VOL. 2
ISSUE 3
2023

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

CANADIAN HEMATOLOGY TODAY

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

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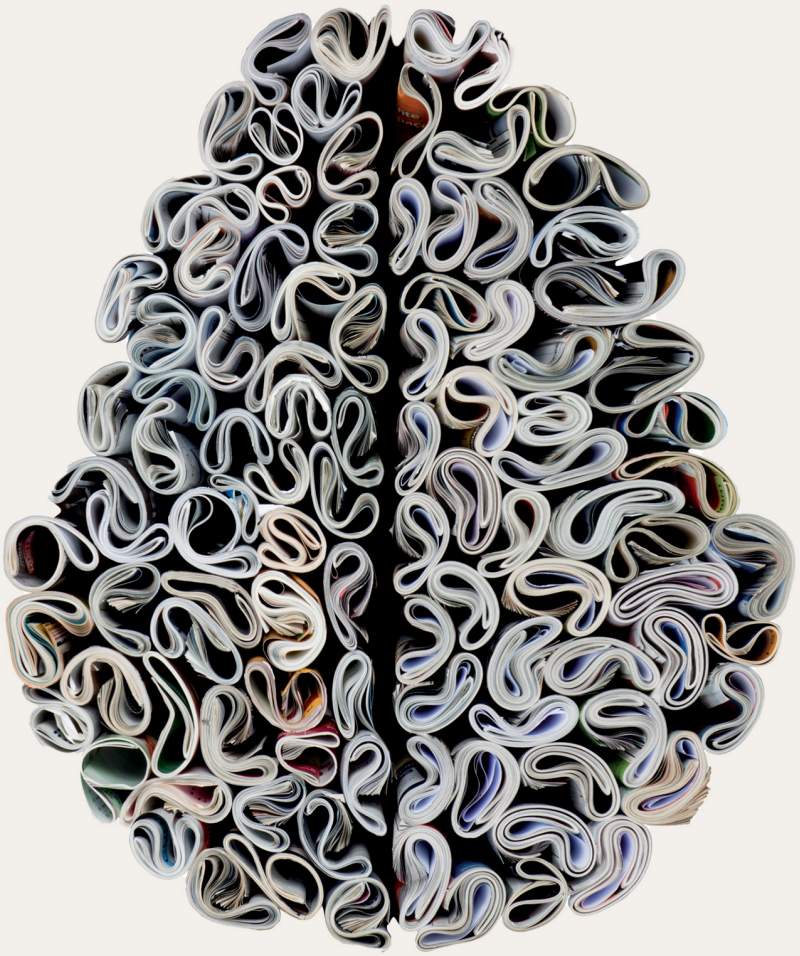
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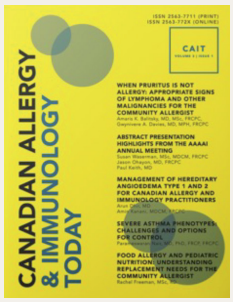
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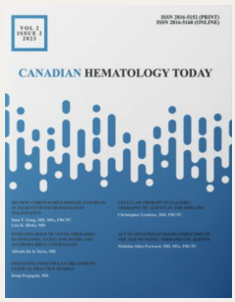




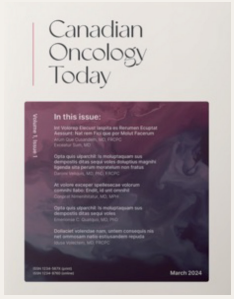


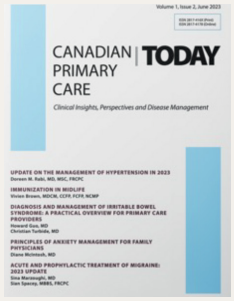




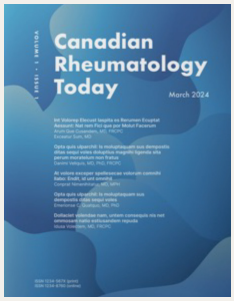


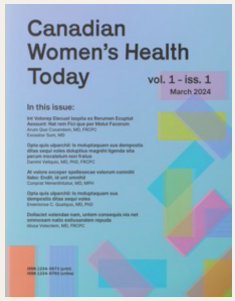












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BISPECIFIC ANTIBODIES AND CHIMERIC ANTIGEN RECEPTOR (CAR) T-CELL THERAPY FOR INDOLENT LYMPHOMA

Introduction

Classic follicular (FL) and marginal zone (MZL) lymphomas are the primary indolent non-Hodgkin lymphomas (iNHL). Once first-line therapy is initiated, the majority of patients eventually experience treatment failure and face progressively shorter disease-free periods following subsequent lines of conventional chemotherapy.[1] Patients with progressive disease within 24 months of first-line therapy (POD24) represent a significant unmet need. The five-year overall survival (OS) for patients with FL and POD24 is only 50% vs 90% for those without POD24.[2] The three-year OS for patients with MZL is 53% and 95% respectively.[3]

Chimeric antigen receptor T cells (CAR-T) and bispecific T-cell engagers (BiTEs) are designed to improve patients' outcome by redirecting their polyclonal T cells against a lymphoma-associated antigen, independently of the major histocompatibility complex. Multicenter Phase II trials with CAR-T and BiTEs in patients with relapse/refractory (R/R) FL and MZL have been published. Key results are summarized in **Table 1**.

CAR-T cells

CAR-T cells are engineered ex vivo to gain a chimeric receptor generated by fusing a single-chain variable fragment derived from a monoclonal antibody, a hinge region, a transmembrane section, and an intracellular domain combining T cell activating and co-stimulatory features.[4] Most CAR-T cells studied in iNHL target CD19 and have one co-stimulatory domain, either CD28 or 4-1BB, and are therefore known as second-generation CAR-T. CD28 and 4-1BB exhibit distinct properties and a distinct toxicity profile.

The manufacturing process involves local non-mobilized leukapheresis and central manufacturing. Following viral transduction, expansion and quality control procedures, cryopreserved CAR-T cells are returned. Bridging therapy (BT) may be needed to facilitate the manufacturing time and may influence CAR-T cell therapy efficacy.[5] Lymphodepleting therapy (LT) precedes CAR-T infusion and contributes to CAR-T expansion and persistence.[5] Three days of fludarabine and cyclophosphamide is the preferred LT regimen over a bendamustine alternative.

CAR-T cells are infused in specialized centres that handle typical early CAR T-related toxicities, namely cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS).[6] Although largely reversible, these syndromes may be severe and fatal, and mandate timely management based on clinical evaluation. CRS presents with fever and constitutional symptoms and may be associated with varying intensities of organ failure. ICANS typically presents with aphasia, impaired fine motor skills and/or reduced level of awareness and may rarely culminate in seizures and/or cerebral edema. CRS and ICANS result from the activation of CAR-T, in addition to bystander immune and nonimmune cells. CAR-T may also be associated with hemophagocytic lymphohistiocytosis-like syndromes.[7]

Hypogammaglobulinemia related to CD19 off-tumor effect and myelosuppression of unpredictable duration may occur. Myelosuppression recovery is expected, but underlying differential diagnosis includes myelodysplastic syndrome.

Nonetheless, we learned from real-world reports in large B-cell lymphoma that CAR-T cell therapy can be safely administered to a broad range of patients with preserved efficacy, including some patients deemed ineligible for the pivotal trial and/or unfit for high-dose chemotherapy and autologous stem cell transplant (HDT-ASCT), but with preserved performance status and no significant organ dysfunction.

Axicabtagene ciloleucel (axi-cel) is a CD28-based CAR-T studied in the ZUMA-5 trial that led to its approval by the FDA.[8] A total of 181 patients with R/R FL and MZL after at least two lines of therapy (LoT), including an anti-CD20 combined with an alkylating agent or with high-risk features were screened; 153 were leukapheresed and 148 were infused. No manufacturing failure occurred. Median time from leukapheresis to axi-cel delivery was 17 days (interquartile range [IQR]: 16–20). Four patients with FL and two with MZL received BT. Hospitalization for seven days following infusion was mandatory. The updated overall response rate (ORR) was 90% and the complete remission rate (CRR) was 75%.[9] Median progression-free survival (PFS) was 40 months and three-year PFS was 54%. CAR-T expansion appeared slightly higher in patients with MZL although outcomes seemed similar with three-year PFS of 56% in patients with MZL and 54% with FL. Outcomes of patients with POD24 were better than expected with a three-year PFS of 59% among patients with POD24 vs 52% without POD24.

Tisagenlecleucel (tisa-cel) is a 4-1BB-based CAR-T cell therapy evaluated in the ELARA trial that led to its approval by the FDA.[10] A total of 119 patients with R/R FL following at least two LoT including an anti-CD20 combined with an alkylating agent, with relapse within six months of second or later LoT or with R/R FL after HDT-ASCT were screened; 98 were enrolled and 97 were infused. Four patients received a lower dose and two received an out-of-specification CAR-T infusion (one low cell viability and one higher cell count). Time from leukapheresis to

infusion was not reported and median time from enrollment to infusion was 46 days (IQR: 38–57); 45% received BT. At the investigator's discretion, 18% of the patients were managed as outpatients and one-third did not require hospitalization. The Independent Review Committee assessed a CRR by independent review (CRRi) of 68% and an objective response rate (ORRi) of 86%.[11] CRR was 59% for patients with POD24. Two-year PFS reached 57%. High tumor burden as measured by the metabolic tumor volume (MTV) was associated with significantly shorter PFS.

