VOL. 3
ISSUE 3
Fall 2024

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

Canadian Hematology Today

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doi.org/10.58931/cht.2024.3356

Relapsed or Refractory Mantle Cell Lymphoma: Available and Emerging Therapies

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Introduction

Mantle cell lymphoma (MCL) is a mature B-cell non-Hodgkin lymphoma (NHL) that accounts for 5–7% of all NHL. In most cases, it is characterized by *t(11;14)* leading to cyclin D1 overexpression.[1] MCL displays a heterogeneous clinical behavior, ranging from a very indolent to a very aggressive clinical course. Biological features associated with aggressive disease include morphology (pleomorphic or blastoid), high proliferation index (Ki67 >30%)[2], adverse clinical scores (Mantle Cell Lymphoma International Prognostic Index [MIPIb])[3], and *TP53* mutation status.[4,5] Patients who relapse within 24 months of initial treatment (POD24) have a poor prognosis with median overall survival (OS) of approximately 12 months.[6,7-9]

Most patients achieve long-term disease control with first-line treatment, which currently involves induction with rituximab-containing chemotherapy[10-15] with or without autologous stem cell transplantation, followed by maintenance rituximab.[16,17] Trials assessing Bruton tyrosine kinase inhibitors (BTKi) and other novel agents in the first-line setting have been recently published[18-20] or are ongoing.[21,22] These options are currently not available in Canada outside of clinical trials but may become standard of care in the future.

Relapse after first-line therapy is inevitable, and curability outside the context of allogeneic stem cell transplant (alloSCT) remains unclear[1], with most patients eventually requiring second and subsequent lines of therapy.[23] In the last decade, new therapies have changed the treatment landscape of relapsed/refractory (R/R) MCL, and their optimal sequencing or combination remain unclear. Treatment options will be described herein, with a proposed treatment algorithm for R/R MCL (**Figure 1**).

Second-line Therapy: Chemoimmunotherapy Retreatment, Non-cytotoxic agents, or BTKi?

Prior to BTKi and chimeric antigen receptor T-cell therapy (CAR-T), treatment options for R/R MCL included agents such as bortezomib or lenalidomide, retreatment with rituximab-based therapy, and alloSCT. The response to these treatments was generally short-lived, especially in those with POD24 (**Table 1**).[24] AlloSCT remains a potentially curative option for fit and younger patients but is associated with significant toxicity, including non-relapse mortality of 10–20% as well as the morbidity associated with graft-versus-host disease.[25]

The covalent, irreversible, first-generation BKTi ibrutinib demonstrated excellent overall responses in R/R MCL.[26] Frequent adverse effects (AEs) include rash, diarrhea, and arthralgia, often low-grade, which may lead to treatment discontinuation in 8–13% of patients.[26-28] With time, serious AEs, such as bleeding, or cardiac events, including higher grade hypertension, atrial fibrillation, but also ventricular arrhythmias, and sudden death, have emerged.[29] Following the SHINE trial[30], which evaluated the addition of ibrutinib to first-line bendamustine and rituximab, the progression-free survival (PFS) benefit was offset by increased mortality from sudden death as well as infectious complications (including coronavirus disease 2019 [COVID-19] deaths). In addition to ~40% of patients crossing over to receive BTKi therapy in the placebo arm, there was also no overall survival (OS) benefit observed in the SHINE trial. Based on these results, the US Food and Drug Administration (FDA) approval for ibrutinib was withdrawn for MCL. Second-generation covalent BTKi, such as acalabrutinib[31] and zanubrutinib[32], have demonstrated similar outcomes with a better

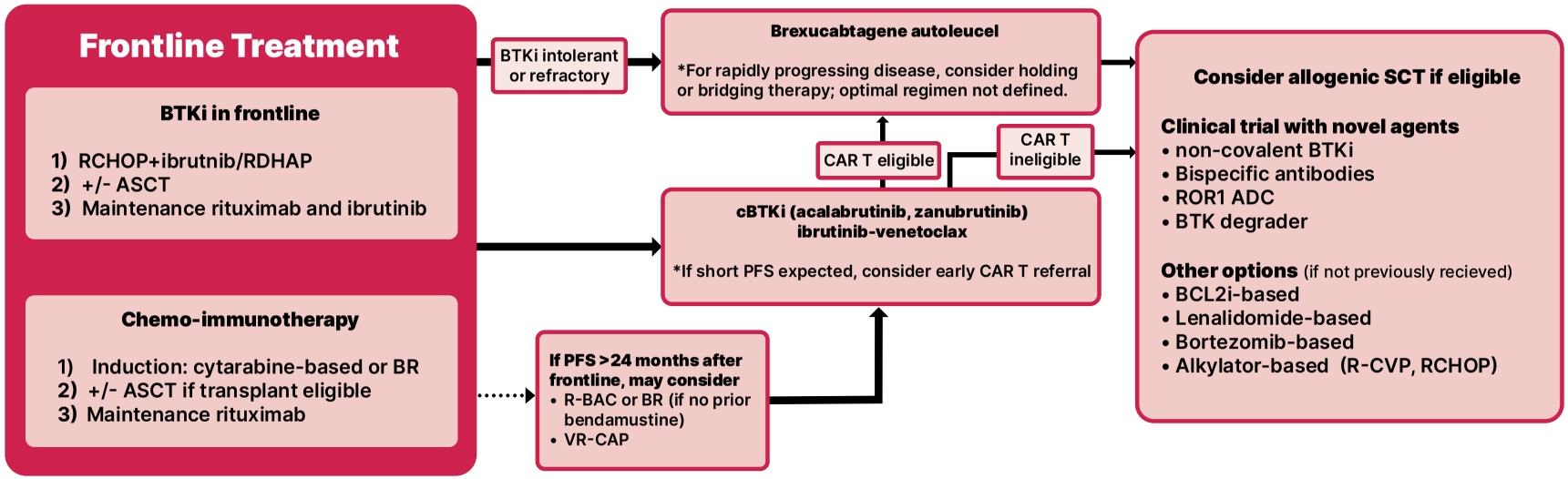


Figure 1. Treatment approach for Mantle Cell Lymphoma; *courtesy of Jean-Nicolas Champagne, MD, FRCPC and Diego Villa, MD, MPH, FRCPC.*

Abbreviations: ADC: antibody-drug conjugate, **ASCT:** autologous stem cell transplant, **BR:** bendamustine and rituximab, **BTKi:** Bruton tyrosine kinase inhibitors, **CAR-T:** chimeric antigen receptor T cell, **PFS:** progression-free survival, **R-BAC:** rituximab, bendamustine, and cytarabine, **RCHOP:** rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone, **R-CVP:** rituximab, cyclophosphamide, vincristine sulfate, and prednisone, **RDHAP:** rituximab, dexamethasone, cytarabine, and cisplatin, **ROR-1:** receptor-tyrosine-kinase-like orphan receptor 1, **SCT:** stem cell transplant, **VR-CAP:** bortezomib, rituximab, cyclophosphamide, doxorubicin, and prednisone.

Class of Therapy	Regimen	Design *(N)*	ORR *(CR)*	Median PFS *(mo)*	Median OS *(mo)*	Reference
Bendamustine-based	BR	Phase 3 (n=47 MCL)	70.8% (37.5%)	17.6 (7.9–30.4)	35.3 (14.9–NR)	60
	R-BAC	Retrospective (n=36; prior BTKi)	83% (60%)	10.1 (6.9–13.3)	12.5 (11.0–14.0)	61
Lenalidomide-based	Lenalidomide, lenalidomide-rituximab, lenalidomide-others	Retrospective (n=58; prior BTKi)	29% (13.8%)	Not reported – DOR: 20 weeks (2.9–NR)	NR	MCL-004[62]
Bortezomib-based	Monotherapy	Phase 2 (n=155; no prior BTKi)	33% (8%)	6.5 (4.0–7.2)	23.5 (20.3–27.9)	PINNACLE study [63, 64]
Lenalidomide and bendamustine-based	Rituximab, lenalidomide and bendamustine	Phase 2 (n=42)	79% (55%)	20	NR OS-24 mo 67% (95%CI 50–79)	65

Table 1. Therapies for R/R MCL prior to BTKi or CAR-T; *courtesy of Jean-Nicolas Champagne, MD, FRCPC and Diego Villa, MD, MPH, FRCPC.*

Abbreviations: **BR:** bendamustine-rituximab, **BTKi:** Bruton tyrosine kinase inhibitor, **CI:** confidence interval, **CR:** complete response, **DOR:** duration of response, **Mo:** months, **NR:** not reached, **ORR:** overall response rate, **OS:** overall survival, **PFS:** progression-free survival, **RBAC:** rituximab, bendamustine, cytarabine.

tolerability profile in cross-trial comparisons, and are increasingly used as second-line therapy in MCL (**Table 2**).[14,15]

No prospective trials have compared BTKi to standard chemoimmunotherapy in the R/R setting. Despite this, the practice pattern is evolving in recent years with increased utilization of BTKi as second-line therapy.[33] The retrospective MANTLE-FIRST study[24] suggests second-line BTKi monotherapy achieves better outcomes compared to traditional therapies for R/R MCL, including R-BAC (rituximab, bendamustine, and cytarabine), and a pooled analysis from three prospective ibrutinib trials showed superior outcomes from BTKi in second-line rather than in later lines (median PFS 24 months vs. 10 months).[26] Therefore, most patients today receive covalent BTKi monotherapy as second line therapy.[14,15]

Venetoclax, an oral Bcl-2 inhibitor, demonstrated deep, yet often short-lived, responses in R/R MCL when used as a monotherapy.[34-36] In preclinical models, it has synergistic effects with BTKi[37] and the combination with ibrutinib was safe in an early phase trial.[38] The phase 3 SYMPATICO trial[39] demonstrated that the addition of 24 months of venetoclax to continuous ibrutinib resulted in an absolute 10-month PFS improvement, with minimal incremental toxicity (**Table 2**). Despite no OS improvement, the clinical benefit from this combination therapy is considered clinically significant, and would likely replace BTKi monotherapy in the R/R setting if available in Canada.

Relapse after BTKi – Cellular Therapy

Relapse after a covalent BTKi has historically been associated with dismal outcomes. Even in those who receive subsequent treatment, historical response rates were ~30% and median overall survival was less than 1 year (8.4 months)[40] with therapies such as chemoimmunotherapy, bortezomib, or lenalidomide. CAR T-cell therapy has dramatically changed the treatment algorithm for R/R MCL. To date, the only Health Canada-approved product is brexucabtagene autoleucel, a CD19-directed CAR T-cell construct with a CD28 costimulatory domain, based on the pivotal phase 2 ZUMA-2 trial.[41] In this study, two-thirds of patients achieved durable complete responses with a median PFS of over 24 months. High-grade toxicities included cytokine release syndrome (CRS) in 15%, immune effector cell-associated neurotoxicity syndrome (ICANS) in 31%, and infections in 32% of patients. CAR T-cell therapy appears effective in patients with adverse biology, including *TP53* mutations or high Ki67 (**Table 2**).[42]

Real-world cohorts from the US (n=189)[42] and Europe (n=74)[43] have shown similar outcomes, even when most patients did not meet the ZUMA-2 inclusion criteria. Although the treatment-related mortality is lower than with alloSCT, it is as high as 9% to 15% in the real-world setting, mainly from infections. More recently, lisocabtagene maraleucel, a CAR T-cell product with a 4-1BB costimulatory domain, has demonstrated high and durable response rates with a similar, and potentially reduced toxicity profile (**Table 2**).[44] The latest American Society for Transplantation and Cellular Therapy (ASTCT), Center for International Blood and Marrow Transplant Research (CIBMTR), and European Society for Blood and Marrow Transplantation (EBMT) guidelines favour CAR T-cell therapy over alloSCT[25], with the limitation that there are no head-to-head comparisons. Despite the durable responses with CAR T-cell therapy, there is currently no evidence that it is curative.

An important challenge to the optimal delivery of CAR T-cell therapy is the timelapse between progressive disease and product infusion. This period includes referral, funding application and approval, candidate evaluation and screening, leukapheresis, manufacturing procedures, and admission for lymphodepleting chemotherapy and product infusion. In real-world studies, the median "vein-to-vein" time from collection to infusion varies between 33 to 41 days.[42,43] During this interval, disease progression may occur, requiring "holding" or "bridging" therapy to stabilize disease in up to 68–82% of patients in real-world cohorts.[42,43] Patients expected to have an early relapse on BTKi, particularly those with a short time to first relapse, Ki67 ≥30%, and MIPI score should be considered for early CAR T-cell therapy or alternate therapies.[9]

New Therapeutic Agents

Relapse after covalent BTKi and CAR T-cell therapy is a major clinical challenge. Emerging options in this setting include non-covalent BTKi, receptor-tyrosine-kinase-like orphan receptor 1 (ROR-1) antibody-drug conjugates (ADC), and bispecific antibodies (**Table 2**). There are multiple ongoing trials with these agents as monotherapy or in combinations (**Table 3**).

