VOL 1
ISSUE 1
2022

ISSN 2816-5152 (PRINT)
ISSN 2816-5160 (ONLINE)

CANADIAN HEMATOLOGY TODAY

Canadian Hematology Today is published 3 times per year in English and French.

The content in *Canadian Hematology Today* qualifies for Section 2 (self-learning) credits towards the maintenance of certification. For information on how this activity fits in the Royal College Maintenance of Certification (MOC) Program, please visit the Royal College's website (royalcollege.ca/moc). For more personalized support, please contact the Royal College Services Centre (1-800-461-9598) or your local CPD Educator.

If you would like to contribute to a future issue of *Canadian Hematology Today* please email us at info@catalytichealth.com

EDITORIAL BOARD

EDITORS WELCOME

Dear Canadian Hematology Community,

It is with great pleasure that we welcome and introduce you to the inaugural issue of *Canadian Hematology Today*. As disease management becomes more complex and as we have more therapies in our arsenal, it is becoming even more important to communicate and share best practices and techniques across the clinical community.

We are tremendously proud of the content in this issue and the forthcoming issues in 2022. We are also incredibly grateful to all the authors who have contributed to this journal. Of course, we would be remiss if we didn't also thank all the advertising partners for their support in helping us launch this exciting peer-to-peer initiative.

As the journal continues to grow, we welcome new ideas, new topics and new submissions which can be sent directly to info@catalytichealth.com. The journal's aim is to provide practical and pragmatic real-world content that helps to inform disease management for Canadian clinicians.

We do sincerely hope you enjoy this first issue, and we look forward to your readership and your ideas for future articles as we grow and expand the reach of this publication!

Best wishes,

Peter Anglin, MD   Laurie H. Sehn, MD   Julie Stakiw, MD   Darrell White, MD

TABLE OF CONTENTS

FROM CANADA.
FOR CANADA.

What happens when you bring together a team of Canadian life sciences specialists with a passion for making a profound difference?

You get the opportunity to unlock Canada's potential as a global life sciences innovator, and the promise of novel treatments to enhance the lives of Canadian hematology-oncology patients.

For science. For Canada. For patients.

FORUS
THERAPEUTICS

ForusTherapeutics.com

ABOUT THE AUTHOR

James A. Kennedy, MD PhD, FRCPC

Dr. Kennedy is a Malignant Hematologist at Sunnybrook Health Sciences Centre and Assistant Professor at the University of Toronto. He completed the combined MD/PhD program in Toronto, where his graduate research focused on developing experimental models of hematologic malignancies. Building on this background, he subsequently completed residency training in Internal Medicine and Hematology, also at the University of Toronto, then enrolled in a combined clinical/research malignant hematology fellowship, splitting time between the Princess Margaret Cancer Centre and Brigham & Women's Hospital / Harvard Medical School. From a research standpoint, James is interested in understanding the genetic events that drive the leukemogenic process and how these can be targeted therapeutically. His clinical focus at Sunnybrook Health Sciences Centre encompasses acute leukemia, bone marrow failure and chronic myeloid malignancies.

NEXT GENERATION SEQUENCING FOR MYELOID MALIGNANCIES – PROGRESS AND PRACTICAL APPLICATIONS

Over the past two decades, next-generation sequencing (NGS) has revolutionized our understanding of the pathogenesis of myeloid neoplasms (MNs) and their clinical management. While traditional Sanger sequencing allows for the interrogation of single loci, NGS enables the parallel sequencing of multiple genomic locations, ranging from targeted sets of genes to the entire genome. Initially, NGS was used predominantly in research, where the ability to interrogate large regions of the genome facilitated the discovery of genes recurrently mutated in myeloid malignancies. Soon thereafter, NGS entered the clinical realm where it is now routinely utilized in diagnosis, prognostication and treatment decision-making. However, the broad availability of clinical NGS comes with a unique set of challenges. Hematologists must interpret complex molecular reports and appropriately apply the provided mutational information to their patients' care in real-time. Consequently, a systematic approach to interpreting NGS reports is crucial; the following will outline one such framework.

1) Understand the range of genetic alterations detectable by your panel

A detailed understanding of the mutational landscape of MNs has emerged over the past 20 years. Whole genome and exome sequencing of patient samples has led to the discovery of a set of ~40 genes recurrently mutated in acute myeloid leukemia (AML), myelodysplastic syndrome (MDS) and myeloproliferative neoplasms (MPN). Importantly, these genes can be organized into a limited number of biological categories, highlighting the key cellular processes whose deregulation drives pathologic myelopoiesis: RNA splicing, epigenetic regulation, the cohesin complex, transcription factors, the DNA damage response, and signal transduction (**Table 1**).[1,2]

By focusing on these recurrently mutated genes, targeted 'myeloid' NGS panels have been developed. The Association of Molecular Pathology has proposed a minimum gene list for chronic myeloid neoplasms (**Table 1, bold genes**).[3] However, the content of myeloid panels can vary with respect to the specific genes included as well as their covered regions (i.e.: hotspot vs. complete coding sequence). Early generation myeloid panels may not contain genes whose relevance to MNs has emerged more recently, such as *PPM1D* (implicated in therapy-related MNs)[4] and *DDX41* (implicated in familial MDS/AML).[5] NGS platforms can also differ from a technical standpoint, influencing their sensitivity and the types of variants that can be detected. For example, by using RNA as a starting material, some panels can detect reciprocal gene rearrangements, such as *PML-RARA, RUNX1-RUNX1T1* and *CBFB-MYH11*, which have previously required standalone RT-PCR based assays or cytogenetics/FISH for their detection.[6]

To assist clinicians, NGS reports contain a wealth of information including the genomic regions being interrogated, the assay technology, the bioinformatic pipeline, as well as the types of genetic alterations that can be detected with their associated

Molecular category	Genes
Splicing factors	***SF3B1, SRSF2, U2AF1, ZRSR2***
Epigenetic regulation	
DNA methylation	***DNMT3A, TET2, IDH1/2***
Histone methylation	***ASXL1, EZH2, BCOR, BCORL1,*** *KMT2A,* ***SETBP1***
Cohesin subunits	***STAG2, RAD21, SMC1A, SMC3***
Transcription factors	***RUNX1, ETV6, CEBPA,*** *CUX1, GATA2,* ***PHF6***
Signal transduction	
JAK-STAT	***JAK2, CALR, MPL, CSF3R***
RAS	***KRAS, NRAS, PTPN11, CBL, NF1,*** *GNAS, BRAF*
Other	***FLT3, KIT***
DNA repair	***TP53, PPM1D***
Miscellaneous	***NPM1,*** *DDX41, ETNK1*

Table 1. *Recurrently mutated genes in myeloid malignancies. Bolded genes are part of the Association of Molecular Pathology recommended minimum gene list for chronic myeloid malignancies; adapted from McClure et al, 2018*

sensitivity limits. Familiarity with these technical details is important for clinicians in order to fully appreciate the strengths and limitations of the NGS platform in use, and how this may impact the variants that are ultimately reported.

2) Review the reported variants and evidence supporting their pathogenicity

Though practices vary, molecular labs follow general guidelines for the reporting of mutations.[7] Genetic variants are listed using Human Genome Variation Society (HGVS) nomenclature (**Table 2**).[8] The detected variants can range from benign germline polymorphisms, to pathogenic driver mutations, to incidental passenger mutations lacking a discernible impact on leukemogenesis. Given this complexity, evidence-based variant annotation performed by molecular diagnostics specialists is a critical upstream analytical step.

For MNs, the ideal method to distinguish between tumor-associated alterations and germline changes is to compare mutation patterns in skin fibroblasts to those present in the blood. However, such analysis is usually limited to the investigation of inherited predisposition syndromes. Instead, probable germline polymorphisms are identified using data from large databases that have pooled genetic information from healthy populations, such as the Genome Aggregation Database (gnomAD).[9] In practice, variants with greater than 1% frequency in the general population are presumed to represent germline polymorphisms and are filtered out prior to clinical reporting. Certain variant allelic frequencies (VAF) can also be suggestive of a germline alterations (i.e.: 40-60% for assumed heterozygosity); however, VAF is not a fully reliable estimate of zygosity as it can be influenced by copy number as well as the relative proportion of the mutant cell clone.[11] Myeloid NGS panels, though primarily focused on the detection of somatic variants, do include genes such as *TP53, RUNX1, GATA2, CEBPA* and *DDX41* whose alteration in the germline can predispose to the development of MNs.[5,10] Identification of such variants in the blood of patients with a suggestive family/clinical history should prompt sequence analysis of skin fibroblasts for confirmation of germline status and genetic counselling.

A second challenge centers around evaluation of the pathogenicity of detected variants. In general, this is performed by pooling evidence from sources including large scale cancer databases (i.e.: The Catalogue of Somatic Mutations in Cancer, COSMIC)[12], healthy population databases (i.e.: gnomAD), clinically annotated mutation databases (i.e.: ClinVar), in silico tools that predict the functional consequences of a given mutation (i.e.: SIFT) and primary scientific literature.[11] An evidence-based tiered system for categorizing variants is in broad use (**Table 3**), and facilitates the identification of variants of clinical significance for hematologists.[7]

3) Clinical application of the provided mutational data

Diagnosis: The 2016 World Health Organization (WHO) MN diagnostic criteria rely heavily on CBC parameters, morphologic assessment of the bone marrow (BM) and cytogenetics, with a relatively smaller role for gene mutations.[13] Though a common cadre of genes are mutated in MNs, disease-defining genetic alterations are rare, with certain notable exceptions. Activating mutations in *JAK2* are present in ~99% of polycythemia vera cases, and the majority of patients with essential thrombocythemia and

Variant Type	Example	Breakdown	Description
Substitution	JAK2 (NM_004972.3) c.1849G>T p.(Val617Phe)	*Gene:* JAK2 *Transcript ID:* NM_004972.3 *cDNA change:* c.1849G>T *Amino acid change:* p.(Val617Phe)	cDNA nucleotide 1849 (G) changed to T Amino acid 617 (Val) changed to Phe
Nonsense	TET2 (NM_001127208.2) c.5298C>G p.Tyr1766*	*Gene:* TET2 *Transcript ID:* NM_001127208.2 *cDNA change:* c.5298C>G *Amino acid change:* p.(Tyr1766*)	cDNA nucleotide 5298 (C) changed to G Amino acid 1766 (Tyr) changed to stop codon
Insertion - frameshift	CALR (NM_004343.3) c.1154_1155insTTGTC p.(Lys385Asnfs*47)	*Gene:* CALR *Transcript ID:* NM_004343.3 *cDNA change:* c.1154_1155insTTGTC *Amino acid change:* p.(Lys385Asnfs*47)	Insertion of TTGTC between cDNA positions 1154 & 1155 Lys385 changed to Asn & reading frame altered with a stop codon 47 amino acids later
Deletion - frameshift	EZH2 (NM_004456.4) c.928delA p.Thr310Leufs*11	*Gene:* EZH2 *Transcript ID:* NM_004456.4 *cDNA change:* c.928delA *Amino acid change:* p.(Thr310Leufs*11)	Deletion of A at cDNA position 928 Thr310 changed to Leu & reading frame altered with a stop codon 11 amino acids later
Duplication – in-frame	SRSF2 (NM_001195427.1) c.281_283dupGCC p.(Arg94dup)	*Gene:* SRSF2 *Transcript ID:* NM_001195427.1 *cDNA change:* c.281_283dupGCC *Amino acid change:* p.(Arg94dup)	Duplication of cDNA nucleotides 281-283 (GCC) Duplication of amino acid 94 (Arg)
Deletion – in-frame	CALR (NM_004343.3) c.1191_1199del p.(Glu398_Asp400del)	*Gene:* CALR *Transcript ID:* NM_004343.3 *cDNA change:* c.1191_1199del *Amino acid change:* p.(Glu398_Asp400del)	Deletion of 9 nucleotides between cDNA positions 1191 & 1199 Deletion of amino acids 398 to 400
Splice site	CBL NM_005188.3 c.1096-1G>C	*Gene:* CBL *Transcript ID:* NM_005188.3 *cDNA change:* c.1096-1G>C	cDNA nucleotide 1096 is the start of exon 8. In the corresponding genomic sequence, 1 nucleotide prior to nt 1096 (the -1 position) is part of the splice acceptor site (AG). Substitution of G to C disrupts the splice acceptor site, resulting in deletion of exon8.[43]

Table 2. *Variant nomenclature examples; adapted from den Dunnen et al, 2016*

Tier		Level of Evidence	Description
I	Variants of Strong Clinical Significance	A	Included in professional guidelines related to disease diagnosis, prognosis and/or therapy Targeted by an FDA-approved therapy
		B	Described in well-powered studies with consensus from experts in the field
II	Variants of Potential Clinical Significance	C	Described in multiple small, published studies with some consensus Targeted by either FDA-approved therapies in different tumor types or investigational therapies
		D	Described in preclinical trials or a few case reports without consensus
III	Variants of Unknown Clinical Significance		Not observed at significant allele frequency in the general or specific subpopulation databases, or pan-cancer or tumor-specific variant databases No convincing published evidence of cancer association
IV	Benign or Likely Benign Variants		Observed at significant allele frequency in the general or specific subpopulation databases No existing published evidence of cancer association

Table 3. *A four-tiered system to categorize somatic sequence variations – based on consensus recommendations from the Association for Molecular Pathology; adapted from Li et al, 2016*

myelofibrosis carry a driver mutation in one of *JAK2, CALR* or *MPL*.[14] In the pediatric realm, more than 90% of cases of juvenile myelomonocytic leukemia carry an activating mutation in genes involved in RAS pathway regulation (*KRAS, NRAS, PTPN11, CB*L or *NF1*), leading to their incorporation into its diagnostic criteria.[13] Lastly, mutations in the splicing factor *SF3B1* are enriched in MN patients with ringed sideroblasts (RS).[15] The specificity of this association is reflected in the WHO diagnostic criteria for MDS-RS, where, in the presence of cytopenias and dysplasia, detection of an *SF3B1* mutation can establish this diagnosis when RS comprise as few as 5% of all nucleated erythroid cells, compared to the traditional cutoff of 15%.[13]

Conversely, the majority of genes recurrently mutated in myeloid malignancies are not specific to a particular disease entity; for example, *TET2* mutations are prevalent in AML, MDS, MPNs and MPN/MDS overlap syndromes.[16] Complicating matters further, recurrent somatic mutations in MN-associated genes have been identified in the blood of individuals without hematologic disease.[17–19] These mutations are a strong independent predictor for the future development of MNs. However, the absolute risk of malignant transformation is low, approximately 0.5-1% per year, leading to this entity being termed "clonal hematopoiesis of indeterminate potential" (CHIP).[20] Thus, clonality, as defined by the presence of MN-associated somatic mutations, should not be considered as definitive evidence of a frank hematologic malignancy in the absence of supporting CBC alterations or BM pathology.

Prognosis: Given the central pathogenic role of gene mutations in MNs, it follows that they have the potential to provide insight into disease risk. The European Leukemia Net (ELN) has proposed a risk stratification schema for AML based on cytogenetic and NGS findings (**Table 4A**).[21] Biallelic mutations in *CEBPA* or *NPM1* alterations confer a favorable prognosis, whereas mutations in *ASXL1, RUNX1, TP53* and *FLT3-ITD* (particularly at a high allelic ratio), confer an adverse risk, prompting clinicians to consider consolidative allogeneic stem cell transplant (allo-SCT) in eligible patients.

Risk category	Genetic abnormality
Favorable	t(8;21)(q22;q22.1); *RUNX1-RUNX1T1* inv(16)(p13.1q22) or t(16;16)(p13.1;q22); *CBFB-MYH11* Mutated *NPM1* without *FLT3-ITD* or with *FLT3-ITD*^{low*} Biallelic mutated *CEBPA*
Intermediate	Wildtype *NPM1* without *FLT3-ITD* or with *FLT3-ITD*^{low**} Mutated *NPM1* with *FLT3-ITD*^{high} t(9;11)(p21.3;q23.3); *MLLT3-KMT2A* Cytogenetic abnormalities not classified as favorable or adverse
Adverse	t(6;9)(q23;q34.1); *DEK-NUP214* t(v;11q23.3); *KMT2A* rearranged t(9;22)(q34.1;q11.2); *BCR-ABL1* inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2); *GATA2, MECOM (EVI1)* -5 or del(5q); -7; -17/abn(17p) Complex or monosomal karyotype§ Wildtype *NPM1* with *FLT3-ITD*^{high} Mutated *RUNX1*¶ Mutated *ASXL1*¶ Mutated *TP53*

Table 4A. *ELN AML risk stratification; adapted from Döhner et al, 2016.*
** Allelic ratio, calculated as FLT3-ITD/FLT3-wildtype; low < 0.5; high ≥ 0.5*
*** without adverse-risk genetic lesions*
§ Complex cytogenetics: 3 or more unrelated chromosomal abnormalities; Monosomal karyotype: 1 single monosomy in association with at least 1 additional monosomy or chromosomal abnormality
¶ Unless occur with favorable-risk AML subtypes

NGS-based risk stratification is also emerging for chronic myeloid malignancies. Mutations in *ASXL1, EZH2, IDH1/2, SRSF2* and *U2AF1* (at Q157) define a high molecular risk group in myelofibrosis,[22,23] and are integrated alongside traditional risk factors in prognostic scoring systems such as the MIPSS70[24] and MIPSS70 plus version 2.0[25] (**Table 4B/C**) which strive to identify patients where allogeneic SCT should be considered. Similarly, for MDS, several groups have developed scoring systems that improve upon the traditional International Prognosis Scoring System (IPSS) and IPSS-R by integrating mutational data.[26–28] While the exact molecular features of these scoring systems vary, common themes have emerged. For example, a higher absolute number of mutated genes as well as TP53 alterations (particularly bi-allelic) confer negative prognostic impact,[29] while SF3B1 alterations are generally associated with lower risk disease, though this can be modulated by co-mutation.[28] A notable strength of these novel scoring systems is that instead of simply classifying patients into broad categories, personalized outcome predictions are generated for each patient, enabling a more refined estimate of disease risk.

***Therapy*:** The genetic profile of a MN can also provide key information regarding responsiveness to therapy. For example, IDH1/2 mutant AML blasts have an intrinsically lower apoptotic threshold, rendering them particularly sensitive to depletion of the anti-apoptotic protein, BCL2.[30] Consequently, IDH mutant AMLs are highly responsive to therapeutic regimens containing the BCL2 inhibitor venetoclax.[31,32] In MDS, there has been much interest in using molecular data to predict responsiveness to hypomethylating agents (HMA). In some studies, TET2 mutations have predicted a favorable treatment response, particularly among individuals where it is an early, clonal mutation.[33–35] However, in a recent study using a machine-learning approach, no single or combination of gene mutations predicted HMA responsiveness; instead, eight genomic combinations predicting HMA resistance were identified. While further validation is required, such analyses

Risk factor	Score
Hemoglobin < 100 g/L	1
Leukocytes > 25 x 10^9/L	2
Platelets < 100 x 10^9/L	2
Circulating blasts ≥ 2%	1
Constitutional symptoms*	1
MF fibrosis grade ≥2	1
HMR category§	1
Absence of CALR type 1 mutation	1
2 or more HMR mutations	2

Risk group	Overall score	Median OS
Low	0-1	27.7 years
Intermediate	2-4	7.1 years
High	≥ 5	2.3 years

Table 4B. *Myelofibrosis - MIPSS70; adapted from Guglielmelli et al, 2018*
** Weight loss >10% of baseline in the year before diagnosis, unexplained fever or excessive sweats persisting for more than 1 month.*
§ HMR category: mutation in any one of ASXL1, EZH2, SRSF2 or IDH1/2

Risk factor	Score
Anemia	
80-99 g/L (women); 90-109 g/L (men)	1
< 80 g/L (women); < 90 g/L (men)	2
Circulating blasts ≥ 2%	1
Constitutional symptoms*	2
HMR category§	2
Absence of CALR type 1 mutation	2
2 or more HMR mutations	3
Cytogenetics¶	
Unfavorable	3
Very high risk	4

Risk group	Overall score	Median OS
Very low	0	Not reached
Low	1-2	16.4 years
Intermediate	3-4	7.7 years
High	5-8	4.1 years
Very high	≥ 9	1.8 years

Table 4C. *Myelofibrosis - MIPSS70 Plus version 2.0; adapted from Tefferi et al, 2018*
** Weight loss >10% of baseline in the year before diagnosis, unexplained fever or excessive sweats persisting for more than 1 month*
§ HMR category: mutation in any one of ASXL1, EZH2, SRSF2, IDH1/2 or U2AF1 at amino acid Q157
¶ Cytogenetic classification as per reference 44
- Favorable: Normal karyotype; Sole 20q−; Sole 13q−; Sole +9; Sole sex chromosome abnormality; Sole chromosome 1 translocation/duplication
- Unfavorable: Sole +8; Sole 7q−; Sole translocations not involving chromosome 1; Two abnormalities not including a VHR abnormality; Single/multiple 5q− abnormalities; Complex karyotype without a VHR abnormality; Monosomal karyotype without a VHR abnormality; Sole abnormalities not otherwise classified
- Very high risk: Single/multiple monosomy 7; Single/multiple inv(3)/3q21 abnormalities; Single/multiple i(17q) abnormalities; Single/multiple 12p−/12p11.2 abnormalities; Single/multiple 11q−/11q23 abnormalities; Single/multiple autosomal trisomies other than +8 or +9 (e.g., +21, +19)

highlight the power of evaluating gene mutations, not in isolation, but in networks to discern their clinical relevance.

Uncovering the mutational landscape of MNs has also fueled the development of novel therapies that target specific gene mutations. The FLT3 inhibitors midostaurin and gilteritinib have emerged as efficacious therapies for newly diagnosed and relapse/refractory (R/R) FLT3-mutant AML, respectively.[36,37] Similarly, ivosidenib and enasidenib have shown promising results for IDH1 and IDH2 mutant R/R AML.[38,39] Additional targeted therapies are currently at early stages of development. For example, eprenetapopt, a small molecule that restores wildtype p53 function to cells bearing TP53 mutations, is currently under study in TP53 mutant MNs.[40] The spliceosome inhibitor H3B-8800 is being evaluated in early phase clinical trials, hoping to exploit the inherent vulnerability of cells with heterozygous splicing factor mutations to further inhibition of the splicing machinery.[41,42] Together, these therapies portend an exciting future where NGS will inform personalized therapeutic approaches in patients with MNs.

Conclusion

The advent of NGS technology has revolutionized our understanding of MN pathogenesis while offering significant potential for clinical application. As evidence continues to accumulate highlighting its utility, physicians must learn to integrate this information into routine practice. In addition to keeping abreast of the ever-expanding literature in this field, a working understanding of the technical and bioinformatic details pertaining to the sequencing platform in use is also required. As clinicians continue to gain familiarity with NGS, the future is extremely bright, as molecular profiling will be central to ongoing efforts to provide personalized care to patients through individualized predictions of disease risk and tailored therapeutic regimens.

Acknowledgements: The author would like to thank Dr. Marta Davidson for critical comments on the manuscript.