Lisocabtagene maraleucel (liso-cel) is a 4-1BB-based CAR-T and is infused in a fixed 1:1 ratio of CD4:CD8. It was studied in patients with R/R FL and MZL in the TRANSCEND-FL trial. In the efficacy set including patients with R/R FL after at least two LoT, 114 patients were leukapheresed, 107 infused and 101 evaluable.[12] Four were excluded due to non-conforming product; 41% received BT. Primary analysis of the efficacy set reports a 97% ORRi, a 94% CRRi, and a 12-month PFS of 81%.

Bispecific T-cell engagers (BiTEs)

BiTEs are recombinant proteins designed to bind simultaneously to T cells and a malignant antigen. They force an immune synapse triggering cell-mediated cytotoxicity. BiTEs with the most mature data in iNHL target CD3 on T cells and CD20 on B cells. They use a full-length IgG-like structure allowing for intermittent dosing. CRS mitigation strategies with an initial step-up dosing and corticosteroid premedication led to a significant reduction in incidence and severity of CRS and neurotoxicity vs CAR-T cell therapy.

Mosunetuzumab was studied in a Phase II trial that led to its approval by the FDA.[13] A total of 90 patients with R/R FL after at least two LoT including an anti-CD20 combined with an alkylating agent received mosunetuzumab intravenously. Dosing was every week (qw) for the first 21-day cycle without mandatory hospitalization and then q3w. Patients with a complete response (CR) at cycle 8 ended their treatment, whereas patients with partial response or stable disease were able to complete 17 cycles. The best ORRi was 80% with a 60% CRRi.[14] Patients with POD24 had an 85% ORRi and a 57% CRRi. The two-year duration of CR was 63% and the two-year PFS was 48%. The median PFS with mosunetuzumab was 24 months whereas it was only 12 months with the last prior therapy. No association between the timing of the first CR and the duration of the response was observed. Two patients discontinued therapy due to related toxicities. Grade ≥2 CRS was greater in patients with bone/bone marrow metabolic disease burden, occurring in 33.3% of patients vs 13.8% if there was no involvement. No correlation was observed between the occurrence of CRS and tumor response. Tumor burden, as measured by the total MTV, did not correlate with response, a finding typically associated with a poorer response rate to CAR-T cell therapy.[15]

Odronextamab was evaluated in the Phase I trial ELM-1 in R/R B-cell NHL.[16] Patients with R/R FL received odronextamab intravenously. CRR was 72% among the 32 patients who received the active dose of odronextamab, with an estimated probability of maintained CR at four years of 54%. The Phase II ELM-2 trial evaluated patients with R/R FL[17] after at least two LoT including an anti-CD20 combined with an alkylating agent. Following the first cycle step-up, odronextamab was dosed qw for the subsequent three 21-day cycles and thereafter q2w until disease progression or significant toxicity. An inpatient 24-hour monitoring period was mandatory after each dosing of cycle 1 and after day 1 of cycle 2. A prespecified analysis of 121 patients reported an 82% ORRi, the primary endpoint, and a 75% CRRi. Median duration of CR was 20.5 months. Ten patients discontinued odronextamab due to related toxicities.

Epcoritamab evidence of single-agent efficacy was observed in 10 patients with R/R FL in the EPCORE NHL-1 trial with a 90% ORR and a 50% CRR.[18] Epcoritamab was administered subcutaneously. Epcoritamab was further evaluated in combination with rituximab and lenalidomide (R2) in patients with R/R FL after at least one LoT in the Phase I/II EPCORE NHL-2 trial.[19] Arm 2a dosed epcoritamab qw in the first three 28 days cycles, then q2w for six cycles and q4w thereafter for a total duration of two years. Arm 2b dosed epcoritamab qw in the first two 28 days cycles then q4w for a total duration of two years. Hospitalization for 24 hours after a full dose at day 15 cycle 1 was mandatory. The primary objective was safety and antitumor activity. The median number of prior LoT was one (range: 1–7). The ORR was 98% with 87% CR in the 104 evaluable patients. This was substantially improved compared to the 85% ORR and 58% CR with immediate prior therapy. Among POD24, the ORR was 98% and the CRR was 75%. The nine-month PFS was 85%. The safety cohort included 111 patients. The incidence of CRS was 48% with only 2% grade 3 and the peak onset was at day 15 cycle 1, corresponding to the first full dose.

Glofitamab is a BiTE unique in its bivalent binding to CD20 and is administered as one infusion of the anti-CD20 obinutuzumab one week prior to initiating BiTE infusion as a CRS mitigation strategy. It is administered intravenously for a fixed duration for up to twelve 21 day cycles. In the Phase I study of 171 R/R B-cell NHL, glofitamab achieved an ORR of 71%, a CR of 48% and a median PFS of 11.8 months in 44 patients with R/R FL.[20]

CAR-T or BiTE?

Retrospective analysis comparing CAR-T cell therapy and BiTE with conventional chemotherapies suggest improvement in PFS and/or OS.[14,21,22]Access, toxicities, sequencing and the financial burden of these novel immunotherapies represent their main challenges. CAR-T cell therapies are logistically more complex than BiTEs and are offered only in limited centres throughout Canada, involving travel considerations for patients and their caregiver(s). Patients in need of rapid treatment initiation may achieve more timely benefit from BiTEs as their toxicity mitigation

	CAR T			BiTE		
	Axicabtagene ciloleucel[8,9]	Tisagenlecleucel[10,11]	Lisocabtagene maraleucel[12]	Mosunetuzumab[13,14]	Odronextamab[17]	Epcoritamab + R2[19]
	CD28	4-1BB	4-1BB	IV fixed-duration C1: qw C2-17: q3w 21d cycle	IV indefinite C1: step-up C2-4: qw 21d cycle C≥5 : q2w 14d cycle	SC fixed-duration 2 arms 28d cycle 2 years total
Pivotal trial	ZUMA-5 NCT03105336	ELARA NCT03568461	TRANSCEND FL NCT04245839	NCT02500407	ELM-2 NCT03888105	EPCORE NHL-2 NCT04663347
Histology	FL and MZL	FL	FL and MZL	FL	FL	FL
N	Efficacy: 127 FL 31 MZL Safety: 124 FL 28 MZL	Efficacy: 94 Safety: 97	FL cohort: Efficacy: 101 Safety: 130	90	Efficacy: 121 Safety: 131	Efficacy: 104 Safety: 111
POD24	81/148 (55%)	61/97 (63%)	58/107 (54%)	47/90 (52%)	60/121 (50%)	42/111 (38%)
Median follow up (m)	40.5	28.9	17.5 for PFS	28.3	22.4	11.4
ORR	90% (94% FL/77% MZL)	86%	97%	80%	82%	98%
CR	75% (79% FL/65% MZL)	68%	94%	60%	75%	87%
PFS	3y PFS 54% FL/56% MZL	2 y PFS 57%	1y PFS 81%	2y PFS 48%	18-month PFS 55%	9-month PFS 85%
OS	3y OS 76% FL/74% MZL	2 y OS 88%	Not reported	2y OS 87%	18-month OS 76%	-
All grade CRS	82% (78% FL/100% MZL)	49%	58%	44%	57%	48%
Grade 3+ CRS	7% (6% FL/8% MZL)	0	1%	2%	2%	2%
All grade ICANS	59% (56% FL/71% MZL)	4%	15%	3%	None with optimized step-up dosing	2%
Grade 3+ ICANS	19% (15% FL/38% MZL)	1%	2%	None	None	None
Infections grade ≥ 3	18%	9%	5%	14%	32%	-
Treatment related mortality (n)	1	None	2	None	3	4

Table 1. *Summary of pivotal Phase II trials of chimeric antigen receptor T cell (CAR T) and bispecific T cell engagers (BiTE) for refractory or relapsing follicular (FL) and marginal zone (MZL) lymphomas, with no direct cross-trial comparison; courtesy of Isabelle Fleury, MD and Eva Laverdure, MD.*
C: Cycle, ***d:*** Days, ***IV:*** Intravenous, ***m:*** months, ***POD24:*** Progression within 24 months of first-line therapy, ***SC:*** Subcutaneous, ***qw:*** Every week.

strategies allow greater availability across Canada in cancer centres in which CRS and ICANS management algorithms are implemented. CAR-T cell therapy, however, offers the opportunity for a single-dose therapy with less care time required, and prolonged remission.

As per the Health Canada product monographs, both axi-cel and tisa-cel are indicated for patients with R/R grade 1–3a FL after at least 2 LoT.[23,24] At the time of writing, Canadian Agency for Drugs and Technologies in Health (CADTH) has published its recommendation to support Canadian access to tisa-cel in this setting and to draft a report to support access to axi-cel as well. Evaluation by Institut national d'excellence en santé et services sociaux (INESSS) for Quebec has not yet been published and access is still, however, pending. Health Canada approval for liso-cel and BiTEs for R/R are not yet available.