1) Non-covalent BTKi

The BTK mutation C481S has emerged as one of the resistance mechanisms to covalent BTKi[45], along with new-onset *TP53* or *NSD2* mutations.[46] Non-covalent BTKi reversibly bind to the ATP pocket in BTK, potentially overcoming the C481S point mutation. Pirtobrutinib, the first-in-class non-covalent BTKi, shows clinical activity in R/R MCL, including in patients with prior BTKi exposure, with an overall response rate (ORR) of 58%, but only 6 months of PFS in the entire study population.[47] However, those who respond may derive significant benefit with a median duration of response of 22 months.[47] The adverse effect profile is comparable to covalent BTKi, including cytopenias, musculoskeletal pain, diarrhea, bruising, and infections. Given the efficacy after BTKi exposure, the ongoing BRUIN-MCL-321 (NCT04662255) trial is currently testing pirtobrutinib against the investigator's choice of covalent BTKi in BTKi-naïve R/R MCL. Nembrabrutinib is another non-covalent BTKi, also with a seemingly similar profile in an early phase trial[48], with ongoing trials testing it as monotherapy (NCT05458297[49]) or in combination (NCT05458297[50]).

Class of therapy	Regimen	Design (N)	ORR (CR)	Median PFS (mo)	Median OS (mo)	References
Covalent BTKi	Ibrutinib	Pooled data from 2 phase 2 and 1 phase 3 trials (N=370)	70% (27%)	if 1 prior line: 25.4 (17.5-51.8) if >1 line: 10.3 mo (8.1-12.5)	if 1 prior line: 61.6 (36.0–NR) if >1 line: 22.5 (16.2–26.7)	Pooled analysis from 3 trials [26] - Phase 2 PCYC-1104 NCT01236391][66, 67] - Phase 2 SPARK [NCT01599949] - Phase 3 RAY [NCT01646021][68]
	Acalabrutinib	Phase 2 N=124	81% (40%)	22 (16.6–33.3)	59.2 (36.5-NR)	ACE-LY-004[31,69]
	Zanubrutinib	Phase 1/2 (n=32)	84.4% (25%)	21.1 (13.2-NR)	24mo OS 64.4%	Phase 1/2[70]
		Phase 2 (n=86)	83.7% (77.9%)	33.0 (19.4-NR)	36mo OS 74.8% (63.7–83.0)	Phase 2 single arm[32,71]
Covalent BTKi + Venetoclax	Ibrutinib + venetoclax	Phase 3 (vs. ibrutinib monotherapy) (N=267)	82% (54%)	31.9	44.9	SYMPATICO trial[39]
Treatment options in relapsed MCL after covalent BTKi						
CAR T-cell therapy	Brexucabtagene autoleucel	Phase 2 (n= 74) Prior treatment with anthracycline or bendamustine, anti-CD20 and BTKi	91% (68%)	25.8 (9.6–47.6)	46.6 (24.9–NR)	ZUMA-2[41,72]
	Lisocabtagene Maraleucel	Phase 1 (n=104 MCL, 88 infused) ≥2 prior lines, including BTKi, an alkylating agent, and anti-CD20	83.1% (72%) * infused patients	15.7 (6.2–24.0)	18.2 (12.9–36.3)	TRANSCEND-NHL 001 [44]
Non-covalent BTKi	Pirtobrutinib	Phase 1/2 (n= 90) *BTKi pretreated	57.8% (20.0%)	7.4 (5.3–12.5)	NR 18mo OS 59.3% (95% CI, 46.1 to 70.2)	BRUIN trial [47]

Class of therapy	Regimen	Design (N)	ORR (CR)	Median PFS (mo)	Median OS (mo)	References
	Epcoritamab (subcutaneous, continuous treatment)	Phase 1/2 (n=4)	50% (25%)	Not reported	Not reported	55
	Glofitamab (intravenous, fixed duration – 12 3-week cycles)	Phase 1/2 (n=37)	83.8% (73.0%)	Not reported	Not reported	54
Bispecific antibodies CD20 x CD3	Mosunetuzumab (intravenous, fixed duration 8 cycles if CR, up to 17 cycles if PR)	Phase 2 (n=15 MCL; 229 total)	Not reported for MCL, overall population 36.4% (21.7%)	Not reported	Not reported	56
	Mosunetuzumab and polatuzumab vedotin (fixed duration)	Phase1b/2 (n=20)	75% (70%)	Not reported	Not reported	73
ROR-1 ADC	Zilovertamab Vedotin	Phase 1 (n=17)	53% (12%)	11.4 (4.0–NR)	18.0 (7.1–NR)	waveLINE-001[74]

Table 2. Selected prospective trials using novel agents in relapsed/refractory MCL; *courtesy of Jean-Nicolas Champagne, MD, FRCPC and Diego Villa, MD, MPH, FRCPC.*

Abbreviations: ADC: antibody-drug conjugate, **BTKi:** bruton tyrosine kinase inhibitor, **CAR:** chimeric antigen receptor, **CR:** complete response, **MCL:** mantle cell lymphoma, **mo:** months, **NR:** not reached, **ORR:** overall response rate, **OS:** overall survival, **ROR-1:** receptor-tyrosine-kinase-like orphan receptor 1, **PFS:** progression-free survival.

Class of drug	Population	Planned accrual	Trial drug	Phase	Comparator	Primary outcome	Trial
Non-covalent BTKi	≥1 prior line BTKi naïve	500	Pirtobrutinib	Phase 3, open-label, randomized 1:1	Investigator's choice of BTKi	PFS	BRUIN MCL-321 NCT04662255[75]
	≥1 prior line BTKi naïve	275	Nemtabrutinib (with ZV)	Phase 2	-	ORR	MK-2140-006, cohort C NCT05458297[49,50]
Bispecific antibodies	≥1 prior line BTKi exposed	182	Glofitamab	Phase 3	Investigator's choice (BR or R-lenalidomide)	PFS	GLOBRYTE NCT06084936[76]
	BTKi refractory excluded	50	Glofitamab + Pirtobrutinib	Phase 2	-	CR	NCT06252675[77]
	≥1 prior line BTKi naive	40	Acalabrutinib, Obinutuzumab, and Glofitamab	Phase 2	-	CR	NCT06054776[78]
BCL2 inhibitor	≥1 prior line BTKi exposed	122	BGB-11417 (sonrotoclax)	Phase 1/2	-	ORR	NCT05471843[79]
ROR-1 ADC	R/R MCL	275	Zilovertamab Vedotin, with various combination	Phase 2	-	ORR	waveLINE-006 NCT05458297[50]
CD79b ADC	≥1 prior line BTKi exposed	16	Polatuzumab vedotin, with bendamustine-rituximab	Phase 2	-	ORR	NCT05868395[80]
BTK degraders	Relapsed B-cell malignancies, including MCL	127 466	BGB-16673	Phase 1/2 Expansion	-	Safety ORR	NCT05294731[81] NCT05006716[82]
		160	NX-2127	Phase 1	-	Safety ORR	NCT04830137[83]
		292	NX-5948	Phase 1	-	Safety ORR	NCT05131022[84]
		128	ABBV-101	Phase 1	-	AE	NCT05753501[85]
		60	AC676	Phase 1	-	AE	NCT05780034[86]

Table 3 . Selected ongoing trials in relapsed/refractory (R/R) MCL; *courtesy of Jean-Nicolas Champagne, MD, FRCPC and Diego Villa, MD, MPH, FRCPC.*

Abbreviations: ADC: antibody-drug conjugate, **AE:** adverse events, **BR:** bendamustine plus rituximab, **BTKi:** bruton tyrosine kinase inhibitor, **CR:** complete response, **MCL:** mantle cell lymphoma, **ORR:** overall response rate, **R-Len:** rituximab plus lenalidomide, **ROR-1:** receptor-tyrosine-kinase-like orphan receptor 1, **PFS:** progression-free survival.

2) ROR-1 ADC

ROR-1 is an oncoprotein expressed across most malignancies[51], including R/R MCL.[52] Zilovertamab vedotin is a ROR-1 targeting ADC with the microtubule inhibitor monomethyl auristatin E-containing (MMAE) as its payload, which is also part of brentuximab vedotin. As a single agent, it demonstrated response in ~50% of patients with R/R MCL.[53] Due to non-overlapping toxicity, combination therapy with nemtabrutinib is being explored in the Waveline-006 trial.[50] As expected with MMAE, toxicity includes neutropenia, infections, and peripheral neuropathy.

3) Bispecific Antibodies (CD20 x CD3)

Glofitamab[54], epcoritamab[55], and mosunetuzumab[56] are CD20-directed bispecific antibodies that simultaneously bind to CD3 to induce T cell-mediated killing of malignant B cells.[57] Despite some differences in the mode of administration (intravenous or subcutaneous) and the schedule (fixed duration or indefinite), they seem comparable in efficacy. In clinical trials including various R/R B-cell malignancies, including MCL, these molecules demonstrated a manageable toxicity profile with frequent, but low-grade CRS and rare ICANS, although the infectious risks remain a serious concern.[58] More experience is needed to better manage the CRS in an outpatient setting, as well as the infectious complications seen with these new treatments, but also to guide optimal treatment duration. In addition, compared to cellular therapy, these antibodies also provide the advantage of being an off-the-shelf treatment that can be deployed in a timely manner for patients presenting with rapidly progressing disease. The GLOBRYTE (NCT06084936) trial is testing glofitamab (CD3 x CD20 bispecific) against the investigator's choice of therapy in relapsed MCL with prior BTKi exposure.

4) Other Emerging Agents

Emerging agents include BTK degraders and other small molecule inhibitors targeting other pathways such as PI3K or NFKB. In addition, combination strategies of the previously described treatments are ongoing, such as mosunetuzumab and polutuzumab vedotin[59], or nemtabrutinib and zilovertamab vedotin[50] (**Table 3**).

Conclusion

Treatment options for R/R MCL have expanded in the last decade with the emergence of several agents with novel mechanisms of action. Clinicians are currently challenged by choosing the optimal sequence, but also ensuring that all treatments are provided to patients in the context of what remains an incurable disease. A proposed treatment algorithm for the management of R/R MCL in the current era is suggested in **Figure 1**. Clinicians will be increasingly challenged by identifying the most effective combinations for specific patients given the biological heterogeneity of MCL. In the Canadian setting, access and funding will remain an additional challenge.

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Financial Disclosures

JNC: Honoraria: BeiGene.
DV: Advisory Boards and Honoraria: Janssen, BeiGene, AstraZeneca, Roche, AbbVie, Kite/Gilead, BMS/Celgene, Merck, and Zetagen; **Research Funding:** Roche and AstraZeneca.

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doi.org/10.58931/cht.2024.3357

Treatment of Philadelphia Chromosome-negative Myeloproliferative Neoplasms in 2024: A Concise Review

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Introduction

In 1951, William Dameshek coined the term myeloproliferative disorders (MPDs) for diseases characterized by abnormal proliferation of one or more terminally differentiated myeloid cell lines in the peripheral blood.[1,2] In 2008, the World Health Organization (WHO) renamed these disorders as myeloproliferative neoplasms (MPNs) in recognition of their clonal nature. There are currently two classification system for MPNs: WHO and International Consensus Classification (ICC), 2022.[3,4] This review will focus on the Philadelphia chromosome-negative MPNs, which include polycythemia vera (PV), essential thrombocythemia (ET), and primary myelofibrosis (PMF).

Genomic changes in MPNs

MPNs result from the constitutive activation of the Janus kinase/signal transducer and activator of transcription (JAK/STAT) signalling pathway. The JAK2 p.V617F mutation, first described in 2005, is detectable in >95% of patients with PV and 50-60% of patients with ET or PMF. In-frame insertions or deletions in exon 12 of the *JAK2* gene are found in the remaining patients with PV but not in those with ET.[5-7] Mutations in the thrombopoietin receptor gene *MPL* were identified in 2006 and are present in 3–5% of ET and 5–10% of PMF, but not in PV cases.[8] Mutations in the calreticulin (*CALR*) gene were identified in 2013 and are found in 20–25% of ET and 25–30% of PMF but not in PV.[9,10] The *CALR* gene encodes for the endoplasmic reticulum chaperone protein (*CALR*). Mutant *CALR* interacts with the MPL protein, which is trafficked to the cell surface thereby activating the JAK-STAT signalling pathway.[11] Mutations in the *CALR* gene consist of insertions or deletions in exon 9 resulting in a positively charged amino acid sequence in the C-terminus. The mutations can be type 1, characterised by a 52-bp deletion that eliminates all the negatively charged amino acids in the C-terminus, or type 2, characterised by 5-bp insertion that eliminates half the negatively charged amino acids from the C-terminus. Type 1 and type 2 mutations constitute 80% of the *CALR* mutations.