References

1. Sperling AS, Gibson CJ, Ebert BL. The genetics of myelodysplastic syndrome: from clonal haematopoiesis to secondary leukaemia. Nat Rev Cancer. 2017;17(1):5-19. doi:10.1038/nrc.2016.112

2. Kennedy JA, Ebert BL. Clinical Implications of Genetic Mutations in Myelodysplastic Syndrome. J Clin Oncol Off J Am Soc Clin Oncol. 2017;35(9):968-974. doi:10.1200/JCO.2016.71.0806

3. McClure RF, Ewalt MD, Crow J, et al. Clinical Significance of DNA Variants in Chronic Myeloid Neoplasms: A Report of the Association for Molecular Pathology. J Mol Diagn JMD. 2018;20(6):717-737. doi:10.1016/j.jmoldx.2018.07.002

4. Lindsley RC, Saber W, Mar BG, et al. Prognostic Mutations in Myelodysplastic Syndrome after Stem-Cell Transplantation. N Engl J Med. 2017;376(6):536-547. doi:10.1056/NEJMoa1611604

5. Feurstein S, Drazer M, Godley LA. Germline predisposition to hematopoietic malignancies. Hum Mol Genet. 2021;30(20):R225-R235. doi:10.1093/hmg/ddab141

6. Ferrone CK, Wong H, Semenuk L, et al. Validation, Implementation, and Clinical Impact of the Oncomine Myeloid Targeted-Amplicon DNA and RNA Ion Semiconductor Sequencing Assay. J Mol Diagn JMD. 2021;23(10):1292-1305. doi:10.1016/j.jmoldx.2021.07.010

7. Li MM, Datto M, Duncavage EJ, et al. Standards and Guidelines for the Interpretation and Reporting of Sequence Variants in Cancer: A Joint Consensus Recommendation of the Association for Molecular Pathology, American Society of Clinical Oncology, and College of American Pathologists. J Mol Diagn JMD. 2017;19(1):4-23. doi:10.1016/j.jmoldx.2016.10.002

8. den Dunnen JT, Dalgleish R, Maglott DR, et al. HGVS Recommendations for the Description of Sequence Variants: 2016 Update. Hum Mutat. 2016;37(6):564-569. doi:10.1002/humu.22981

9. Karczewski KJ, Francioli LC, Tiao G, et al. The mutational constraint spectrum quantified from variation in 141,456 humans. Nature. 2020;581(7809):434-443. doi:10.1038/s41586-020-2308-7

10. DiNardo CD, Routbort MJ, Bannon SA, et al. Improving the detection of patients with inherited predispositions to hematologic malignancies using next-generation sequencing-based leukemia prognostication panels. Cancer. 2018;124(13):2704-2713. doi:10.1002/cncr.31331

11. Bacher U, Shumilov E, Flach J, et al. Challenges in the introduction of next-generation sequencing (NGS) for diagnostics of myeloid malignancies into clinical routine use. Blood Cancer J. 2018;8(11):113. doi:10.1038/s41408-018-0148-6

12. Tate JG, Bamford S, Jubb HC, et al. COSMIC: the Catalogue Of Somatic Mutations In Cancer. Nucleic Acids Res. 2019;47(Database issue):D941-D947. doi:10.1093/nar/gky1015

13. Arber DA, Orazi A, Hasserjian R, et al. The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia. Blood. 2016;127(20):2391-2405. doi:10.1182/blood-2016-03-643544

14. Marneth AE, Mullally A. The Molecular Genetics of Myeloproliferative Neoplasms. Cold Spring Harb Perspect Med. 2020;10(2):a034876. doi:10.1101/cshperspect.a034876

15. Papaemmanuil E, Cazzola M, Boultwood J, et al. Somatic SF3B1 mutation in myelodysplasia with ring sideroblasts. N Engl J Med. 2011;365(15):1384-1395. doi:10.1056/NEJMoa1103283

16. Delhommeau F, Dupont S, Della Valle V, et al. Mutation in TET2 in myeloid cancers. N Engl J Med. 2009;360(22):2289-2301. doi:10.1056/NEJMoa0810069

17. Xie M, Lu C, Wang J, et al. Age-related mutations associated with clonal hematopoietic expansion and malignancies. Nat Med. 2014;20(12):1472-1478. doi:10.1038/nm.3733

18. Genovese G, Kähler AK, Handsaker RE, et al. Clonal hematopoiesis and blood-cancer risk inferred from blood DNA sequence. N Engl J Med. 2014;371(26):2477-2487. doi:10.1056/NEJMoa1409405

19. Jaiswal S, Fontanillas P, Flannick J, et al. Age-related clonal hematopoiesis associated with adverse outcomes. N Engl J Med. 2014;371(26):2488-2498. doi:10.1056/NEJMoa1408617

20. Steensma DP, Bejar R, Jaiswal S, et al. Clonal hematopoiesis of indeterminate potential and its distinction from myelodysplastic syndromes. Blood. 2015;126(1):9-16. doi:10.1182/blood-2015-03-631747

21. Döhner H, Estey E, Grimwade D, et al. Diagnosis and management of AML in adults: 2017 ELN recommendations from an international expert panel. Blood. 2017;129(4):424-447. doi:10.1182/blood-2016-08-733196

22. Vannucchi AM, Lasho TL, Guglielmelli P, et al. Mutations and prognosis in primary myelofibrosis. Leukemia. 2013;27(9):1861-1869. doi:10.1038/leu.2013.119

23. Tefferi A, Finke CM, Lasho TL, et al. U2AF1 mutation types in primary myelofibrosis: phenotypic and prognostic distinctions. Leukemia. 2018;32(10):2274-2278. doi:10.1038/s41375-018-0078-0

24. Guglielmelli P, Lasho TL, Rotunno G, et al. MIPSS70: Mutation-Enhanced International Prognostic Score System for Transplantation-Age Patients With Primary Myelofibrosis. J Clin Oncol Off J Am Soc Clin Oncol. 2018;36(4):310-318. doi:10.1200/JCO.2017.76.4886

25. Tefferi A, Guglielmelli P, Lasho TL, et al. MIPSS70+ Version 2.0: Mutation and Karyotype-Enhanced International Prognostic Scoring System for Primary Myelofibrosis. J Clin Oncol Off J Am Soc Clin Oncol. 2018;36(17):1769-1770. doi:10.1200/JCO.2018.78.9867

26. Nazha A, Komrokji R, Meggendorfer M, et al. Personalized Prediction Model to Risk Stratify Patients With Myelodysplastic Syndromes. J Clin Oncol Off J Am Soc Clin Oncol. 2021;39(33):3737-3746. doi:10.1200/JCO.20.02810

27. Bersanelli M, Travaglino E, Meggendorfer M, et al. Classification and Personalized Prognostic Assessment on the Basis of Clinical and Genomic Features in Myelodysplastic Syndromes. J Clin Oncol. 2021;39(11):1223-1233. doi:10.1200/JCO.20.01659

28. Bernard E. Molecular International Prognosis Scoring System for Myelodysplastic Syndromes. In: ASH; 2021. Accessed February 12, 2022. https://ash.confex.com/ash/2021/webprogram/Paper150554.html

29. Bernard E, Nannya Y, Hasserjian RP, et al. Implications of TP53 allelic state for genome stability, clinical presentation and outcomes in myelodysplastic syndromes. Nat Med. 2020;26(10):1549-1556. doi:10.1038/s41591-020-1008-z

30. Chan SM, Thomas D, Corces-Zimmerman MR, et al. Isocitrate dehydrogenase 1 and 2 mutations induce BCL-2 dependence in acute myeloid leukemia. Nat Med. 2015;21(2):178-184. doi:10.1038/nm.3788

31. DiNardo CD, Jonas BA, Pullarkat V, et al. Azacitidine and Venetoclax in Previously Untreated Acute Myeloid Leukemia. N Engl J Med. 2020;383(7):617-629. doi:10.1056/NEJMoa2012971

32. Wei AH, Montesinos P, Ivanov V, et al. Venetoclax plus LDAC for newly diagnosed AML ineligible for intensive chemotherapy: a phase 3 randomized placebo-controlled trial. Blood. 2020;135(24):2137-2145. doi:10.1182/blood.2020004856

33. Itzykson R, Kosmider O, Cluzeau T, et al. Impact of TET2 mutations on response rate to azacitidine in myelodysplastic syndromes and low blast count acute myeloid leukemias. Leukemia. 2011;25(7):1147-1152. doi:10.1038/leu.2011.71

34. Bejar R, Lord A, Stevenson K, et al. TET2 mutations predict response to hypomethylating agents in myelodysplastic syndrome patients. Blood. 2014;124(17):2705-2712. doi:10.1182/blood-2014-06-582809

35. Traina F, Visconte V, Elson P, et al. Impact of molecular mutations on treatment response to DNMT inhibitors in myelodysplasia and related neoplasms. Leukemia. 2014;28(1):78-87. doi:10.1038/leu.2013.269

36. Stone RM, Mandrekar SJ, Sanford BL, et al. Midostaurin plus Chemotherapy for Acute Myeloid Leukemia with a FLT3 Mutation. N Engl J Med. 2017;377(5):454-464. doi:10.1056/NEJMoa1614359

37. Perl AE, Martinelli G, Cortes JE, et al. Gilteritinib or Chemotherapy for Relapsed or Refractory FLT3-Mutated AML. N Engl J Med. 2019;381(18):1728-1740. doi:10.1056/NEJMoa1902688

38. Stein EM, DiNardo CD, Pollyea DA, et al. Enasidenib in mutant IDH2 relapsed or refractory acute myeloid leukemia. Blood. 2017;130(6):722-731. doi:10.1182/blood-2017-04-779405

39. DiNardo CD, Stein EM, de Botton S, et al. Durable Remissions with Ivosidenib in IDH1-Mutated Relapsed or Refractory AML. N Engl J Med. 2018;378(25):2386-2398. doi:10.1056/NEJMoa1716984

40. Sallman DA, DeZern AE, Garcia-Manero G, et al. Eprenetapopt (APR-246) and Azacitidine in TP53-Mutant Myelodysplastic Syndromes. J Clin Oncol Off J Am Soc Clin Oncol. 2021;39(14):1584-1594. doi:10.1200/JCO.20.02341

41. Lee SCW, Dvinge H, Kim E, et al. Modulation of splicing catalysis for therapeutic targeting of leukemia with mutations in genes encoding spliceosomal proteins. Nat Med. 2016;22(6):672-678. doi:10.1038/nm.4097

42. Steensma DP, Wermke M, Klimek VM, et al. Phase I First-in-Human Dose Escalation Study of the oral SF3B1 modulator H3B-8800 in myeloid neoplasms. Leukemia. 2021;35(12):3542-3550. doi:10.1038/s41375-021-01328-9

43. Niemeyer CM, Kang MW, Shin DH, et al. Germline CBL mutations cause developmental abnormalities and predispose to juvenile myelomonocytic leukemia. Nat Genet. 2010;42(9):794-800. doi:10.1038/ng.641

44. Tefferi A, Nicolosi M, Mudireddy M, et al. Revised cytogenetic risk stratification in primary myelofibrosis: analysis based on 1002 informative patients. Leukemia. 2018;32(5):1189-1199. doi:10.1038/s41375-018-0018-z

ABOUT THE AUTHOR

Roopesh Kansara, MD, FRCPC

Dr. Roopesh Kansara is a staff Hematologist within the Department of Internal medicine, University of Manitoba. He is appointed as an assistant professor and is also the Program Director for Adult Hematology subspecialty program at the University of Manitoba. He pursued his Medicine and Hematology subspecialty training at the University of Manitoba followed by further training in Lymphoproliferative disorders at the British Columbia Cancer Agency (Vancouver). He treats both malignant and benign hematologic disorders but with special focus on Lymphoproliferative neoplasms especially CNS B-cell lymphomas.

MANAGEMENT OF FOLLICULAR LYMPHOMA AT FIRST RELAPSE

Follicular lymphoma (FL) is the most common subtype of indolent B-cell non-Hodgkin's lymphoma (NHL). Histologically, it is subcategorized as grade 1, 2, 3A or 3B[1]. FL, grade 3B is considered an aggressive form of the disease and is managed similar to diffuse large B-cell lymphoma (DLBCL). The intent of this article is to discuss the management of FL at first relapse. However, the knowledge of upfront management strategy is crucial in planning treatment in the event of a relapse.

FL lymphoma is an incurable disease except for small subset patients with limited stage disease (Stage I/II); with local radiotherapy, these patients may attain a 50 to 70% chance of cure[2]. For those with advanced stage disease (Stage III/IV), upfront management strategies include a wait and watch (WW) approach[3–6], monotherapy with rituximab[7] or a combination of anti-CD20 monoclonal antibodies and systemic chemotherapy/oral agents. WW and monotherapy with rituximab are typically pursued for patients with stage III/IV (including extensive limited stage not amenable to radiation) who are asymptomatic and do not meet criteria for treatment.

For patients meeting the indications for upfront treatment, several options are available that combine anti-CD20 monoclonal antibodies with either systemic chemotherapy or oral agents (lenalidomide). R-CHOP (rituximab, cyclophosphamide, vincristine, prednisone)[8], R-CVP (rituximab, cyclophosphamide, vincristine, prednisone)[9] and R-FM (rituximab, fludarabine, mitoxantrone)[10] have been widely used for upfront management of FL. Both R-CHOP and R-FM have demonstrated similar outcomes but superior 3-year progression free survival (PFS) and time to treatment failure (TTF) compared to R-CVP[11]. Trials comparing bendamustine and rituximab (BR) to R-CHOP and/or R-CVP show superior PFS and lesser toxicities with the BR[12,13] regimen. Therefore, BR is, the most preferred choice for upfront treatment of patients with FL, grades 1 to 2. Some centers have extrapolated the results of the STiL and BRIGHT trials to include FL, grade 3A (who were excluded in both of these studies) whereas some offer R-CHOP therapy to this subset of patients. The current body of data does not support upfront stem cell transplantation (SCT) following induction chemo-immunotherapy[14]. Instead, following upfront systemic therapy, maintenance rituximab (MR) is pursued for patients who attain a complete response (CR) or partial (PR) response to induction therapy based on improved PFS[15]. It should be noted that there are currently no definitive studies demonstrating an OS benefit with MR and there is a paucity of prospective data to support the use of MR versus observation following BR, however several retrospective studies support MR following BR[16].

The management of patients with untreated FL continues to evolve. In a multicenter, international, phase 3 superiority trial to evaluate rituximab plus lenalidomide, as compared with rituximab plus chemotherapy, in patients with previously untreated follicular lymphoma, patients were randomly assigned to receive one of the two regimens, followed by maintenance monotherapy with rituximab. Lenalidomide plus rituximab (R2) when compared to R-chemotherapy (BR, R-CHOP, R-CVP) showed similar 3-year PFS between the two groups with the interim 3-year rate of progression-free survival being 77% (95% CI, 72 to 80) and 78% (95% CI, 74 to 82), in the R2 group compared with the R-chemotherapy group[17] making a new chemo-free treatment option available for patients with FL, grades 1 to 3A (**Table 1)**. This R2 regimen has not been approved for frontline use as the trial was not powered to show non-inferiority.

A novel anti-CD20 monoclonal antibody, obinutuzumab (O), is now available in the first-line management of FL. A study from 2017 compared O-chemotherapy (BO, O-CHOP, O-CVP) followed by O-maintenance (MO) to R-chemotherapy (BR, R-CHOP, R-CVP) followed by MR in treatment of FL, grades 1-3A and demonstrated a significantly better 3-year PFS in the O-chemotherapy group with the estimated 3-year rate of progression-free survival at 80.0% in the O-chemotherapy group compared with 73.3% in the R-chemotherapy group (hazard ratio for progression, relapse, or death, 0.66; 95% confidence interval [CI], 0.51 to 0.85; P=0.001)[18]. Lenalidomide with obinutuzumab (GALEN) also appears to show efficacy in an upfront setting[19].

Treatment at first relapse is determined by numerous factors including the patient's age, performance status, evidence of histologic transformation, first-line approach, type of monoclonal antibody received, whether a maintenance regimen was pursued and the time to first relapse. Among these variables, age and performance status allow for an assessment of eligibility for high dose systemic therapy/ SCT following second-line treatment. The time to relapse is also a critical

Variable	Rituximab-Lenalidomide Group (N= 513)	Rituximab-Chemotherapy Group (N=517)	Hazard Ratio (95%= CI)	P Value
Response status at 120 weeks, as assessed by independent review committee				
Overall response - no. (% [95% CI])	312 (61 [56-65])	336 (65 [61-69])		
Confirmed or unconfirmed complete response - no. (%[95% CI])	247 (48 [44-53])	274 (53 [49-57])		0.13
Complete response, confirmed - no. (%)	142(28)	169 (33)		
Complete response, unconfirmed - no. (%)	105 (20)	105 (20)		
Partial response - no. (%)	65 (13)	62 (12)		
Stable disease - no. (%)	2(<1)	0		
Progressive disease or death - no. (%)*	87 (17)	79 (15)		
Not evaluated or data missing - no. (%)	112 (22)	102(20)		
Response status at 120 weeks, as assessed by investigator				
Overall response - no. (% [95% CI])	335 (65 [61-69])	353 (68 [64-72])		
Confirmed or unconfirmed complete response - no. (%[95% CI)	283 (55 [51-60])	299 (58 [53-62])		0.38
Complete response, confirmed - no. (%)	201 (39)	242(47)		
Complete response, unconfirmed - no. (%)	82(16)	57(11)		
Partial response - no. (%)	52(10)	54(10)		
Stable disease - no. (%)	0	0		
Progressive disease or death - no. (%)*	90(18)	94(18)		
Not evaluated or missing -no. (%)	88(17)	70(14)		
Progression-free survival at 3 years				
Rate, as assessed by independent review committee - %(95% CI)	77(72-80)	78(74-82)	1.10 (0.85-1.43)	0.48
Rate, as assessed by investigator - % (95% CI)	77 (72-80)	78(74-81)	0.94 (0.73-1.22)	0.63
Overall survival rate at 3 years - % (95% CI)	94(91-96)	94(91-96)	1.16 (0.72-1.861	

Table 1. *Efficacy (Intention-to-Treat Population); adapted from Morschhauser F, 2018.*

determinant as patients who relapse within 2 years of initial therapy tend to have poorer overall outcomes requiring the consideration of more aggressive salvage therapies[20,21].

Alternate combination chemotherapy is usually the treatment of choice at relapse. Bendamustine as a second-line treatment option for patients without prior exposure to bendamustine may be considered provided there is no histologic transformation. In a study from 2010, 161 patients were enrolled with a median of 2 previous chemotherapy regimens. Histologies included follicular (68%), small lymphocytic (20%), marginal zone (11%), and lymphoplasmacytic (1%) lymphoma. Sixty patients (34.1%) were refractory to their last chemotherapy, 53 (30.1%) were alkylating agent refractory. The overall response rate (ORR) was 76% with a median 10-month duration of response[22]. Considering monoclonal antibodies are widely available, bendamustine can be combined with rituximab (if not refractory) or obinituzumab (if refractory to rituximab). The use of BR in the treatment of patients with relapsed indolent or mantle cell lymphoma (excluding rituximab refractory patients) produced superior median PFS with BR compared to fludarabine-rituximab (FR) (54.5 months versus 22.9 months, respectively, p= 0.01)[23]. For patients who are rituximab-refractory, bendamustine may be combined with obinutuzumab (BO) based on the outcomes seen in the GADOLIN trial that included patients with indolent B-cell NHL, including FL, grades 1 to 3A[24]. In this study, patients were randomized to receive either BO followed by MO or to bendamustine monotherapy. After a median observation time of 32.6 months (range 0.4 to 65.9) in the obinutuzumab plus bendamustine group and 29.3 months (0 to 65.1) in the bendamustine monotherapy group, progression-free survival was significantly longer with obinutuzumab plus bendamustine (median 25.3 [95% CI 17.4 - 36 months) than with bendamustine monotherapy (14 months [11.3-15.3]; hazard ratio 0.52 [95% CI 0.39-0.69]; p=0.0001). It also showed an OS benefit in the obinutuzumab-arm (Not estimate able versus 53.9 months, p= 0.0061)[24]. Another study recently compared the efficacy of bendamustine in combination with ofatumumab, a second generation anti-CD20 antibody, to bendamustine monotherapy in patients with rituximab-refractory indolent NHL (including FL, grades 1-3A)[25]. Unlike the results seen in the GADOLIN trial, this study showed no benefit to the addition ofatumumab to bendamustine with median IRC-assessed PFS at 16.7 and 13.8 months in the combination and monotherapy arms respectively [hazard ratio (HR) = 0.82; P = 0.1390]. Additionally, the median overall survival (OS) was 58.2 and 51.8 months in the combination and monotherapy arms respectively (HR = 0.89, P = 0.4968). For patients who had already received BR as initial therapy but were not refractory, retreatment with BR may be a reasonable approach at the time of first relapse. Both the StilNHL2 and GADOLIN trials allowed retreatment with bendamustine in the relapse setting if patients were deemed to have been responsive to bendamustine. However, further research is needed to better understand the cumulative long-term effects of re-exposure to bendamustine, and as a result, retreatment is rare.

Given that many patients may have received first-line BR followed by MR, many clinicians choose alternate second-line options such as CHOP, CVP or lenalidomide in combination with rituximab or obinutuzumab (depending on rituximab-refractory status). A small phase II study showed a median time to progression of approximately 47 months for patients with relapsed FL treated with RCHOP[26]. The CALGB 50401 trial comparing lenalidomide with rituximab (LR) to lenalidomide alone (L) showed that LR produced a superior median time to progression (TTP) compared to L alone (2 years versus 1.1 years, respectively)[27]. The same group published results from the AUGMENT trial in which patients with recurrent iNHL (including FL, grades 1 to 3A) were randomized to either the LR arm or the placebo-rituximab arm. The results from this study showed superior PFS in the LR arm compared to the placebo-rituximab arm (**Figure 1**) with a secondary analysis showing favorable OS for FL patients who received LR (hazard ratio 0.45, p= 0.02)[28]. It should be noted that this subgroup analysis was not powered to assess definite OS benefit. Lenalidomide-based combinations have not yet received regulatory approval from Health Canada.

Lenalidomide in combination with obinutuzumab (LO) has also been studied in patients with recurrent FL, grades 1 to 3A. A phase II trial treated recurrent FL patients with LO followed by 1 year of L and 2 years of MO and showed an ORR at the end of induction in the 86 evaluable patients of 79% (95% CI 69–87) with 38% of subjects achieving a CR (95% CI 28–50)[29].

In the event of evident transformed relapsed FL, a CHOP regimen (with R) would be standard for DLBCL[30–32] histology and dose-adjusted EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin) (with R) may be used if the histology shows high-grade B-cell lymphoma with double or triple hit gene rearrangements[33]. Management of these patients however becomes challenging if the patients experience transformed FL after initial treatment with R-CHOP. In this scenario such patients may be managed with salvage combination agents utilized in the management of DLBCL such as GDP (gemcitabine, dexamethasone, cisplatin)[34], ICE (ifosfamide, carboplatin, etoposide)[35], DHAP (dexamethasone, high dose cytarabine, cisplatin)[34,35] with or without monoclonal antibodies. In patients who have experienced transformed FL after initial treatment with R-CHOP, salvage therapy followed by ASCT may be considered.