The most favourable sequence for recruiting patients' T cells through CAR-T cell therapy or BiTE along the patient's journey has yet to be defined. From large B cell and mantle cell lymphoma studies, we know that BiTE therapy has demonstrated efficacy irrespective of prior CAR T-cell therapy exposure and response, and that recent exposure to bendamustine may hamper CAR-T cell therapy efficacy.[25,26] Data on BiTE rechallenge after response loss will also contribute to guiding our therapeutic choice.

Both CAR-T and BiTE are being evaluated in combination with other agents and are being studied in earlier LoT. Clinical studies with new BiTE and immune effector cells are also ongoing. The design of these trials and the better understanding of the resistance mechanism will be paramount in optimizing their use.

CAR-T and BiTE have launched a new era for patients with R/R FL and MZL with a rapidly evolving treatment landscape and a promising future for patients in Canada.

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Financial Disclosures:

I.F.: Advisory board and conference: Abbvie, BMS, Kite-Gilead, Novartis, and Roche.

E.L.: None declared

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THE ROLE OF FDG-PET SCANNING AND PET-ADAPTED THERAPY IN THE PRIMARY TREATMENT OF HODGKIN LYMPHOMA: A PRIMER FOR CLINICIANS

Introduction

The evolving treatment paradigm for classical Hodgkin lymphoma (cHL) remains focused on maintaining high rates of progression-free survival (PFS) and overall survival (OS), while seeking to reduce both short-term and late toxicities from chemotherapy and radiation. Functional imaging with fluoro-deoxyglucose (FDG)-positron emission tomography (PET) combined with computed tomography (CT) is recognized as standard for staging and response evaluation of Hodgkin lymphoma (HL).[1,2] Recent randomized controlled trials evaluating FDG-PET-guided therapy for patients with limited stage and advanced stage Hodgkin lymphoma provide clinicians and patients with meaningful data upon which to base individualized treatment approaches.[3-9] FDG-PET scanning after two cycles of therapy (interim PET or PET2) represents the most important determinant of further appropriate treatment and subsequent outcomes, and is now the cornerstone of risk-adapted therapy for all patients receiving curative-intent initial therapy for Hodgkin lymphoma. For patients with limited stage cHL, post-chemotherapy assessment (after two or four cycles of treatment depending on the regimen used) is also a key determinant of the need for the addition of involved site or nodal radiation as part of combined modality therapy. This review summarizes the important role of interim and end of chemotherapy FDG-PET scanning to guide individualized initial therapy for patients to achieve optimal treatment outcomes.

FDG-PET CT scanning has an established role in the staging of patients with Hodgkin lymphoma prior to therapy. It is more accurate than cross-sectional imaging with contrast CT scanning[1] and has a high positive and negative predictive value for the presence of bone marrow involvement. This renders bone marrow biopsy unnecessary as part of baseline staging,[10,11] other than in cases of unexplained cytopenias without specific uptake on PET scan.

Total metabolic tumour volume (TMTV) at baseline provides an accurate measure of overall tumour burden and has been shown to be prognostic in early stage HL, with patients having greater TMTV experiencing worse PFS.[12,13] Baseline PET scanning also greatly facilitates the interpretation of interim and end-of-treatment scans used for clinical decision-making as described below and should be standard for all patients with cHL.

Clinical tools such as the international prognostic score (IPS) and baseline serum thymus and activation-regulated chemokine/CCL17 (TARC) levels provide information regarding prognosis with currently available chemotherapy regimens for the treatment of cHL.[14,15] Efforts to improve our ability to identify patients at diagnosis who have a high risk of treatment failure, such as by gene expression profiling of tumour samples, have yet to reliably define

a group of patients who would benefit from treatment intensification vs those who can be prescribed standard or reduced intensity therapy.[16,17] Evaluation of circulating tumour DNA together with FDG-PET scanning appears to hold promise as part of early response assessment but is beyond the scope of this review.

Interim and End-of-Treatment PET Scanning in Early Stage cHL

Early favourable

Initial observations of the poor prognosis associated with a persistent positive PET scan after two cycles of ABVD and the desire to reduce the need for local radiotherapy for patients with limited stage HL led to three landmark prospective randomized clinical trials (RCTs) based on interim PET assessment. In all three trials (**Figure 1**)—the UK-NCRI RAPID study,[3] EORTC/LYSA/FIL H10[5] and the GHSG HD16[8] trials—patients with a negative PET2 scan who had omission of end-of-treatment radiation had inferior PFS vs those treated with involved field radiation therapy (IFRT) or involved node radiation therapy (INRT). Omission of radiation in the per protocol analysis populations showed a reduction in PFS between 7% and 12%, although no OS difference has been reported in these studies. The largest reduction in PFS was observed in patients with early favourable HL enrolled in H10, where five-year PFS was 87.1% without INRT vs 99% for patients receiving radiation.[5] These data allow individualized treatment decisions, tailoring duration of chemotherapy and inclusion or omission of radiation, depending on individual circumstances. For example, it is appropriate to avoid extended field radiation therapy (EFRT) or IFRT for presentations involving the axilla, infraclavicular fossa and mediastinum in young women with cHL to reduce the excess breast cancer risk in this population, or if the potential cardiac dose would be high. Conversely, when the risk of secondary breast cancer is low (women over the age of 35 to 40 years[18] and in other circumstances where secondary cardiovascular or cancer risks are lower, and risk of

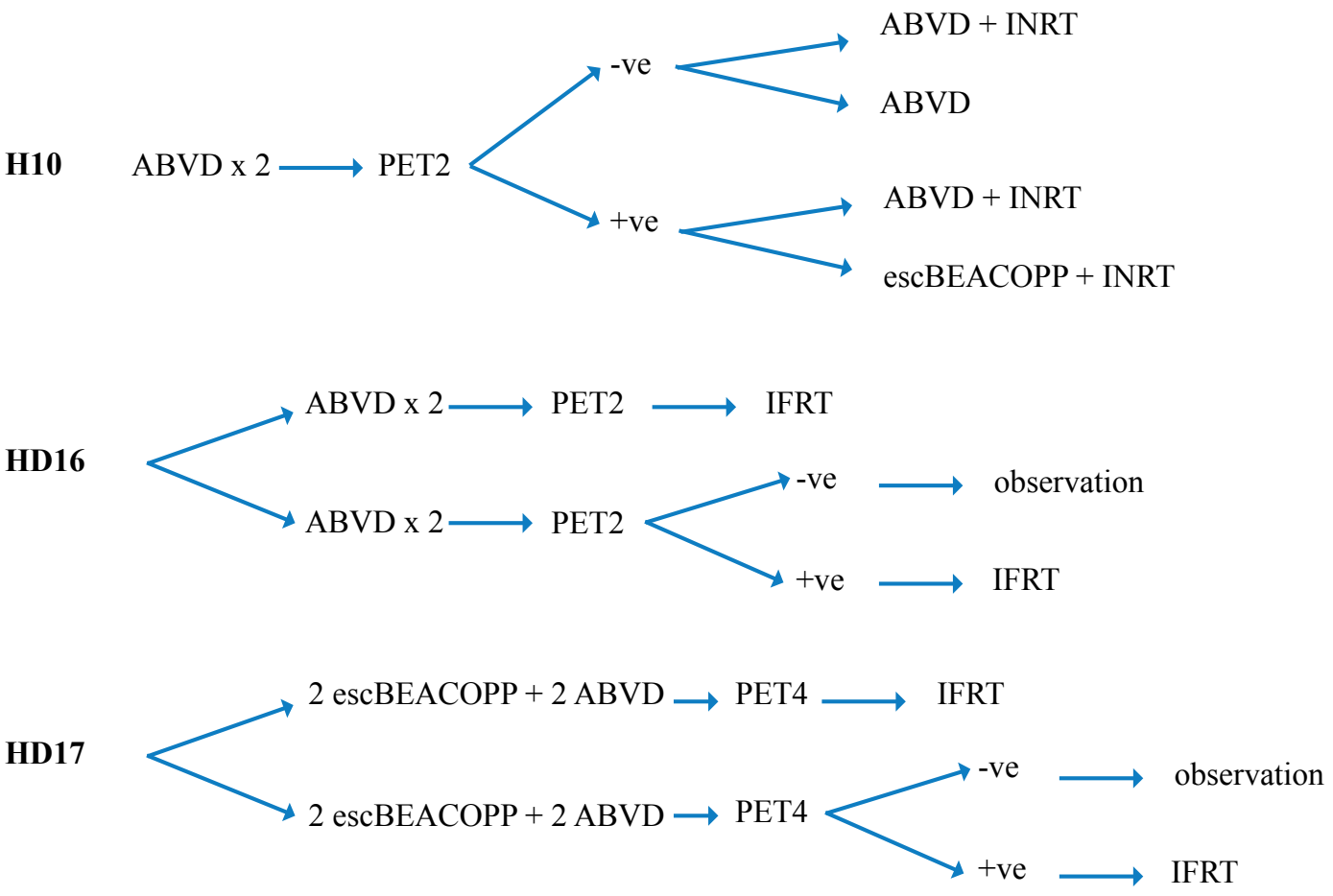


Figure 1. *Recent FDG-PET-adapted trials in early stage HL: H10 depicts the per-protocol analysis of patients with early favourable or unfavourable HL and negative PET2 after two cycles ABVD; and the combined analysis of patients in both subgroups with positive PET2; HD16 and HD17 compared outcomes of PET-adapted omission of IFRT for patients with a negative end-of-treatment PET scan after two (early favourable patients) or four (early unfavourable patients) cycles of chemotherapy vs standard CMT; per protocol analyses compared outcomes for patients with negative PET scans with or without radiation; courtesy of Michael Crump, MD, FRCPC.*
INRT: *involved nodal radiation;* ***IFRT:*** *involved field radiation.*

treatment failure is higher (e.g., women or men over age 50), radiotherapy should be included to provide optimal PFS.