In addition to the above three driver mutations, other somatic myeloid mutations are also found in MPNs. Common somatic mutations involve genes regulating DNA methylation (*TET2, DNMT3A,* and *IDH1/IDH2*), histone modification (*ASXL1* and *EZH2*), RNA splicing (S*F3B1, U2AF1, ZRSR2,* and *SRSF2*), and the RAS pathway (*NRAS* and *KRAS*). These mutations are common in PMF and the blast phase of PV and ET. While these mutations do not cause MPN, they may modify the disease phenotype. Mutations in *ASXL1, EZH2, SRSF2, U2AF1,* and *IDH1/2* are denoted as resulting in the "high molecular risk" phenotype.[12]

Management of PV

PV is a clonal hematopoietic stem cell neoplasm characterized by panmyelosis, disease-related symptoms, increased risk for thrombosis, and risk of transformation to post-PV myelofibrosis (MF) or acute leukemia. Goals of treatment for PV include prevention of thrombosis, reducing symptom burden, and prevention of disease progression.

PV-related thrombosis is multifactorial and related to hyperviscosity, increased red cell mass, and increased thrombin generation by platelets.[13]

JAK2 positivity contributes to thrombosis risk in MPN[14], as does increased allele burden.[15] Once-daily aspirin (81 mg/day; acetylsalicylic acid [ASA]) is recommended for all patients with PV without contraindications.[16] In addition, phlebotomies are performed to achieve a target hematocrit level of <45%.[17,18]

Beyond phlebotomy and aspirin, cytoreductive treatment is indicated for individuals with high-risk disease.[19] Traditionally, patients who are over 60 years of age and/or have a history of thrombosis are considered to have high-risk disease, while those without these factors are considered low risk.[19] In certain scenarios cytoreductive therapy may be considered even in patients with low-risk disease (**Figure 1.**):

1. Frequent phlebotomies with suboptimal hematocrit control or poor tolerability
2. Symptoms of PV (microvascular, pruritis) not controlled with ASA or phlebotomies
3. Phlebotomies leading to symptomatic iron deficiency anemia
4. Extreme thrombocytosis leading to acquired von Willebrand syndrome

Cytoreductive therapy

Over the years, hydroxyurea (HU) has been the standard cytoreductive agent in PV. HU is usually started at a dose of 500 mg once or twice daily, and titrated based on response. Another option, interferon alfa (IFNα), has long been shown to have cytoreductive and disease-modifying potential. However, its toxicity and need for frequent parenteral administration has been a deterrent to its usage. This has changed with the availability of pegylated forms of IFNα. The only formulation currently available in Canada is peginterferon alfa-2a (Pegasys). Another formulation is ropeginterferon alfa-2b (rIFN), which is a monopegylated form of IFNα. This formulation is characterised by an extended elimination half-life, resulting in less frequent dosing, better tolerability, and improved compliance.[20] This formulation is FDA-approved.

Phase 3 trials have established the role of IFNα in high-risk PV. The MPD-RC-112 trial, in which randomized patients with high-risk ET/PV received Pegasys or HU[21], and the PROUD-PV and CONTINUATION PV studies randomized patients with high-risk PV to receive rIFN or HU.[22,34] IFNα was non-inferior to HU in terms of complete hematological response (CHR) at 12 months in both these trials.[21-23] In the CONTINUATION-PV study, CHR was higher for the rIFN group in long-term follow-up.[23] JAK2 allele burden decreased consistently over time with both IFNα drugs, which was associated with improved event-free survival (EFS).[24] The starting dose for Pegasys is 45 mcg subcutaneously weekly. Doses are titrated with 45 mcg monthly increments to a maximum of 180 mcg.[21] rIFN is administered subcutaneously every 2 weeks at a starting dose of 100 or 50 mcg (for HU-exposed patients). Dosing increments of 50 mcg are made every 2 weeks up to a maximum of 500 mcg.[22,25]

Treatment of patients with HU-intolerant, resistant disease

A significant number of patients are intolerant to HU due to hematologic or non-hematologic toxicity or their disease is resistant to this therapy due to a lack of effective cytoreduction. HU intolerance or resistance has been defined by the European LeukemiaNet (ELN; **Table 1**)[26,27]:

1. Need for phlebotomy to maintain hematocrit levels <45% after 3 months of at least 2 g/day of hydroxyurea **OR**
2. Uncontrolled myeloproliferation (i.e. platelet count >400 × 10^9/L and white blood cell count >10 × 10^9/L) after 3 months of at least 2 g/day of hydroxyurea **OR**
3. Failure to reduce massive splenomegaly by more than 50% as measured by palpation or failure to completely relieve symptoms related to splenomegaly, after 3 months of at least 2 g/day of hydroxyurea **OR**
4. Absolute neutrophil count <1.0 × 10^9/L, or platelet count <100 × 10^9/L, or hemoglobin <100 g/L at the lowest dose of hydroxyurea required to achieve complete or partial clinical hematological response **OR**
5. Presence of leg ulcers or other hydroxyurea-related non-hematological toxicities like mucocutaneous manifestations, gastrointestinal symptoms, pneumonitis, or fever at any dose of hydroxyurea

Table 1. Definition of clinical resistance and intolerance to hydroxyurea in polycythemia vera and myelofibrosis; *adapted from Barosi, G, et al., 2007 and Barosi, G, et al., 2010.*

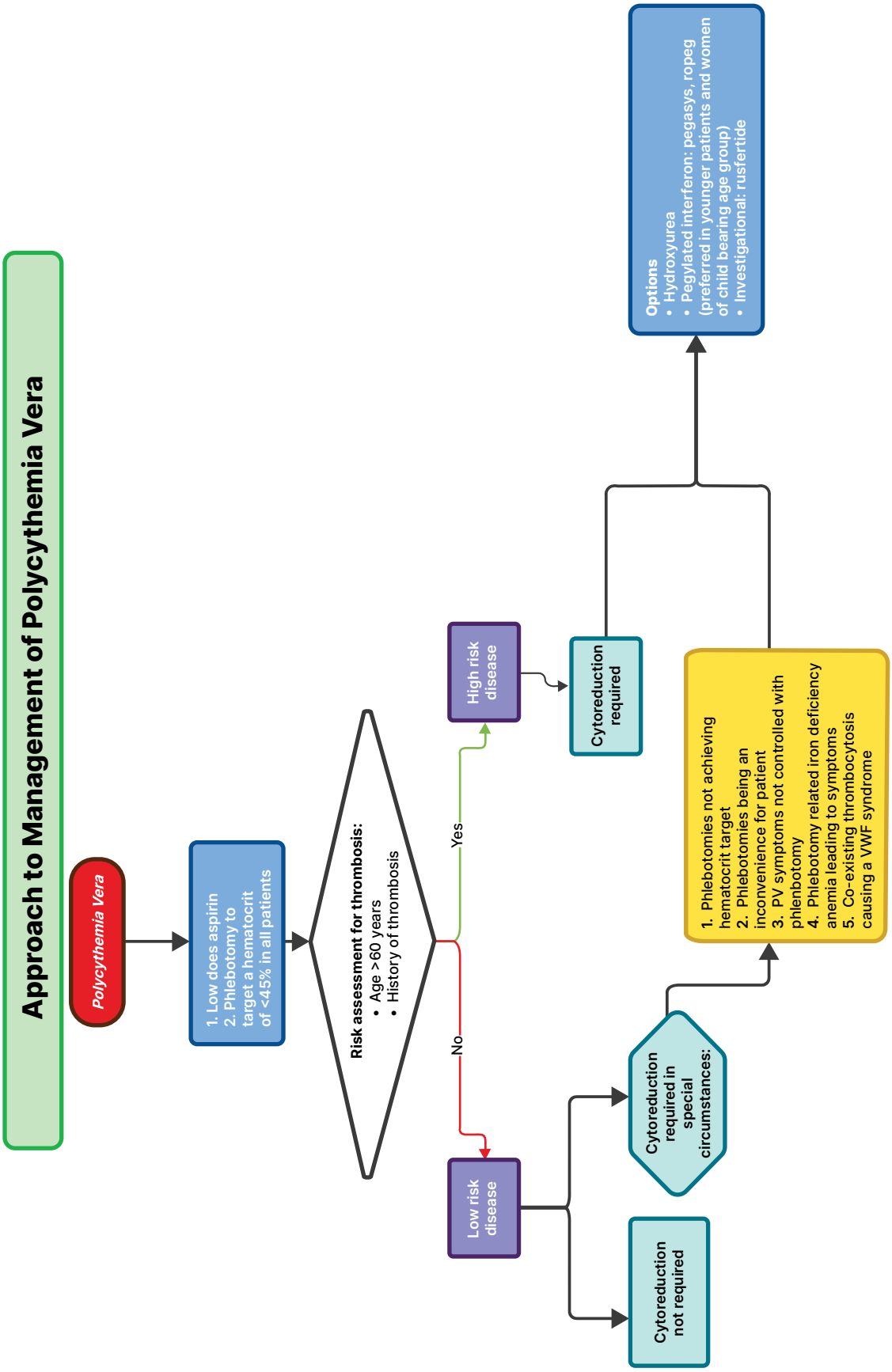


Figure 1. Approach to management of polycythemia vera; *adapted from Tefferi and Barbui, 2008.*[19]

In the MPD-RC-111 trial, a single-arm Phase 2 study, patients with HU-resistant or -intolerant disease were treated with Pegasys, which resulted in a 12-month overall response rate (ORR) of 60% and spleen normalisation in 32.7% of cases.[28] Ruxolitinib, an oral JAK inhibitor, was also assessed in this population in three randomized trials: the RESPONSE trial (with splenomegaly)[29], the RESPONSE-2 trial (without splenomegaly)[30], and the MAJIC-PV study (Phase 2). The comparator arm in these trials was the best available therapy (BAT). All three trials showed that ruxolitinib was better at achieving hematocrit control and spleen volume reduction compared to BAT. The MAJIC-PV trial also showed better EFS with ruxolitnib.[31] However, IFNα-based therapy constituted only 11.6%, 13%, and 15% of BATs.[29-31] Thus, whether ruxolitinib or pegIFNα is the best agent for those with HU-resistant/intolerant disease remains unknown. Future trials must focus on the appropriate sequencing of these agents for this group of patients.

Novel approaches

IFNα in low-risk PV

The role of rIFN in low-risk PV was studied in the LOW PV study which was a Phase 2 randomized trial comparing rIFN with phlebotomy. The group receiving rIFN had better hematologic response,[32,33] (rIFN was dosed 100 mcg every 2 weeks with no escalation).

Hepcidin-mimetic (rusfertide) in PV

Hepcidin binds to ferroportin, blocking the export of intracellular iron to the blood leading to reduced serum iron levels and decreased erythropoiesis.[34] In the Phase 2 REVIVE trial involving patients with phlebotomy-dependent PV, rusfertide was associated with a significant decline in phlebotomies and better hematological response.[35] The ongoing Phase 3 VERIFY trial is evaluating its efficacy and safety in PV.[36]

In summary, patients with low-risk PV are managed with aspirin and phlebotomy to achieve hematocrit levels of <45%. Cytoreductive therapy is indicated in patients with high-risk PV. In certain scenarios in low-risk PV, cytoreductive therapy can be instituted. Both the National Comprehensive Cancer Network (NCCN) and ELN recommend either HU or pegIFNα/rIFN as first line cytoreductive therapies. pegIFNα or rIFN are favoured in younger patients (<60 years) and women of child-bearing age.[37] In the HU-resistant/intolerant population, both pegIFN and ruxolitinib can be used.

Management of ET

ET is characterised by predominantly thrombocytosis, occurrence of thrombosis, and microcirculatory symptoms, and occasionally disease transformation to fibrosis or leukemia.