Following systemic second-line chemo-immunotherapy, further consolidative strategies may be pursued such as SCT or maintenance therapy if patients are deemed to be eligible. If patients are candidates for stem cell transplant therapy, then autologous stem cell transplant (ASCT) or allogeneic stem cell transplant (alloSCT) is considered-- especially

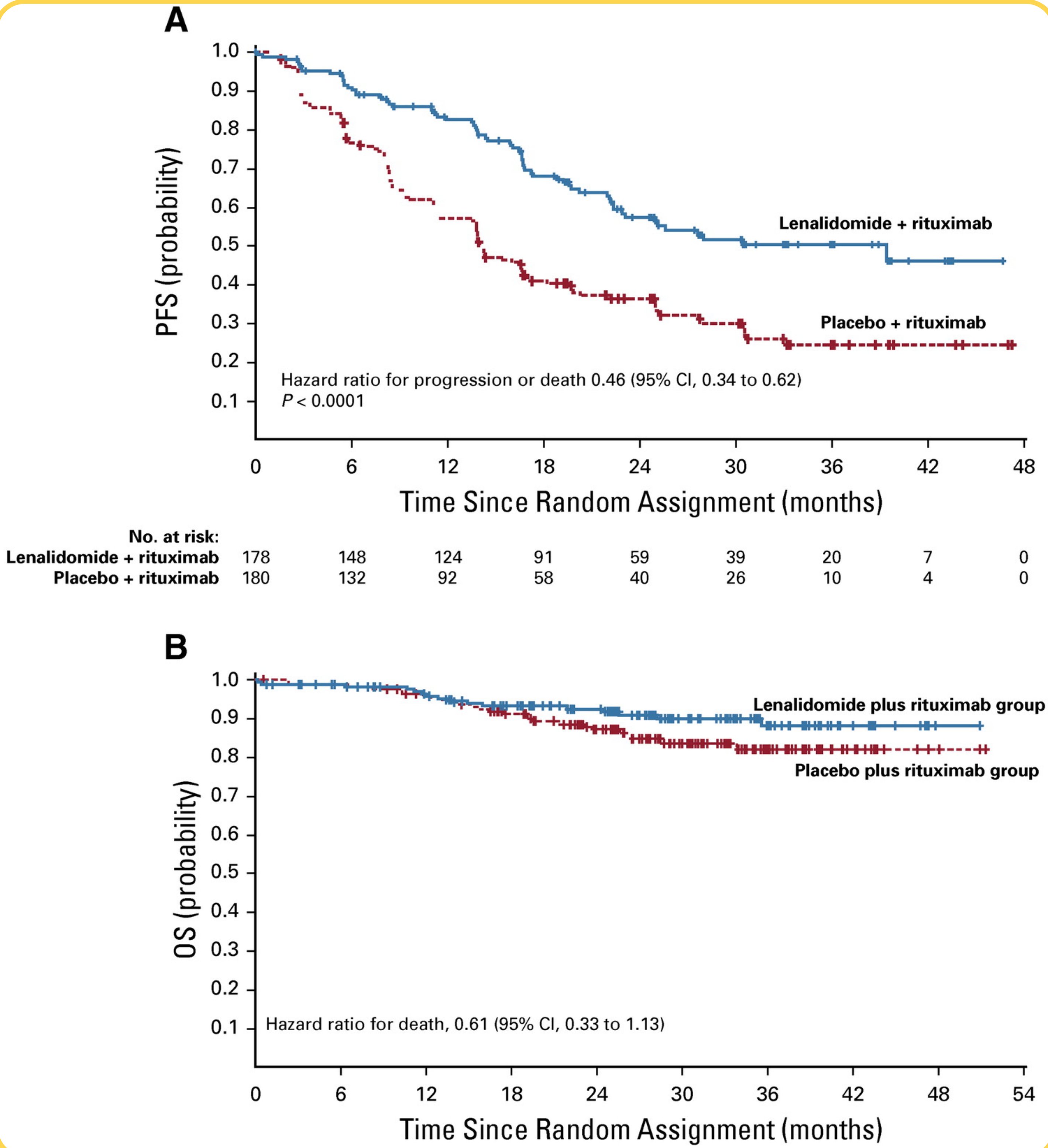

Figure 1. *Survie sans progression (SSP) et survie globale (SG) évaluées par un comité d'examen indépendant auprès de la population en intention de traiter : (A) survie sans progression ; (B) survie globale. Adapté de Leonard, JP et al, 2019*

for those with early relapse. The CUP trial demonstrated significant improvement in PFS and OS for patients who received ASCT compared to chemotherapy alone[36]. The benefit of ASCT was also demonstrated at first relapse in both rituximab-naïve and rituximab re-treated patients[37] in the GELA/GOELAMS FL2000 study which showed a 3-year OS of 92% (95%CI 78-97%) versus 63% (95%CI 51-72%) (P=0.0003), for those that received ASCT versus chemotherapy alone. There is also retrospective evidence demonstrating a survival benefit with early transplant in patients with early treatment failure[38–40]. It should be noted that the benefit of ASCT in the modern era is unclear and there may be varied practices across different centers. In our center we pursue ASCT following second-line therapy at first relapse especially for patients who relapsed within 24 months of first-line treatment. AlloSCT can offer a potential cure due to its graft versus lymphoma (GVL) effect however only few patients would be eligible. Several studies have demonstrated a benefit to alloSCT over ASCT but with higher transplant related mortality (TRM)[41–43]. For patients with early treatment failure both ASCT and matched sibling alloSCT produce a similar 5-year OS (~70%) but with a higher rate of TRM in the alloSCTgroup[44]. The role of alloSCT even in a few select young patients with refractory/relapsed FL, is unclear in the modern era of emerging therapeutic agents. The optimal transplant strategy thus continues to remain unclear.

For patients who are not transplant candidates, maintenance therapy with monoclonal antibodies following salvage chemo-immunotherapy is recommended if maintenance has not been previously given or was administered using a different monoclonal antibody. Maintenance should also be considered post-ASCT if warranted. MR following (R)-salvage therapy in patients with relapsed/refractory FL significantly improved PFS[15]. Even though evidence is lacking on the utility of MR post-ASCT, a recent consensus publication on maintenance therapy after ASCT recommended post-autologous maintenance rituximab for chemo-sensitive, rituximab-naïve patients with FL at relapse[45]. Clinicians may consider the use of MO in patients who received O-chemotherapy followed by ASCT for rituximab refractory FL patients. However, there are no prospective trials to inform this potential therapeutic approach, nor any evidence about potential post-SCT toxicities.

The management at first relapse will continue to evolve as more and more novel therapies are studied in a first relapse setting. Novel chimeric antigen receptor T-cell therapy (CAR-T) is showing promising results in patients with relapsed FL[46]. Additionally, data is also beginning to emerge on the use of bispecific antibodies in FL[47]. In the end, the management of FL at first relapse will undoubtedly consider advances in management strategies as clinicians continue to strive for optimal outcomes for their relapsed FL patients.

References

1. Swerdlow SH, Campo E, Harris NL. WHO Classification of Tumors. Vol 2. WHO Press

2. Brady JL, Binkley MS, Hajj C, et al. Definitive radiotherapy for localized follicular lymphoma staged by 18F-FDG PET-CT: a collaborative study by ILROG. Blood. 2019;133(3):237-245. doi:10.1182/blood-2018-04-843540

3. El-Galaly TC, Bilgrau AE, de Nully Brown P, et al. A population-based study of prognosis in advanced stage follicular lymphoma managed by watch and wait. Br J Haematol. 2015;169(3):435-444. doi:10.1111/bjh.13316

4. Solal-Céligny P, Bellei M, Marcheselli L, et al. Watchful waiting in low-tumor burden follicular lymphoma in the rituximab era: results of an F2-study database. J Clin Oncol. 2012;30(31):3848-3853. doi:10.1200/JCO.2010.33.4474

5. Ardeshna KM, Smith P, Norton A, et al. Long-term effect of a watch and wait policy versus immediate systemic treatment for asymptomatic advanced-stage non-Hodgkin lymphoma: a randomised controlled trial. Lancet. 2003;362(9383):516-522. doi:10.1016/s0140-6736(03)14110-4

6. Advani R, Rosenberg SA, Horning SJ. Stage I and II follicular non-Hodgkin's lymphoma: long-term follow-up of no initial therapy. J Clin Oncol. 2004;22(8):1454-1459. doi:10.1200/JCO.2004.10.086

7. Ardeshna KM, Qian W, Smith P, et al. Rituximab versus a watch-and-wait approach in patients with advanced-stage, asymptomatic, non-bulky follicular lymphoma: an open-label randomised phase 3 trial. Lancet Oncol. 2014;15(4):424-435. doi:10.1016/S1470-2045(14)70027-0

8. Hiddemann W, Kneba M, Dreyling M, et al. Frontline therapy with rituximab added to the combination of cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) significantly improves the outcome for patients with advanced-stage follicular lymphoma compared with therapy with CHOP alone: results of a prospective randomized study of the German Low-Grade Lymphoma Study Group. Blood. 2005;106(12):3725-3732. doi:10.1182/blood-2005-01-0016

9. Marcus R, Imrie K, Solal-Celigny P, et al. Phase III study of R-CVP compared with cyclophosphamide, vincristine, and prednisone alone in patients with previously untreated advanced follicular lymphoma. J Clin Oncol. 2008;26(28):4579-4586. doi:10.1200/JCO.2007.13.5376

10. Federico M, Luminari S, Dondi A, et al. R-CVP versus R-CHOP versus R-FM for the initial treatment of patients with advanced-stage follicular lymphoma: results of the FOLL05 trial conducted by the Fondazione Italiana Linfomi. J Clin Oncol. 2013;31(12):1506-1513. doi:10.1200/JCO.2012.45.0866

11. Luminari S, Ferrari A, Manni M, et al. Long-Term Results of the FOLL05 Trial Comparing R-CVP Versus R-CHOP Versus R-FM for the Initial Treatment of Patients With Advanced-Stage Symptomatic Follicular Lymphoma. J Clin Oncol. 2018;36(7):689-696. doi:10.1200/JCO.2017.74.1652

12. Flinn IW, van der Jagt R, Kahl BS, et al. Randomized trial of bendamustine-rituximab or R-CHOP/R-CVP in first-line treatment of indolent NHL or MCL: the BRIGHT study. Blood. 2014;123(19):2944-2952. doi:10.1182/blood-2013-11-531327

13. Rummel MJ, Niederle N, Maschmeyer G, et al. Bendamustine plus rituximab versus CHOP plus rituximab as first-line treatment for patients with indolent and mantle-cell lymphomas: an open-label, multicentre, randomised, phase 3 non-inferiority trial. Lancet. 2013;381(9873):1203-1210. doi:10.1016/S0140-6736(12)61763-2

14. Bruna R, Benedetti F, Boccomini C, et al. Prolonged survival in the absence of disease-recurrence in advanced-stage follicular lymphoma following chemo-immunotherapy: 13-year update of the prospective, multicenter randomized GITMO-IIL trial. Haematologica. 2019;104(11):2241-2248. doi:10.3324/haematol.2018.209932

15. Vidal L, Gafter-Gvili A, Salles G, et al. Rituximab maintenance improves overall survival of patients with follicular lymphoma-Individual patient data meta-analysis. Eur J Cancer. 2017;76:216-225. doi:10.1016/j.ejca.2017.01.021

16. Roschewski M, Hill BT. One Size Does Not Fit All: Who Benefits From Maintenance After Frontline Therapy for Follicular Lymphoma? Am Soc Clin Oncol Educ Book. 2019;39:467-476. doi:10.1200/EDBK_239065

17. Morschhauser F, Fowler NH, Feugier P, et al. Rituximab plus Lenalidomide in Advanced Untreated Follicular Lymphoma. N Engl J Med. 2018;379(10):934-947. doi:10.1056/NEJMoa1805104

18. Marcus R, Davies A, Ando K, et al. Obinutuzumab for the First-Line Treatment of Follicular Lymphoma. N Engl J Med. 2017;377(14):1331-1344. doi:10.1056/NEJMoa1614598

19. Bachy E, Houot R, Feugier P, et al. Obinutuzumab plus lenalidomide (GALEN) in advanced, previously untreated follicular lymphoma in need of systemic therapy. Blood. Published online December 22, 2021:blood.2021013526. doi:10.1182/blood.2021013526

20. Maurer MJ, Bachy E, Ghesquières H, et al. Early event status informs subsequent outcome in newly diagnosed follicular lymphoma. Am J Hematol. 2016;91(11):1096-1101. doi:10.1002/ajh.24492

21. Casulo C, Byrtek M, Dawson KL, et al. Early Relapse of Follicular Lymphoma After Rituximab Plus Cyclophosphamide, Doxorubicin, Vincristine, and Prednisone Defines Patients at High Risk for Death: An Analysis From the National LymphoCare Study. J Clin Oncol. 2015;33(23):2516-2522. doi:10.1200/JCO.2014.59.7534

22. Cheson BD, Friedberg JW, Kahl BS, Van der Jagt RH, Tremmel L. Bendamustine produces durable responses with an acceptable safety profile in patients with rituximab-refractory indolent non-Hodgkin lymphoma. Clin Lymphoma Myeloma Leuk. 2010;10(6):452-457. doi:10.3816/CLML.2010.n.079

23. Rummel M, Kaiser U, Balser C, et al. Bendamustine plus rituximab versus fludarabine plus rituximab for patients with relapsed indolent and mantle-cell lymphomas: a multicentre, randomised, open-label, non-inferiority phase 3 trial. Lancet Oncol. 2016;17(1):57-66. doi:10.1016/S1470-2045(15)00447-7

24. Cheson BD, Chua N, Mayer J, et al. Overall Survival Benefit in Patients With Rituximab-Refractory Indolent Non-Hodgkin Lymphoma Who Received Obinutuzumab Plus Bendamustine Induction and Obinutuzumab Maintenance in the GADOLIN Study. J Clin Oncol. 2018;36(22):2259-2266. doi:10.1200/JCO.2017.76.3656

25. Rummel MJ, Janssens A, MacDonald D, et al. A phase 3, randomized study of ofatumumab combined with bendamustine in rituximab-refractory iNHL (COMPLEMENT A + B study). Br J Haematol. 2021;193(6):1123-1133. doi:10.1111/bjh.17420

26. Czuczman MS, Weaver R, Alkuzweny B, Berlfein J, Grillo-López AJ. Prolonged clinical and molecular remission in patients with low-grade or follicular non-Hodgkin's lymphoma treated with rituximab plus CHOP chemotherapy: 9-year follow-up. J Clin Oncol. 2004;22(23):4711-4716. doi:10.1200/JCO.2004.04.020

27. Leonard JP, Jung SH, Johnson J, et al. Randomized Trial of Lenalidomide Alone Versus Lenalidomide Plus Rituximab in Patients With Recurrent Follicular Lymphoma: CALGB 50401 (Alliance). J Clin Oncol. 2015;33(31):3635-3640. doi:10.1200/JCO.2014.59.9258

28. Leonard JP, Trneny M, Izutsu K, et al. AUGMENT: A Phase III Study of Lenalidomide Plus Rituximab Versus Placebo Plus Rituximab in Relapsed or Refractory Indolent Lymphoma. J Clin Oncol. 2019;37(14):1188-1199. doi:10.1200/JCO.19.00010

29. Morschhauser F, Le Gouill S, Feugier P, et al. Obinutuzumab combined with lenalidomide for relapsed or refractory follicular B-cell lymphoma (GALEN): a multicentre, single-arm, phase 2 study. Lancet Haematol. 2019;6(8):e429-e437. doi:10.1016/S2352-3026(19)30089-4

30. Pfreundschuh M, Kuhnt E, Trümper L, et al. CHOP-like chemotherapy with or without rituximab in young patients with good-prognosis diffuse large-B-cell lymphoma: 6-year results of an open-label randomised study of the MabThera International Trial (MInT) Group. Lancet Oncol. 2011;12(11):1013-1022. doi:10.1016/S1470-2045(11)70235-2

31. Pfreundschuh M, Schubert J, Ziepert M, et al. Six versus eight cycles of bi-weekly CHOP-14 with or without rituximab in elderly patients with aggressive CD20+ B-cell lymphomas: a randomised controlled trial (RICOVER-60). Lancet Oncol. 2008;9(2):105-116. doi:10.1016/S1470-2045(08)70002-0

32. Habermann TM, Weller EA, Morrison VA, et al. Rituximab-CHOP versus CHOP alone or with maintenance rituximab in older patients with diffuse large B-cell lymphoma. J Clin Oncol. 2006;24(19):3121-3127. doi:10.1200/JCO.2005.05.1003

33. Dunleavy K, Fanale MA, Abramson JS, et al. Dose-adjusted EPOCH-R (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin, and rituximab) in untreated aggressive diffuse large B-cell lymphoma with MYC rearrangement: a prospective, multicentre, single-arm phase 2 study. Lancet Haematol. 2018;5(12):e609-e617. doi:10.1016/S2352-3026(18)30177-7

34. Crump M, Kuruvilla J, Couban S, et al. Randomized comparison of gemcitabine, dexamethasone, and cisplatin versus dexamethasone, cytarabine, and cisplatin chemotherapy before autologous stem-cell transplantation for relapsed and refractory aggressive lymphomas: NCIC-CTG LY.12. J Clin Oncol. 2014;32(31):3490-3496. doi:10.1200/JCO.2013.53.9593

35. Hagberg H, Gisselbrecht C, CORAL study group. Randomised phase III study of R-ICE versus R-DHAP in relapsed patients with CD20 diffuse large B-cell lymphoma (DLBCL) followed by high-dose therapy and a second randomisation to maintenance treatment with rituximab or not: an update of the CORAL study. Ann Oncol. 2006;17 Suppl 4:iv31-32. doi:10.1093/annonc/mdj996

36. Schouten HC, Kvaloy S, Sydes M, Qian W, Fayers PM. The CUP trial: a randomized study analyzing the efficacy of high dose therapy and purging in low-grade non-Hodgkin's lymphoma (NHL). Ann Oncol. 2000;11 Suppl 1:91-94.

37. Le Gouill S, De Guibert S, Planche L, et al. Impact of the use of autologous stem cell transplantation at first relapse both in naive and previously rituximab exposed follicular lymphoma patients treated in the GELA/GOELAMS FL2000 study. Haematologica. 2011;96(8):1128-1135. doi:10.3324/haematol.2010.030320

38. Manna M, Lee-Ying R, Davies G, et al. Autologous transplantation improves survival rates for follicular lymphoma patients who relapse within two years of chemoimmunotherapy: a multi-center retrospective analysis of consecutively treated patients in the real world. Leuk Lymphoma. 2019;60(1):133-141. doi:10.1080/10428194.2018.1473576

39. Casulo C, Friedberg JW, Ahn KW, et al. Autologous Transplantation in Follicular Lymphoma with Early Therapy Failure: A National LymphoCare Study and Center for International Blood and Marrow Transplant Research Analysis. Biol Blood Marrow Transplant. 2018;24(6):1163-1171. doi:10.1016/j.bbmt.2017.12.771

40. Jurinovic V, Metzner B, Pfreundschuh M, et al. Autologous Stem Cell Transplantation for Patients with Early Progression of Follicular Lymphoma: A Follow-Up Study of 2 Randomized Trials from the German Low Grade Lymphoma Study Group. Biol Blood Marrow Transplant. 2018;24(6):1172-1179. doi:10.1016/j.bbmt.2018.03.022

41. Khouri IF, Milton DR, Gulbis AM, et al. Nine-Year Follow-up of Patients with Relapsed Follicular Lymphoma after Nonmyeloablative Allogeneic Stem Cell Transplant and Autologous Transplant. Clin Cancer Res. 2021;27(21):5847-5856. doi:10.1158/1078-0432.CCR-21-1377

42. Hosing C, Saliba RM, McLaughlin P, et al. Long-term results favor allogeneic over autologous hematopoietic stem cell transplantation in patients with refractory or recurrent indolent non-Hodgkin's lymphoma. Ann Oncol. 2003;14(5):737-744. doi:10.1093/annonc/mdg200

43. van Besien K, Loberiza FR, Bajorunaite R, et al. Comparison of autologous and allogeneic hematopoietic stem cell transplantation for follicular lymphoma. Blood. 2003;102(10):3521-3529. doi:10.1182/blood-2003-04-1205

44. Smith SM, Godfrey J, Ahn KW, et al. Autologous transplantation versus allogeneic transplantation in patients with follicular lymphoma experiencing early treatment failure. Cancer. 2018;124(12):2541-2551. doi:10.1002/cncr.31374

45. Kanate AS, Kumar A, Dreger P, et al. Maintenance Therapies for Hodgkin and Non-Hodgkin Lymphomas After Autologous Transplantation: A Consensus Project of ASBMT, CIBMTR, and the Lymphoma Working Party of EBMT. JAMA Oncol. 2019;5(5):715-722. doi:10.1001/jamaoncol.2018.6278

46. Hirayama AV, Gauthier J, Hay KA, et al. High rate of durable complete remission in follicular lymphoma after CD19 CAR-T cell immunotherapy. Blood. 2019;134(7):636-640. doi:10.1182/blood.2019000905

47. Assouline SE, Kim WS, Sehn LH, et al. Mosunetuzumab Shows Promising Efficacy in Patients with Multiply Relapsed Follicular Lymphoma: Updated Clinical Experience from a Phase I Dose-Escalation Trial. Blood. 2020;136:42-4

IMBRUVICA® (ibrutinib) is indicated:

- For the treatment of adult patients with previously untreated chronic lymphocytic leukemia (CLL), including those with 17p deletion.

  Clinical effectiveness of IMBRUVICA® in previously untreated adult patients with CLL with 17p deletion is based on the benefit observed in patients with CLL with 17p deletion who have received ≥1 prior therapy. Clinical trial data in previously untreated patients with CLL with 17p deletion are very limited.
- In combination with obinutuzumab for the treatment of adult patients with previously untreated CLL, including those with 17p deletion.
- In combination with rituximab for the treatment of adult patients with previously untreated CLL.

  Clinical trial data with IMBRUVICA® in combination with rituximab in adult patients with CLL with 17p deletion are limited.
- For the treatment of adult patients with CLL who have received ≥1 prior therapy, including those with 17p deletion.
- In combination with bendamustine and rituximab for the treatment of adult patients with CLL who have received ≥1 prior therapy.

  Clinical trial data with IMBRUVICA® in combination with bendamustine and rituximab in adult patients with CLL with 17p deletion are limited.
- For the treatment of adult patients with relapsed or refractory mantle cell lymphoma (MCL).
- For the treatment of adult patients with marginal zone lymphoma (MZL) who require systemic therapy and have received ≥1 prior anti-CD20-based therapy.
- For the treatment of adult patients with Waldenström's macroglobulinemia (WM).

  Clinical effectiveness of IMBRUVICA® is based on response rates demonstrated in a single-arm study in adult patients who had received ≥1 prior therapy.
- In combination with rituximab for the treatment of adult patients with WM.
- For the treatment of adult patients with steroid dependent or refractory chronic graft versus host disease (cGVHD).

Consult the Product Monograph at http://www.janssen.com/canada/products for information regarding warnings, precautions, adverse reactions, interactions, dosing and conditions of clinical use. The Product Monograph is also available by calling 1-800-567-3331 or 1-800-387-8781.

Reference: IMBRUVICA® Product Monograph, Janssen Inc., December 14, 2020.

ABOUT THE AUTHOR

Dawn Maze, MD, FRCPC, MSc

Dawn Maze, MD, FRCPC, MSc is a member of the Leukemia Program and the Elizabeth and Tony Comper MPN Program at the Princess Margaret Cancer Centre. Dr. Maze earned her medical degree and master's degree in clinical epidemiology from Memorial University. She completed postgraduate training in hematology at Queen's University, followed by a fellowship in blood and marrow transplantation and transfusion medicine research at The Ottawa Hospital.

Dr. Maze's current research interests include MPN management in the adolescent and young adult population, particularly around pregnancy. She is also interested in optimizing transfusion support for patients with hematologic malignancies and is Medical Director for the Malignant Hematology Day Unit. She is the primary investigator or co-investigator on numerous clinical trials of treatment and supportive care of patients with hematologic malignancies.

MYELOPROLIFERATIVE NEOPLASMS IN 2022: A CONCISE REVIEW

Introduction

The Philadelphia chromosome(Ph)-negative myeloproliferative neoplasms (MPN) are comprised of a heterogenous group of disorders of myeloid hematopoietic stem cells that include polycythemia vera (PV), essential thrombocythemia (ET), and idiopathic myelofibrosis (MF). MPN are characterized by constitutional and other disease-related symptoms, an increased risk for thrombotic and hemorrhagic events, and a propensity to transform to acute myeloid leukemia (AML). Progress in our understanding of the molecular pathophysiology of MPN has led to improved prognostic tools, and increasingly personal risk-stratification. In PV, there has been renewed interest in interferon (IFN) for its potential to directly target the malignant clone and exert a disease-modifying effect. In MF, the introduction of Janus Kinase (JAK) inhibitors has significantly altered the therapeutic landscape over the past decade. Ongoing development in the area of JAK inhibitor therapy, as well as several novel pathways, holds promise for improved hematologic responses, lessening of overall burden of illness, increased quality of life, and application to a broader cohort of patients.