For the 15% to 20% of patients with Stage I-II cHL treated with ABVD who have a positive interim PET scan, intensification of treatment with two cycles of escalated BEACOPP followed by INRT is considered standard based on the significant PFS and possible OS benefit demonstrated in EORTC H10.[5] To date, this is the only patient subgroup in which therapy escalation has been shown to improve outcomes in a randomized trial. Furthermore, it established this as an important consideration for all patients with a positive PET2 not already receiving intensive induction therapy such as escBEACOPP.

Early unfavourable (early stage intermediate)

Prior to the routine use of PET guided therapy, standard approaches for patients with Stage I-II HL and risk factors (**Table 1**), based on RCTs, included four cycles of ABVD and 30 Gray IFRT, or two cycles of escalated BEACOPP followed by two cycles of ABVD (2+2) with IFRT.[19,20] The PFS advantage for the latter strategy in the GHSG HD14 trial, compared to four cycles of ABVD, was approximately 7%, with no demonstrated difference in OS. To identify whether or not IFRT could be safely omitted, the GHSG conducted HD17, randomizing patients to either a standard approach (2+2 followed by radiation) or a PET-adapted approach where patients with a negative PET scan following completion of chemotherapy (PET4) were observed without radiation, and those positive PET scan (Deauville score 4) completed IFRT (**Figure 1**). PFS was 97% at five years in the standard combined-modality treatment arm and 95% in the PET-guided arm, meeting the study's non-inferiority endpoint.[6] PFS among patients with a negative end-of-treatment (EOT) (PET4) scan was 97.7% and 95.9%, respectively. For those with a positive PET4 scan (Deauville score 4), five-year PFS was only 81.6% with the inclusion of IFRT. However, the overall treatment results were excellent with the standard combined modality therapy (CMT) or PET-guided approaches, with a 5-year OS of 98.8% among the patients in the per protocol analysis and 98.6% in the intention to treat (ITT) population.

EORTC favourable*	GHSG favourable*
No large mediastinal adenopathy (MTR <0.35)	No large mediastinal adenopathy (MTR <0.33)
ESR <50 (or <30 with B symptoms)	ESR <50 (or <30 with B symptoms)
Age <50	No extranodal disease
1–3 lymph node sites involved	1–2 lymph node sites involved

Table 1. *Prognostic factors in Stage I and II Hodgkin lymphoma; courtesy of Michael Crump, MD, FRCPC.*
** Presence of any one of these factors designates the presentation as early unfavourable with regard to treatment planning*
EORTC: *European Organization for Research and Treatment of Cancer;* ***GHSG:*** *German Hodgkin Study Group;* ***MTR:*** *mediastinal thoracic ratio (at T5/6).*

As reported in HD17, chemotherapy dose reductions for acute toxicities occurred in 17% of patients during the escBEACOPP cycles and in 22% of patients during the ABVD cycles.[6] Importantly, only 1% percent of patients in both arms developed a second cancer; however, follow-up for this important outcome is still too short to capture all potential events.

When a more intensive induction chemotherapy approach is warranted, patients with a negative PET scan after two escalated BEACOPP + 2 ABVD may have radiation safely omitted without detriment to tumour control. Conversely, following the approach of EORTC H10, starting with two cycles of ABVD, approximately 20% of patients will be expected to have a positive interim PET scan and require therapy escalation and inclusion of radiotherapy. For those with a negative PET2 after ABVD, the decision to continue with four cycles of AVD (omitting bleomycin as was done in the U.K. RATHL trial[4]) which has a higher risk of treatment failure with omission of radiation[22]; or two more cycles of chemotherapy plus INRT will depend on individual patient characteristics, and the tradeoff of local control vs the potential risk of late cardiac toxicity and second cancers.

Interim and end-of-treatment PET scanning in advanced cHL

There are currently two treatment approaches in the management of Stage III/IV cHL that are founded on therapy modification according to the results of PET2 tested in prospective trials. For patients commencing therapy with ABVD, the U.K. Response-Adjusted Therapy for Advanced Hodgkin Lymphoma (RATHL) trial provided guidance for treatment following two cycles of ABVD.[4] Patients with a negative PET2 scan (Deauville 1–3) were randomized between four more cycles of ABVD or bleomycin omission with AVD, while those with a positive PET2 scan were assigned to six cycles of BEACOPP-14 or four cycles of escBEACOPP. Consolidative radiotherapy was not recommended for PET2 negative patients but was allowed at the treating physician's discretion and was administered to 35/937 patients with a negative PET2 scan and 43/182 patients with a positive PET2 scan. One hundred fifty-four of 1088 patients enrolled (14%) had therapy escalated. Following a median follow-up of 69 months, the five-year PFS of the entire cohort was 81.4% and OS was 95.2%.[4]

A second approach starts with escBEACOPP, and treatment is either de-escalated in those with a negative PET2 (Deauville 1–3), or maintained for those where the PET2 scan is positive (Deauville 4). The GHSG HD18 trial randomized patients with Stages IIB-IV disease and negative PET2 to receive four additional cycles of escBEACOPP (total 6 cycles, standard arm), or two additional cycles (total four cycles, de-escalation arm).[7] PET2-positive patients (uptake greater than mediastinal blood pool) were randomized to receive four additional cycles escBEACOPP with or without the CD20 antibody

rituximab. The primary objectives of the study were to assess superiority of the escalation arm with a 5-year PFS improvement of at least 15% and non-inferiority of the de-escalated arm with a margin of 6%.

After a median follow-up of 66 months, the HD18 study met its primary end-point in the PET2 negative cohort, with 5-year PFS of 92% vs 91% and OS of 98% vs 95% for patients receiving four vs six cycles of chemotherapy, respectively. The addition of rituximab did not improve PFS for patients with a positive PET2 scan.[7]

The second trial of de-escalation of therapy for PET2 responders, Lymphoma Study Association (LYSA) AHL 2011, compared outcomes in Stage III/IV cHL using the standard six cycles of escBEACOPP, to a PET-guided strategy, where patients with a negative PET2 scan received four cycles of ABVD, while patients with a positive scan continued to complete four additional cycles of escBEACOPP. After a median follow-up of 50.4 months, the five-year PFS was 86% in both the standard and PET2 modified arms; OS was similar in both arms, 95.5%. Radiation was not part of the treatment protocol in this trial for those with positive end-of-treatment PET scan, but would be appropriate to apply to localized residual areas of FDG uptake as was performed in HD18.

Studies incorporating novel agents into front-line therapy of classical HL—an opportunity for PET-guided therapy?

RCTs incorporating brentuximab vedotin and nivolumab are poised to provide new therapeutic approaches to improve outcomes in cHL. The ECHELON1 trial comparing brentuximab vedotin (BV) added to AVD to ABVD for six cycles in Stage III/IV cHL demonstrated improved six-year PFS (82.3% vs 74.5%) and OS (93.9% vs 89.4%).[23] This study included assessment of response to therapy by FDG-PET after cycle two, but did not modify treatment based on these results. Six-year PFS for those with a negative PET2 scan was superior for BV-AVD compared to ABVD (85.0% vs 78.1%, HR 0.66 [0.50-0.87]). However, for patients with a positive PET2 scan, PFS was only 61% for those in the BV-AVD arm and 46% for ABVD. This suggests that patients receiving BV-AVD should have an early PET scan with consideration of escalation of therapy, such as switching to escBEACOPP as performed in the RATHL trial if the scan is positive, rather than continuing the same therapy, to ensure optimal outcomes.

The results of a planned interim analysis of the recently completed North American Intergroup trial S1826/CCTG HDC.1 in patients with Stage III/IV cHL comparing six cycles of nivolumab + AVD (n=489) to six cycles of BV-AVD (n=487) were recently reported at the International Conference on Malignant Lymphoma (ICML17).[24] The complete molecular response rate (CMR) by FDG-PET at EOT was 85.1% for nivo-AVD and 71.7% for BV-AVD. After a median follow-up of 12 months, PFS at one year was 94% in the nivo-AVD arm compared to 86% in patients receiving BV-AVD (HR 0.48, one sided P=0.0005). Data on outcomes according to interim PET scanning after two cycles to address prognostic value when treatment includes a PD1 antibody, or need for treatment modification, were not reported.