Risk-stratified treatment

Similar to PV, treatment in ET is focused on thrombosis prevention. Traditional risk factors include age over 60 years and history of thrombosis.[38] More recently, the international prognostic score for ET (IPSET), has refined risk stratification in ET by incorporating *JAK2* mutation status. In its latest iteration the revised IPSET thrombosis score categorises patients into four risk groups (**Table 2**).[39,40]

Despite the lack of randomized evidence, low-dose aspirin is used for thrombosis prevention in ET. Recommendations are based on non-randomized studies[41,42] and by extrapolation from studies in PV.[16] In the absence of contraindications, low-dose aspirin is a reasonable choice in patients with low, intermediate, and high-risk disease and in those with very low-risk disease with microvascular symptoms. In a recent study of low-risk patients with mutated *CALR*, no benefit was observed for the use of low-dose aspirin, while it was associated with increased risk of bleeding.[41] In patients with extreme thrombocytosis (>1000 × 10^9/L), aspirin should be used with caution due to the risk of bleeding and acquired von Willebrand factor deficiency (**Figure 2**).

Cytoreductive therapy

The first line cytoreductive therapy of choice for ET is HU. Similar to PV, pegylated IFN can be used in ET. The MPD-RC-112 trial compared Pegasys with HU in high-risk ET. The percentage of patients with complete remissions (CR) at 12 months were 44% and 45% with Pegasys and HU, respectively.[21] Anagrelide, an oral imidazoquinoline, when compared with HU in the first line, resulted in higher rates of thrombosis (arterial and venous), hemorrhage, and transformation to myelofibrosis than HU.[43]

For the HU intolerant/resistant population, the MPD-RC-111 trial showed that Pegasys produces reasonable responses (ORR of 69% at 12 months).[28] On the other hand, in the

Risk	Attributes	Management
Very low	Age ≤60 years, *JAK2* wild type, no prior thrombosis	Observation Low-dose aspirin (in the presence of cardiovascular risk factors)
Low	Age ≤60 years, *JAK2* V617F mutated, no prior thrombosis	Low-dose aspirin
Intermediate	Age >60 years, *JAK2* V617F wild type, no prior thrombosis	Low-dose aspirin +/- cytoreductive therapy
High	Age >60 years and *JAK2* V617F mutated **OR** Prior thrombosis regardless of other factors	Low-dose aspirin + cytoreductive therapy

Table 2. Revised international prognostic score for ET; *adapted from Barbui et al., 2015.*[46]

MAJIC-ET trial, when ruxolitinib was compared to BAT in this population, the ORR, and rates of thrombosis, hemorrhage, and transformation were similar. The BAT used were IFNα, anagrelide, busulfan, and HU.[44]

Thus, in patients with high-risk ET, the first line cytoreductive therapy of choice is HU. Pegylated IFN should be considered in younger patients and individuals of child-bearing age. Either of these agents (HU or IFNα) can be used in the second line if not previously used and anagrelide is an alternative option. Ruxolitinib has activity in ET and may be considered in certain circumstances. Results of the SURPASS-ET trial, comparing ruxolitinib with anagrelide in HU-intolerant/resistant ET are pending.[45]

Treatment of PMF and post-PV/ET MF

Primary myelofibrosis (PMF) is characterised by progressive cytopenia, marrow fibrosis, cytokine-driven inflammatory symptoms, and extramedullary hematopoiesis. A disease phenotype similar to PMF is observed in advanced phases of PV and ET and is defined as post-PV-MF and post-ET-MF, respectively. Aberration in the JAK/STAT signaling pathways is crucial to the pathogenesis of MF, which in 90% of patients is driven by mutually exclusive mutations in *JAK2, CALR,* or *MPL* genes.[47] Somatic mutations in the myeloid genes (mentioned under genomic changes) additionally influence MF biology.[48]

Risk stratification

Management of MF begins with risk stratification. Earlier risk models include the International Prognostic Scoring System (IPSS), Dynamic International Prognostic Scoring System (DIPSS), and DIPSS-plus.[49-51] Better genomic understanding has led to the incorporation of genetic mutations into the risk stratification. Mutations in *ASXL1, SRSF2, IDH1/2,* and *EZH2* confer poorer prognosis.[51] Mutational data has been integrated into the Mutation-enhanced (M) IPSS70, MIPSS70-plus, and MIPSS70+ version 2.0 risk stratification models.[53,54] Mutations in the *TP53* gene are not included in these risk systems. Seminal work by Grinfeld *et al.* showed that *TP53*-mutated MF has a high risk of leukemic transformation and very poor median overall survival (OS) of 2.4 years.[48] These risk models have been validated in primary myelofibrosis but not in secondary myelofibrosis. In clinical practice, these models are frequently used in secondary MF. The Myelofibrosis Secondary to PV and ET – Prognostic Model (MYSEC-PM) is a prognostic model developed specifically for secondary MF.[55]

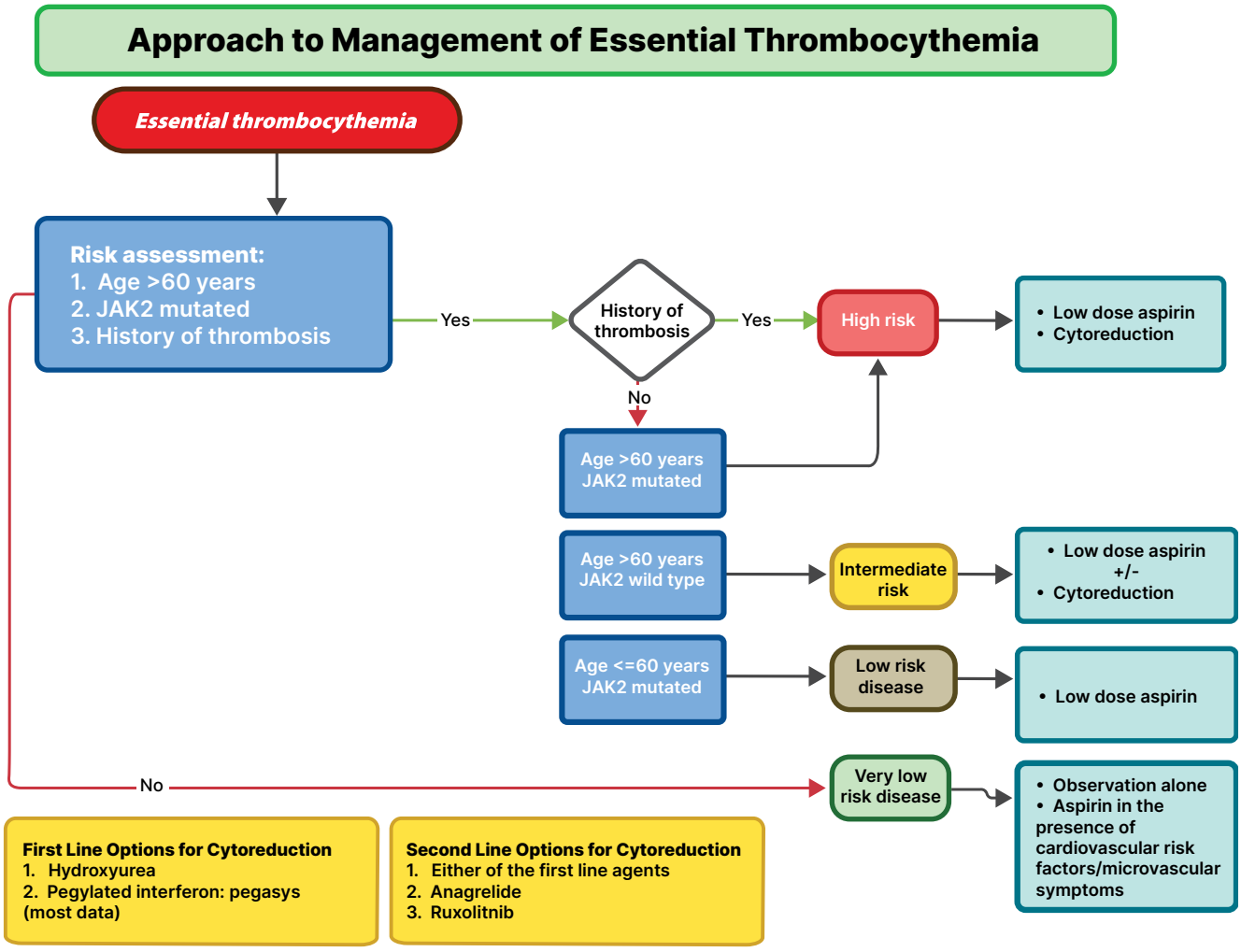


Figure 2. Approach to management of essential thrombocythemia; *adapted from Barbui et al., 2015.*[46]

Treatment of MF

Patients with DIPSS scores intermediate 2 or higher, MIPSS70 or MIPSS70-plus version 2.0 high risk, MYSEC-PM intermediate 2 or higher, and *TP53* mutations have a predicted median overall survival of <5 years and should be considered for allogeneic stem cell transplantation (**Figure 3**).[56] Peri-transplant management is directed at symptoms and splenomegaly and a bridging JAK inhibitor (JAKi) can be considered. Timing of the transplant in the JAKi era is controversial and is covered in other publications.[57-59] For patients who are ineligible for transplant, do not have a suitable donor, or prefer non-transplant therapy, JAKi have been the mainstay of therapy for symptomatic management. Patients who are not high risk per the above models can be monitored if asymptomatic, receive symptom-directed management, or refered to clinical trials as appropriate.

Choice of JAKi

There are currently four FDA-approved JAKi for myelofibrosis: ruxolitinib, fedratinib, pacritinib, and momelotinib, the first two of which are Health Canada approved. Ruxolitinib, a non-selective JAK1/JAK2 inhibitor, approved in the US in 2011 and in Canada in 2012, has the largest body of evidence. In the COMFORT-I and COMFORT-II trials comparing ruxolitinib to placebo and BAT, respectively, ruxolitinib resulted in a spleen volume reduction of 35% (SVR35) at 24 weeks (SVR35@24) in 41.9% and 32% of patients, respectively.[60,61] Anemia and thrombocytopenia are important side effects

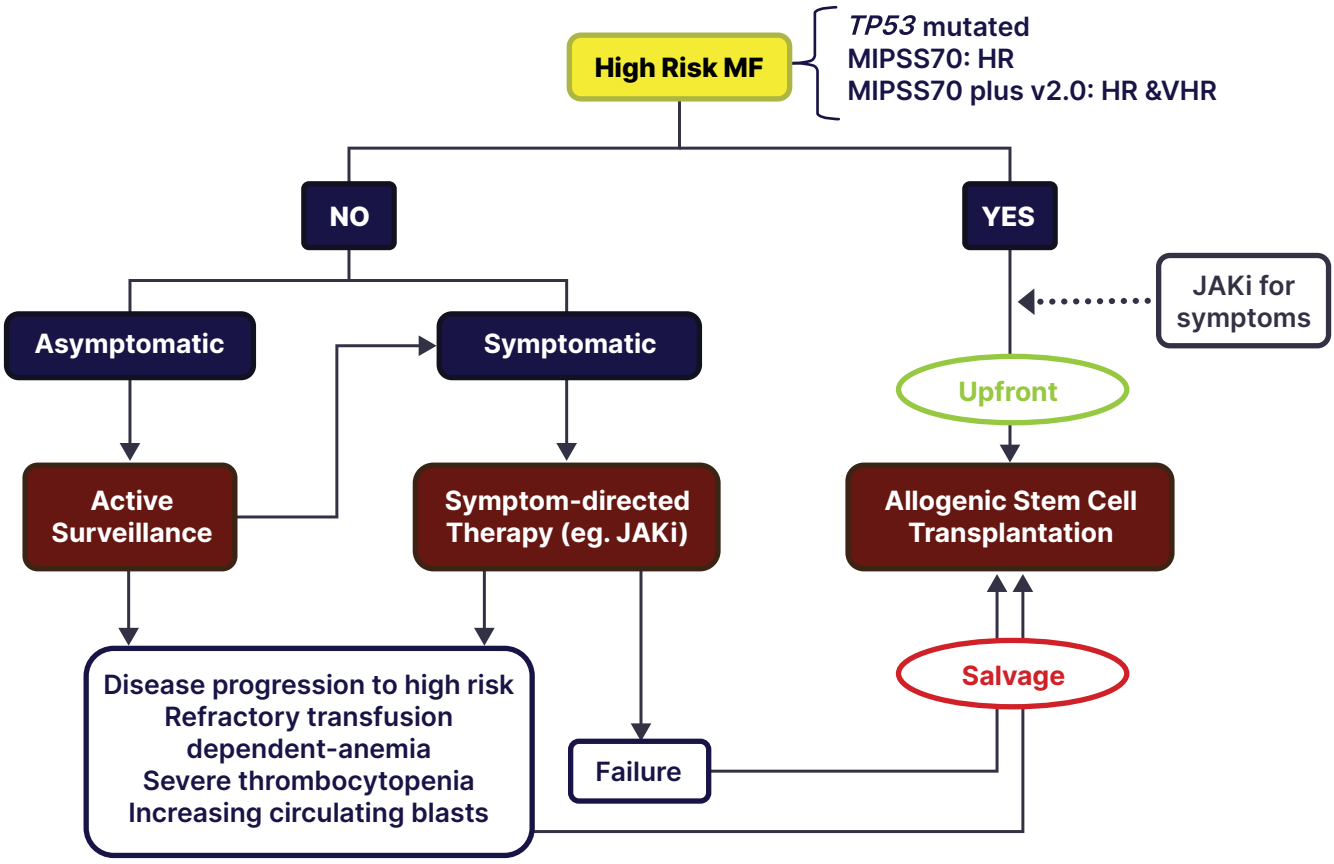


Figure 3. Management algorithm for transplant-eligible patients with MF in the chronic phase; *used with permission from Davidson and Gupta, 2021.*[58]

of ruxolitinib, which lead to dose reductions or treatment interruptions. At 3 years, 50% of patients had discontinued ruxolitinib, and this rate increased to 75% at 5 years.[62]