Molecular Pathogenesis

MPN result from constitutive activation of the JAK/STAT signalling pathway. In the majority of cases, a driver mutation in *JAK2, CALR* or *MPL* can be identified, and those without one of these mutations are classified as "triple negative". The first discovered, in 2005, was a point mutation in exon 14 of the *JAK2* gene which results in a valine to phenylalanine substitution at position 617 (V617F). This mutation results in constitutive activation of the JAK/STAT pathway independent of ligand activation of the erythropoietin (EPO), thrombopoietin (TPO) or granulocyte-colony stimulating factor (G-CSF) and as such, can drive the phenotype of either of the classical World Health Organization (WHO)-defined MPN. In comparison, the second type of driver mutation in JAK2, comprised of a variety of insertions and deletions in exon 12, activates primarily the EPO receptor. JAK2V617F is detected in 95% of PV cases and 50-60% of ET and MF.[1,2] JAK2 exon 12 mutations can be identified in most of the remaining 5%.[3]

Calreticulin (CALR) is a chaperone protein that prevents exportation of misfolded proteins in the endoplasmic reticulum.[4-5] Multiple mutations have been described, but 80% are either type 1, a 52-bp deletion, or type 2, a 5-bp insertion in exon 9. These frameshift mutations result in pathogenic binding of the CALR lectin-binding domain to thrombopoietin receptor (MPL, also known as TPOR) , which activates JAK/STAT signalling. CALR mutations are identified in 20-25% of ET cases and 25-30% of MF cases.[6-7] MPL is the receptor for TPO and gain of function mutations in tryptophan at position 515 (W515) in exon 10 of the *MPL* gene are identified in approximately 3-8% of ET and MF cases.[8]

In addition to driver mutations, the MPN phenotype and evolution over time is modulated by additional mutations such as those in genes involved in epigenetic regulation (e.g., *EZH2, ASXL1*), spliceosome machinery (e.g., *SRSF2, U2AF1*) and the RAS pathway (e.g., *NRAS, KRAS*). Mutations in *ASXL1, EZH2, SRSF2* and *IDH1/29*, denoted "high molecular risk (HMR)", as well as those in *TP53*[10], predict leukemic progression or shortened survival. In addition to these genetic drivers, there is growing evidence that proinflammatory processes play a role in MPN progression, from clonal hematopoiesis to chronic phase MPN to accelerated and blast phase disease.[11,12]

Goals of Therapy and Risk Stratification

The goals of treatment in MPN include symptom improvement, prevention of vascular events, control of abnormal blood counts, reduction in splenomegaly and delayed disease progression. Potential consequences of treatment must also be considered and may include side effects, impact on fertility, and the risk of second cancers. The MPN Landmark survey involving 813 patient respondents who had MPNs and 457 hematologist/oncologist respondents who treated patients with these conditions uncovered frequent discordance regarding treatment goals between patients and physicians.[13] Indeed, the goals of treatment may vary depending on the MPN and its clinical and genetic features, as well as an individual's life stage, values, and preferences. Hence, effective patient-physician communication is vital to treatment decision making.

An important component of therapeutic decision making is accurate risk stratification. Traditional stratification in PV and ET is based on age and history of thrombosis, with patients over the age of 60 years or with prior thrombosis considered high risk, and those without either of these factors considered low risk.[14] In ET, the newer International Prognostic Score of Thrombosis for ET (IPSET-thrombosis)[15], which also incorporates the *JAK2V617F* mutation and conventional cardiovascular risk factors as risk factors for thrombosis, is the preferred scoring system.[16,17] In MF, newer risk models incorporating both clinical and genetic information are recommended, particularly to inform decisions around allogeneic stem cell transplantation (SCT). In primary myelofibrosis (PMF), the Mutation-Enhanced International Prognostic Score System (MIPSS-70)[18] or MIPSS-70+ Version 2.0[19] are preferred if both molecular profile and karyotype are available, and the MYelofibrosis SECondary to PV and ET prognostic model (MYSEC-PM)[20] is a validated tool for post-ET or post-PV MF. The Dynamic International Prognostic Scoring System (DIPSS) continues to be the recommended scoring system in clinical practice if genetic information is unavailable.[21]

Treatment of PV and ET: The Old and the New

The mainstay of therapy for low-risk PV is low dose acetylsalicylic acid (ASA) and phlebotomy to maintain a hematocrit below 45%.[22] However, in clinical practice, it can be challenging to maintain target hematocrit values with intermittent phlebotomies. Further, phlebotomies do not control progressive thrombocytosis or leukocytosis, and may result in symptomatic iron deficiency.[23] Hydroxyurea is commonly used in this setting for patients who are poorly tolerant or require frequent phlebotomies, however, new strategies are being explored. In the Low-PV study, in which 127 patients with low-risk PV were randomized to receive standard therapy with ASA (100 mg daily) and phlebotomy (300mL for each phlebotomy) with or without ropeginterferon alfa-2b (rIFN) administered subcutaneously every 2 weeks in a fixed dose of 100 µg, more patients treated with rIFN maintained a median hematocrit of 45% or lower without progressive disease during a 12-month period than those receiving standard therapy (84% vs. 60%, p=0.0075). There was no significant difference between grade 3 or higher adverse events, and serum ferritin concentrations progressively increased over time in the rIFN group.[24] Another promising approach to hematocrit control is with the hepcidin mimetic, rusfertide (PTG-300). In a phase 2 study, rusfertide was effective at limiting the number of phlebotomies and maintaining hematocrit below 45%, while the serum ferritin levels increased throughout the treatment period reflecting increase in iron stores.[25]

In high-risk PV, either hydroxyurea or IFN are the currently recommended first-line cytoreductive therapies for patients of any age, however the initial choice is often strongly influenced by cost and drug availability.[15] In Canada, IFN is most often considered in younger patients and in patients who are pregnant and require cytoreduction. In the PROUD-PV study, and its extension phase, CONTINUATION-PV, patients with high-risk PV were randomized to receive rIFN or hydroxyurea. While responses to rIFN occurred later, by 36 months hematologic responses without normalization of spleen size were seen in 71% of patients treated with rIFN vs. 51% of those treated with hydroxyurea (p=0.012).[26] At the 60-month follow-up, 56% of evaluable patients treated with rIFN had a decrease in their JAK2 allele burden to under 10%. Younger age and lower allele burden predicted a better molecular response, suggesting early treatment initiation may result in the greatest long-term benefit.[27]

Most patients with ET likely benefit from ASA for prevention of vascular events. However, in a retrospective review of 433 patients with low-risk ET, in patients with a CALR mutation, antiplatelet therapy did not affect the risk of thrombosis, but was associated with a higher incidence of bleeding (12.9 vs. 1.8 episodes per 1000 patient-years, p=0.03).[28] Patients with high-risk disease according to the IPSET-thrombosis should receive low dose ASA, while those with low- or intermediate-risk disease should receive ASA if they are 60 years of age or older, have the JAK2V617F mutation, or uncontrolled cardiovascular risk factors.[15] Cytoreduction is recommended for patients aged 60 years and older, those with a history of thrombosis and for a platelet count above 1500 x 109/L. Cytoreduction is recommended for extreme thrombocytosis primarily to reduce the risk of acquired Von Willebrand syndrome and major hemorrhage, as the risk of thrombosis does not appear to be increased.[29] Hydroxyurea is generally favoured as first-line therapy in ET. Anagrelide and IFN are recommended as second line treatments, and the ongoing SURPASS ET study, comparing rIFN to anagrelide in patients with resistance or intolerance to hydroxyurea, may help inform the optimal treatment in this setting (NCT04285086).

Treatment of MF: JAK Inhibitors and Beyond

Management of MF starts with risk assessment, as described below (**Figure 1**). In patients with lower risk disease, who have no or minimal disease-related symptoms, active surveillance is recommended. For patients with splenomegaly or MF-related symptoms, ruxolitinib may be beneficial; IFN or hydroxyurea may be indicated if cytoreduction is required,[17,30] and erythropoiesis-stimulating agents may be useful in patients with symptomatic anemia in whom the serum erythropoietin level is under 500 mU/mL.

In patients with higher risk disease, who are eligible for hematopoietic cell transplantation (HCT) and have an available donor, referral for consideration of upfront HCT is recommended.[31,32] For patients with higher risk MF who are ineligible for HCT, do not have a suitable donor, or prefer non-HCT therapy, ruxolitinib has been the mainstay of treatment for nearly a decade. Several studies have demonstrated that ruxolitinib may improve disease-related symptoms, splenomegaly and quality of life.[33,34] Since ruxolitinib's approval, a number of other JAK inhibitors have been developed, most notably fedratinib, which was approved in Canada in September 2020. Momelotinib and pacritinib, which aim to improve the incidence of adverse events such as anemia and thrombocytopenia, respectively, are currently being evaluated in phase 3 trials.

In addition to novel JAK inhibitors, a number of investigational agents are being studied in combination with a JAK inhibitor. The bromodomain and extra-terminal domain inhibitor, pelabresib (CPI-0610), the BCL-2/BCL-XL inhibitor, navitoclax, and the phosphatidylinositol 3-kinase inhibitor, parsaclisib, have all shown clinical benefit in phase 2 studies and are currently in phase 3 trials

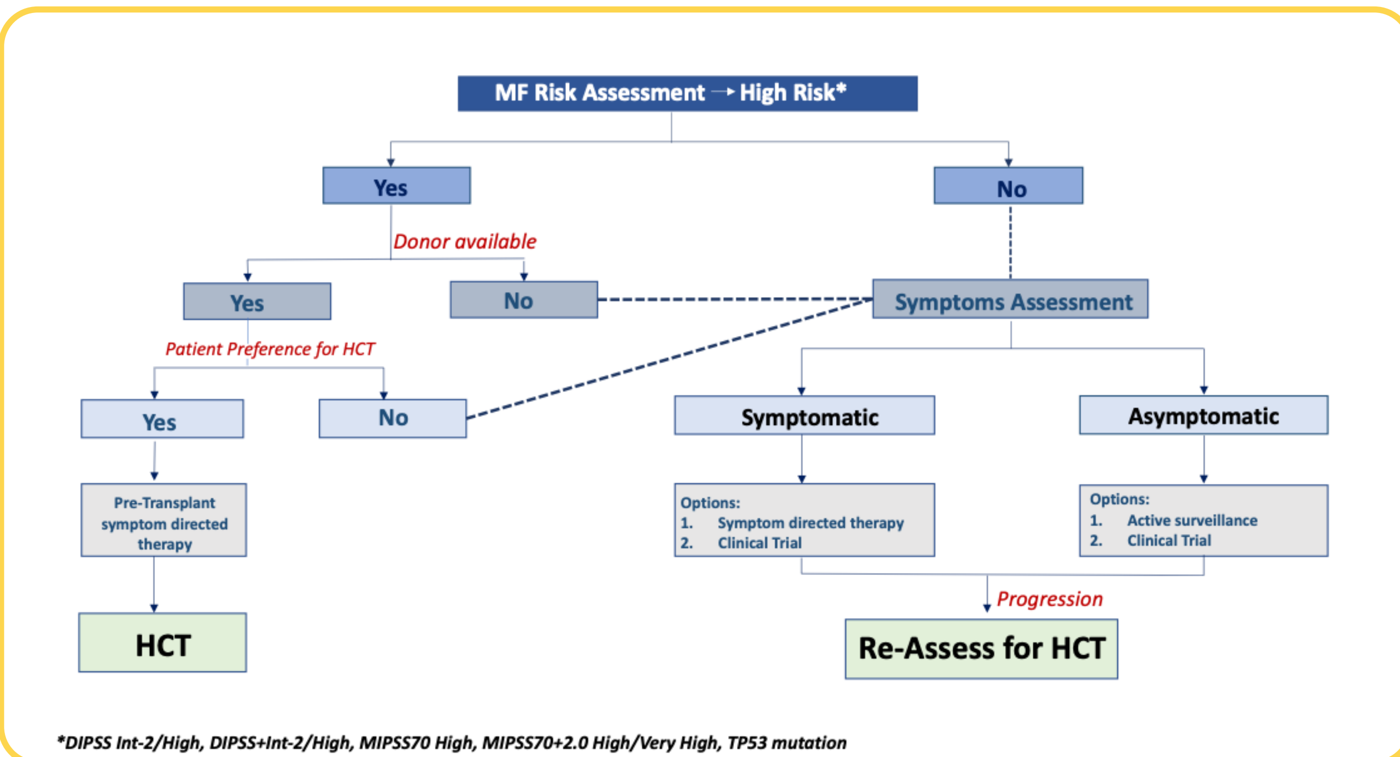

Figure 1. *Management Algorithm for Transplant eligible MF Patients in chronic phase (used with permission from England J, Gupta V. Novel therapies vs hematopoietic cell transplantation in myelofibrosis: who, when, how? Hematology Am Soc Hematol Educ Program 2021; 2021(1): 453-462.)*

(NCT04603495, NCT04472598, NCT04551066). Another agent of interest is luspatercept, which has been demonstrated to improve hemoglobin and reduce transfusion requirements in patients with myelodysplastic syndrome.[35] Symptomatic anemia is an unmet clinical need in MF and in a phase 2 study, luspatercept in combination with ruxolitinib resulted in 27% transfusion-independence for 12 consecutive weeks.[36] This drug is also in phase 3 testing for patients with MF and red cell transfusion dependence in combination with ruxolitinib (NCT04717414).

Conclusions and Future Directions

The past decade has seen major shifts in diagnosis, prognostication, and management of MPN. Driver mutations lead to constitutive activation of the JAK-STAT signalling pathway, and the clinical phenotype and disease evolution likely results from a complex interplay of host genomic background, inflammatory pressures, and acquisition of new mutations. There has been renewed interest in IFN for its disease-modifying potential and ongoing trials with long-term follow-up will help inform its place in the MPN therapeutic algorithm. Management of MF begins with risk assessment and a clear understanding of the patient's goals and preferences. For higher risk patients who are ineligible for, or chose not to undergo, HCT, there are several promising new agents and patients should be offered clinical trial participation whenever possible.

References:

1. Baxter EJ, Scott LM, Campbell PJ, East C, Fourouclas N, Swanton S, et al. Acquired mutation of the tyrosine kinase JAK2 in human myeloproliferative disorders. Lancet 2005; 365(9464): 1054–61.

2. Mejia-Ochoa M, Acevedo Toro PA, Cardona-Arias JA. Systematization of analytical studies of polycythemia vera, essential thrombocythemia and primary myelofibrosis, and a meta-analysis of the frequency of JAK2, CALR and MPL mutations: 2000–2018. BMC Cancer 2019; 19(1): 590.

3. Scott LM, Tong W, Levine RL, Scott MA, Beer PA, Stratton MR, et al. JAK2 exon 12 mutations in polycythemia vera and idiopathic erythrocytosis. N Engl J Med 2007; 356(5): 459–68.

4. Merlinsky TR, Levine RL, Pronier E. Unfolding the role of calreticulin in myeloproliferative neoplasm pathogenesis. Clinical Cancer Research 2019; 25(10): 2956-62.

5. How J, Hobbs GS, Mullally A. Mutant calreticulin in myeloproliferative neoplasms. Blood 2019; 134(25): 2242–8.

6. Nangalia J, Massie CE, Baxter EJ, et al. Somatic CALR mutations in myeloproliferative neoplasms with nonmutated JAK2. N Engl J Med 2013; 369(25): 2391–2405.

7. Klampfl T, Gisslinger H, Harutyunyan AS, et al. Somatic mutations of calreticulin in myeloproliferative neoplasms. N Engl J Med 2013; 369(25): 2379–90.

8. Staerk J, Lacout C, Sato T, Smith SO, Vainchenker W, Constantinescu SN. An amphipathic motif at the transmembrane-cytoplasmic junction prevents autonomous activation of the thrombopoietin receptor. Blood 2006; 107(5): 1864–71.

9. Vannucchi AM, Lasho TL, Guglielmelli P, Biamonte F, Pardanani A, Pereira A, et al. Mutations and prognosis in primary myelofibrosis. Leukemia 2013; 27(9):1 861–9.

10. Lundberg P, Karow A, Nienhold R, Looser R, Hao-Shen H, Nissen I, et al. Clonal evolution and clinical correlates of somatic mutations in myeloproliferative neoplasms. Blood 2014; 123(14): 2220–8.

11. Hasselbalch H. The role of cytokines in the initiation and progression of myelofibrosis. Cytokine & Growth Factor Reviews 2013; 24(2): 133-45.

12. Bjørn ME, Hasselbalch HC. The role of reactive oxygen species in myelo¬fibrosis and related neoplasms. Mediators of Inflammation 2015; 2015(October): 648090.

13. Mesa RA, Miller CB, Thyne M, Mangan J, Goldberger S, Fazal S et al. Differences in treatment goals and perception of symptom burden between patients with myeloproliferative neoplasms (MPNs) and hematologists/oncologists in the United States: Findings from the MPN Landmark survey. Cancer 2017; 123(3): 449-58.

14. Tefferi A, Barbui T. Polycythemia vera and essential thrombocythemia: 2021 update on diagnosis, risk-stratification and management. American Journal of Hematology 2020; 95: 1599-1613.

15. Barbui T, Finazzi G, Carobbio A, Thiele J, Passamonti F, Rumi E, et al. Development and validation of an International Prognostic Score of thrombosis in World Health Organization-essential thrombocythemia (IPSET-thrombosis). Blood 2012; 120: 5128–33.

16. Barbui T, Terreri A, Vannucchi AM, Passamonti F, Silver RT, Hoffman R, et al. Philadelphia chromosome-negative classical myeloproliferative neoplasms: revised management recommendations from European LeukemiaNet. Leukemia 2018; 32: 1057-69.

17. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology. Myeloproliferative Neoplasms Version 2.2021. 2021 Aug 18;National Comprehensive Cancer Network. Available from: https://www.nccn.org/professionals/physician_gls/pdf/mpn.pdf.

18. Guglielmelli P, Lasho TL, Rotunno G, Mudireddy M, Mannarelli C, Nicolosi M et al. MIPSS70: Mutation-enhanced international prognostic score system for transplantation-age patients with primary myelofibrosis. Journal of Clinical Oncology 2018; 36(4): 310-18.

19. Tefferi A, Guglielmelli P, Lasho TL, Gangat N, Ketterling RP, Pardanani A, Vannucchi AM. MIPSS70+ version 2.0: Mutation and karyotype-enhanced international prognostic scoring system for primary myelofibrosis. Journal of Clinical Oncology 2018; 36(17): 1769-70.

20. Passamonti F, Giorgino T, Mora B, Guglielmelli P, Rumi E, Maffioli M, et al.

A clinical-molecular prognostic model to predict survival in patients with post polycythemia vera and post essential thrombocythemia myelofibrosis. Leukemia 2017; 31(12): 2726-31.

21. Passamonti F, Cervantes F, Vannucchi AM, Morra E, Rumi E, Cazzola M, et al. A dynamic prognostic model to predict survival in primary myelofibrosis: a study by the IWG-MRT (International Working Group for Myeloproliferative Neoplasms Research and Treatment). Blood 2010; 115: 1703–08.

22. Marchioloi R, Finazzi G, Specchia G, Cacciola R, Cavazzina R,Cilloni D, et al. Cardiovascular events and intensity of treatment in polycythemia vera. New England Journal of Medicine 2013; 368: 22-33.

23. Scherber RM, Geyer HL, Dueck AC, Kosiorek HE, Finzzi G, Cavazzina R, et al. The potential role of hematocrit control on symptom burden among polycythemia vera patients: Insights from the CYTO-PV and MPN-SAF patient cohorts. Leukemia & Lymphoma 2017; 58(6): 1481-7.

24. Barbui T, Vannucchi AM, De Stefano V, Masciulli A, Carobbio A, Ferrari A, et al. Ropeginterferon alfa-2b versus phlebotomy in low-risk patients with polycythaemic vera (Low-PV study): a multicentre, randomized phase 2 trial. The Lancet Haemology 2021; 8(3): e175-84.

25. Ginzburg Y, Kremyanskaya M, Kuykendall AT, Yacoub A, Yang J, Gupta SK, et al. Hepcidin Mimetic (PTG-300) reverses iron deficiency while controlling hematocrit in polycythemiavera patients. Blood 2020; 136(Supplement 1): 40-1.

26. Gisslinger H, Klade C, Georgiev P, Krochmalczyk D, Gercheva-Kyuchukova L, Egyed M, et al. Ropeginterferon alfa-2b versus standard therapy for polycythemia vera (PROUD-PV and CONTINUATION-PV): A randomised, non-inferiority, phase 3 trial and its extension study. Lancet Haematology 2020; 7: e196-208.

27. Kiladjian JJ, Klade C, Georgiev P, Krochmalczyk D, Gercheva-Kyuchukova L, Egyed, M, et al. Towards a potential operational cure in patients with polycythaemia vera? Results from five years' ropeginterferon alpha-2b therapy in a randomized setting. EHA 2021. EP1076.

28. Alvarez-Larran A, Pereira A, Guglielmelli P, Hernandez-Bolunda JC, Arellano-Rodrigo E, Ferrer-Marin F, et al. Antiplatelet therapy versus observation in low-risk essential thrombocythemia with a CALR mutation. Haematologica 2016; 101(8): 926-31.

29. Gangat N, Szuber N, Jawaid T, Hanson CA, Pardanani A, Tefferi A. Young platelet millionaires with essential thrombocythemia. American Journal of Hematology 2021; 96(4): E93-5.

30. Gupta V, Griesshammer M, Martino B, et al. Analysis of predictors of response to ruxolitinib in patients with myelofibrosis in the phase 3b expanded-access JUMP study. Leukemia & Lymphoma 2021; 62(4):918-26.

31. Maze D, Arcasoy MO, Henrie R, Cerquozzi S, Damble R, Al Hadidi SA, et al. Role of Allogeneic Hematopoietic Cell Transplant in Patients with Myelofibrosis in the JAK Inhibitor Era. Blood 2020; 136(Supplement 1): 52-3.

32. Gowin K, Ballen K, Ahn KW, Hu ZH, Ali H, Arcasoy MO, et al. Survival following allogeneic transplant in patients with myelofibrosis. Blood Advances 2020; 4(9): 1965-73.

33. Harrison C, Kiladjian J-J, Al-Ali H-K, et al. JAK inhibition with ruxolitinib versus best available therapy for myelofibrosis. New England Journal of Medicine 2012; 366(9): 787-798.

34. Verstovsek S, Mesa RA, Gotlib J, et al. A double-blind, placebo-controlled trial of ruxolitinib for myelofibrosis. New England Journal of Medicine 2012; 366(9):799-807.

35. Fenaux P, Platzbecker U, Mufti GJ, Garcia-Manero G, Buckstein R, Santini V, et al. Luspatercept in patients with lower-risk myelodysplastic syndromes. New England Journal of Medicine 2020; 382: 140-51.

36. Gerds A, Vannucchi A, Passamonti F, Kremyanskaya M, Gotlib J, Palmer JM, et al. Duration of response to luspatercept in patients requiring red blood cell transfusions with myelofibrosis: Updated data from the phase 2 ACE-536-MF-001 Study. Blood 2020; 136(Supplement 1): 47-8.

abbvie

Pr VENCLEXTA®
venetoclax tablets

DISCOVER THE POWER OF VENCLEXTA[1]

POWERED BY V*

VENCLEXTA (venetoclax), in combination with obinutuzumab, is indicated for the treatment of patients with previously untreated CLL.[1]

VENCLEXTA, in combination with rituximab, is indicated for the treatment of adult patients with CLL who have received at least one prior therapy.[1]

DEMONSTRATED PFS[1]

In an open-label study (CLL14), VENCLEXTA + obinutuzumab demonstrated superior PFS compared with obinutuzumab + chlorambucil in previously untreated CLL patients[1†]

- 65% reduction in the risk of disease progression or death vs. obinutuzumab + chlorambucil (HR: 0.35 [95% CI: 0.23–0.53]; $p<0.0001$)[1‡]
  - Number of events was 30/216 for VENCLEXTA + obinutuzumab vs. 77/216 for obinutuzumab + chlorambucil[1]

Visit venclextareimbursement.ca!

In an open-label study (MURANO), VENCLEXTA + rituximab demonstrated superior PFS compared with bendamustine + rituximab in patients with R/R CLL[1§]

- 81% reduction in instantaneous risk of progression or death vs. bendamustine + rituximab (HR: 0.19 [95% CI: 0.13–0.28]; $p<0.0001$)[1¶]
  - The 2-year rates of PFS for the VENCLEXTA + rituximab and bendamustine + rituximab arms were 82.76% (95% CI: 76.62–88.90) and 39.42% (95% CI: 31.03–47.82), respectively (IRC-assessed in the ITT population)[1,2]

Clinical use:
No safety and efficacy data for VENCLEXTA in children and adolescents below 18 years of age are available.

Contraindication:
In patients with CLL, concomitant use with strong CYP3A inhibitors at initiation and during ramp-up phase.