The GHSG trial HD21 incorporating BV into front-line therapy of advanced cHL was also reported at ICML17.[9] This trial evaluated a new regimen consisting of brentuximab vedotin, etoposide, doxorubicin, cyclophosphamide, dacarbazine, and dexamethasone (BrECADD)[24] compared to escBEACOPP in nearly 1500 patients with Stage IIB-IV cHL. HD21 used a PET2-guided design, with a reduction of number of cycles of therapy from six to four in patients with CMR after cycle two, which was achieved in 57% of patients in both arms. The trial met both of its co-primary endpoints, demonstrating superiority of BrECADD over escBEACOPP in treatment-related morbidity (any CTCAE Grade three or four organ toxicity or Grade four khematological toxicity [anemia, thrombocytopenia, infection]), and non-inferiority in three-year PFS (94.7% vs 92.3%).[9]

This latest PET-adapted approach yielded a treatment that meets the objectives of providing both less toxic and more effective therapy for patients with advanced cHL, and BrECADD has become the new standard for advanced stage cHL for the GHSG. PET-adapted strategies incorporating new agents into the treatment of early stage cHL[25] are being tested in the recently activated international RADAR study (CCTG HD.12; **Figure 2**) comparing BV-AVD to ABVD, and in the upcoming North American Lymphoma Intergroup trial adding nivolumab and BV to initial therapy in patients with Stage I-II disease.

Conclusion

The integration of functional imaging during and at end of treatment has transformed the delivery of chemotherapy and radiation for the treatment of classical HL. PET-guided treatment is the current standard that allows clinicians to provide individualized care for patients with a clearer depiction of the balance between toxicities and efficacy (summarized in **Table 2**). Functional imaging with FDG-PET will continue to inform the next generation of trials of new approaches integrating novel treatment regimens incorporating immune checkpoint inhibitors in the front-line and relapse/second-line setting

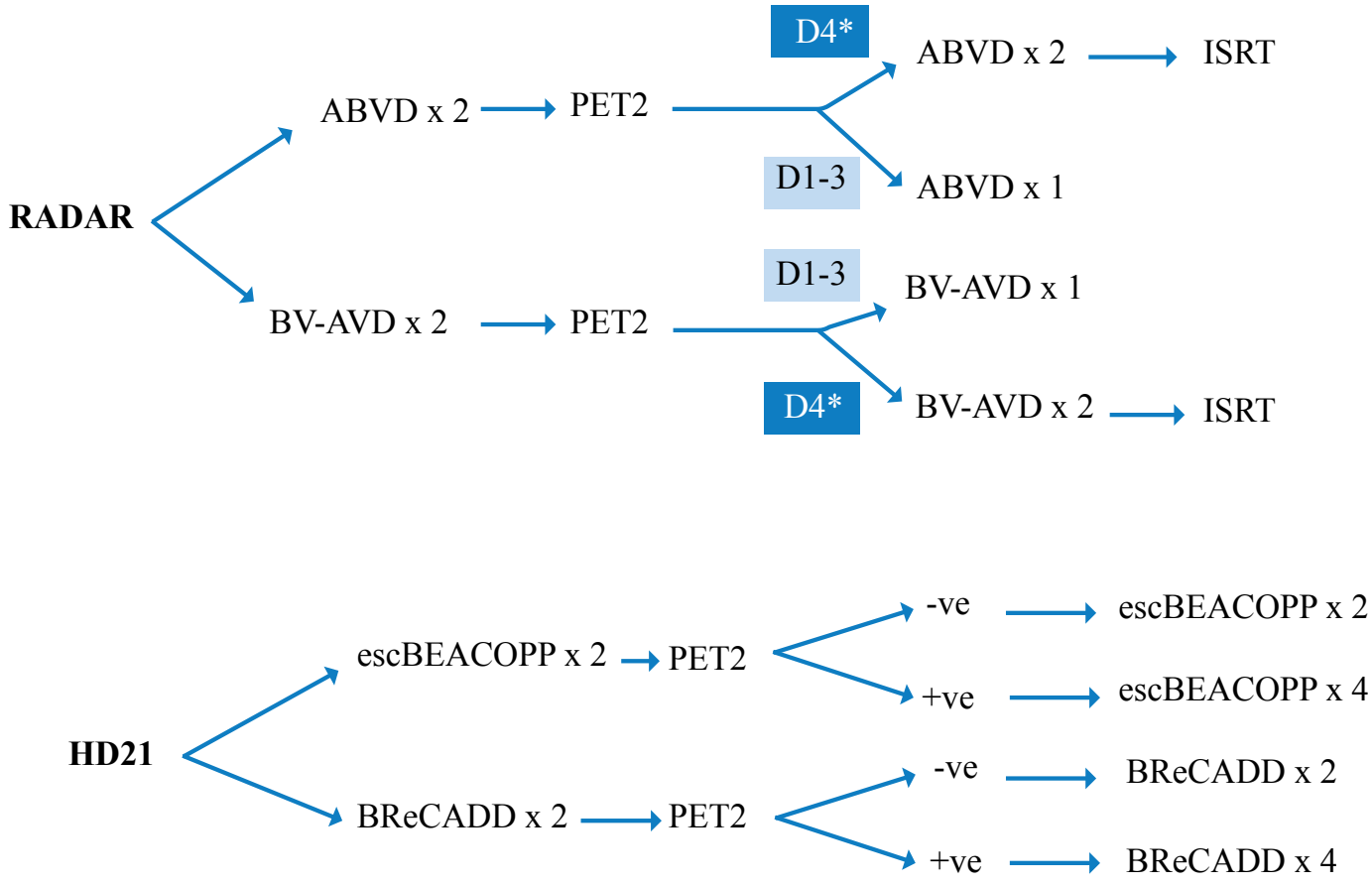


Figure 2. *PET-adapted trials incorporating brentuximab vedotin (BV) into therapy for Stage I-II cHL (RADAR; opened to accrual 2022) and Stage IIE-IV cHL (GHSG HD21).*[9]
**Patients with Deauville (D) score 5 receive alternative therapy.*
ISRT: *involved site radiation;* ***BrECADD:*** *brentuximab vedotin, etoposide, doxorubicin, cyclophosphamide, dacarbazine, dexamethasone;* ***escBEACOPP:*** *escalated bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone.*

Baseline assessment of disease extent	Interim response assessment after two cycles of chemotherapy (PET2)	End-of-treatment response assessment:
• "Upstaging" of 5%–15% of patients presenting with clinical and CT scan evidence of limited stage HL • Assessment of presence or absence of bone marrow involvement: bone marrow biopsy no longer required for routine staging	• Limited stage cHL (I,II): After two cycles ABVD identification of patients for whom INRT could be omitted (Deauville score 1–3) and treatment completed with 2–4 additional cycles or patients with inadequate response for whom treatment should be escalated (Deauville score 4,5) • Advanced stage cHL (III,IV): Treatment reduction/de-escalation to reduce toxicity without decrease in PFS following favourable early response to therapy (Deauville score 1–3) ◊ Initial treatment with two cycles escBEACOPP: Continue with two further cycles (vs four cycles) or continue with four cycles A(B)VD ◊ Initial treatment with two cycles ABVD: Continue treatment with four cycles AVD (omission of bleomycin to reduce potential pulmonary toxicity) • Treatment intensification/continuation following unfavourable early response (Deauville 4) ◊ Positive PET2 after ABVD: Intensify therapy with four cycles escBEACOPP ◊ Positive PET2 after escBEACOPP: Continue with 4 cycles escBEACOPP	• Early favourable cHL: Identification of patients with incomplete response (Deauville 4) who may benefit from therapy escalation after two cycles ABVD (vs standard CMT), despite favourable characteristics at presentation • Early unfavourable cHL: Identification of patients after two cycles escBEACOPP + two cycles ABVD with complete metabolic response for whom INRT can be omitted without reduction in PFS. • Advanced stage (including IIB with risk factors) cHL: Identification of patients with bulky disease at presentation and favourable response after completion of chemotherapy (Deauville 1–3) for whom consolidative radiation can be omitted without reduction in PFS. • Advanced stage (including IIB with risk factors) cHL with less than CMR at end-of-treatment (PMR, Deauville 4) for whom further follow-up imaging is warranted or for whom a biopsy must be performed before change in therapy (Deauville 5)

Table 2. *Summary of role of FDG-PET scanning in primary treatment of classical Hodgkin lymphoma; courtesy of Michael Crump, MD, FRCPC.* ***INRT:*** *involved nodal radiation therapy;* ***CMR:*** *complete metabolic response;* ***PMR:*** *partial metabolic response;* ***RT:*** *radiation therapy;* ***CMT:*** *combined modality treatment.*

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Financial Disclosures:

Consultancy fees: Kite-Gilead, Novartis and Epizyme/Epson
Research funding to author's institution: Roche and Epizyme/Epson.

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MONOCLONAL GAMMOPATHY OF CLINICAL AND UNDETERMINED SIGNIFICANCE

Introduction

Monoclonal gammopathy of undetermined significance (MGUS) is a pre-malignant condition that arises when clonal B-lymphocytes or plasma cells secrete a monoclonal immunoglobulin protein (m-protein). To be diagnosed with MGUS, patients must have bone marrow clonal cell involvement of less than 10%, an m-protein concentration of <30 g/L, and no signs or symptoms related to the clonal proliferative process.