Fedratinib is a JAK2-FLT3-BRD4 inhibitor that has been studied in both ruxolitinib-naïve and -exposed patients in the JAKARTA and JAKARTA-2 trials. To be included in these trials, platelet levels had to be ≥50 × 10^9/L. Fedratinib resulted in a SVR35@24 of 36% and 55%, respectively, with good symptom burden reduction.[63-66] Even though fedratinib is effective in the first line setting, ruxolitinib is most often used in clinical practice. The Health Canada approval for fedratinib is for patients with MF with disease-related symptoms or splenomegaly, including those who have been previously exposed to ruxolitinib.[67]

Momelotinib is a JAK1/JAK2 inhibitor that has additional inhibitory effects against activin A receptor type 1 (ACVR1). ACVR1 is involved in SMAD2/3 signalling, which upregulates hepcidin production. Momelotinib has been found to have significant anemia benefits. In the SIMPLIFY-1 trial, momelotinib was found to be non-inferior to ruxolitinib in terms of the SVR35@24, but not for symptom score reduction.[68] In addition, this trial showed that red blood cell (RBC) transfusion independence and conversion to transfusion independence was better with momelotinib.[69] Momelotinib is an exciting option for the treatment of symptomatic MF with anemia. Approval in Canada is anticipated in the near future.

The fourth JAKi is pacritinib, which was studied in the PERSIST-1 and PERSIST-2 trials that included patients with platelet counts <50×10^9/L (both JAKi-naïve and JAKi-exposed). Pacritinib achieved SVR35@24 of 23.1% and symptom control in 25% of patients.[70]

Combination therapy

A number of novel agents have been combined with JAKi therapy in clinical trials. In the MANIFEST-2 trial, patients with treatment-naïve symptomatic MF with an enlarged spleen (DIPSS intermediate-1 or higher) were randomized to receive ruxolitinib + pelabresib (BET inhibitor) or ruxolitinib + placebo.[71] In the TRANSFORM-1 trial, the combination of ruxolitinib + navitoclax (BCL-2 inhibitor) was compared with ruxolitinib + placebo.[72] Both combinations resulted in a doubling of the SVR35@24 in comparison to ruxolitinib + placebo. However, neither combinations significantly reduced the symptom burden in comparison to ruxolitinib + placebo. Therefore, the place of these combinations for treatment remains unclear and longer follow-up studies are awaited. These two trials also highlight the need for better endpoints to evaluate therapies in MF. In addition, the combination of ruxolitinib + pelabresib showed improvement of bone marrow fibrosis.[73] This could be evidence of disease modification with the BET inhibitor. Other therapies with disease-modifying potential are required.

Agents addressing anemia

Transfusion dependence is a major symptom in MF. Transfusion dependence is associated with poorer overall survival in patients with MF.[74,75] Apart from momelotinib and pacritinib, which positively affect anemia due to *ACVR1* inhibition, there are other adjunctive therapies that have been used in patients with MF and anemia. RBC transfusion is the most commonly used strategy in clinical practice. Erythropoietin (EPO)-stimulating agents can be used in patients with EPO levels <500 U/L with an expected response ranging from 40–60%.[76-78] Androgens (danazol), steroids, immunomodulatory agents (lenalidomide, thalidomide), and splenectomy are other strategies that have been used.[79] Recently, the Phase 2 open label ACE-536-MF-001 trial tested luspatercept in patients with MF. Luspatercept resulted in improvement of the primary endpoint (anemia response) in transfusion-dependent (9.5%) and non-transfusion-dependent (13.6%) patients and in patients who were on ruxolitinib (26.3% and 14.3%, respectively).[80]

In summary, management of MF begins with risk stratification. Patients with high-risk disease should be offered a transplant. JAKi can be used in peri-transplant symptom management. In patients who are ineligible for transplant or decline transplant, management is symptom-directed using JAKi. Ruxolitinib is the JAKi with the most clinical experience. Newer JAKi, such as momelotinib and pacritinib, have a role in the setting of co-existing cytopenia. Trials are assessing agents that modify the disease biology and also address anemia.

Conclusions and future directions

The past decade has seen major shifts in the diagnosis, prognostication, and management of MPN. The focus of treatment for PV and ET is thrombosis prevention and monitoring for disease progression. New data support the use of IFNα therapy for cytoreduction, especially in PV, and also appears to result in sustained decline in JAK2 allele burden in a proportion of patients. Management of MF begins with risk assessment. Patients with high-risk disease should be considered for transplant. Symptom management of MF has seen the availability of several JAK inhibitors which may help address the co-existing cytopenia in MF. With the availability of many agents, sequencing of therapies will become increasingly important in the future. Several agents are focused on addressing anemia in MF, which continues to be an area of unmet need. Patients should be offered clinical trial participation whenever possible.

Disclaimer: At the time of publishing this review, there is a global shortage in the supply of Pegasys, which is expected to last until the second half of 2025.

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Financial Disclosures

A.R.: None declared.
D.M.: None declared.

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doi.org/10.58931/cht.2024.3358

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Front-line Treatment of Older Patients with Hodgkin Lymphoma

Kelly Davison, MD

Introduction

The evolution of treatment for classical Hodgkin lymphoma (cHL) represents a great success in oncology, with disease outcomes evolving from universally fatal to vastly curable. However, not all patients benefit equally from modern therapies, which include response-adapted regimens and the addition of novel, targeted agents to the front-line setting. Although patients older than 60 years account for the later peak in cHL's characteristic bimodal age distribution and represent approximately 20–25% of all patients with cHL, their outcomes remain inferior compared to younger patients.[1] A retrospective study including 401 patients >60 years treated in British Columbia between 2000 and 2019 revealed modest progression-free survival (PFS) and disease-specific survival rates of 50% and 63%, respectively, with a median follow-up of nine years. While these outcomes have improved relative to cohorts treated prior to 2000, they nevertheless fall short of those experienced by younger patients. Furthermore, the gap in outcomes between young and older patients progressively worsens with each increasing age decile, with patients >70 years having a particularly poor prognosis.[2] This shortfall has been attributed in part to patient-specific factors such as comorbidities and frailty, which may limit treatment tolerance, but also to differing disease biology, with negative prognostic features including advanced stage disease, Epstein-Barr virus positivity, and mixed cellularity histology often present in those with older age.[3] Adding to the challenges in treating older patients is the fact that this group is frequently underrepresented in clinical trials, or excluded altogether, making their optimal treatment ill-defined.

Treatment of Anthracycline-eligible Patients

For several decades, the multiagent ABVD (adriamycin, bleomycin, vinblastine, and dacarbazine) regimen has represented a North American standard for the front-line treatment of fit patients with cHL. However, ABVD is more toxic for older patients, with rates of bleomycin-induced lung toxicity (BLT) as high as 35% in this subpopulation. The risk of BLT rises with increased age, resulting in mortality rates that approach 30%.[4] The randomized RATHL trial aimed to minimize pulmonary toxicity through a positron emission tomography (PET)-directed approach wherein bleomycin was omitted from ABVD after two cycles for patients with advanced-stage disease achieving an early metabolic complete response. While this study reported decreased pulmonary events (3.2% vs. 0.6% in cycles 3–6 for ABVD and AVD, respectively) with similar 3-year PFS for patients who were PET-negative after two cycles (PET2-negative), only 9% of enrolled patients were >60 years of age, challenging the extrapolation of these results to routine clinical practice.[5]

The impact of omitting bleomycin from the ABVD backbone has likewise been evaluated in the limited-stage setting. The German Hodgkin Study Group (GHSG) HD13 trial randomized favourable risk patients with early-stage disease to one of four arms: two cycles of ABVD with or without bleomycin, dacarbazine, or both, prior to consolidative radiotherapy. Freedom from treatment failure was not found to be non-inferior for patients receiving AVD (93.1% vs. 89.2%), leading investigators to conclude that ABVD remained the preferred regimen in this setting.[6] Older patients, for whom the slight loss in treatment efficacy may be offset by decreased toxicity and improved treatment-related mortality, comprised only a small proportion of the enrolled population (13%). A subsequent analysis of patients >60 years enrolled in GHSG trials was undertaken, all of whom were meant to receive 2–4 cycles of ABVD (HD10 and HD13 trials) or two cycles of AVD (HD13). This pooled analysis of 287 patients demonstrated no significant increase in BLT for patients receiving ABVD compared to AVD when chemotherapy was limited to two cycles (1.5% vs. 0.0%, respectively), but showed a striking increase (10%, including three fatal cases among the seven reported) when ABVD was extended to four cycles. Response and efficacy outcomes were similar across groups and not different from the main HD13 analysis, including both young and older patients.[7] These data suggest that bleomycin may be safe and tolerable for fit older patients, but should be limited to two cycles, beyond which the risk of BLT becomes unacceptably high. Ultimately, the decision to include bleomycin in the treatment of older patients should be individualized, with careful consideration of additional patient-specific risk factors for the development of BLT.

More recently, the anti-CD30-directed antibody-drug conjugate, brentuximab vedotin (BV), has presented an additional treatment option for cHL. In addition to its use in the relapsed setting, BV is licensed for use in combination with AVD as front-line treatment for patients with advanced-stage disease in the US and for patients with stage IV disease in Canada. The BV-AVD regimen was evaluated against standard ABVD in the randomized ECHELON-1 trial, which enrolled newly diagnosed patients irrespective of age. The overall analysis revealed a modified PFS advantage and, with longer follow-up, a small but statistically significant OS advantage favouring BV-AVD. However, these benefits appeared to be limited to younger patients. In a subgroup analysis of patients >60 years, BV-AVD conferred a trend toward improved 5-year modified PFS; however, this was not statistically significant (67.1% vs. 61.6% for ABVD; p=0.443)[8] and no OS benefit was observed (hazard ratio [HR] for death 0.83, 95% CI 0.47–1.47).[9] Rates of treatment-emergent adverse events were similar among patients treated with ABVD vs. BV-AVD; however, pulmonary toxicity was predictably less frequent in the absence of bleomycin. In contrast, treatment with BV-AVD was associated with increased rates of neuropathy and febrile neutropenia, particularly in older patients, mandating the use of granulocyte colony-stimulating factor (G-CSF) prophylaxis. Collectively, these data suggest that BV-AVD may be an effective regimen for selected fit older patients with advanced stage cHL, but its use requires careful supportive care and toxicity monitoring.

An alternative strategy aimed at improving the tolerability of BV has been to use it sequentially rather than in combination with AVD. In a phase 2 study of patients >60 years with stage II-IV cHL, a lead-in phase of two cycles of single-agent BV was followed by six cycles of AVD and an additional four cycles

of consolidative BV for patients responding to treatment. Encouragingly, rates of neuropathy and neutropenia appeared more favourable than those reported in the ECHELON-1 study, suggesting better tolerability with this sequential treatment approach. The 2-year PFS and OS were compelling, at 84% and 93%, respectively.[10]

The escBEACOPP (escalated bleomycin, etoposide, adriamycin, cyclophosphamide, vincristine, procarbazine, and prednisone) regimen, established by the GHSG for front-line treatment of advanced-stage cHL, has long been recognized as prohibitively toxic for older individuals, limiting its use to those <60 years of age. Recent efforts to decrease acute and late toxicity with this regimen have resulted in the development of the novel BrECADD (brentuximab vedotin, etoposide, cyclophosphamide, doxorubicin, dacarbazine, and dexamethasone) regimen, which incorporates BV into a modified, less toxic version of the escBEACOPP backbone. When used in a PET-adapted manner for the treatment of patients with advanced-stage disease, including those having stage 2 disease with risk factors, BrECADD was shown to be better tolerated and non-inferior with respect to PFS to escBEACOPP, leading investigators to declare it a new treatment standard.[11] While HD21 did not enrol patients >60 years, the improved toxicity profile associated with BrECADD has led to its evaluation in an older cohort of patients, the results of which are expected soon.