Most serious warnings and precautions:
- **VENCLEXTA should only be prescribed by a qualified physician who is experienced in the use of anti-cancer agents.**
- **VENCLEXTA is only available through specialty pharmacies and/or retail oncology pharmacies that are part of AbbVie's managed distribution program.**
- **Tumour lysis syndrome (TLS)**
  - Weekly dosage ramp-up over a period of 5 weeks with CLL, with blood chemistry monitoring on each dose ramp-up is required.
  - Patients must receive prophylaxis for TLS, including hydration and anti-hyperuricemics prior to initiating treatment.
  - In patients with CLL, concomitant use of strong CYP3A inhibitors at initiation and during ramp-up phase is contraindicated.
- **Serious infections that may lead to hospitalization or death.**

Other relevant warnings and precautions:
- Second primary malignancies: monitor patients for the appearance of non-melanoma skin cancers.
- Monitor patients more frequently for signs of VENCLEXTA toxicities.
- Neutropenia; dose interruption/reduction recommended for severe neutropenia; prophylactic use of growth factors (e.g. G-CSF) may be considered.
- Immunization using live vaccines should be avoided during treatment and thereafter until B-cell recovery.
- Monitor for signs of infection and have their complete blood counts monitored throughout treatment.
- Recommended dose not determined for patients with severe renal impairment (CrCl <30 mL/min) or on dialysis.
- Females of reproductive potential: test to exclude pregnancy before treatment; use of effective contraceptives during treatment and for at least 30 days after last dose.
- Male fertility may be compromised.
- Avoid use during pregnancy.
- Breastfeeding should be discontinued.
- No overall difference in effectiveness and safety observed in patients ≥65 years of age compared to younger patients. In the combination study (MURANO), patients ≥65 years of age experienced higher incidences of diarrhea, peripheral oedema, dizziness, blood creatinine increased, constipation, pyrexia and fall than those <65 years of age.
- Patients with hepatic impairment should be monitored more closely for signs of toxicity.
  - Severe hepatic impairment: A 50% reduction in VENCLEXTA dose is recommended throughout the initiation, ramp-up phase and steady state once daily dose.
- Monitoring and laboratory tests: tumour burden assessment; blood chemistry monitoring; signs of infection; complete blood counts; baseline renal function and hepatic status; bleeding events. Treatment should be interrupted as appropriate.

For more information:
Please consult the Product Monograph at abbvie.ca/content/dam/abbvie-dotcom/ca/en/documents/products/VENCLEXTA_PM_EN.pdf for important information relating to adverse reactions, drug interactions and dosing information which have not been discussed in this piece. The Product Monograph is also available by calling 1-888-704-8271 or 514-906-9771.

Please refer to the study parameters[†§] and reference list at: **meddocs.ca/CA-VENC-210030.html**.

* V: VENCLEXTA.
‡ The median follow-up at the time of analysis was 28 months (range: 0 to 36 months).
¶ The median follow-up at the time of primary analysis was 24.8 months (range: 0.3 to 37.4 months) in the VENCLEXTA + rituximab arm and 22.1 months (range: 0 to 33.8 months) in the bendamustine + rituximab arm (data cut-off date May 8, 2017).

CLL: chronic lymphocytic leukemia; PFS: progression-free survival; HR: hazard ratio; CI: confidence interval; R/R: relapsed/refractory; IRC: independent review committee; ITT: intention-to-treat; G-CSF: granulocyte-colony stimulating factor; CrCl: creatinine clearance.

abbvie.ca
1-888-703-3006
Printed in Canada

CA-VENC-210030A – January 2022

ABOUT THE AUTHOR

Victor H Jimenez-Zepeda, MD

Dr Victor H Jimenez Zepeda is a hematologist practicing in Calgary, AB and a member of the Arnie Charbonneau Cancer Research Institute and Tom Baker Cancer Center. He is co-director of the Amyloidosis Program of Calgary. He serves as a member of the steering committee for the Myeloma Canada Research Network Database and is a member of other prestigious international societies such as the International Myeloma Society, International Society of Amyloidosis, European Hematology Association, and the American Society of Hematology among others.

DIAGNOSIS AND TREATMENT OF AL AMYLOIDOSIS IN 2022

Introduction

Light chain (AL) amyloidosis is a rare, progressive and typically fatal disease (when advanced) characterized by organ dysfunction secondary to deposition of misfolded fibrils of immunoglobulin light chains that are produced by clonal plasma cells or B cells.[1] Although less than 10% of AL patients qualify for CRAB criteria of symptomatic myeloma (**C**alcium elevation, **R**enal dysfunction, **A**nemia, and **B**one disease),[2] the majority of these patients have significant impairment of vital organs, such as the heart, kidney and liver. This implies that the common risk factors used for the assessment of multiple myeloma (MM) are not applicable to AL. AL amyloidosis affects 8-12 individuals per million person-years.[3,4] and its clinical presentation is variable depending on the extent and number of vital organs affected. The locations of amyloid deposits can vary among patients, thus contributing to the heterogeneity of the clinical manifestations. The heart and kidney, which are the most affected organs, can lead to renal failure, cardiomyopathy, and pericardial and pleural effusions.[1] Initial symptoms at onset are often non-specific (e.g., weight loss, fatigue). Despite advances in the diagnostic tools and treatment options, early mortality rates remain high; the expected one-year mortality is approximately 30%.[5] Unfortunately, by the time the AL diagnosis is made, and treatment is initiated, the disease has often become advanced.

The diagnosis of AL amyloidosis requires histological demonstration of amyloid deposits in biopsy tissue, followed by amyloid typing to identify the precursor protein associated with the amyloid formation.[6] The tissue source can be the involved organ by amyloid formation. However, a more accessible tissue, such as subcutaneous fat, should initially be pursued when suspicion for amyloidosis is raised.[7] Fat pad aspirate in combination with a bone marrow biopsy will yield the diagnosis in approximately 90% of patients. Congo red is the gold standard staining for recognition of amyloid deposits. Tissue stained by congo red under polarized light demonstrates apple-green birefringence, illustrating the highly organized ultrastructure of the amyloid fibrils. Once the amyloid diagnosis is established, the next step is to type and determine the precursor protein associated to fibril deposition. Several methods of typing are available. The gold standard technique is laser microdissection, followed by mass spectrometry–based proteomic analysis, which has high sensitivity and specificity.[8] Alternative typing methods include antigen-antibody–based analyses, such as immunofluorescence, immunohistochemistry, and immunogold.[9] It should be emphasized that the presence of a monoclonal protein in a patient with amyloidosis does not prove AL type[10] as monoclonal gammopathy of undetermined significance (MGUS) can be found in 30-40% of patients with either wild type or hereditary systemic transthyretin amyloidosis (ATTR).[11] Finally, the distinction between 'localized' and 'systemic' AL amyloidosis is required. The designation localized applies to AL amyloidosis in which the precursor protein is produced at the site of amyloid deposition and is typically not associated with a detectable circulating monoclonal protein in the serum or urine. The common sites of localized amyloidosis are the tracheobronchial tree, lungs, urinary tract, skin and soft tissue, oropharynx, gastrointestinal tract, and eyes.[12,13]

Due to the protein clinical manifestations and insidious onset of the disease, indications for diagnostic testing includes a broad range of features including non-diabetic nephrotic range proteinuria, non-dilated cardiomyopathy, increased NT-pro-BNP, unexplained hepatosplenomegaly, carpal tunnel syndrome, edema, purpura, or macroglossia. Biomarkers are also essential in making the diagnosis, as well as in determining the prognosis and evaluating response to therapy. Given the significant prognostic impact of cardiac involvement with early death, several markers of cardiac injury and dysfunction have been reported.[14] Serum levels of NT-pro-BNP and cardiac troponin T (cTnT) were first found to predict survival in several cohorts of patients with AL.[15-17] They were later incorporated into the first widely used staging system for AL amyloidosis (Mayo 2004).[17] The composition and biomarker thresholds were subsequently revised and two modifications of the original score are widely accepted.[18] The European version of the 2004 Mayo system identifies patients with very high NT-pro-BNP levels as having very poor outcomes and splits stage III into two stages (IIIa and IIIb) based on a cutoff of 8500 ng/L for the values of NT-pro-BNP. More recently, the Boston group reported on the use of BNP and troponin I (TnI) for staging.[19] BNP higher than 81 pg/mL and TnI higher than 0.1 ng/mL were used in this validated staging system.

Assessment of the monoclonal protein associated to AL amyloidosis
The screening for a monoclonal protein is done by serum and urine electrophoresis with immunofixation studies as well as serum free light chain (FLC) levels.[20] More recently at the Mayo Clinic, immunofixation has been replaced by the mass spectrometry method (Mass-Fix).[21] The Mass-Fix assay has the ability to detect M-proteins with light chain glycosylation, which has been reported to be a risk factor for progression of AL amyloidosis and other plasma cell disorders.[22] In addition, bone marrow aspiration and biopsy and fluorescence in-situ hybridization (FISH) testing are indicated and can affect treatment decisions during the disease course.

Immunophenotyping
Multidimensional flow cytometry (MFC) has emerged as a potential tool highly sensitive for the detection of aberrant plasma cells in the bone marrow. Research has demonstrated that monoclonal plasma cells >2.5% at the time of diagnosis, as detected by MFC was associated with shorter survival.[23] More recently another group developed an automated computerized algorithm to assess clonality and identified three subgroups with different survival outcomes.[24]

Cytogenetics of the aberrant plasma cells
FISH abnormalities have been detected in patients with AL amyloidosis. A study conducted in 2009[25] was one of the first to describe the utility of this approach in identifying t(11;14) as an adverse risk factor for AL. Other researchers[26] described the degree of plasma cell burden and their relationship to survival an advanced cardiac disease. Additional research has[27] further stratified patients with t(11;14) who received bortezomib and IMiD-containing regimens showing that this group had an inferior survival compared to those without this translocation. It is important to note that high risk cytogenetics seen in MM (t(4;14), t(14;16) and del17p) are not common in AL. More complex karyotype clones, however, and presence of del17p have an impact on outcomes. Gain of 1q21 has also been described as an independent adverse prognostic factor in a series of 103 AL patients treated with melphalan, dexamethasone, standard chemotherapy, and daratumumab as first-line therapy.[28]

Treatment of AL amyloidosis
The aim of treatment of AL amyloidosis is to eradicate the underlying plasma cell clone in order to rapidly reduce the production of misfolded FLC proteins, mitigate further organ damage, and improve overall survival.[29]

Supportive care
Supportive measures are key in the management of AL amyloidosis, with the goal of improving quality of life, symptoms and sustaining organ function while the plasma directed therapy takes place.[30] The main pillar of supportive care is the use of diuretics. It should be noted that, in amyloidosis, cardiac function is preload dependent, and thus, avoiding reduction of intravascular volume is fundamental. Angiotensin-converting enzyme inhibitors are usually poorly tolerated due to hypotension. Similarly, calcium channel blockers are contraindicated due to their negative inotropic effects.[31] Patients with severe neurogenic orthostatic hypotension will require therapy with midodrine and/or droxidopa to facilitate diuretic dose titration.

Intracardiac thrombi are another possible complication in AL amyloidosis despite sinus rhythm.[32] Atrial thrombus, mainly located in the right or left atrial appendages, was found by transesophageal echocardiography in 35% of patients with this disease.[33] The incidence of thromboembolism is higher in patients with atrial fibrillation in the presence of cardiac AL amyloidosis than in other more common forms of atrial fibrillation. Therefore, anticoagulation must be considered on an individualized basis counterbalancing the higher hemorrhagic risk of this population due to the potential association of vascular amyloid deposition, factor X deficiency and liver involvement. As a general recommendation, anticoagulation should be given for any atrial arrhythmia and in patients with sinus rhythm whose echocardiography shows features of left atrial mechanical dysfunction.[34]

Further, organ transplantation should be carefully assessed by a multidisciplinary team since the risk of recurrence of amyloid in the graft and progression of fibril deposition in other organs is often observed. For instance, cardiac transplantation could be considered in young patients with isolated severe cardiac involvement where effective anti-plasma cell therapy is only expected to be delivered if organ replacement occurs. The implantation of left ventricular assist devices is technically feasible for patients with severe heart failure caused by advanced cardiac amyloidosis, but the possible benefit is unclear.[35,36]

Autologous stem cell transplantation
In clinical practice, the first question to be asked is whether an AL patient is a candidate for autologous stem cell transplantation (auto-SCT). Among eligible patients, auto-SCT is an excellent option with potential for long-term survival. There are, however, no randomized trial data to support that it is superior to conventional chemotherapy. On the contrary, a phase 3 study concluded that high dose intravenous melphalan followed by auto-SCT rescue was inferior to standard-dose melphalan plus high-dose dexamethasone (MDex) in newly diagnosed patients.[37] On an intention-to-treat (ITT) basis, the median survival for MDex was 57 months vs 22 months for the auto-SCT arm (P=0.04). However, of the 50 patients randomized to receive ASCT, only 37 actually received the planned transplant and 9 of those died within 100 days, indicating an unacceptably high (24%) treatment-related mortality (TRM) rate. In a 6-month landmark analysis, no difference in survival was noted between treatment arms, thus accounting for the survival disadvantage of ASCT to the very high TRM rate. Current clinical trials demonstrate a TRM of less than 5%,[38-40] suggesting inappropriate selection of patients in that study, which in turn limits its conclusions.

Non transplant therapies
Historically, therapy for AL amyloidosis was based on targeting the plasma cell clone and treatments that were used in MM were incorporated into the management of AL patients. Treatment should be risk-adapted, considering the severity of organ involvement, characteristic of the clone, and comorbidities and should seek to deliver the most rapid and effective therapy patients can safely tolerate.[30] Early and profound reductions of the amyloid LC are associated with the greatest chance of organ improvement and prolongation of survival outcomes.[41-43] The optimal end point of therapy is still a matter of debate. However, achievement of organ response and profound hematological response should be the long-term goal of therapy. Novel definitions of response and minimal residual disease (MRD) assessment are currently being investigated for AL.[41,44,45]

Most patients with AL amyloidosis are not eligible for auto-SCT. Melphalan with steroids has historically been the first-line approach for the treatment of AL.[46] However, given the efficacy of proteasome inhibition in MM, bortezomib was evaluated in AL amyloidosis. Real-world studies of CyBorD (cyclophsophamide, bortezomib and dexamethasone) demonstrate a need for more effective therapies for AL amyloidosis, with hematologic responses reported in 60-65%, cardiac responses in 17-32%, and renal responses in 15-25% of patients[45,47]. Encouragingly, the phase III ANDROMEDA trial showed that the addition of daratumumab to a CyBorD regimen significantly increased the rates of hematologic complete response (CR) (53% vs 18%, p<0.001), cardiac response (42% vs 22%), and renal response (53% vs 24%), with median time to hematologic CR of 60 days in the daratumumab-CyBorD group compared to 85 days in the CyBorD group (**Figure 2**)[48].

Treatment intensification with high dose melphalan is an option in a subset of patients and it has been suggested as a sequential response-driven approach for patients undergoing CyBorD who don't exhibit a satisfactory response after induction therapy.[49] In addition, a phase 3 study in intermediate risk AL patient demonstrated that bortezomib, melphalan and dexamethasone (BMD) induced a significantly higher HR rate (81% vs 57%, CR, 23% vs 20%; VGPR 42% vs 20%) than MDex, with prolonged overall survival. Cardiac and renal responses were observed in 38% and 44% of cases with BMDex and in 28% and 43% of cases with MDex, respectively.[50]

Approximately 20% of patients have advanced cardiac stage at the time of diagnosis. Treatment of these patients considered high-risk and remains an unmet need. Initially, the European collaborative study reported lower haematological response rates in patients with stage IIIb disease.[51] This is likely a reflection of very advanced cardiac disease. Further, studies have reported on the importance of rapid responses in patients with stage IIIb, demonstrating an improvement in survival for patients treated with CyBorD compared to CTD (cyclophosphamide, thalidomide and dexamethasone); but most importantly described how patients with rapid haematological response in 1-month are associated with improved survival.[52] Based on these reports, recent studies have explored the possible benefit of the substitution of dexamethasone by methylprednisolone with the aim of decreasing toxicity.[53]

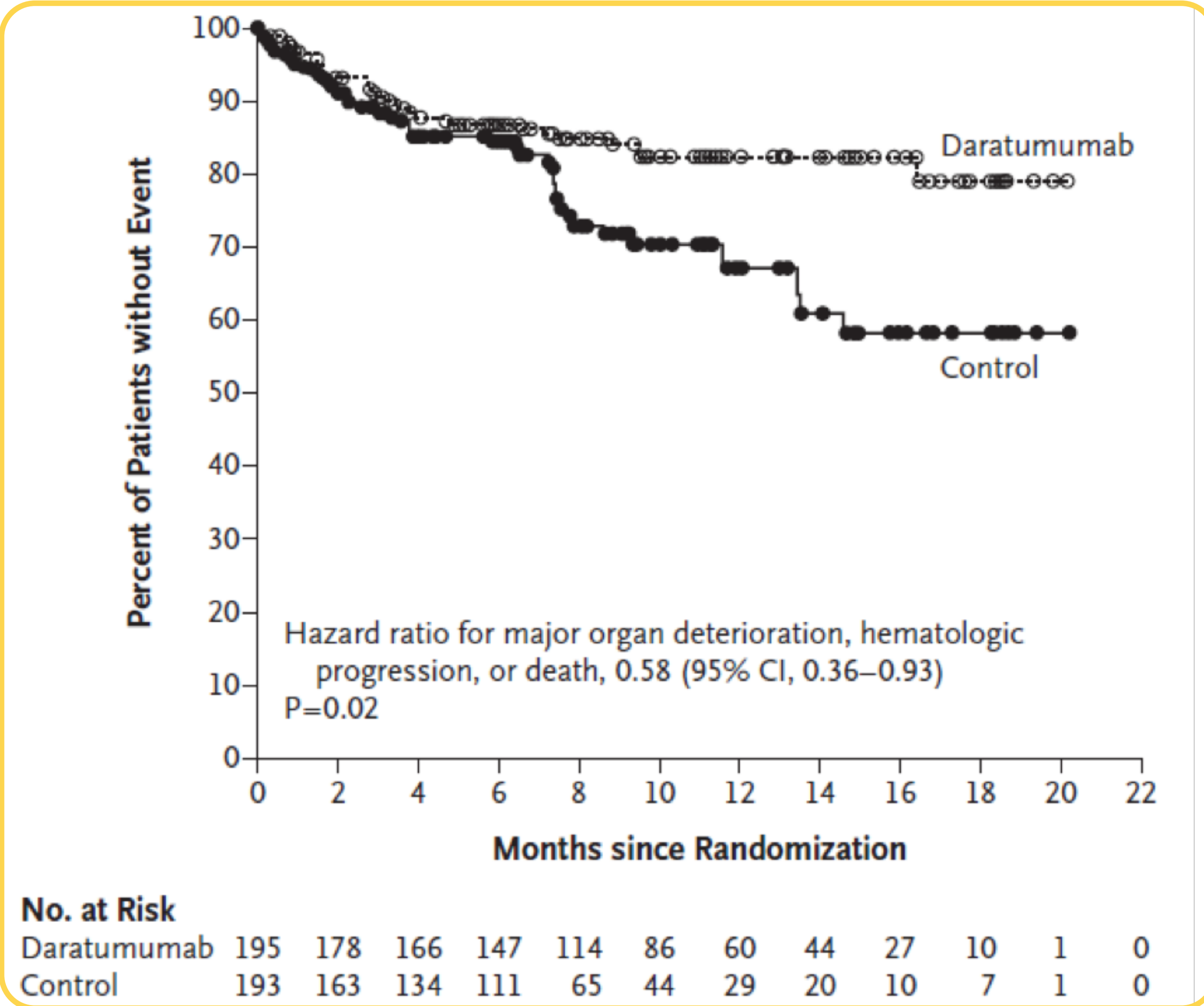

Figure 2. *Kaplan–Meier Estimates of Survival Free from Major Organ Deterioration or Hematologic Progression. Shown are the results of the Kaplan–Meier estimates of survival from major organ deterioration or hematologic progression among patients in the intention- to-treat population. Major organ deterioration was defined as end stage cardiac or renal failure; adapted from Kastritis et al, 2021*

Notably, patients treated with methylprednisolone exhibited faster responses which translated into a better survival rate (2-year OS of 65% versus 43%). Our group presented a preliminary report on the use of CyBorMe (cyclophosphamide, bortezomib and methylprednisolone) for newly diagnosed AL amyloidosis patients treated at a single referral center and compared with a historic group of patients treated with a standard CyBorD regimen used at our institution. Overall response rates (ORR) were similar among the CyBorD and CyBorMe groups (90.6% vs 100%, p=0.7). However, patients in the CyBorMe group had a faster time to first (4 vs 6 weeks) and best response compared to CyBorD (p=0.003 and 0.047, respectively). In addition, a trend towards lower dFLC after one month and higher cardiac response rate was noted (44% and 31% of patients treated with CyBorMe and CyBorD, respectively). Out of 7 evaluable cases for cardiac involvement, 3 patients exhibited cardiac response at a median of 8 weeks.[54]

Venetoclax is also an appealing option for patients with t(11;14), but few data are available to date. Although a change in AL amyloidosis therapy is typically prompted by the occurrence of hematologic or organ progression, there is growing consensus that failure to achieve an optimal response within the first few cycles of treatment should also lead to a change in therapy[55]. Given the poor prognosis of patients with suboptimal response to first-line therapy and the encouraging findings of these studies, further research is warranted to identify the optimal timing of response assessment and to better understand the role for early switch to second-line therapy in AL amyloidosis.

Anti-fibril directed therapy

Treatment of AL amyloidosis has been directed at reducing the circulating precursor LC's by targeting the malignant B-cell clone. Recently, two anti-amyloid antibodies have been tested in clinical trials for AL amyloidosis, but despite encouraging preliminary results, further clinical studies were discontinued due to futility or unfavorable toxicity.[56,57] Recently, CAEL-101, a monoclonal antibody that reacts with a conformational epitope present on partially denatured and fibrillar LC's was investigated in phase1a/b study. All patients were exposed to 1 to 10 lines of therapy, and median times from last chemotherapy administration were 2.6 and 7.4 months in the phase 1a and 1b portions of the study. Twenty patients (74%) demonstrated VGPR at the time of first infusion of CAEL-101. Fifteen of 24 patients (63%) had a therapeutic response to CAEL-101 as evidenced by serum biomarkers or objective imaging modalities with a median time of response of 3 weeks.[58] This study provides rationale for the development of a phase 3 clinical trial program for patients with AL amyloidosis with stage IIIa and IIIB that are randomized to CAEL-101 plus CyBorD or CyBorD alone.

Conclusion

AL amyloidosis is a rare disease often associated with devastating outcomes due to advanced cardiac disease. As delays in the diagnosis of AL amyloidosis are common, finding biomarkers that could potentially help us diagnose this entity is crucial. Recently, CyBorD plus daratumumab was approved by FDA and Health Canada becoming the first and only treatment approved for patients with newly diagnosed AL amyloidosis. Based on this exciting approval more work is needed to improve awareness and advance research that could potentially lead to early diagnosis and innovative use of novel drug combinations.

References:

1. McCausland KL, White MK, Guthrie SD, et al. Light Chain (AL) Amyloidosis: The Journey to Diagnosis. Patient. 2018 Apr;11(2):207-216.

2. Kourelis TV, Kumar SK, Gertz MA, et al. Coexistent multiple myeloma or increased bone marrow plasma cells define equally high-risk populations in patients with immunoglobulin light chain amyloidosis. J Clin Oncol. 2013 Dec 1;31(34):4319-24.

3. Kyle RA, Linos A, Beard CM, et al. Incidence and natural history of primary systemic amyloidosis in Olmsted County, Minnesota, 1950 through 1989. Blood. 1992 Apr 1;79(7):1817-22.

4. Pinney JH, Smith CJ, Taube JB, et al. Systemic amyloidosis in England: an epidemiological study. Br J Haematol. 2013 May;161(4):525-32.

5. Lousada I, Comenzo RL, Landau H, et al. Light Chain Amyloidosis: Patient Experience Survey from the Amyloidosis Research Consortium. Advances in therapy. 2015 Oct;32(10):920-8.

6. Nuvolone M, Merlini G. Systemic amyloidosis: novel therapies and role of biomarkers. Nephrol Dial Transplant. 2017 May 1;32(5):770-780.

7. Muchtar E, Dispenzieri A, Lacy MQ, et al. Overuse of organ biopsies in immunoglobulin light chain amyloidosis (AL): the consequence of failure of early recognition. Ann Med. 2017 Nov;49(7):545-551.