MGUS is a common condition and its prevalence increases with age; a large population screening study has shown that the prevalence of MGUS is approximately 3% among individuals above the age of 50, and increases to 5% among those above the age of 70.[1] Currently, the standard of care is not to screen for MGUS; therefore, patients often are incidentally diagnosed during the work-up of other comorbid conditions. Patients with MGUS are, by definition, asymptomatic and do not require treatment. However, recognizing this disorder is clinically relevant as there is a small (~1% per year) risk that MGUS will progress to multiple myeloma, a lymphoproliferative disorder, or systemic light-chain (LC) (AL) amyloidosis.[2] Therefore, expert consensus guidelines recommend that patients diagnosed with MGUS undergo lifelong serial clinical and laboratory monitoring for signs or symptoms of disease progression.[3] It is becoming increasingly recognized that there is a small subset of patients with a small B-cell or plasma-cell clone that would otherwise have met the criteria for MGUS; however, these patients have debilitating symptoms due to organ damage from the circulating m-protein. Therefore, the term "monoclonal gammopathy of clinical significance" (MGCS) was coined to differentiate these patients from asymptomatic patients with MGUS. The objective of this review is to broadly highlight when to investigate further for MGCS when evaluating a patient with a monoclonal protein.

Unlike with multiple myeloma or B-cell lymphoma, where symptoms are most often related to uncontrolled clonal cell proliferation resulting in high tumor burden and m-protein production, quiescent MGCS clonal cells cause symptoms from other mechanisms including cytokine production or the production of toxic m-proteins. Multiple mechanisms of tissue injury have been described: organized m-protein deposition into target tissues (i.e., systemic AL amyloidosis, Type 1 cryoglobulinemia); disorganized m-protein deposits (i.e., monoclonal immunoglobulin deposition disease [MIDD], proliferative glomerulonephritis with monoclonal IgG deposits [PGMNID]); auto reactivity of the m-protein (i.e., C1 inhibitor deficiency resulting in angioedema; IgM-associated peripheral neuropathy resulting in an anti-MAG [myelin-associated glycoprotein] ataxic polyneuropathy); complement pathway activation (i.e., C3 glomerulonephritis); and cytokine-mediated damage (i.e., vascular endothelial growth factor [VEGF] production in POEMS [Polyneuropathy, Organomegaly, Endocrinopathy, Monoclonal plasma cell disorder, Skin changes] syndrome).[4] MGCS clinical syndromes can affect multiple organs simultaneously; however, commonly involved organs include the kidneys, nerves and skin. To diagnose MGCS, a thorough review of systems and physical

examination, and a high index of suspicion, are required when evaluating patients with a monoclonal gammopathy to identify red flags (**Table 1**).

Monoclonal Gammopathy of Renal Significance

MGCS affecting the kidneys is termed monoclonal gammopathy of renal significance (MGRS). Given that renal failure is a common manifestation of multiple myeloma, it is important to distinguish between a diagnosis of MGRS and multiple myeloma. The International Myeloma Working Group clearly states that only renal failure caused by cast nephropathy is considered a myeloma-defining renal event.[5] All other causes of renal injury due to plasma cell disorders are classified as MGRS. MGRS is a broad term for several different disorders that arise when an m-protein causes renal damage, and the underlying B-cell or plasma-cell clone does not meet criteria for treatment due to other end-organ damage (including patients with smoldering multiple myeloma or indolent Waldenström macroglobulinemia).[6] MGRS-related disorders include amyloid LC amyloidosis; MIDD; PGMNID; C3 glomerulopathy; thrombotic microangiopathy; monoclonal immunotactoid glomerulonephritis; Type 1 cryoglobulinemia; and LC proximal tubulopathy. A renal biopsy is required to identify the underlying disorder based on the location of m-protein damage within the nephron, the type of m-protein deposit (i.e, organized fibrils, immunoglobulin crystals, cryoglobulins, microtubules), and other characteristics of renal damage.

Cast nephropathy occurs when free LCs (FLCs) aggregate with uromodulin (Tamm-Horsfall glycoprotein) causing intratubular renal casts and resulting in acute kidney injury. Patients with cast nephropathy typically have an involved FLC >1500 mg/L, high serum creatinine, and proteinuria due to renal excretion of LCs (also known as Bence-Jones proteinuria), resulting in abnormally high urine protein to creatine ratio (uPCR) relative to the urine albumin to creatinine ratio (uACR).[7] In contrast, MGRS-related disorders most commonly present with low m-protein levels, proteinuria (typically >1.5 g/day, and predominantly albuminuria given that the majority of MGRS-related disorders cause glomerular injury) even with a preserved glomerular filtration rate (GFR), microscopic hematuria or a rapid loss of kidney function.[8]

Clinical features associated with MGCS			
Dermatologic Findings	**Consider...**	**Neurologic Findings**	**Consider...**
Yellow plaques	Necrobiotic xanthogranuloma	Ascending length-dependent sensory neuropathy (parasthesia), autonomic neuropathy, carpal tunnel syndrome	AL amyloid
Angioedema	Acquired C1 esterase deficiency	length-dependent demyelinating motor >> sensory neuropathy	POEMS
Chronic urticaria	Schnitzler's syndrome	Ataxia	CANOMED
Acrocynanosis, purpura, livedo reticularis	Type 1 cryo.	Polyneuropathy	Cryoglobulinemia
Hyperpigmentation, hypertrichosis, white nails, acrocyanosis, flushing, hemangiomas, plethora	POEMS	Distal ascending symmetric neuropathy, sensory ataxia	DADS-M
Renal Findings	**Consider...**	**Cardiac Findings**	**Consider...**
Proteinuria (mainly albuminuria), CKD, microscopic hematuria, hypertension	MGRS (AL amyloid, MIDD, PGMNID, C3 glomerulopathy, TMA, MIGN, type 1 cryo., LCPT)	HFpEF, concentric LVH, low QRS on ECG, arrythmia	AL amyloid, MIDD

Table 1. *A summary ok key clinical features (if unexplained base on concomitant medical history) that should prompt further evaluation for MGCS in patients with MGUS.*
Abbreviations: ***cryo:*** *cryoglobulinemia ,* ***AL:*** *light chain,* ***CKD:*** *chronic kidney disease,* ***MIDD:*** *monoclonal immunoglobulin deposition disease,* ***TMA:*** *thrombotic microangiopathy,* ***MIGN:*** *monoclonal immunotactoid glomerulonephritis,* ***LCPT:*** *light chain proximal tubulopathy,* ***POEMS:*** *polyneuropathy organomegaly endocrinopathy m-protein sclerotic lesions,* ***DADS-M:*** *distal ascending demyelinating symmetric lgM ,* ***CANOMAD:*** *chronic ataxic neuropathy ophthalmoplegia lgM m-protein cold agglutinins disialosyl antibodies.*

These red flags should prompt an evaluation with a renal biopsy, as MGRS without other systemic features is ultimately a pathologic diagnosis.

Neurological MGCS

Although neurological symptoms are common in the general population, MGCS-related syndromes have classical neurologic presentations. AL amyloidosis can be associated with a progressive length-dependent, small fiber, axonal neuropathy presenting with burning, pain and paresthesias, autonomic dysfunction (postural hypotension, gastrointestinal [G] dysmotility, erectile dysfunction), and carpal-tunnel syndrome from median nerve compression due to soft tissue enlargement.[9] Isolated neurological manifestations with AL amyloidosis are rare, therefore a thorough review of systems (as described below) is needed to identify other potential organ involvement. POEMS syndrome is characterized by progressive, length-dependent, ascending, symmetrical, sensorimotor demyelinating peripheral neuropathy, where motor symptoms are often dominant and debilitating.[10] IgM-related neuropathy classically presents as a distal, acquired, demyelinating, symmetric (DADS-M) neuropathy affecting large sensory fibers and presenting with sensory ataxia. DADS-M neuropathy classically affects older males and is a diagnosis of exclusion among patients with an IgM m-protein. Anti-myelin-associated glycoprotein (MAG) antibodies have been associated with DADS-M neuropathy, however the presence of anti-MAG auto-antibodies is a not a specific finding.[9] CANOMAD is a rare condition characterized by chronic sensory ataxia, ophthalmoplegia, an IgM m-protein, cold agglutinins, and disialosyl antibodies.[11]

Cutaneous MGCS

MGCS-related dermatological disorders have a wide variety of manifestations. Schnitzler syndrome is characterized by chronic urticaria, an IgM monoclonal protein, recurrent fevers, bone remodelling, and neutrophilic infiltrates on skin biopsy.[12] Patients with scleromyxedema have generalized papular and sclerodermoid cutaneous eruptions,[13] whereas patients with necrobiotic xanthogranulomas present with yellow-orange papules and nodules typically involving the eyelids.[14] TEMPI syndrome is a rare disorder characterized by telangiectasias, an elevated erythropoietin level along with erythrocytosis, perinephric fluid collections, and intrapulmonary shunting, in addition to a monoclonal gammopathy.[15] MGCS-related cryoglobulinemia is most commonly Type I, and cutaneous findings occur due to small vessel vascular occlusion and include cold-induced purpura, urticaria, livedo reticularis, and ulceration. Palpable purpura, as a manifestation of small-vessel-vasculitis, is more commonly found in patients with Type 2/3 cryoglobulinemia, which is less common in patients with underlying lymphoproliferative or plasma cell disorders.[16] POEMS syndrome, described in greater detail below, can also present with hyperpigmentation, hypertrichosis, white nails, acrocyanosis, flushing, hemangiomas, and plethora.[10]