Another promising approach to the management of older patients with cHL has emerged from the US intergroup study S1826, which evaluated the role of programmed cell death protein 1 (PD-1) inhibition in combination with chemotherapy as a first line of treatment.[12] This randomized, phase 3 trial compared six cycles of BV-AVD to six cycles of nivolumab-AVD (N-AVD). Patients >60 years accounted for only 10% of the 994 patients enrolled, all of whom had advanced-stage disease. A pre-planned analysis of outcomes among older patients revealed a dramatic improvement in PFS favouring N-AVD. With a median follow-up of 12.1 months, the 1-year PFS was 93% for N-AVD, compared with 64% for BV-AVD (HR: 0.35, 95% CI: 0.12–1.02; p=0.022). Remarkably, the PFS observed in this study mirrored the one observed in the overall cohort, where the median age was 27 years. Among older patients, fewer deaths were observed in the N-AVD group, leading to improved 1-year OS, though this did not reach statistical significance (95% vs. 83%, HR: 0.35, 95% CI: 0.07-1.75, p=0.091). Predictably, rates of neuropathy were significantly lower with the absence of BV. Immune-related toxicities were similar between arms, except for hypothyroidism (15% vs. 0.0%) and rash (16.0% vs. 2.0%), which were predominantly low-grade.[13] Although longer follow-up is eagerly awaited and PD-1 inhibitors are not yet approved in the front-line setting, the very promising results from S1826 and other trials incorporating these drugs into front-line therapy[14], have led to the early adoption of N-AVD as a treatment of choice in the US, for older, fit patients with advanced stage cHL.

Treatment of Anthracycline-ineligible Older Patients

Older individuals unfit for anthracycline-based chemotherapy represent a challenging group of patients. Given the important contribution of anthracyclines in achieving cure through conventional front-line chemotherapy regimens, it is paramount to determine which patients are fit enough to receive anthracycline-based therapy. Geriatric assessment (GA) has been increasingly recognized as valuable in the pre-treatment evaluation of older patients with cHL. While few trials have prospectively incorporated GA, a growing body of retrospective data underscores the utility of standardized tools in predicting treatment response and outcomes, including the cumulative illness rating scale – geriatric (CIRS-G), the adult comorbidity evaluation 27 (ACE-27), the Charleston Comorbidity Index, screens for impaired activities of daily living, and the presence of geriatric syndromes. The use of GA may ultimately guide treatment decisions, sparing patients unlikely to benefit from more intensive and more toxic therapies, while offering them alternatives with more favourable risk-to-benefit profiles.[15,16]

Treatment outcomes for unfit older patients are largely informed by non-randomized trials that enrolled small numbers of patients, leaving this demographic without a clearly defined treatment standard. Given the poor outcomes for low-intensity multi-agent chemotherapy regimens such as ChlVPP (chlorambucil, vinblastine, procarbazine, and prednisone), for which 5-year event-free survival (EFS) and OS rates are reported to be only 24% and 30%, respectively, there has been great interest in developing more rational novel approaches.[17] To this end, targeted agents, including BV and PD-1

inhibitors, have been assessed in the front-line setting as monotherapies and doublets. While both BV and nivolumab (or pembrolizumab) have shown disappointing results when administered alone, combinations of BV or PD-1 inhibitors with chemotherapy or with each other have shown more promise. The SGN-015 phase 2 trial evaluated BV in cohorts of older patients with cHL, either alone or in combination with other agents (dacarbazine, bendamustine, or nivolumab). Recently reported results from the combination cohorts receiving BV plus dacarbazine or BV plus nivolumab revealed that with a median follow-up of over four years, the median PFS was a remarkable 47.2 months and not reached, respectively.[18] This compares favourably to a cohort receiving BV monotherapy, in which only a modest median PFS of 10.5 months was observed, despite a high overall response rate of 92%.[19] Responses to doublet therapy were more durable, and the median OS was not reached in either group. Furthermore, for patients who received no further therapy beyond the end of the study treatment (a median of 12.5 cycles in the dacarbazine cohort, and 10 cycles in the nivolumab cohort), the 5-year OS was 90% in the dacarbazine and 78% in the nivolumab cohort, invoking the possibility of cure for a subset of patients treated with these regimens. Neuropathy rates were high, however, underscoring the need to carefully select and monitor patients for this common side effect of BV. These data support the use of novel agent-containing doublet therapies for the treatment of patients with cHL who are unfit to receive more intensive therapy, which merits further investigation.

Conclusion

The treatment of cHL in elderly patients presents a unique set of challenges necessitating a tailored approach that considers the individual's overall health, comorbidities, and treatment preferences. While traditional chemotherapy regimens remain the backbone of therapy, incorporating novel agents into the front-line setting is poised to raise the bar, improving both outcomes and tolerability. GAs will likely become increasingly important in defining which patients are fit for standard treatment versus those requiring novel approaches. For those patients unfit to receive conventional treatments, novel doublet therapies may offer hope for long-term disease control. Together, these approaches promise to improve outcomes for this vulnerable patient population.

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Financial Disclosures

Consulting: Abbvie, AstraZeneca, Beigene, BMS, Gilead/Kite, Incyte, Janssen, Roche, Pfizer, Sobi;
Research funding: Novartis, Merck, Roche

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doi.org/10.58931/cht.2024.3359

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The Evolving Landscape of DLBCL Treatment Beyond the First Line in 2024

Mark Bosch, MD

Introduction

The landscape for treating relapsed or refractory (R/R) diffuse large B-cell lymphoma (DLBCL) in 2024 is rapidly evolving, with various treatment options emerging. Traditionally, salvage chemotherapy followed by autologous stem cell transplant (ASCT) has been the primary treatment for young, fit patients with R/R DLBCL, and only limited options exist for those ineligible for transplant. However, recent research and regulatory approvals, such as chimeric antigen receptor (CAR) T-cell and bispecific antibody therapies, have significantly improved our ability to treat patients previously considered palliative for R/R DLBCL.

Moreover, further research has demonstrated that these advanced technologies are not only effective in the transplant setting but also in individuals who are not traditionally eligible for ASCT and those with comorbid conditions. One anticipated development has been the provincial approvals of bispecific T-cell engagers (BiTEs), such as epcoritamab and glofitamab, which target CD20 and CD3. BiTE therapy holds promise as an off-the-shelf treatment option, potentially offering wider availability to patients compared to CAR T-celll therapy or even post-CAR T-cell failure.[1,2]

With advancements in treatments, physicians may be unfamiliar with the safety profiles and potential toxicities. Concerns about CAR T-cell and BiTE treatments have been raised, particularly regarding the risk of cytokine release syndrome (CRS) and/or immune effector cell-associated neurotoxicity syndrome (ICANS). Despite these concerns, the ability to manage CRS and ICANS improves with increasing experience and advancements in treatment algorithms.[3,4]

In addition to CAR T-cell therapy and BiTEs, targeted approaches for R/R DLBCL have seen recent approvals for patients who are not ideal candidates for ASCT or CAR T-cell therapy. These include combinations, such as

tafasitamab (an anti-CD19 monoclonal antibody) and lenalidomide, or polatuzumab vedotin (an anti-CD79b-conjugated monoclonal antibody) with bendamustine, rituximab, and selinexor, an oral inhibitor of exportin 1. Unfortunately, there are disparities in drug access in different provinces in Canada. For example, institut national d'excellence en santé et services sociaux (INESSS) in Quebec has approved the funding of tafasitamab, while Canada's Drug Agency (CDA) did not recommend reimbursement, and therefore, the rest of the country does not have access. The reverse is true for polatuzumab-rituximab-bendamustine. Selinexor is not Health Canada approved or funded for this indication.

Table 1 outlines many of the latest advancements for R/R DLBCL. It is essential to highlight that three major CAR T-cell-producing companies currently treat patients with regulatory approval in the third-line setting, which may provide a potential cure. These products include Tisa-Cel, Axi-Cel, and Liso-Cel, each with the potential to significantly impact the future of DLBCL treatment. In Canada, Tisa-Cel, Axi-Cel, and Liso-Cel are approved for third-line therapy, while only Axi-Cel and Liso-Cel are available for second-line therapy, as Tisa-Cel did not demonstrate benefits in the second-line setting.

Regarding safety, it is unclear whether the differences in toxicity are related to the design of the CAR T-cell construct, as none of the constructs have been compared in clinical trials. The understanding of CRS diagnosis and management was still evolving during the studies. Despite this limitation, a retrospective study from the French real-life registry DESCAR-T compared Axi-Cel with Tisa-Cel using a propensity score-matched comparison. This study showed that Axi-Cel may demonstrate higher efficacy but more toxicity than Tisa-Cel, regarding the incidence and severity of CRS, ICANS, and prolonged cytopenias. As a result, some centres may prefer Tisa-Cel for less fit patients in third-line.[5]

BiTE therapy is also rapidly advancing, yet a comprehensive understanding of its therapeutic potential remains to be discovered. The current data does not decisively indicate curative capabilities comparable to CAR T-cell therapy. Future research should explore the potential of BiTE therapy to deliver curative benefits and ascertain the parameters for treatment cessation. Additionally, investigating the necessity of a fixed duration strategy (glofitamab)[2] versus a continuation strategy (epcoritamab)[6] will provide valuable insights for clinical practice and patient care.

In the context of second-line relapse treatment, the data indicate that Axi-Cel[7] and Liso-Cel[8] are excellent options and show superiority over ASCT. However, Tisa-Cel[9] did not demonstrate statistically significant improvement in the second-line setting and thus is not expected to be marketed in Canada in the second-line-setting.

Understanding when and to whom to provide these new therapies is rapidly evolving. In the early stages, CAR T-cell therapy clinical trials had strict criteria and were only offered to fit individuals with Eastern Cooperative Oncology Group (ECOG) performance score (PS) 0–1 and clearly defined normal organ function.[10,11] As these therapies became more common in clinical practice, many of these restrictions were lifted, and most centres now consider adequate organ function to allow more patients to benefit from the therapy. Real-world data analysis using Center for International Blood and Marrow Transplant Research (CIBMTR) data has shown that Axi-Cel is effective for those over 65 years. However, those with ECOG PS ≥2 had inferior outcomes and a higher incidence of ICANS.[12]

In the transplant-ineligible population, CAR T-cell therapy has been studied in two other clinical trials: the Pilot[13] (Liso-Cel) and Alycante[14] (Axi-Cel) trials, which specifically examined the use of CAR T-cell therapy in older and historically transplant-ineligible populations in the second-line setting. In the Alycante study with Axi-Cel, a phase II trial, patients were eligible if they had an ECOG PS of 0–2 and were considered ineligible for transplant based on age ≥65 years, Hematopoietic Cell Transplantation (HCT)-specific Comorbidity Index (HCT-CI) ≥3, or prior ACST. In the Pilot study using Liso-Cel, patients only required adequate vascular access and one of the following criteria to be considered transplant ineligible: age ≥70 years, ECOG PS of 2, diffusion capacity of the lung for carbon monoxide (DLCO) <60%, left ventricular ejection fraction (LVEF) ≤40%, creatine clearance (CrCL) between 30–60, and liver function tests showing aspartate transaminase (AST) and alanine aminotransferase (ALT) >2 and ≤5 times the upper limit of normal. Despite the increase in age and comorbidities, both toxicity and outcomes were comparable to data obtained from studies in younger and healthier patients.