8. Dasari S, Theis JD, Vrana JA, et al. Amyloid Typing by Mass Spectrometry in Clinical Practice: a Comprehensive Review of 16,175 Samples. Mayo Clin Proc. 2020 Sep;95(9):1852-1864.

9. Fernandez de Larrea C, Verga L, Morbini P, et al. A practical approach to the diagnosis of systemic amyloidoses. Blood. 2015 Apr 2;125(14):2239-44.

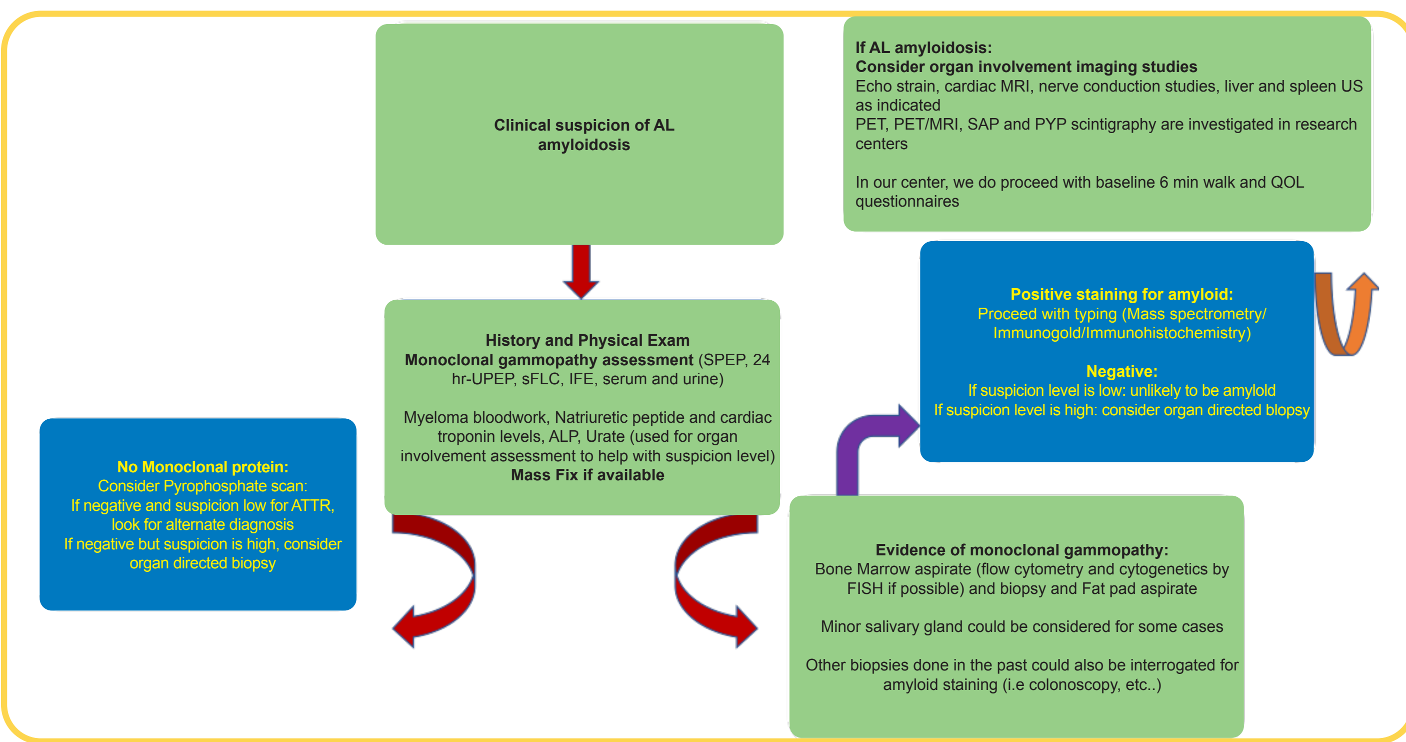

Figure 1. *Diagnostic algorithm for AL Amyloidosis; courtesy of Victor Zepeda, MD*

10. Sidiqi MH, Dasari S, McPhail ED, et al. Monoclonal gammopathy plus positive amyloid biopsy does not always equal AL amyloidosis. Am J Hematol. 2019 May;94(5):E141-E143.

11. Phull P, Sanchorawala V, Connors LH, et al. Monoclonal gammopathy of undetermined significance in systemic transthyretin amyloidosis (ATTR). Amyloid. 2018 Mar;25(1):62-67.

12. Mahmood S, Bridoux F, Venner CP, et al. Natural history and outcomes in localised immunoglobulin light-chain amyloidosis: a long-term observational study. Lancet Haematol. 2015 Jun;2(6):e241-50.

13. Dispenzieri A, Gertz MA, Kyle RA, et al. Prognostication of survival using cardiac troponins and N-terminal pro-brain natriuretic peptide in patients with primary systemic amyloidosis undergoing peripheral blood stem cell transplantation. Blood. 2004 Sep 15;104(6):1881-7.

14. Fotiou D, Theodorakakou F, Kastritis E. Biomarkers in AL Amyloidosis. Int J Mol Sci. 2021 Oct 9;22(20).

15. Palladini G, Foli A, Milani P, et al. Best use of cardiac biomarkers in patients with AL amyloidosis and renal failure. Am J Hematol. 2012 May;87(5):465-71.

16. Palladini G, Milani P, Merlini G. Predicting survival in light chain amyloidosis. Haematologica. 2019 Jul;104(7):1294-1296.

17. Dispenzieri A, Gertz MA, Kyle RA, et al. Serum cardiac troponins and N-terminal pro-brain natriuretic peptide: a staging system for primary systemic amyloidosis. J Clin Oncol. 2004 Sep 15;22(18):3751-7.

18. Kumar S, Dispenzieri A, Lacy MQ, et al. Revised prognostic staging system for light chain amyloidosis incorporating cardiac biomarkers and serum free light chain measurements. J Clin Oncol. 2012 Mar 20;30(9):989-95.

19. Lilleness B, Ruberg FL, Mussinelli R, et al. Development and validation of a survival staging system incorporating BNP in patients with light chain amyloidosis. Blood. 2019 Jan 17;133(3):215-223.

20. Katzmann JA, Kyle RA, Benson J, et al. Screening panels for detection of monoclonal gammopathies. Clin Chem. 2009 Aug;55(8):1517-22.

21. Dispenzieri A, Larson DR, Rajkumar SV, et al. N-glycosylation of monoclonal light chains on routine MASS-FIX testing is a risk factor for MGUS progression. Leukemia. 2020 Oct;34(10):2749-2753.

22. Kourelis T, Murray DL, Dasari S, et al. MASS-FIX may allow identification of patients at risk for light chain amyloidosis before the onset of symptoms. Am J Hematol. 2018 Nov;93(11):E368-E370.

23. Muchtar E, Jevremovic D, Dispenzieri A, et al. The prognostic value of multiparametric flow cytometry in AL amyloidosis at diagnosis and at the end of first-line treatment. Blood. 2017 Jan 5;129(1):82-87.

24. Puig N, Paiva B, Lasa M, et al. Flow cytometry for fast screening and automated risk assessment in systemic light-chain amyloidosis. Leukemia. 2019 May;33(5):1256-1267.

25. Bryce AH, Ketterling RP, Gertz MA, et al. Translocation t(11;14) and survival of patients with light chain (AL) amyloidosis. Haematologica. 2009 Mar;94(3):380-6.

26. Warsame R, Kumar SK, Gertz MA, et al. Abnormal FISH in patients with immunoglobulin light chain amyloidosis is a risk factor for cardiac involvement and for death. Blood Cancer J. 2015 May 1;5:e310.

27. Muchtar E, Dispenzieri A, Kumar SK, et al. Interphase fluorescence in situ hybridization in untreated AL amyloidosis has an independent prognostic impact by abnormality type and treatment category. Leukemia. 2017 Jul;31(7):1562-1569.

28. Bochtler T, Hegenbart U, Kunz C, et al. Gain of chromosome 1q21 is an independent adverse prognostic factor in light chain amyloidosis patients treated with melphalan/dexamethasone. Amyloid. 2014 Mar;21(1):9-17.

29. Jimenez-Zepeda VH, Lee H, McCulloch S, et al. Treatment response measurements and survival outcomes in a cohort of newly diagnosed AL amyloidosis. Amyloid. 2021 Sep;28(3):182-188.

30. Palladini G, Milani P, Merlini G. Management of AL amyloidosis in 2020. Hematology Am Soc Hematol Educ Program. 2020 Dec 4;2020(1):363-371.

31. Gertz MA, Falk RH, Skinner M, et al. Worsening of congestive heart failure in amyloid heart disease treated by calcium channel-blocking agents. Am J Cardiol. 1985 Jun 1;55(13 Pt 1):1645.32. Dubrey S, Pollak A, Skinner M, et al. Atrial thrombi occurring during sinus rhythm in cardiac amyloidosis: evidence for atrial electromechanical dissociation. Br Heart J. 1995 Nov;74(5):541-4.

33. Feng D, Syed IS, Martinez M, et al. Intracardiac thrombosis and anticoagulation therapy in cardiac amyloidosis. Circulation. 2009 May 12;119(18):2490-7.

34. Falk RH, Alexander KM, Liao R, et al. AL (Light-Chain) Cardiac Amyloidosis: A Review of Diagnosis and Therapy. J Am Coll Cardiol. 2016 Sep 20;68(12):1323-41.

35. Patel KS, Hawkins PN, Whelan CJ, et al. Life-saving implantable cardioverter defibrillator therapy in cardiac AL amyloidosis. BMJ Case Rep. 2014 Dec 22;2014.

36. Varr BC, Zarafshar S, Coakley T, et al. Implantable cardioverter-defibrillator placement in patients with cardiac amyloidosis. Heart Rhythm. 2014 Jan;11(1):158-62.

37. Jaccard A, Moreau P, Leblond V, et al. High-dose melphalan versus melphalan plus dexamethasone for AL amyloidosis. N Engl J Med. 2007 Sep 13;357(11):1083-93.

38. Sidiqi MH, Aljama MA, Buadi FK, et al. Stem Cell Transplantation for Light Chain Amyloidosis: Decreased Early Mortality Over Time. J Clin Oncol. 2018 May 1;36(13):1323-1329.

39. D'Souza A, Dispenzieri A, Wirk B, et al. Improved Outcomes After Autologous Hematopoietic Cell Transplantation for Light Chain Amyloidosis: A Center for International Blood and Marrow Transplant Research Study. J Clin Oncol. 2015 Nov 10;33(32):3741-9.

40. Sharpley FA, Petrie A, Mahmood S, et al. A 24-year experience of autologous stem cell transplantation for light chain amyloidosis patients in the United Kingdom. Br J Haematol. 2019 Dec;187(5):642-652.

41. Milani P, Basset M, Nuvolone M, et al. Indicators of profound hematologic response in AL amyloidosis: complete response remains the goal of therapy. Blood Cancer J. 2020 Sep 1;10(8):90.

42. Sidana S, Milani P, Binder M, et al. A validated composite organ and hematologic response model for early assessment of treatment outcomes in light chain amyloidosis. Blood Cancer J. 2020 Apr 14;10(4):41.

43. Palladini G, Dispenzieri A, Gertz MA, et al. New criteria for response to treatment in immunoglobulin light chain amyloidosis based on free light chain measurement and cardiac biomarkers: impact on survival outcomes. J Clin Oncol. 2012 Dec 20;30(36):4541-9.

44. Palladini G, Paiva B, Wechalekar A, et al. Minimal residual disease negativity by next-generation flow cytometry is associated with improved organ response in AL amyloidosis. Blood Cancer J. 2021 Feb 16;11(2):34.

45. Manwani R, Cohen O, Sharpley F, et al. A prospective observational study of 915 patients with systemic AL amyloidosis treated with upfront bortezomib. Blood. 2019 Dec 19;134(25):2271-2280.

46. Palladini G, Perfetti V, Obici L, et al. Association of melphalan and high-dose dexamethasone is effective and well tolerated in patients with AL (primary) amyloidosis who are ineligible for stem cell transplantation. Blood. 2004 Apr 15;103(8):2936-8.

47. Palladini G, Sachchithanantham S, Milani P, et al. A European collaborative study of cyclophosphamide, bortezomib, and dexamethasone in upfront treatment of systemic AL amyloidosis. Blood. 2015 Jul 30;126(5):612-5.

48. Kastritis E, Palladini G, Minnema MC, et al. Daratumumab-Based Treatment for Immunoglobulin Light-Chain Amyloidosis. N Engl J Med. 2021 07 01;385(1):46-58.

49. Basset M, Milani P, Nuvolone M, et al. Sequential response-driven bortezomib-based therapy followed by autologous stem cell transplant in AL amyloidosis. Blood Adv. 2020 Sep 8;4(17):4175-4179.

50. Kastritis E, Leleu X, Arnulf B, et al. Bortezomib, Melphalan, and Dexamethasone for Light-Chain Amyloidosis. J Clin Oncol. 2020 Oct 1;38(28):3252-3260.

51. Wechalekar AD, Schonland SO, Kastritis E, et al. A European collaborative study of treatment outcomes in 346 patients with cardiac stage III AL amyloidosis. Blood. 2013 Apr 25;121(17):3420-7.

52. Manwani R, Foard D, Mahmood S, et al. Rapid hematologic responses improve outcomes in patients with very advanced (stage IIIb) cardiac immunoglobulin light chain amyloidosis. Haematologica. 2018 Apr;103(4):e165-e168.

53. Mahmood A SS, Harrison S, Manwani R, Sharpley F, Quarta C, Rezk T, Martinez A, Yoong K, Rabin N, Popat R, Kyriacou C, Papanikolau X, D'Sa S, Lachmann H, Whelan C, Gillmore J, Fontana M, Hawkins P and Wechaleckar A. Bortezomib-High dose Methylprednisolone offers improved hematological response and overall survival compared to Bortezomib-Dexamethasone in Systemic Light Chain Amyloidosis. EHA Library. 2019 [cited PB2127 p.]. Abstract available at

54. Jimenez-Zepeda VH, Lee H, Fine N, et al. Cyclophosphamide, Bortezomib and Methylprednisolone (CyBorMe) for the Treatment of AL Amyloidosis: Initial Experience From a Single Center. Indian J Hematol Blood Transfus. 2021 Oct;37(4):675-678.

55. Palladini G, Milani P, Merlini G. Management of AL amyloidosis in 2020. Blood. 2020 12 03;136(23):2620-2627.

56. Richards DB, Cookson LM, Berges AC, et al. Therapeutic Clearance of Amyloid by Antibodies to Serum Amyloid P Component. N Engl J Med. 2015 Sep 17;373(12):1106-14.

57. Gertz MA, Landau H, Comenzo RL, et al. First-in-Human Phase I/II Study of NEOD001 in Patients With Light Chain Amyloidosis and Persistent Organ Dysfunction. J Clin Oncol. 2016 Apr 1;34(10):1097-103.

58. Edwards CV, Rao N, Bhutani D, et al. Phase 1a/b study of monoclonal antibody CAEL-101 (11-1F4) in patients with AL amyloidosis. Blood. 2021 Dec 23;138(25):2632-2641.

POLIVY®
polatuzumab vedotin

Roche

PICTURE THE **POSSIBILITIES**

^{Pr}POLIVY® (polatuzumab vedotin) in combination with bendamustine and rituximab (BR) is indicated for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (R/R DLBCL), not otherwise specified, who are not eligible for autologous stem cell transplant (ASCT) and have received at least one prior therapy. POLIVY has been issued marketing authorization with conditions, pending the results of trials to verify its clinical benefit. Patients should be advised of the nature of the authorization.

POLIVY: A combination treatment option for R/R DLBCL patients who are not candidates for ASCT

Clinical use:

Pediatrics (< 18 years of age):
Based on the data submitted and reviewed by Health Canada, the safety and efficacy of POLIVY in pediatric patients has not been established; therefore, Health Canada has not authorized an indication for pediatric use.

Geriatrics (≥ 65 years of age):
Patients aged 65 and older had a higher incidence of adverse events ≥ Grade 3 and POLIVY discontinuation compared with younger patients. There is insufficient evidence from clinical studies to determine if there are meaningful differences in response to POLIVY in patients 65 years and older compared to a younger patient population.

Most serious warnings and precautions:

Clinically significant and life-threatening adverse events
Fatal, life-threatening or serious infections, including opportunistic infections, have been reported in patients treated with POLIVY.

Serious and severe myelosuppression
Neutropenia, febrile neutropenia, thrombocytopenia and anemia have been reported in patients treated with POLIVY.

Administration
POLIVY should only be administered by a qualified healthcare professional experienced in the use of antineoplastic therapy.

Other relevant warnings and precautions:

- Infusion-related reactions
- Tumour Lysis Syndrome (TLS)
- Hepatic toxicity
- Peripheral neuropathy
- Progressive Multifocal Leukoencephalopathy (PML)
- Pregnancy testing: The pregnancy status of female patients of reproductive potential should be verified prior to initiating POLIVY
- Contraception: Female patients of reproductive potential should be advised of the potential harm to the fetus. Female patients of reproductive potential should be advised to use effective contraception during treatment with POLIVY and for at least 9 months after the last dose
- Breastfeeding: Nursing women should be advised not to breastfeed during treatment with POLIVY and for at least 3 months after the last dose
- Fertility: Based on findings from animal studies, POLIVY may impair male reproductive function and fertility
- Renal impairment
- Hepatic impairment
- Caution when driving or operating machinery

For more information:
Please consult the Product Monograph at: https://www.rochecanada.com/content/dam/rochexx/roche-ca/products/ConsumerInformation/MonographsandPublicAdvisories/polivy/Polivy_PM_E.pdf for important information relating to contraindications, warnings, precautions, adverse reactions, interactions, dosing and conditions of clinical use. The Product Monograph is also available by calling Roche Drug Information at 1-888-762-4388.

REFERENCE: Current POLIVY® Product Monograph, Hoffmann-La Roche Limited.

If you require this information in an accessible format, please contact Roche at 1-800-561-1759.

Roche Hoffmann-La Roche Limited
Mississauga (Ontario) L5N 5M8

5936E21v

ABOUT THE AUTHOR

Richard LeBlanc, MD

Dr Richard LeBlanc is a hematologist and medical oncologist at Maisonneuve-Rosemont hospital. He obtained his MD degree at Laval University in 1995. He was certified in internal medicine in 1998 and in hematology in 2000 at Laval University. Thereafter, he spent two years as a research fellow at the Dana Farber Cancer Institute, Harvard Medical School in Boston, from 2000 to 2002, to develop an expertise in multiple myeloma. In 2004, he completed his training in medical oncology at Montreal University. He is an associate professor of medicine at the department of medicine, Université de Montréal. Since 2012, he is the Myeloma Canada Chair at the Université de Montréal. His practice and interests focus on improvements in care, teaching and research in multiple myeloma.

TO TRANSPLANT OR NOT TO TRANSPLANT IN MULTIPLE MYELOMA

Introduction and benefits of autologous stem cell transplantation

Multiple myeloma (MM) is the second most common hematologic cancer resulting from proliferation and accumulation of abnormal plasma cells (myeloma cells) with a preferential homing in the bone marrow. It causes significant morbidity including lytic bone lesions, renal insufficiency, anemia and infections to name just a few.[1] Although MM remains largely incurable, it is a chemo-sensitive disease. The use of high-dose intravenous melphalan (100-140 mg/m2) in the treatment of MM was first studied almost 4 decades ago.[2] Subsequently, the dose of melphalan was increased and was followed by autologous hematopoietic stem cell to decrease the aplasia-associated toxicity.[3,4] Results from phase 3 studies comparing chemotherapy alone to chemotherapy followed by high-dose melphalan and autologous stem cell transplantation appeared in the mid-90s with the publication of the IFM-90 study[5] demonstrating significant clinical benefits on response rate, event-free survival and even overall survival in a cohort of two hundred previously untreated patients under the age of 65 years. This landmark study was followed by confirmatory studies in the early 2000's.[6-8] Within the last 2 decades, although improvement in the treatment of transplant-eligible patients is mostly the result of better induction regimens[9,10] and due to the addition of maintenance therapies,[11-13] autologous stem cell transplantation remains a cornerstone treatment for MM patients. Indeed, despite novel and more effective treatments for MM, autologous stem cell transplantation continues to demonstrate clinical benefits (**Table 1**).[9,10,14-17] Moreover, tandem autologous transplantation has demonstrated progression-free survival and overall survival benefits for some patients with poor risk cytogenetics.[17]

In 2022, with better knowledge of MM, awareness of potential consequences of high-dose melphalan and with novel and more effective treatment modalities, the role of autologous stem cell transplantation is certainly becoming a question for debate. The purpose of this article is to present the pros and cons of autologous stem cell transplantation in our Canadian reality (**Figure 1**). This article aims to better assess its role as a therapeutic option considering our health system's limited resources in which many novel drugs will not be available/accessible in Canada for several more years to come.

Risk of high-dose melphalan

High-dose melphalan is well known for significant risk of adverse effects such as severe bone marrow suppression which can result in infection or bleeding, severe gastrointestinal toxicity such as nausea, vomiting, diarrhea and mucositis with ulceration that further increase the risk of infection via bacterial translocation, among other risks.[18] The risk of early mortality within the first few months after autologous stem cell transplantation is approximately 1-2%[5] and predominantly the result of infectious complications.

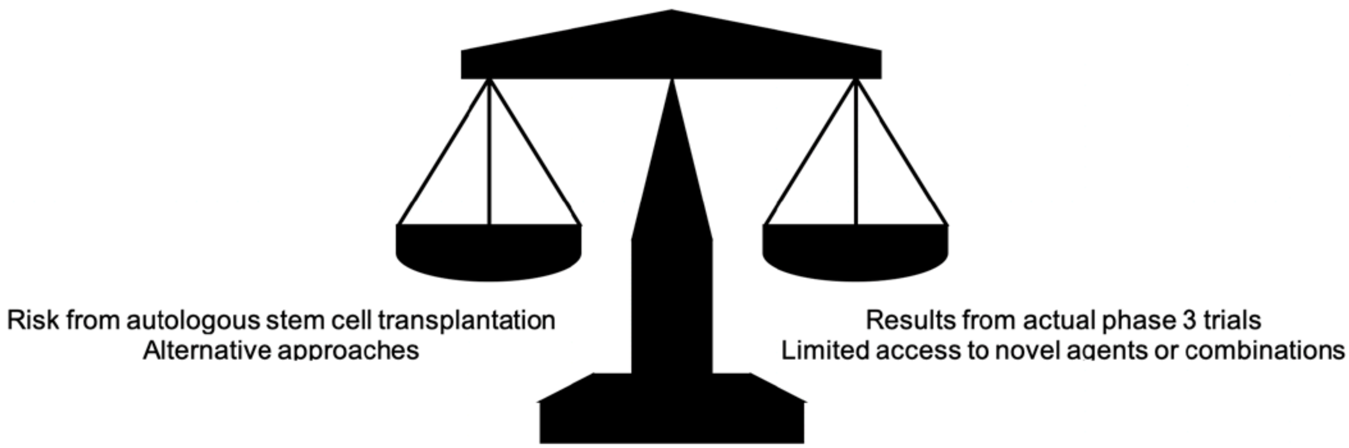

Figure 1. *Weighing the pros and cons of autologous stem cell transplantation; courtesy of Richard LeBlanc, MD*

Beyond the risk of complications and mortality associated with high-dose melphalan is the risk of second primary malignancy. In a retrospective cohort study looking at 841 consecutive MM patients who underwent autologous stem cell transplantation between 1989 and 2009, the overall cumulative incidence of second primary malignancies was found to be 5.3% at 5 years and 11.2% at 10 years when nonmelanoma skin cancers were excluded from the final analysis.[19] In addition, this risk is further increased with the use of lenalidomide in maintenance therapy.[19,20] Melphalan as an alkylating agent that induces DNA damage and high-dose melphalan exposure increases mutational burden detected between diagnosis and relapse by 10-20%.[21] Clinically, melphalan has been shown to increase the relative risk of acute myeloid leukemia by 10-50 fold and the risk of myelodysplastic syndrome by 100 fold in a database analysis of over 9,000 recipients of hematopoietic cell autotransplants between 1995 and 2010 for Hodgkin lymphoma (n = 916), non-Hodgkin lymphoma (n = 3546) and MM (n = 4566), reported to the Center for International Blood and Marrow Transplant Research.[22] This is particularly important since overall survival of myeloma patients is improving. In a recent analysis of 14,532 myeloma patients, the 10-year survival rate favored patients who did not receive transplant.[23] In addition, for long term survivors after autologous stem cell transplantation, the 10-year cumulative incidence of severe and/or life-threatening chronic health conditions is approaching 60%, representing a significant morbidity burden for these patients.[24] As non-transplant regimens become more effective, autologous stem cell transplantation might eventually be regarded as unnecessary and may require a re-examination of its risk-benefit profile.