Multisystem MGCS: Systemic Light-Chain Amyloidosis

Amyloidosis is characterized by the deposition of misfolded proteins in a proteolysis-resistant beta-pleated sheet. Although multiple proteins are amyloidogenic, systemic AL amyloidosis is caused by the deposition of monoclonal light-chain proteins. The clinical symptoms of systemic AL amyloidosis can vary and can mimic chronic complications of other common disorders such as Type 2 diabetes mellitus and hypertension, which can lead to prolonged delays in diagnosis.[17] Most commonly, AL amyloidosis presents with cardiac involvement (heart failure with preserved ejection fraction [HFpEF], thickened ventricular walls with low voltages on electrocardiogram, dyspnea on exertion, arrythmias and renal involvement (nephrotic syndrome, renal failure). Other signs and symptoms include soft tissue deposition (macroglossia, obstructive sleep apnea, carpal tunnel syndrome); liver involvement (hepatomegaly and increased alkaline phosphatase); peripheral or autonomic neuropathy; GI involvement; periorbital purpura; and coagulopathy due to an acquired factor X deficiency.[18]. A diagnosis of amyloidosis requires histological evidence of apple-green birefringent amyloid fibrils when the biopsied tissue is stained with Congo red and viewed under polarized light. In patients with clinical symptoms of AL amyloidosis and a detectable serum or urine m-protein, a combined fat pad aspirate and bone marrow biopsy stained for Congo red has a sensitivity of 90% for detecting amyloid deposits.[19] Once Congo red positive amyloid deposits have been found, the type of amyloid needs to be identified; mass spectrometry is the preferred method for isotyping as it has a high sensitivity and specificity.[20]

Multisystem MGCS – POEMS

Patients with POEMS syndrome present with polyneuropathy and a monoclonal (almost always lambda-restricted) plasma-cell proliferative disorder. Patients also require at least one major criteria (sclerotic bone lesions, an elevated vascular EGF level or concomitant Castleman disease) and one minor criteria (organomegaly; extravascular volume overload; endocrinopathy excluding Type 2 diabetes mellitus and thyroid disorders; skin changes as described above; papilledema; thrombocytosis; or polycythemia).[10] Patients diagnosed with chronic inflammatory demyelinating polyneuropathy (CIDP) who do not respond to conventional CIDP treatment should flag a high clinical suspicion for POEMS syndrome, as POEMS syndrome is often misdiagnosed as CIDP.

Conclusion

Although specific treatments for MGCS-related disorders are beyond the scope of this review, significant symptoms related to MGCS often warrant the use of clone-directed therapy to inhibit the production of the problematic m-protein. Therefore, having a high clinical suspicion for MGCS-related disorders is necessary to allow early identification and treatment prior to the onset of debilitating symptoms.

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Financial Disclosures:

Consultancy/Honoraria fees: Janssen, Sanofi, Pfizer, Apotex

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FRONTLINE TREATMENT OF AGGRESSIVE B-CELL LYMPHOMA

Introduction

Aggressive B-cell non-Hodgkin lymphoma, which most often manifests as diffuse large B-cell lymphoma (DLBCL), is the most common non-Hodgkin lymphoma, accounting for up to 30% of diagnosed cases. It is responsible for considerable morbidity and mortality worldwide, with a global burden of approximately 150,000 new patients annually.[1] Large B-cell lymphoma encompasses a group of lymphomas with significant clinical and biological heterogeneity. While there are approximately 18 variations of large B-cell lymphoma in the upcoming 5th edition of the World Health Organization classification of lymphoid neoplasms (WHO-HAEM5), for the purposes of this review the aggressive B-cell lymphomas will refer to the most common entity, diffuse large B-cell lymphoma, not otherwise specified (DLBCL), as well as diffuse large B-cell lymphoma/high-grade B-cell lymphoma with MYC and BCL2 rearrangements (DLBCL/HGBL-MYC/BCL2), and high-grade B-cell lymphoma, not otherwise specified (HGBL,NOS).[2]

More than 60% of patients may be cured of their DLBCL with front-line treatment, a figure that has not increased measurably for decades despite attempts to improve outcomes by adding to or adjusting the established standard of care regimen of rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP).[3] R-CHOP can also be effective in the setting of high-grade B-cell lymphoma (HGBL), but in that context outcomes are worse than those in DLBCL.[3] There is no established standard of care for HGBL, and while there is evidence to suggest that intensified regimens such as dose-adjusted rituximab, etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin (DA-R-EPOCH) may improve outcomes, this has not been tested in randomized controlled trials (RCTs).

Given substantial efforts to improve DLBCL outcomes following first-line therapy, and the lack of a clear standard of care in treatment of HGBL, this review seeks to outline current front-line treatment of aggressive B-cell non-Hodgkin lymphoma.

Diffuse Large B-cell Lymphoma (DLBCL)

While many DLBCL patients may be cured of their lymphoma with front-line R-CHOP, more than 30% of patients will have relapsed or refractory disease leaving significant room for improvement in front-line treatment outcomes.[3] Significant effort has been made to identify drivers of chemotherapy-resistant disease in an attempt to highlight patients unlikely to respond to standard front-line therapy. Cases of DLBCL with rearrangements of MYC and BCL2, and those with high-grade histology without other clearly distinct molecular features, have been recognized by the WHO as distinct disease entities and studies have shown they benefit from a more intensive treatment approach.[2] Gene expression profiling (GEP) studies have identified two main subgroups of DLBCL based on the cell of origin (COO): germinal center B-cell-like (GCB) and activated B-cell-like (ABC); outcomes in ABC DLBCL have been shown to be significantly worse than those of GCB DLBCL following R-CHOP, with five-year progression-free survival (PFS) and overall survival (OS) of 48% and 56% vs 73% and 78%.[4,5] However, COO does not tell the entire story: GEP reveals an “unclassified” category that is missed by the IHC algorithms, such as the Hans algorithm used in routine clinical practice.[2] Using further molecular analysis, researchers are working to define distinct genetic subtypes

of DLBCL which may be better able to risk stratify patients and guide future treatment.[2,6]

Numerous clinical trials have been undertaken to improve outcomes with R-CHOP. Studies, including the GOYA trial, have looked at changing the anti-CD20 antibody from rituximab to obinutuzumab in combination with CHOP chemotherapy. They have shown no significant difference in PFS or OS, and increased toxicity with obinutuzumab.[7] R-CHOP14 was compared to R-CHOP21 to see if more frequent or dose-dense administration resulted in better outcomes; no significant difference was found, but there was an increased need for transfusions in the R-CHOP14 group.[8] The intensified regimen of dose-adjusted rituximab, etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin (DA-R-EPOCH) was compared to R-CHOP in DLBCL patients and no significant difference in PFS or OS was found between regimens; however, significantly increased toxicity was seen in the R-EPOCH arm.[9]

A series of clinical trials, both completed and ongoing, seek to determine whether there is a novel or targeted agent that, when added to the R-CHOP backbone, would more effectively treat the approximately 30% of patients undertreated by R-CHOP alone, without overtreating the R-CHOP-sensitive patients and causing excess toxicity.

The REMoDL-B trial studied R-CHOP plus bortezomib vs R-CHOP; to be randomized patients needed to have adequate biopsy samples for GEP in order to stratify by COO.[10] The primary analysis of the trial showed no benefit from the addition of bortezomib, but the five-year follow-up data shows that while there is still no overall benefit, COO analysis demonstrates a PFS and OS benefit in patients with ABC DLBCL.[10,11] Retrospective analysis using a gene-expression-based classifier identified a subset of disease with a high-grade molecular signature which also demonstrated improvement in PFS and OS with the addition of bortezomib.[11]

The PHOENIX trial investigated the addition of ibrutinib to R-CHOP in non-GCB DLBCL and did not demonstrate improved outcomes vs R-CHOP.[12] Interestingly, a subgroup analysis of the PHOENIX trial showed improved event-free survival (EFS), PFS, and OS as well as increased toxicity in patients under age 60. Conversely, patients age 60 or older had inferior EFS, PFS and OS and increased toxicity from the addition of ibrutinib to R-CHOP.[12]

Lenalidomide plus RCHOP (or R2CHOP) has been studied in Phase II and Phase III trials. The Phase 2 ECOG-ACRIN E1412 study encouragingly showed improved PFS and OS in patients treated with R2CHOP vs RCHOP.[13] Unfortunately, the Phase III ROBUST study of R2CHOP vs RCHOP failed to meet its primary end point, with no difference in PFS seen between groups.[14]

The POLARIX trial is the only study to date that demonstrates an overall improvement in PFS vs standard of care R-CHOP. The study examined the addition of the CD79b monoclonal antibody-drug conjugate polatuzumab vedotin to R-CHOP but with vincristine omitted due to overlapping neurologic toxicity - the pola-R-CHP regimen. The researchers compared pola-R-CHP to R-CHOP and found that PFS was improved with pola-R-CHP vs R-CHOP with two-year PFS of 76.7% in the pola-R-CHP arm vs 70.2% in the R-CHOP arm.[15] There was no significant difference in OS and toxicity was similar between arms.[15] Subgroup analysis suggests that pola-R-CHP may not offer incremental benefit to patients 60 years or younger, patients with GCB DLBCL, and patients with lower international prognostic index (IPI) scores.[15]

Based on the available data, R-CHOP remains the front-line standard of care for treatment of DLBCL, although pola-R-CHP could shift the treatment paradigm in Canada. Already adopted as the preferred regimen in some European centres, if polatuzumab is funded for front-line treatment of DLBCL in Canada, it would challenge R-CHOP as the optimal initial therapy for older patients with high-risk non-GCB DLBCL.