When determining the best treatment options for patients with R/R lymphoma, the practitioner must consider the availability and

Drug	Study *(n)*	Administration	ORR	mPFS or mEFS *(months)*	Toxicity Grade ≥3 of Special Interest
2L					
Axi-cel[7]	Zuma-7 (359)	IV - Fixed	ORR 83%, CR 65%	8.3 EFS	CRS: 6%, ICANS 21%
Axi-cel[14]	ALYCANTE (62)	IV - Fixed	ORR 76%, CR 60%	12.3 EFS	CRS: 8%, ICANS 15%
Liso-cel[8]	Transform (184)	IV - Fixed	ORR 87%, CR 74%	10.1 EFS	CRS: 1%, ICANS 4%
Liso-cel[13]	Pilot (74)	IV - Fixed	ORR 80%, CR 54%	9.03 PFS	CRS: 1%, ICANS 4%
Tisa-cel[9]	Belinda (322)	IV - Fixed	ORR 46%, CR 28%	3.0 EFS	CRS: 5%, ICANS 2%
≥ 2L					
Pola-BR[16]	NCT02257567 (152)	IV - Fixed	ORR 42%, CR 39%	6.6 PFS	NA
Tafa-Len[17]	L-MIND (81)	IV- Continuous	ORR 58%, CR 40%	11.6 PFS	NA
≥ 3L					
Tisa-cel[10]	Juliet (165)	IV - Fixed	ORR 52%, CR 40%	3.5 PFS	CRS: 22%, ICANS 12%
Axi-cel[18]	Zuma-1 (111)	IV - Fixed	ORR 82%, CR 54%	5.8 PFS	CRS: 13%, ICANS 28%
Liso-cel[5]	Transcend (269)	IV - Fixed	ORR 73%, CR 53%	6.8 PFS	CRS 2%, ICAN 10%
Glofitamab[2]	NP30179 (154)	IV - Fixed	ORR 52%, CR 39%	4.9 PFS	CRS: 4%, ICANS 3%
Epicoritamab[6]	EPCORE (157)	SC-Continuous	ORR 63%, CR 39%	4.4 PFS	CRS: 2.5%, ICANS 0.6%
Selinexor[19]	SADAL (127)	PO	ORR 28%, CR 12%	3.5 PFS	NA

Table 1. Therapeutic advancements for R/R DLBCL; *courtesy of Mark Bosch, MD.*

Abbreviations: CR: complete response, **CRS:** cytokine release syndrome, **DLBCL:** diffuse large B-cell lymphoma, **EFS:** event-free survival, **ICANS:** immune effector cell-associated neurotoxicity syndrome, **IV:** intravenous; **NA:** not applicable, **ORR:** overall response rate, **PFS:** progression-free survival, **R/R:** relapsed/refractory, **2L:** second line, **3L:** third line

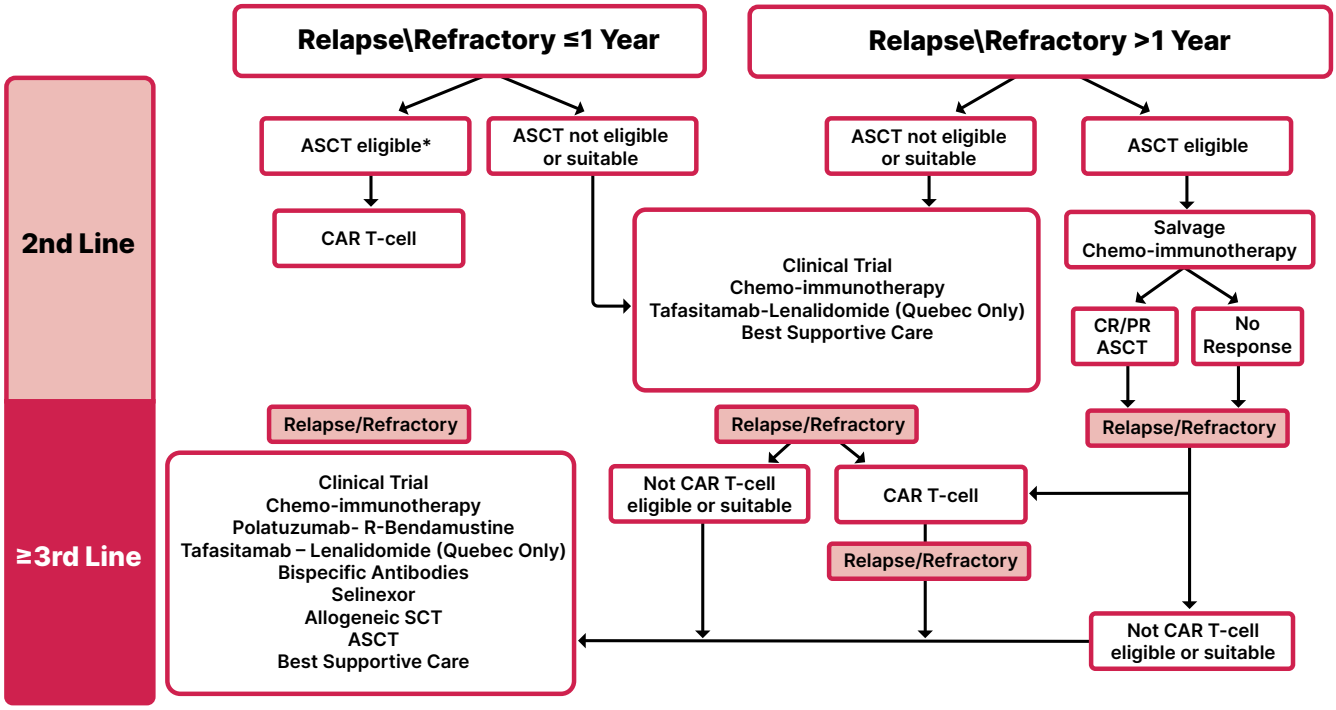


Figure 1. Algorithm for the treatment of patients with relapsed/refractory diffuse large B-cell lymphoma; *adapted from Barca*[20].

*Access to second-line CAR T therapy in Canada is currently limited to patients deemed "transplant-eligible," as per Health Canada's approval and provincial funding. The definition of what constitutes transplant eligibility for patients is recognized as a complex issue.

Abbreviations: ASCT: autologous stem cell transplant, **BiTE:** bispecific T cell engager, **CAR:** chimeric antigen receptor, **CR:** complete response, **PR:** partial response.

funding of the latest treatments. CAR T-cell therapy is approved for second-line treatment and is currently funded in British Columbia, Alberta, Saskatchewan, Ontario, and Quebec, with additional provinces expected to follow in the future.

In addition, further clarity will need to be sought on whether we will have the same access to CAR T-cell therapy in all large B-cell lymphomas (LBCL). For example, LBCL, like Richter's transformation and primary central nervous system (CNS) lymphoma, still does not have the data to support provincial funding. In addition, not all second-line relapses were eligible for CAR T-cell therapy based on trials in the second-line. For instance, the original trials only included those who relapsed within one year from treatment. Whether this strict definition will be adhered to by the provinces and if this will change over time will need to be seen.

Above is an example of an algorithm that could guide treatment (**Figure 1**).

Factors Affecting Treatment Choice:

Various factors must be considered when determining the optimal treatment approach for patients with R/R DLBCL to achieve the best possible outcomes. These factors encompass the specifics of the disease, the patient's health status, and practical considerations that influence the choice between CAR T-cell therapy, bispecific antibodies, and other therapies.

Disease Characteristics:

The specific characteristics of the disease significantly influence treatment choice. Factors such as the stage of the disease, genetic mutations, tumour burden, and the

aggressiveness of the lymphoma play a crucial role in determining the most appropriate treatment strategy. For instance, patients with high tumour burden or aggressive disease may benefit more from the potent and rapid response offered by off-the-shelf products like BiTEs instead of waiting for the lengthy CAR T-cell assessment, collection, manufacture, and infusion process.

When treating this disease, it is essential to consider the speed and timing of therapy. For example, initiating CAR T-cell therapy earlier, such as in the second line instead of waiting until the third line, may expand the number of patients benefitting from this curative technology. Treating patients before their disease becomes more aggressive can also be crucial, as aggressive disease may cause patients to lose eligibility to receive their CAR T-cell infusion.

Treatment Characteristics:

Apart from disease characteristics, changes in how patients have been treated in the past are increasingly showing significant impacts on outcomes, especially in the context of immunotherapies. Previously, the number of cycles and lines of chemotherapy used could affect the patient's ability to gather stem cells. In current practice, there is much greater concern about the specific type of chemotherapy that patients may have been exposed to before cellular therapy. Current literature indicates that bendamustine impacts the quality of the cell manufacturing.[15] These data also suggest that using bendamustine up to nine months before collection produces a lower overall response rate ([ORR], 53% vs. 72%; P <0.01) and overall survival ([OS], 10.3 vs. 23.5 months; P = 0.01) in comparison with the bendamustine-naïve group.[15]

Patient-Specific Factors:

Considering the patient's characteristics and health status is crucial when selecting the proper treatment. Factors such as biological age, performance status, presence of comorbidities, and overall health condition play a significant role in determining the suitability of CAR T-cell or BiTE therapy. Younger patients with good performance status and fewer comorbidities may be better candidates for the potentially more intensive and personalized approach of CAR T-cell therapy. In contrast, older patients or those with significant comorbidities may benefit more from the targeted and potentially less toxic nature of off-the-shelf bispecific antibodies. Further data will be needed to delineate this. Our ability to manage side effects of interest, such as CRS and ICANS, will play a significant role in determining who are considered to qualify for these therapies. The exact specifics remain unknown; however, this will evolve with time.

Prioritizing Treatment Goals and Preferences:

When deciding between CAR T-cell therapy, BiTEs, or other therapies, it is crucial to grasp the patient's treatment goals, preferences, and expectations. Some patients may prioritize achieving a swift and profound response to treatment, even if it entails a higher risk of side effects, favouring CAR T-cell therapy. Others may prioritize a more targeted and potentially less toxic approach, favouring bispecific antibodies. Additionally, in a large geographic area, some patients may prefer to stay in their home setting and opt for treatments that may not be considered the standard of care, presenting unique challenges. Engaging patients in shared decision-making and considering their preferences can assist in customizing the treatment approach to align with their objectives and values.

Availability and Cost Considerations:

Practical and financial considerations, such as the availability of CAR T-cell or BiTE therapy in a given healthcare setting, can impact treatment choice. For example, CAR T-cell therapy may have limited availability in certain regions or healthcare facilities, making it necessary to explore alternative options like BiTEs. Additionally, the cost of treatment, including the price of the therapy itself, supportive care, and monitoring, can influence decision-making, especially in settings where cost-effectiveness is a significant concern.

It is also essential to consider the cost of these therapies in a clinical context. For instance, CDA has determined the incremental cost-effectiveness ratio (ICER) for Axi-Cel, a CAR T-cell therapy in the second line, is $404,418 per quality-adjusted life year (QALY) compared with the standard of care. At the same time, the ICER for the BiTE glofitamab is $230,682 per QALY gained compared to salvage chemotherapy. Clearly, these new therapies come with substantial costs.

Conclusion

In conclusion, the decision-making process regarding choosing CAR T-cell or BiTE therapy involves a comprehensive assessment that considers disease characteristics, patient-specific factors, treatment goals and preferences, and availability and cost considerations. This multifaceted approach aims to provide patients with the most suitable and effective treatment while considering their circumstances. With more significant data, regulatory approvals, and experience, a new paradigm will be unlocked for relapsed patients who were once difficult to treat and cure.

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Financial Disclosures

None declared.

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doi.org/10.58931/cht.2024.3360

Minimal Residual Disease in Myeloma in 2024: Where We are Today

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Introduction

Minimal residual disease (MRD) refers to a small population of cancer cells that persists in the body after treatment. Often undetectable using traditional diagnostic methods, these cells can eventually cause relapse in patients who appear to have achieved a complete response (CR) to treatment. For that reason, MRD has become a vital parameter in evaluating the effectiveness of cancer therapies, particularly in hematological malignancies, such as multiple myeloma (MM), and certain solid tumours.[1,2]

Detection of MRD represents a challenge, as the disease may not cause symptoms or be detected through traditional methods (i.e., visible under a microscope). Nevertheless, these cells are often responsible for disease relapse; alternatively, sustained absence of these cells may portend a prolonged remission and presumably be required for disease cure. Therefore, monitoring and detecting MRD are increasingly recognized as essential for long-term patient care and treatment planning.[3,4]

Importance of MRD Detection and Monitoring

MRD detection and monitoring play a critical role in the following:

- **Assessing the depth of treatment response:** by measuring how much residual disease remains after treatment, physicians can gauge the true effectiveness of therapy.
- **Predicting relapse:** MRD-positive patients are at a higher risk of relapse. Continuous monitoring can help identify early signs of recurrence, even before clinical symptoms arise.
- **Tailoring treatment plans:** MRD detection allows personalized treatment approaches, such as intensifying or de-escalating therapy based on a patient's MRD status.