Alternative approaches

The combination of immunomodulatory drugs and proteasome inhibitors in addition to dexamethasone have been shown to have substantial activity against MM.[25,26] These observed benefits from the combination raise questions about the role of autologous stem cell transplantation. The IFM 2009 study compared the bortezomib-lenalidomide-dexamethasone (VRD) combination in induction and consolidation with or without autologous stem cell transplantation, followed by lenalidomide maintenance as a first line treatment for transplant-eligible patients. Although median progression-free survival was significantly longer in the transplant group (50 months vs 36 months; HR 0.65; p<0.001),[9] a long-term follow-up analysis at 95 months, demonstrated median PFS2 to be similar (HR 0.96; p=0.751) between the two groups as well as the rate of overall survival at 60.2% in the VRD arm compared with 62.2% in the transplant arm (HR 1.03; p=0.815).[27] However, 77% of patients randomized in the non-transplant group in first line treatment received autologous stem cell transplantation at time of relapse.[27] Similarly, the FORTE trial compared the carfilzomib-lenalidomide-dexamethasone (KRd) combination in induction and consolidation with or without autologous stem cell transplantation followed by maintenance therapy in first line treatment for transplant-eligible patients with newly-diagnosed MM and who were aged 65 years or younger. Although the overall response rate was similar in both groups, sustained minimal residual disease negativity rate and progression-free survival were in favor of the transplantation group.[10] These trials still suggest a potential role for autologous stem cell transplantation, although, perhaps, not as first-line treatment (**Table 1**).

Studies References	n	Induction	Intensification	Consolidation	Maintenance	≥PR	≥VGPR	≥CR	MRD	PFS (months)	OS (%)
RV-MM-PI-209[14]	273	Rd x 4	**ASCT x 2 vs MPR x 6**	None	**Len vs none**	- -	- -	36% 34%	NE NE	m: 43.0 m: 22.4	@4y: 81.6% @4y: 65.3%
EMN-441[15]	389	Rd x 4	**ASCT x 2 vs RCd x 6**	None	**Len+pred vs Len alone**	- -	- -	33-37% 23-27%	NE NE	m: 43.3 m: 28.6	@4y: 86% @4y: 73%
EMN02[17]	1197	VCD x 3-4	**ASCT x 1-2 vs VMP x 4**	**VRD x 2 vs none**	Len	95% 95%	84% 77%	44% 40%	NA NA	m: 56.7 m: 41.9	@5y: 75.1% @5y: 71.6%
IFM2009[9]	700	VRD x 3	**ASCT x 1 vs VRD x 3**	VRD x 2	Len x 1y	99% 97%	88% 77%	59% 48%	79%* 65%*	m: 50 m: 36	@4y: 81% @4y: 82%
FORTE[10]	474	**KRd x 4 vs KRd x 4 vs KCd x 4**	**ASCT x 1 KRd x 4 ASCT x 1**	**KRd x 4 KRd x 4 KCd x 4**	**K-Len vs Len alone**	97% 94% 91%	89% 87% 76%	54% 57% 42%	80%# 69%# 73%#	m: NR m: 55.3 m: 53	@4y: 86% @4y: 85% @4y: 76%
MANHATTAN[40]	41	DKRd x 8	As per SoC	-	As per SoC	100%	95%	95%	71%∞	@1y:98%	@1y: 100%

Table 1. *Studies influencing the decision for autologous stem cell transplantation; courtesy of Richard LeBlanc, MD*

** Performed for patients achieving ≥VGPR after consolidation and maintenance (sensitivity level of 10^{-4})*
 # Performed for patients achieving ≥VGPR before maintenance and every 6 months during maintenance (sensitivity level of 10^{-5})
∞ Performed after DKRd for 8 28-day cycles (sensitivity level of 10^{-5})
***Abbreviation**: ASCT, autologous stem cell transplantation; CR, complete response; DKRd, daratumumab-carfilzomib-lenalidomide-dexamethasone; K, carfilzomib; KCd, carfilzomib-cyclophosphamide-dexamethasone; KRd, carfilzomib-lenalidomide-dexamethasone; Len, lenalidomide; m, median; MPR, melphalan-prednisone-lenalidomide; MRD, minimal residual disease; OS, overall survival; PFS, progression-free survival; PR, partial response; pred, prednisone; RCd, lenalidomide-cyclophosphamide-dexamethasone; Rd, lenalidomide-dexamethasone; SoC, standard of care; VCD, bortezomib-cyclophosphamide-dexamethasone; VGPR, very good partial response; VMP, bortezomib-melphalan-prednisone; VRD, bortezomib-lenalidomide-dexamethasone; y, year; @, at.*
*Characters **in bold** represent part of randomization for these studies*

Aside from immunomodulatory drugs and proteasome inhibitors, monoclonal antibodies against CD38 have emerged as very effective therapeutic options available to clinicians. In randomized phase 3 trials, daratumumab has been shown to significantly improve progression-free survival and overall survival, both in first-line treatment[28-31] and in a relapsed setting.[32-38] Specifically in transplant-eligible patients, the randomized phase 2 GRIFFIN trial comparing lenalidomide, bortezomib, and dexamethasone (RVd) with or without daratumumab (quadruplet) in induction and consolidation treatment in addition to autologous stem cell transplantation and maintenance therapy, demonstrated an impressive 99% overall response rate of daratumumab-based treatment. The daratumumab arm (D-RVd) also achieved a ≥CR of 51.5% compared to the RVd arm at 42.3% , a ≥VGPR of 90.9% compared with 73.2% for the RVd arm and a significantly higher minimal residual disease negativity rate of 51% compared to 20.4% in the RVd arm ($P<0.0001$).[39] After a median follow-up of 22.1 months, the estimated 24-month progression-free survival was 95.8% (95% CI, 89.2-98.4) in the D-RVd group and 89.8% (95% CI, 77.1-95.7) in the RVd group. Based on these promising results, the phase 2 MANHATTAN nonrandomized clinical trial evaluated the efficacy of the quadruplet treatment daratumumab-KRd in newly-diagnosed transplant-eligible myeloma patients in the absence of high-dose melphalan and autologous stem cell transplantation. Treatment was administered for eight 28-day cycles and resulted in a minimal residual disease negativity rate of 71%, (29 of 41 patients) with a 1-year progression-free survival rate and overall survival rate of 98% and 100%, respectively (**Table 1**).[40]

Discussion

Over the last few decades, myeloma patients have achieved longer survival rates as a result of the discovery and approval of novel therapies and combinations.[41] However, in Canada, accessibility to many of these treatments are limited and varies from one province to another. For example, most centers still use cyclophosphamide-bortezomib-dexamethasone (CyBorD) as an induction treatment for transplant-eligible myeloma patients instead of the more effective RVd or KRd combinations.[42] Also, daratumumab-based therapies as first line treatment options, such as those used in the CASSIOPEIA[31], GRIFFIN[39] and MANHATTAN[40] trials, are not available in Canada, nor are the use of quadruplet treatments. In the context of these access limitations and considering the literature showing randomized trials with currently-available agents in Canada still demonstrating clinical benefit with the use of autologous stem cell transplantation, it is prudent to continue the use of transplantation for transplant-eligible myeloma patients as part of the therapeutic armamentarium.

However, impressive results from the MANHATTAN trial with the absence of high-dose melphalan followed by autologous stem cell transplantation are certainly noteworthy. Based on these results, a large randomized, multicenter, 3-arm, phase 2 (ADVANCE) study (NCT04268498) comparing initial treatment with VRd vs KRd vs daratumumab-KRd is presently recruiting. After 8 cycles, patients achieving minimal residual disease negativity will receive maintenance therapy with lenalidomide for up to 2 years. Those with minimal residual disease positivity will have the option to receive an autologous stem cell transplant if available, before initiating the same maintenance therapy. To better evaluate the role of autologous stem cell transplantation, a similar minimal residual disease adapted strategy will be used in the phase 3 MIDAS IFM 2020-02 trial (NCT04934475). After induction treatment with isatuximab-KRd for 6 cycles, patients who achieve minimal residual disease negativity will be randomized to the same treatment as a consolidation for 6 cycles vs high-dose melphalan and autologous stem cell transplantation followed by isatuximab-KRd consolidation for 2 cycles. All patients will receive 3 years of maintenance therapy with lenalidomide. The results of this study may eventually elucidate a sub-population for whom autologous stem cell transplantation can be avoided.

Numerous novel therapies are also emerging with certain immunotherapeutic modalities demonstrating particularly promising results, such as chimeric antigen receptor (CAR)-T and bispecific antibodies. Although still early in their development lifecycle, these therapeutic modalities have shown impressive results in heavily pre-treated relapsed/refractory MM patients.[43-52] Their benefits in earlier use have yet to be demonstrated in clinical trials which will take several more years, but certainly the clinical efficacy of these new agents will have to be compared with that achieved using autologous stem cell transplantation before they are widely adopted.

Conclusion

Without doubt, the role of autologous stem cell transplantation will be open for discussion based on the rapid improvement of myeloma therapies. The day may soon arrive when the risks of autologous stem cell transplantation will outweigh its clinical benefits in light of the availability of novel, more effective and safer therapeutic options. Until such time as clinical trials clearly demonstrate that autologous stem cell transplantation can be avoided and alternative therapeutic modalities are fully available for Canadian patients, autologous stem cell transplantation will remain the standard of care in Canada despite the associated morbidity, mortality and second primary malignancy risks. The eligibility criteria for patients who may be candidates for transplantation are more stringent than those criteria for patients undergoing chemo-immunotherapy alone and, as such, autologous stem cell transplantation as first line treatment should be considered in eligible patients to avoid subsequent ineligibility.

References:

1. Palumbo A, Anderson K. Multiple myeloma. N Engl J Med. 2011;364(11):1046-1060.

2. McElwain TJ, Powles RL. High-dose intravenous melphalan for plasma-cell leukaemia and myeloma. Lancet. 1983;2(8354):822-824.

3. Barlogie B, Hall R, Zander A, Dicke K, Alexanian R. High-dose melphalan with autologous bone marrow transplantation for multiple myeloma. Blood. 1986;67(5):1298-1301.

4. Barlogie B, Alexanian R, Dicke KA, et al. High-dose chemoradiotherapy and autologous bone marrow transplantation for resistant multiple myeloma. Blood. 1987;70(3):869-872.

5. Attal M, Harousseau JL, Stoppa AM, et al. A prospective, randomized trial of autologous bone marrow transplantation and chemotherapy in multiple myeloma. Intergroupe Francais du Myelome. N Engl J Med. 1996;335(2):91-97.

6. Child JA, Morgan GJ, Davies FE, et al. High-dose chemotherapy with hematopoietic stem-cell rescue for multiple myeloma. N Engl J Med. 2003;348(19):1875-1883.

7. Fermand JP, Katsahian S, Divine M, et al. High-dose therapy and autologous blood stem-cell transplantation compared with conventional treatment in myeloma patients aged 55 to 65 years: long-term results of a randomized control trial from the Group Myelome-Autogreffe. J Clin Oncol. 2005;23(36):9227-9233.

8. Blade J, Rosinol L, Sureda A, et al. High-dose therapy intensification compared with continued standard chemotherapy in multiple myeloma patients responding to the initial chemotherapy: long-term results from a prospective randomized trial from the Spanish cooperative group PETHEMA. Blood. 2005;106(12):3755-3759.

9. Attal M, Lauwers-Cances V, Hulin C, et al. Lenalidomide, Bortezomib, and Dexamethasone with Transplantation for Myeloma. N Engl J Med. 2017;376(14):1311-1320.

10. Gay F, Musto P, Rota-Scalabrini D, et al. Carfilzomib with cyclophosphamide and dexamethasone or lenalidomide and dexamethasone plus autologous transplantation or carfilzomib plus lenalidomide and dexamethasone, followed by maintenance with carfilzomib plus lenalidomide or lenalidomide alone for patients with newly diagnosed multiple myeloma (FORTE): a randomised, open-label, phase 2 trial. Lancet Oncol. 2021;22(12):1705-1720.

11. McCarthy PL, Owzar K, Hofmeister CC, et al. Lenalidomide after stem-cell transplantation for multiple myeloma. N Engl J Med. 2012;366(19):1770-1781.

12. McCarthy PL, Holstein SA, Petrucci MT, et al. Lenalidomide Maintenance After Autologous Stem-Cell Transplantation in Newly Diagnosed Multiple Myeloma: A Meta-Analysis. J Clin Oncol. 2017;35(29):3279-3289.

13. Gay F, Jackson G, Rosinol L, et al. Maintenance Treatment and Survival in Patients With Myeloma: A Systematic Review and Network Meta-analysis. JAMA Oncol. 2018;4(10):1389-1397.

14. Palumbo A, Cavallo F, Gay F, et al. Autologous transplantation and maintenance therapy in multiple myeloma. N Engl J Med. 2014;371(10):895-905.

15. Gay F, Oliva S, Petrucci MT, et al. Chemotherapy plus lenalidomide versus autologous transplantation, followed by lenalidomide plus prednisone versus lenalidomide maintenance, in patients with multiple myeloma: a randomised, multicentre, phase 3 trial. Lancet Oncol. 2015;16(16):1617-1629.

16. Gay F, Oliva S, Petrucci MT, et al. Autologous transplant vs oral chemotherapy and lenalidomide in newly diagnosed young myeloma patients: a pooled analysis. Leukemia. 2017;31(8):1727-1734.

17. Cavo M, Gay F, Beksac M, et al. Autologous haematopoietic stem-cell transplantation versus bortezomib-melphalan-prednisone, with or without bortezomib-lenalidomide-dexamethasone consolidation therapy, and lenalidomide maintenance for newly diagnosed multiple myeloma (EMN02/HO95): a multicentre, randomised, open-label, phase 3 study. Lancet Haematol. 2020;7(6):e456-e468.

18. Melphalan for Injection Product Monograph. Apotex Inc. https://pdf.hres.ca/dpd_pm/00041663.PDF. 2017.

19. Krishnan AY, Mei M, Sun CL, et al. Second primary malignancies after autologous hematopoietic cell transplantation for multiple myeloma. Biol Blood Marrow Transplant. 2013;19(2):260-265.

20. Palumbo A, Bringhen S, Kumar SK, et al. Second primary malignancies with lenalidomide therapy for newly diagnosed myeloma: a meta-analysis of individual patient data. Lancet Oncol. 2014;15(3):333-342.

21. Maura F, Weinhold N, Diamond B, et al. The mutagenic impact of melphalan in multiple myeloma. Leukemia. 2021;35(8):2145-2150.

22. Radivoyevitch T, Dean RM, Shaw BE, et al. Risk of acute myeloid leukemia and myelodysplastic syndrome after autotransplants for lymphomas and plasma cell myeloma. Leuk Res. 2018;74:130-136.

23. Miles B, Mackey JD. Increased Risk of Second Primary Malignancy and Mortality at ten Years After Stem Cell Transplant for Multiple Myeloma: An Analysis of 14,532 Patients. Cureus. 2021;13(7):e16372.

24. Arora M, Chen Y, Hageman L, et al. Morbidity burden in survivors of multiple myeloma who underwent autologous transplantation: A Bone Marrow Transplantation Survivor Study. Cancer. 2020;126(14):3322-3329.

25. Roussel M, Lauwers-Cances V, Robillard N, et al. Front-line transplantation program with lenalidomide, bortezomib, and dexamethasone combination as induction and consolidation followed by lenalidomide maintenance in patients with multiple myeloma: a phase II study by the Intergroupe Francophone du Myelome. J Clin Oncol. 2014;32(25):2712-2717.

26. Richardson PG, Weller E, Lonial S, et al. Lenalidomide, bortezomib, and dexamethasone combination therapy in patients with newly diagnosed multiple myeloma. Blood. 2010;116(5):679-686.

27. Perrot AL-C, V.; Cazaubiel, T.; Facon, T.; Caillot, D.; Clement-Filliatre, L. Early Versus Late Autologous Stem Cell Transplant in Newly Diagnosed Multiple Myeloma: Long-Term Follow-up Analysis of the IFM 2009 Trial. ASH 2020, abstract 143.

28. Mateos MV, Dimopoulos MA, Cavo M, et al. Daratumumab plus Bortezomib, Melphalan, and Prednisone for Untreated Myeloma. N Engl J Med. 2018;378(6):518-528.

29. Mateos MV, Cavo M, Blade J, et al. Overall survival with daratumumab, bortezomib, melphalan, and prednisone in newly diagnosed multiple myeloma (ALCYONE): a randomised, open-label, phase 3 trial. Lancet. 2020;395(10218):132-141.

30. Facon T, Kumar S, Plesner T, et al. Daratumumab plus Lenalidomide and Dexamethasone for Untreated Myeloma. N Engl J Med. 2019;380(22):2104-2115.

31. Moreau P, Attal M, Hulin C, et al. Bortezomib, thalidomide, and dexamethasone with or without daratumumab before and after autologous stem-cell transplantation for newly diagnosed multiple myeloma (CASSIOPEIA): a randomised, open-label, phase 3 study. Lancet. 2019;394(10192):29-38.

32. Palumbo A, Chanan-Khan A, Weisel K, et al. Daratumumab, Bortezomib, and Dexamethasone for Multiple Myeloma. N Engl J Med. 2016;375(8):754-766.

33. Spencer A, Lentzsch S, Weisel K, et al. Daratumumab plus bortezomib and dexamethasone versus bortezomib and dexamethasone in relapsed or refractory multiple myeloma: updated analysis of CASTOR. Haematologica. 2018;103(12):2079-2087.

34. Mateos MV, Sonneveld P, Hungria V, et al. Daratumumab, Bortezomib, and Dexamethasone Versus Bortezomib and Dexamethasone in Patients With Previously Treated Multiple Myeloma: Three-year Follow-up of CASTOR. Clin Lymphoma Myeloma Leuk. 2020;20(8):509-518.

35. Dimopoulos MA, Oriol A, Nahi H, et al. Daratumumab, Lenalidomide, and Dexamethasone for Multiple Myeloma. N Engl J Med. 2016;375(14):1319-1331.

36. Bahlis NJ, Dimopoulos MA, White DJ, et al. Daratumumab plus lenalidomide and dexamethasone in relapsed/refractory multiple myeloma: extended follow-up of POLLUX, a randomized, open-label, phase 3 study. Leukemia. 2020;34(7):1875-1884.

37. Dimopoulos M, Quach H, Mateos MV, et al. Carfilzomib, dexamethasone, and daratumumab versus carfilzomib and dexamethasone for patients with relapsed or refractory multiple myeloma (CANDOR): results from a randomised, multicentre, open-label, phase 3 study. Lancet. 2020;396(10245):186-197.

38. Dimopoulos MA, Terpos E, Boccadoro M, et al. Daratumumab plus pomalidomide and dexamethasone versus pomalidomide and dexamethasone alone in previously treated multiple myeloma (APOLLO): an open-label, randomised, phase 3 trial. Lancet Oncol. 2021;22(6):801-812.

39. Voorhees PM, Kaufman JL, Laubach J, et al. Daratumumab, lenalidomide, bortezomib, and dexamethasone for transplant-eligible newly diagnosed multiple myeloma: the GRIFFIN trial. Blood. 2020;136(8):936-945.

40. Landgren O, Hultcrantz M, Diamond B, et al. Safety and Effectiveness of Weekly Carfilzomib, Lenalidomide, Dexamethasone, and Daratumumab Combination Therapy for Patients With Newly Diagnosed Multiple Myeloma: The MANHATTAN Nonrandomized Clinical Trial. JAMA Oncol. 2021;7(6):862-868.

41. Corre J, Perrot A, Hulin C, et al. Improved survival in multiple myeloma during the 2005-2009 and 2010-2014 periods. Leukemia. 2021.

42. Cherniawsky HM, Kukreti V, Reece D, et al. The impact of lenalidomide maintenance on second-line chemotherapy in transplant eligible patients with multiple myeloma. Eur J Haematol. 2021;106(5):673-681.

43. Berdeja JG, Madduri D, Usmani SZ, et al. Ciltacabtagene autoleucel, a B-cell maturation antigen-directed chimeric antigen receptor T-cell therapy in patients with relapsed or refractory multiple myeloma (CARTITUDE-1): a phase 1b/2 open-label study. Lancet. 2021;398(10297):314-324.

44. Munshi NC, Anderson LD, Jr., Shah N, et al. Idecabtagene Vicleucel in Relapsed and Refractory Multiple Myeloma. N Engl J Med. 2021;384(8):705-716.

45. Usmani SZ, Garfall AL, van de Donk N, et al. Teclistamab, a B-cell maturation antigen x CD3 bispecific antibody, in patients with relapsed or refractory multiple myeloma (MajesTEC-1): a multicentre, open-label, single-arm, phase 1 study. Lancet. 2021;398(10301):665-674.

46. Trudel SC, AD; Krishnan, AY; Fonseca, R; Spencer, A; Berdeja, et al. Cevostamab Monotherapy Continues to Show Clinically Meaningful Activity and Manageable Safety in Patients with Heavily Pre-Treated Relapsed/ Refractory Multiple Myeloma (RRMM): Updated Results from an Ongoing Phase I Study. ASH 2021, abstract 157.

47. Krishnan AM, MC; Berdeja, JG; Oriol, A; van de Donk, NWCJ; Rodriguez-Otero, P; et al. Updated Phase 1 Results from MonumenTAL-1: First-in-Human Study of Talquetamab, a G Protein-Coupled Receptor Family C Group 5 Member D x CD3 Bispecific Antibody, in Patients with Relapsed/Refractory Multiple Myeloma. ASH 2021, abstract 158.

48. Zonder JR, J; Bumma, N; Brayer, J; Hoffman, JE; Bensinger, WI; et al. Early, Deep, and Durable Responses, and Low Rates of Cytokine Release Syndrome with REGN5458, a BCMAxCD3 Bispecific Monoclonal Antibody, in a Phase 1/2 First-in-Human Study in Patients with Relapsed/Refractory Multiple Myeloma (RRMM). ASH 2021, abstract 160.

49. Li CW, D; Song, Y; Li J; Huang, H; Chen, B; et al. A Phase 1/2 Study of a Novel Fully Human B-Cell Maturation Antigen-Specific CAR T Cells (CT103A) in Patients with Relapsed and/or Refractory Multiple Myeloma. ASH 2021, abstract 547.

50. Raje NS, N; Jagannath, S; Kaufman, JL; Siegel, DS; Munshi, NC; et al. Updated Clinical and Correlative Results from the Phase I CRB-402 Study of the BCMA-Targeted CAR T Cell Therapy bb21217 in Patients with Relapsed and Refractory Multiple Myeloma. ASH 2021, abstract 548.

51. Sebag MR, NS; Bahlis, NJ; Costello, C; Dholaria, B; Solh, M; et al. Elranatamab (PF-06863135), a B-Cell Maturation Antigen (BCMA) Targeted CD3-Engaging Bispecific Molecule, for Patients with Relapsed or Refractory Multiple Myeloma: Results from Magnetismm-1. ASH 2021, abstract 895.

52. Kumar SDS, A; Shah, N; Rodriguez, C; Voorhees, PM; Bueno, OF; et al. A Phase 1 First-in-Human Study of Tnb-383B, a BCMA x CD3 Bispecific T-Cell Redirecting Antibody, in Patients with Relapsed/ Refractory Multiple Myeloma. ASH 2021, abstract 900.

ABOUT THE AUTHOR

Anthea Peters, MD

Dr. Anthea Peters is a hematologist based at the Cross Cancer Institute in Edmonton, Alberta and an Associate Professor in the Department of Oncology at the University of Alberta. She completed her MD at the University of Saskatchewan, internal medicine residency training at the University of Alberta and hematology training as well as a lymphoma fellowship at the University of Calgary. Her clinical and research interests are centered around lymphoma and chronic lymphocytic leukemia (CLL), with a special interest in post-transplant lymphoproliferative disorders. She is currently the clinical lead for lymphoma and CLL for Northern Alberta.