In the realm of MM, achieving MRD-negative status—meaning no residual disease is detected—is increasingly viewed as the gold standard for treatment success. The absence of detectable MRD correlates strongly with improved outcomes, such as progression-free survival (PFS) and overall survival (OS).[3-6]

Methods for Detecting MRD

Several advanced techniques have been developed for detecting MRD, each offering varying degrees of sensitivity and specificity:

1. ***Real-time quantitative polymerase chain reaction (RQ-PCR):*** this method detects residual disease by measuring specific genetic abnormalities, such as fusion genes, overexpressed genes, or mutations, that are unique to cancer cells. Although highly sensitive, it is limited by the requirement for specific primers and probes designed to target individual tumour characteristics.[2,7,8]

2. ***Multiparametric flow cytometry (MFC):*** this approach uses antibodies tagged with fluorescent markers to identify cancer cells based on their surface proteins. A laser beam analyzes these cells, making it possible to detect multiple markers simultaneously. MFC can detect one cancer cell among 10,000 to 100,000 normal cells (10^{-4} to 10^{-5} sensitivity), and a more advanced version, next-generation flow cytometry (NGF), offers even higher sensitivity.[2,4,9]

3. ***Next-generation sequencing (NGS):*** NGS examines thousands of genes simultaneously to detect residual disease with extremely high sensitivity (10^{-6} to 10^{-7}). This method is highly specific and has been increasingly adopted for monitoring MRD in various cancers, including MM.[2,10]

MRD in MM

MM is a cancer of plasma cells that primarily affects the bone marrow. MRD testing has become critical in evaluating treatment outcomes in MM, especially as newer therapies result in deeper responses. Traditionally, treatment responses in MM were measured by evaluating monoclonal protein levels in the blood and urine or assessing bone marrow plasma cell involvement. However, the introduction of highly effective agents like proteasome inhibitors, immunomodulatory drugs, and monoclonal antibodies has increased the frequency of CRs, necessitating more sensitive methods to track MRD.[1,2]

Therapeutic Advances and MRD in MM

Over the last two decades, MM treatment has significantly advanced with the approval of drugs like:

- **Proteasome inhibitors** (e.g., bortezomib, carfilzomib, ixazomib)
- **Immunomodulatory drugs** (e.g., lenalidomide, pomalidomide)
- **Monoclonal antibodies** (e.g., daratumumab, isatuximab)

The use of daratumumab combined with carfilzomib, lenalidomide, and dexamethasone (Dara-KRd) has led to deeper treatment responses, with CR rates as high as 95% in newly diagnosed patients.[11]

The increasing depth of response induced by these novel therapies has made MRD testing more crucial than ever for determining long-term outcomes. Studies have demonstrated that MRD-negative patients have significantly longer PFS and OS compared to those who remain MRD-positive, even if they achieve CR by conventional measures.[3,4]

MRD Testing: NGF vs. NGS

In MM, MRD-negative status is defined by the absence of detectable cancer cells, typically using highly sensitive methods such as Next-Generation Flow Cytometry (NGF) or NGS (**Table 1**).

1. ***NGF:*** This method is capable of detecting MRD with a sensitivity of 10^-6 and is increasingly used in clinical practice to monitor residual disease in patients with MM. NGF does not require a baseline sample, making it particularly useful in clinical settings.

2. ***NGS:*** This method uses primers to amplify immunoglobulin gene segments, allowing for the detection of clonal plasma cells with high sensitivity. NGS requires a baseline sample to track the cancer clone but offers superior sensitivity, detecting one cancer cell among a million normal cells (10^{-6} to 10^{-7}).

Studies have shown high concordance between NGF and NGS, with both methods yielding similar results in over 80% of cases. However, NGS requires a baseline sample, while NGF does not, giving each method certain advantages depending on the clinical scenario. MRD detection methods like NGS and NGF are proving to be highly predictive of long-term patient outcomes, particularly in patients with newly diagnosed MM.[9,10,12]

MRD and Patient Prognosis

MRD status has become a key factor in determining patient prognosis in MM. For example, a recent meta-analysis of clinical trials demonstrated that MRD-negative status was associated with:

- A hazard ratio (HR) of 0.33 for PFS, meaning MRD-negative patients had a 67% lower risk of disease progression or death compared to MRD-positive patients.[3]
- An HR of 0.45 for OS, meaning patients with MRD-negative disease had a 55% lower risk of death compared to MRD-positive patients.[13]

These findings apply across various subgroups, including patients with high-risk disease or those with relapsed MM.

	Next-generation flow cytometry (NGF)	Next-generation sequencing (NGS)
Reproducibility among centers	High	Limited Centers available
Baseline assessment	Not required	Required
Processing requirements	Fresh Samples <36 h	Fresh and stored samples
Standardization	EuroFlow Consortium	Commercial companies. (Adaptative Biotechnologies)
Quantitative	Yes	Yes
Sensitivity	1 in 10^{-5} -10^{-6}	1 in 10^{-5} -10^{-6}
Time to processing	<24 hours	1–2 weeks
Clonal evolution evaluation	Not evaluable	Evaluable
Cost	300 USD	700–1500 USD

Table 1. Minimal Residual Disease Assessment Techniques; a*dapted from Pavia et al.*[24] *and Mina et al.*[25]

Challenges and Limitations of MRD Testing

While MRD testing offers significant prognostic value, several limitations and challenges remain:

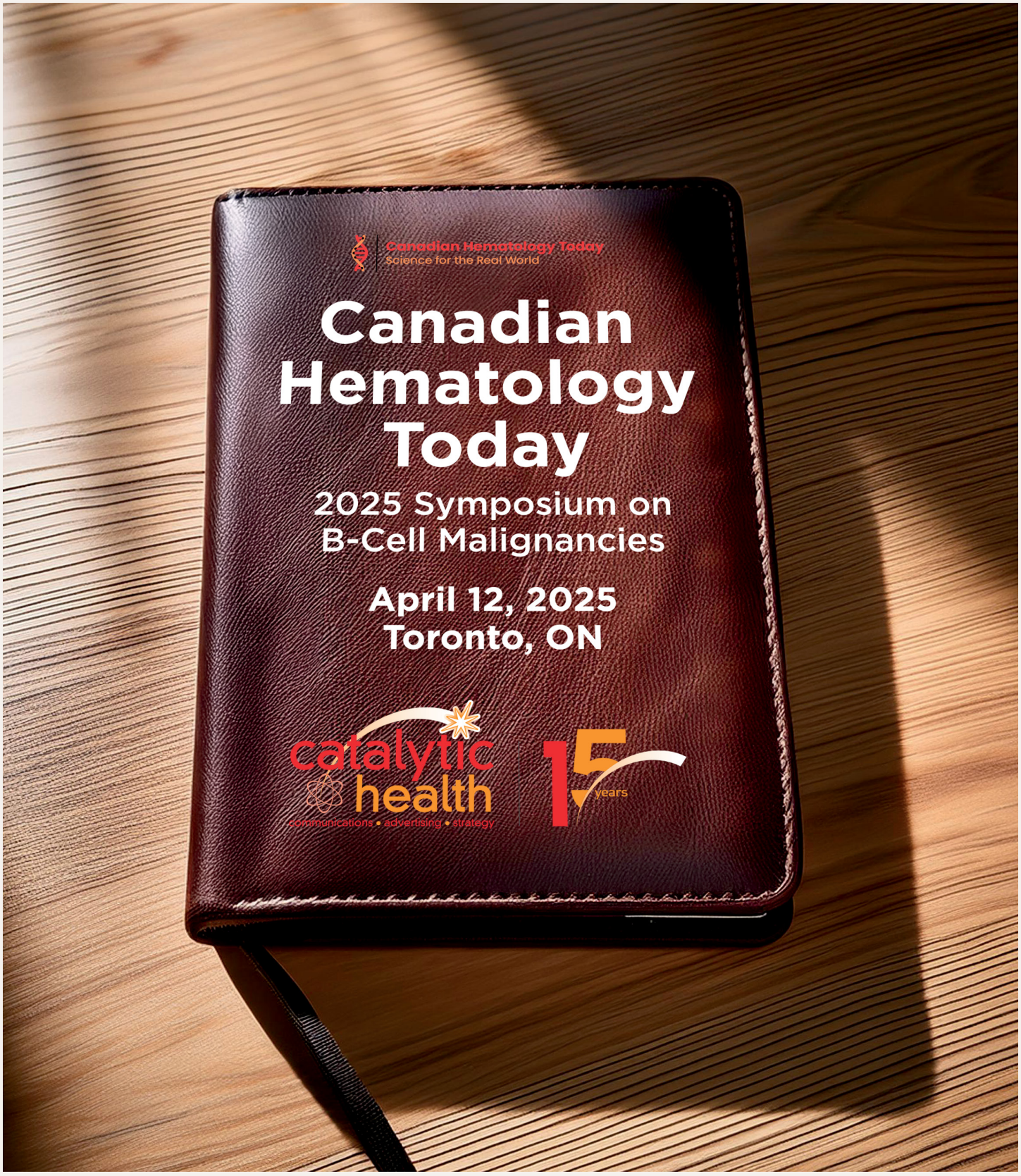
1. ***Bone marrow sampling:*** MRD testing often requires bone marrow aspirates, which can be invasive and painful. Furthermore, bone marrow involvement in MM may not be uniform, leading to variability in MRD test results.[14]

2. ***Extramedullary disease:*** MRD testing primarily focuses on the bone marrow, but MM can present as extramedullary disease (i.e., disease outside the bone marrow). For instance, some patients who are MRD-negative in the bone marrow still show signs of disease in imaging studies, such as positron emission tomography-computed tomography (PET-CT) scans. This discrepancy highlights the importance of using multiple diagnostic modalities to fully assess disease status.[1,14]

3. ***Relapse prediction:*** one of the key advantages of MRD testing is its ability to predict relapse before clinical symptoms appear. Patients who remain MRD-positive after treatment are at higher risk of relapse, often several months before biochemical or clinical indicators emerge. This raises the question of whether early intervention at the point of MRD detection could improve long-term outcomes.[15]

4. ***Liquid biopsies:*** a less invasive alternative to bone marrow sampling is the use of liquid biopsies to detect circulating tumour DNA (ctDNA) or plasma cells in the peripheral blood. While this method is less invasive, its sensitivity is currently lower than that of bone marrow-based tests.[16,17]

5. **Mass spectrometry:** emerging technologies like mass spectrometry are also being explored as potential tools for detecting MRD. Mass spectrometry can measure low levels of monoclonal protein in the blood, and it has shown promise as a highly sensitive technique for identifying residual disease in patients with MM.[18]



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MRD as a Clinical Endpoint and Surrogate Marker

MRD status is increasingly being used as a prognostic tool in clinical trials. Many trials now include MRD as an endpoint, and its presence or absence can help stratify patients based on their risk of relapse and overall prognosis.[19,20] Guidelines from the International Myeloma Working Group (IMWG) recommend a sensitivity threshold of 10^{-5} for MRD testing. Sustained MRD negativity, defined as maintaining MRD-negative status for at least one year, is now considered the optimal endpoint in assessing long-term treatment efficacy.[2]

Several ongoing trials are using MRD to guide treatment decisions, with different strategies under investigation:

1. ***Intensification of therapy:*** some trials are investigating whether intensifying treatment can improve outcomes for patients who remain MRD-positive after initial therapy. The AURIGA trial, for example, is evaluating the role of adding daratumumab to lenalidomide maintenance to deepen responses in patients who remain MRD-positive.[19,21]

2. ***De-escalation of therapy:*** other trials are exploring whether patients who achieve sustained MRD negativity can safely discontinue treatment. For example, the DRAMMATIC trial is investigating whether MRD-negative patients can stop maintenance therapy without compromising outcomes.[22]

3. ***Early treatment of MRD relapse:*** some trials, like the REMNANT study, are investigating whether treating patients at the time of MRD relapse—before biochemical or clinical relapse—can improve long-term outcomes. This approach aims to intervene at the earliest sign of disease recurrence, potentially preventing full clinical relapse.[23]

Conclusion

MRD detection has become an essential tool in the management of MM and other hematological malignancies. The development of sensitive techniques like NGS and NGF has revolutionized our ability to measure disease burden, allowing the detection of even the smallest number of remaining cancer cells. Achieving MRD-negative status is associated with significantly improved outcomes in MM, including longer PFS and OS.

Despite the remarkable advancements in MRD testing, several challenges remain, particularly in detecting extramedullary disease and developing less invasive diagnostic techniques. Nonetheless, the ongoing integration of MRD testing into clinical trials and treatment strategies provides critical insights into disease management, helping tailor therapy to individual patient needs and improve long-term survival.

As MRD testing continues to evolve, it will likely play an increasingly important role in personalized medicine, guiding treatment decisions and helping predict relapse before it occurs. The ultimate goal is to use MRD testing not only as a prognostic tool but also as a guide for real-time treatment modifications, helping to achieve the best possible outcomes for patients with MM.

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Financial Disclosures

A.D.T: Advisory Board: Janssen, Amgen, Forus Therapeutics, Sanofi, Apobiologix, BMS, Incyte, Pfizer
A.R.I: None declared

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Canadian Hematology Today
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VOL. 3
ISSUE 3
Fall 2024

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