EMERGING THERAPEUTIC AGENTS IN THE TREATMENT OF RELAPSED OR REFRACTORY DIFFUSE LARGE B CELL LYMPHOMA

Diffuse large B cell lymphoma (DLBCL) is the most common type of aggressive non-Hodgkin lymphoma (NHL). The median age at diagnosis of DLBCL is 65, and about one-third of patients are older than age 75 at diagnosis.[1,2] The standard of care for frontline treatment is chemoimmunotherapy, consisting of rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (RCHOP). Approximately 60% of patients are cured with standard treatment, but it is inaccessible for up to 25% of patients due to advanced age and underlying comorbidities, including cardiac dysfunction.[2,3] Several biologic factors confer risk of treatment failure, including activated B cell (ABC) cell of origin[4-6] and double expressor phenotype (i.e. and overexpression of c-MYC and BCL2[7,8]).

Patients with DLBCL who relapse or are refractory to RCHOP have a poor prognosis. Currently, the standard approach is platinum-based salvage chemotherapy, such as rituximab, gemcitabine, dexamethasone, and cisplatin (R-GDP), to which approximately half of patients will respond, followed by consolidation with autologous stem cell transplant (ASCT). However this aggressive approach, which yields an overall cure rate of 25 to 35%[2,9], is restricted to younger patients without concurrent medical conditions, leaving a paucity of treatment options for patients ineligible for ASCT. Outcomes for those refractory to frontline or subsequent chemotherapy are particularly poor, with overall response rates (ORR) to salvage treatment of 26% and a median overall survival (OS) of 6 months.[10] Without a curative standard, lower intensity treatment options cited for patients ineligible for ASCT include rituximab, gemcitabine and oxaliplatin (R-GemOx) and bendamustine and rituximab (BR)[1] or lenalidomide[11], but access to these therapeutic agents is not consistent across Canadian treatment centres.

Adoptive cellular therapy using CAR-T cells has recently emerged as a potentially curative option for R/R DLBCL, and it may even supplant ASCT as the preferred second line option for R/R DLBCL. The phase 3 randomized controlled trial (RCT) ZUMA-7 reported superior response rates and event-free survival (EFS) with axicabtagene ciloecel (axi-cel) compared to standard of care (two or three cycles of platinum-based chemoimmunotherapy followed by high-dose chemotherapy with ASCT) in patients who were refractory to or had relapsed no more than 12 months after first-line chemoimmunotherapy.[12] Both axi-cel and tisagenlecleucel have obtained Health Canada approval for R/R DLBCL after two or more lines of systemic therapy.[13] While eligibility for CAR-T is more inclusive than ASCT, Canadian patients have limited access to CAR-T therapies due to a lack of qualified centres, the limitations of CAR-T product supply and prohibitive cost. Toxicity is also a concern, with a significant incidence of cytokine release syndrome (CRS) and neurologic adverse events (AEs).[14] Therefore R/R DLBCL continues to be an area of unmet therapeutic need with no standard of care, particularly for those patients ineligible for ASCT or CAR-T.

Recently there has been unprecedented development of novel agents for patients with R/R DLBCL who are ineligible for ASCT.[2,14] Select agents are discussed in this article (summarized in **Table 1**), with particular attention to the Canadian regulatory landscape.

Monoclonal Antibodies:
Tafasitamab (MOR208) is an Fc-enhanced, humanized monoclonal antibody directed against CD19 approved by Health Canada in 2021.[15] In a phase II open label trial, adults (n=80) with R/R DLBCL who had received no more than three prior lines of therapy and were transplant-ineligible were treated with tafasitamab and lenalidomide (25 mg daily) for up to 12 cycles (28 days each) followed by tafasitamab monotherapy until disease progression.[15] Primary refractory patients were excluded. The initially reported overall response rate (ORR) was impressive at 60% with 43% complete response (CR) (**Figure 1**). The median duration of response (DoR) of 43.9 months was reported in the long term follow up in subjects with at least 35-months of data.[16], and median PFS and OS were 11.6 and 33.5 months respectively. Toxicity was mild with the most common grade 3 or higher AE being neutropenia (48%). After discontinuation of lenalidomide Grade 3 or higher AEs dropped to 29% (from 70%) in the study population.

Antibody-drug conjugates:
Polatuzumab vedotin (pola), an antibody-drug conjugate that delivers microtubule inhibitor monomethyl auristatin E (MMAE) directly to mature B cells with its target CD79b was approved by Health Canada

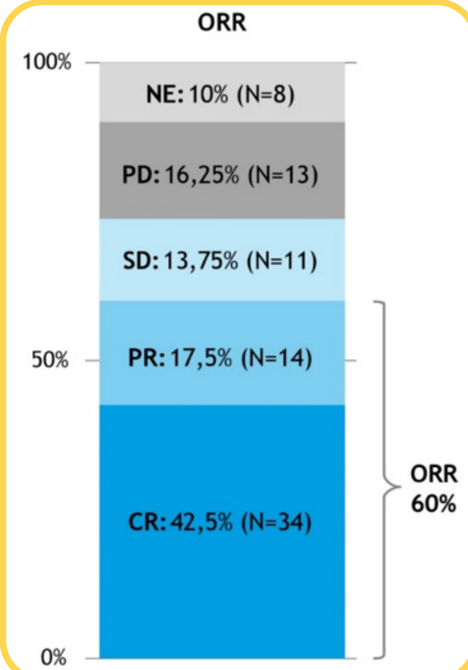

Figure 1. *Response rates with tafasitamab, lenalidomide, and rituximab from L-MIND; Salles et al., 2020.*
CR, complete response; NE, not evaluable; ORR, overall response rate; PR, partial response; PD, progressive disease; SD, stable disease.

in 2020.[17] The efficacy of pola was established in a phase II trial that randomized patients with R/R DLBCL who were ASCT-ineligible or had prior ASCT to receive pola in combination with BR versus BR alone[17]. Patients in the pola-BR arm had superior ORR (45% vs. 17.5%) and CR rates (40% vs. 17.5%). The addition of pola to BR also improved both PFS (median 9.5 vs. 3.7 months) and OS (median, 12.4 vs. 4.7 months). There was a higher rate of grade 3-4 AEs in the group that received pola-BR, with the most common being neutropenia (46% vs. 33%) followed by anemia (28.2% v 17.9%), and thrombocytopenia (41% v 23.1%), but a similar rate of grade 3-4 infections (23% vs. 22%). Peripheral neuropathy, a known side effect of MMAE-based drug conjugates, was common (44% pola-BR vs. 8% BR), but all were classified as grade 1-2 and resolved in most patients. The addition of Pola to standard chemoimmunotherapy also enhances response rates and PFS in previously untreated DLBCL.[18] It is also being studied in combination with R-GemOx for R/R.[19]

Another antibody-drug conjugate is loncastuximab tesirine (lonca), a humanized anti-CD19 antibody conjugated to SG3199, a pyrrolobenzodiazepine dimer cytotoxin that causes intrastrand DNA crosslinks.[20] A phase II single-arm open label clinical trial enrolled adults with R/R DLBCL, high grade lymphoma with BCL2+/- BCL6 rearrangements or primary mediastinal BCL; the study population was heavily pretreated with 32% having received more than 3 prior lines of systemic therapy. After receiving lonca as a single agent once every 3 weeks for 1 year or until disease progression, an ORR of 48.3% with a 24.1% CR rate was observed. In this study, patients were allowed to continue their use of lonca beyond the one year timepoint. Median PFS was 4.9 months and median OS was 9.9 months. The most common grade 3 or higher AE was neutropenia (26%) followed by thrombocytopenia (18%), and increased gamma-glutamyltransferase (17%). Eight patients (6%) died while on treatment, but none of the fatalities were deemed to have been drug-related. Lonca tesirine is approved in the U.S. for the treatment of adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy. It is not yet approved by Health Canada.

Despite CD30 not being universally expressed on B-cell lymphomas, brentuximab vedotin (BV), a monoclonal antibody against CD30 with MMAE drug conjugate, does produce objective responses in R/R DLBCL. In a phase 2 study that enrolled R/R B-cell non-Hodgkin lymphoma patients, 44% of subjects with DLBCL responded and 17% had CR. The median DoR was 5.6 months (16.6 months for complete responders).[21] Neutropenia (37%) was the most common grade 3 and higher AE followed by peripheral neuropathy (28%). BV has also been studied in combination with lenalidomide in a phase 1 dose expansion trial[22], showing an ORR of 57%, a CR rate of 35%, median PFS of 10.2 months and median OS of 14.3 months. Responses were higher in CD30+ DLBCLs (73%) in this study but in the previous study there was no statistical correlation between response and level of CD30 expression.[21] The toxicities observed were consistent with those seen with single agent use, but most patients required G-CSF support. These promising results have led to the current ECHELON3 trial, a phase 3 RCT studying lenalidomide plus rituximab with or without BV.[23]

Novel Agent	Ab Target or Drug Class	Regimen (comparator)	Phase	ORR % (CRR %)	Median PFS (months)	Median OS (months)
Tafasitamab[15]	CD19	Tafasitamab + Lenalidomide*	2 open label	58 (40)	11.6	33.5
Loncastuximab tesirine[20]	CD19	Loncastuximab tesirine	2	48 (24)	4.9	9.9
Brentuximab vedotin[21]	CD30	Brentuximab vedotin	2	44 (17; not reported for PFS and OS)		
Brentuximab vedotin[22]	CD30	Brentuximab vedotin + Lenalidomide	1/ dose expansion trial	57 (35)	10.2	14.3
Polatuzumab vedotin[31]	CD79b	Polatuzumab vedotin + R	2 (randomized)	54 (21)	5.6	20.1
Polatuzumab vedotin[17]	CD79b	Polatuzumab vedotin + BR* vs. BR	2 (randomized)	45 (40)	9.5	12.4
Blinatumomab[24]	CD19-CD3	Blinatumomab	2	35 (17)	3.7	5.0
Mosunetuzumab[25]	CD20-CD3	Mosunetuzumab	1/1b	45 (25)	Not reported	Not reported
Selinexor[26]	XPO1	Selinexor	2b	28 (12)	2.6	9.1
Venetoclax[29]	BCL2	Venetoclax	1	18 (12)	1	32 at 12 months
Lenalidomide[32]		Lenalidomide	2/3	27.5	13.6	31.0
Umbralisib[30]	PI3K	umbra; U2; U2 + benda-mustine	2	Umbra 13 (3); U2 32 (11); 43 (17)	Not reported	Not reported
Ibrutinib[28]	Bruton's Tyrosine Kinase	Ibrutinib + Lenalidomide + R	1b/2	44 (28)	5.5	9.5

Table 1. *Select Agents for Treatment of Relapsed/Refractory DLBCL; courtesy of Anthea Peters, MD*

BR, bendamustine + rituximab; C, cycle; D, day; NR, not reached; R, rituximab; umbra, umbralisib; U2, umbralisib + ublituximab
**indicates Health Canada approval*

Bispecific antibodies:
Bispecific antibodies, or bispecific T-cell engagers (BiTEs), target B (CD19 or CD20) cells and T (CD3) cells, thereby redirecting T cells to engage with and eliminate malignant B cells. The agent in this class furthest in development is blinatumomab, which targets CD19 and CD3. Blinatumomab has received regulatory approval for adult patients with relapsed or refractory B-cell precursor acute lymphoblastic leukemia (ALL) and an approval with conditions for pediatric patients with Philadelphia chromosome-negative relapsed or refractory B-cell precursor ALL. In a phase 2 trial of R/R DLBCL, blinatumomab produced a moderate response rate but relatively short survival.[24] There was a high rate of neurologic AEs, including grade 3 encephalopathy and aphasia. Another consideration for the use of this agent is its requirement to be dosed as a continuous intravenous infusion.

Mosenetuzumab is a bispecific antibody with a much longer half-life allowing dosing every three weeks. Durable responses in aggressive and indolent B-cell NHLs in a phase 1 dose escalation study have been recently reported.[25] Despite a heavily pretreated aggressive NHL population in the study, with 34% of subjects having had prior ASCT and 12% having received prior CAR-T, 35% of subjects responded with 20% CRs, and DoR in those with CR was a median of 23 months. Cytokine release syndrome occurred in 27% of all patients but only 1% were classified as grade 3 or higher.

Other mechanisms:
Selinexor is an oral selective inhibitor of nuclear export of oncoproteins mediated by XPO1.[26] This agent is already approved in the U.S. for use in multiple myeloma, and was evaluated in patients with R/R DLBCL in the phase 2b SADAL trial in which heavily pretreated patients (n=127) were given selinexor 60 mg taken on days 1 and 3 weekly until disease progression or unacceptable toxicity. Responses with this single oral drug were promising, with an ORR of 28% (36/127) and a CR rate of 12% (15/127). The most common grade 3-4 adverse events were hematologic in nature. The median PFS reported in the SADAL trial was 2.6 months. Selinexor shows promise and is being combined with other agents in further studies, such as a phase 2/3 study in progress using R-GDP with or without selinexor.[27]

Ibrutinib, best-known for its use in chronic lymphocytic leukemia (CLL), does have activity in DLBCL, as shown in a phase 1b/2 trial in combination with lenalidomide and rituximab. The ORR in this study was higher in non-germinal center B-cell-like (non-GCB)DLBCL at 65% vs. 44% in the entire cohort.[28] Another drug typically used for CLL, BCL-2 inhibitor venetoclax, has minimal single agent activity in DLBCL.[29] Umbralisib, a PI3K-inhibitor, has objective activity alone and in combination with ublituximab with or without bendamustine, but results using this agent are preliminary and currently only available in abstract form.[30]

Conclusions:
Options for tolerable treatment are needed in R/R DLBCL in patients who are ineligible for ASCT or unable to access CAR-T cell therapy. Herein, several emerging novel agents with promise for further development as single agents or in combination regimens were reviewed. Many of these are monoclonal antibody-based and have a toxicity profile that makes them desirable particularly for the elderly and comorbid patient. The sequencing of agents that target CD19 with regards to CAR-T will be a question of interest.

References:

1. Di M, Huntington SF, Olszewski AJ. Challenges and Opportunities in the Management of Diffuse Large B-Cell Lymphoma in Older Patients. Oncologist. 2021;26(2):120-32.

2. Sehn LH, Salles G. Diffuse Large B-Cell Lymphoma. N Engl J Med. 2021;384(9):842-58.

3. Coiffier B, Lepage E, Briere J, Herbrecht R, Tilly H, Bouabdallah R, et al. CHOP chemotherapy plus rituximab compared with CHOP alone in elderly patients with diffuse large-B-cell lymphoma. N Engl J Med. 2002;346(4):235-42.

4. Lenz G, Wright GW, Emre NC, Kohlhammer H, Dave SS, Davis RE, et al. Molecular subtypes of diffuse large B-cell lymphoma arise by distinct genetic pathways. Proc Natl Acad Sci U S A. 2008;105(36):13520-5.

5. Rosenwald A, Wright G, Chan WC, Connors JM, Campo E, Fisher RI, et al. The use of molecular profiling to predict survival after chemotherapy for diffuse large-B-cell lymphoma. N Engl J Med. 2002;346(25):1937-47.

6. Leonard JP, Martin P, Roboz GJ. Practical Implications of the 2016 Revision of the World Health Organization Classification of Lymphoid and Myeloid Neoplasms and Acute Leukemia. J Clin Oncol. 2017;35(23):2708-15.

7. Johnson NA, Slack GW, Savage KJ, Connors JM, Ben-Neriah S, Rogic S, et al. Concurrent expression of MYC and BCL2 in diffuse large B-cell lymphoma treated with rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone. J Clin Oncol. 2012;30(28):3452-9.

8. Green TM, Young KH, Visco C, Xu-Monette ZY, Orazi A, Go RS, et al. Immunohistochemical double-hit score is a strong predictor of outcome in patients with diffuse large B-cell lymphoma treated with rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone. J Clin Oncol. 2012;30(28):3460-7.

9. Crump M, Kuruvilla J, Couban S, MacDonald DA, Kukreti V, Kouroukis CT, et al. Randomized comparison of gemcitabine, dexamethasone, and cisplatin versus dexamethasone, cytarabine, and cisplatin chemotherapy before autologous stem-cell transplantation for relapsed and refractory aggressive lymphomas: NCIC-CTG LY.12. J Clin Oncol. 2014;32(31):3490-6.

10. Crump M, Neelapu SS, Farooq U, Van Den Neste E, Kuruvilla J, Westin J, et al. Outcomes in refractory diffuse large B-cell lymphoma: results from the international SCHOLAR-1 study. Blood. 2017;130(16):1800-8.

11. Zinzani PL, Rodgers T, Marino D, Frezzato M, Barbui AM, Castellino C, et al. RE-MIND: Comparing Tafasitamab + Lenalidomide (L-MIND) with a Real-world Lenalidomide Monotherapy Cohort in Relapsed or Refractory Diffuse Large B-cell Lymphoma. Clin Cancer Res. 2021;27(22):6124-34.

12. Locke FL, Miklos DB, Jacobson CA, Perales MA, Kersten MJ, Oluwole OO, et al. Axicabtagene Ciloleucel as Second-Line Therapy for Large B-Cell Lymphoma. N Engl J Med. 2021.

13. Schuster SJ, Bishop MR, Tam CS, Waller EK, Borchmann P, McGuirk JP, et al. Tisagenlecleucel in Adult Relapsed or Refractory Diffuse Large B-Cell Lymphoma. N Engl J Med. 2019;380(1):45-56.

14. Maddocks K. Novel targets in aggressive lymphoma. Hematology Am Soc Hematol Educ Program. 2020;2020(1):101-6.

15. Salles G, Duell J, Gonzalez Barca E, Tournilhac O, Jurczak W, Liberati AM, et al. Tafasitamab plus lenalidomide in relapsed or refractory diffuse large B-cell lymphoma (L-MIND): a multicentre, prospective, single-arm, phase 2 study. Lancet Oncol. 2020;21(7):978-88.

16. Duell J, Maddocks KJ, Gonzalez-Barca E, Jurczak W, Liberati AM, De Vos S, et al. Long-term outcomes from the Phase II L-MIND study of tafasitamab (MOR208) plus lenalidomide in patients with relapsed or refractory diffuse large B-cell lymphoma. Haematologica. 2021;106(9):2417-26.

17. Sehn LH, Herrera AF, Flowers CR, Kamdar MK, McMillan A, Hertzberg M, et al. Polatuzumab Vedotin in Relapsed or Refractory Diffuse Large B-Cell Lymphoma. J Clin Oncol. 2020;38(2):155-65.

18. Tilly H, Morschhauser F, Sehn LH, Friedberg JW, Trneny M, Sharman JP, et al. Polatuzumab Vedotin in Previously Untreated Diffuse Large B-Cell Lymphoma. N Engl J Med. 2021.

19. Matasar MJ, Haioun C, Sancho J-M, Viardot A, Hirata J, Perretti T, et al. POLARGO: Randomized Phase III Study of Polatuzumab Vedotin Plus Rituximab, Gemcitabine, and Oxaliplatin in Relapsed/Refractory Diffuse Large B-Cell Lymphoma. Blood. 2021;138(Supplement 1):3568-.

20. Caimi PF, Ai W, Alderuccio JP, Ardeshna KM, Hamadani M, Hess B, et al. Loncastuximab tesirine in relapsed or refractory diffuse large B-cell lymphoma (LOTIS-2): a multicentre, open-label, single-arm, phase 2 trial. Lancet Oncol. 2021;22(6):790-800.

21. Jacobsen ED, Sharman JP, Oki Y, Advani RH, Winter JN, Bello CM, et al. Brentuximab vedotin demonstrates objective responses in a phase 2 study of relapsed/refractory DLBCL with variable CD30 expression. Blood. 2015;125(9):1394-402.

22. Ward J, Berrien-Elliott MM, Gomez F, Luo J, Becker-Hapak M, Cashen AF, et al. Phase I/Dose Expansion Trial of Brentuximab vedotin/Lenalidomide in Relapsed or Refractory Diffuse Large B-cell Lymphoma. Blood. 2021.

23. Bartlett NL, Yasenchak CA, Ashraf K, Harwin W, Sims R, Nowakowski GS. Brentuximab Vedotin in Combination with Lenalidomide and Rituximab in Patients with Relapsed or Refractory Diffuse Large B-Cell Lymphoma (DLBCL) (ECHELON-3, Trial in Progress). Blood. 2021;138(Supplement 1):3564-.

24. Viardot A, Goebeler ME, Hess G, Neumann S, Pfreundschuh M, Adrian N, et al. Phase 2 study of the bispecific T-cell engager (BiTE) antibody blinatumomab in relapsed/refractory diffuse large B-cell lymphoma. Blood. 2016;127(11):1410-6.

25. Budde LE, Assouline S, Sehn LH, Schuster SJ, Yoon SS, Yoon DH, et al. Single-Agent Mosunetuzumab Shows Durable Complete Responses in Patients With Relapsed or Refractory B-Cell Lymphomas: Phase I Dose-Escalation Study. J Clin Oncol. 2021:JCO2100931.

26. Kalakonda N, Maerevoet M, Cavallo F, Follows G, Goy A, Vermaat JSP, et al. Selinexor in patients with relapsed or refractory diffuse large B-cell lymphoma (SADAL): a single-arm, multinational, multicentre, open-label, phase 2 trial. Lancet Haematol. 2020;7(7):e511-e22.

27. Lee ST, Pinto A, Yimer H, Stevens D, Knopinska Posluszny W, Shum MK, et al. A Phase 2/3, Multicenter Randomized Study of Rituximab-Gemcitabine-Dexamethasone-Platinum (R-GDP) with or without Selinexor in Patients with Relapsed/Refractory Diffuse Large B-Cell Lymphoma (RR DLBCL). Blood. 2021;138(Supplement 1):1420-.

28. Goy A, Ramchandren R, Ghosh N, Munoz J, Morgan DS, Dang NH, et al. Ibrutinib plus lenalidomide and rituximab has promising activity in relapsed/refractory non-germinal center B-cell-like DLBCL. Blood. 2019;134(13):1024-36.

29. Davids MS, Roberts AW, Seymour JF, Pagel JM, Kahl BS, Wierda WG, et al. Phase I First-in-Human Study of Venetoclax in Patients With Relapsed or Refractory Non-Hodgkin Lymphoma. J Clin Oncol. 2017;35(8):826-33.

30. Burke JM, Fonseca G, Jurczak W, Melear J, Islas-Ohlmayer M, Reeves JA, et al. Efficacy and Safety of Umbralisib, Ublituximab (U2), and U2 Plus Bendamustine in Patients with Relapsed or Refractory Diffuse Large B-Cell Lymphoma (DLBCL). Blood. 2021;138(Supplement 1):527-.

31. Morschhauser F, Flinn IW, Advani R, Sehn LH, Diefenbach C, Kolibaba K, et al. Polatuzumab vedotin or pinatuzumab vedotin plus rituximab in patients with relapsed or refractory non-Hodgkin lymphoma: final results from a phase 2 randomised study (ROMULUS). Lancet Haematol. 2019;6(5):e254-e65.

32. Czuczman MS, Trneny M, Davies A, Rule S, Linton KM, Wagner-Johnston N, et al. A Phase 2/3 Multicenter, Randomized, Open-Label Study to Compare the Efficacy and Safety of Lenalidomide Versus Investigator's Choice in Patients with Relapsed or Refractory Diffuse Large B-Cell Lymphoma. Clin Cancer Res. 2017;23(15):4127-37.

VOL 1
ISSUE 1
2022

CANADIAN HEMATOLOGY TODAY

SHARE OUR WEBLINK ON YOUR SOCIAL MEDIA PLATFORM:

REGISTER FOR FUTURE DIGITAL AND PRINT ISSUES BY VISITING US AT CANADIANHEMATOLOGYTODAY.COM

CALLING ALL AUTHORS! DO YOU HAVE A TOPIC THAT YOU WOULD LIKE TO SEE COVERED IN 2022?

DROP US A LINE AND TELL US ABOUT IT OR SEND US A SHORT ABSTRACT

INTERESTED IN RECORDING A PODCAST? WE WANT TO EXPLORE TOPICS WITH YOU!

EMAIL US: INFO@CATALYTICHEALTH.COM