Investigation of other novel or targeted agents in combination with R-CHOP such as venetoclax, acalabrutinib, zanubrutinib, and the combination of tafasitamab and lenalidomide are ongoing.

High-Grade B-cell Lymphoma (HGBL)

Although it shares features with DLBCL, HGBL displays higher grade, Burkitt-like morphology but with histologic and genetic features inconsistent with Burkitt lymphoma.[16] The disease entities formerly referred to as "double-" or "triple-hit" lymphoma have been reclassified in order to better reflect their histologic and genetic features. These were initially referred to jointly as HGBL with dual rearrangements of MYC and BCL2 and/or BCL6; the WHO-HAEM5 uses the label diffuse large B-cell lymphoma/high-grade B-cell lymphoma with MYC and BCL2 rearrangements (DLBCL/HGBL-MYC/BCL2) to include large B-cell lymphomas with MYC and BCL2 rearrangements, composed of large, intermediate, or blastoid cells.[2] DLBCL/HGBL-MYC/BCL2 lymphomas are homogenous and are exclusively GCB by GEP.[2] Lymphomas with rearrangements of MYC and BCL6 are more heterogenous with variable molecular, genetic and GEP features, therefore the WHO-HAEM5 classifies them as either DLBCL, NOS or HGBL, NOS according to their morphological features.[2]

There is no established front-line standard of care treatment for patients with HGBL and outcomes are inferior vs those in DLBCL.[17] Several retrospective analyses have suggested that patients with HGBL experience improved outcomes when treated with intensive regimens vs standard R-CHOP.[18-21] Interestingly, a retrospective, multicentre, pooled analysis conducted in 2023 evaluating 259 patients with DLBCL/HGBL with rearrangements of MYC and BCL2/BCL6 suggested no significant difference in outcomes between intensive regimens and R-CHOP, although the author acknowledges there is a large amount of missing patient data which may impact results.[22] The same authors subsequently conducted a more recently published

systematic review and meta-analysis, again studying retrospective studies of front-line therapy for DLBCL/HGBL with rearrangements of MYC and BCL2/BCL6. The objective was to compare outcomes in patients treated with intensive regimens vs R-CHOP; a review of 876 patients found that PFS and OS were improved with intensified regimens.[23]

The body of existing retrospective data supports intensive front-line treatment over R-CHOP for patients with HGBL, but with very little prospective data on treatment of HGBL, and a lack of randomized, controlled Phase III trials, the intensive regimen associated with the best outcomes is unclear. While there are various intensive treatment regimens described in the literature, the two regimens most frequently reported in this patient population are DA-R-EPOCH and rituximab, cyclophosphamide, vincristine, doxorubicin, and methotrexate alternating with ifosfamide, etoposide, and cytarabine (R-CODOX-M/R-IVAC), also called the Magrath protocol.

The prospective LY10 trial studied the efficacy of the intensive Magrath protocol without rituximab (CODOX-M/IVAC) in patients with Burkitt lymphoma and DLBCL/HGBL.[24] The two-year PFS and OS for the high-risk patients were 54% and 62% respectively, and subgroup analysis showed the patients with Burkitt lymphoma had significantly better outcomes than those with high-risk DLBCL/HGBL.[24] A Phase II study conducted in the United Kingdom examined the Magrath protocol including rituximab (R-CODOX-M/R-IVAC) in patients with high-risk DLBCL and HGBL. It demonstrated good outcomes with four-year PFS and OS of 66.9% and 72.8% respectively, although only 52% of patients underwent cytogenetic studies and only 12% of patients had confirmed rearrangements of MYC, BCL2, and/or BCL6.[25] Toxicity is high with this intensive regimen with frequent grade 3 and 4 adverse events, most commonly neutropenia, thrombocytopenia and infections, and these events were more often observed in older patients.[24,25]

In addition, there is some prospective evidence supporting the use of R-EPOCH in HGBL, with a Phase II study of R-EPOCH in HGBL with MYC rearrangements at 48 months achieving EFS and OS of 71% and 77%, respectively.[26] A small, prospective study examined R-EPOCH followed by consolidative autologous stem cell transplant and found similar outcomes in terms of PFS and OS with no additional benefit offered by consolidative transplant.[27] A retrospective analysis of the use of DA-R-EPOCH in DLBCL/HGBL patients, including those expressing MYC and BCL2 by IHC, as well as those with rearrangements of MYC and BCL2/BCL6, had particularly good outcomes. It demonstrated two-year PFS and OS of 74% and 84%, respectively. However, the study included a population of low-risk patients and some who had DLBCL, NOS with no high-grade features; therefore, efficacy may be exaggerated.[28] A recently published real-world analysis of treatment trends and patient outcomes in DLBCL and HGBL in the United States showed that the patients with rearrangements of MYC and BCL2/BCL6 who received R-EPOCH as first-line treatment had significantly longer OS vs those receiving R-CHOP.[29] DLBCL patients without those cytogenetic findings who were treated with R-CHOP or R-EPOCH had no difference in OS.[29]

There is a body of evidence supporting the use of intensive regimens like DA-R-EPOCH and R-CODOX-M/R-IVAC as front-line treatment for HGBL with a suggestion of improved outcomes over R-CHOP in these patients. However, this has not been proven in RCTs and the intensive regimens have not been compared to each other. There remains no standard of care for front-line treatment of HGBL. DA-R-EPOCH is a commonly described intensive regimen which may improve outcomes over R-CHOP for patients with HGBL. R-CODOX-M/R-IVAC may also be a reasonable choice, although, given the increased toxicity, this may be most appropriate for select younger, fit patients.

Summary

Aggressive B-cell lymphoma is the most commonly diagnosed lymphoma with a significant burden of disease globally. The classification of aggressive B-cell lymphoma continues to evolve as we continue to delineate subtypes based on genetic features. Despite our improved understanding of the disease, we have yet to make substantial improvement in treatment outcomes.

R-CHOP remains the preferred front-line treatment for DLBCL, although pola-R-CHP demonstrates an improvement in PFS over R-CHOP. It may be a preferred initial treatment if it becomes available for this indication in Canada, especially for patients over 60 years of age with non-GCB DLBCL.

Trials investigating therapies in HGBL are limited by the rare nature of the disease, and much of the available evidence for treatment is retrospective or pulled from subgroup analyses. Despite these limitations, there is evidence supporting intensive regimens over R-CHOP as front-line treatment for HGBL. There is no established standard of care in this setting, but DA-R-EPOCH and R-CODOX-M/R-IVAC are both reasonable intensive treatment regimens for HGBL in front-line, with DA-R-EPOCH most frequently described. Additional prospective data and RCTs are needed to confirm the optimal front-line approach in HGBL.

As we continue to advance our knowledge of the molecular landscape of DLBCL and HGBL beyond COO into detailed genetic analysis with next generation sequencing, we may be able to identify the impact of these detailed disease genetics on treatment outcomes, and perhaps target treatments on the basis of molecular classification.[5,6] We await further evidence from clinical trials to inform this approach.

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Financial Disclosures:

Honoraria/Consultancy/Advisory Boards: Abbvie, BeiGene, Novartis

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CHIMERIC ANTIGEN RECEPTOR (CAR) T-CELL THERAPY IN MULTIPLE MYELOMA: THE EVOLVING CANADIAN LANDSCAPE

Introduction

Multiple myeloma (MM) is a hematologic malignancy characterized by excessive production and improper function of plasma cells.[1] This results in an abnormal high M protein or immunoglobulin protein which can result clinically in lytic lesions, anemia, renal dysfunction, and hypercalcemia. Multiple myeloma is not curable; however, there has been a rapid evolution of therapies in the past two decades, leading to an improvement in overall survival (OS).[2]

Despite the rapid improvement in the treatment options for myeloma, the outcomes among relapsed/refractory (RR) patients remains poor. The MAMMOTH study, a retrospective review of 275 patients at 14 academic centres with MM refractory to a monoclonal CD38 antibody, demonstrated that penta-refractory patients had a median OS of 5.6 months and patients refractory to a CD38 monoclonal antibody had a median OS of 8.6 months. The median progression-free survival (PFS) to the next line of therapy in this study was 3.4 months.[3] The LocoMMotion trial was a prospective study of real-life standard of care (SoC) in triple-class exposed (received at least a proteasome inhibitor [PI], immunomodulatory agent [IMiD] and anti-CD38 monoclonal antibody [mAb]) patients with relapsed/refractory multiple myeloma (RRMM).[4] This trial examined the outcomes of 248 patients and found that the response rate (RR) to next treatment was 29.8%; the median PFS and median OS were 4.6 and 12.4 months respectively. These studies demonstrate an unmet need for patients with triple-class exposed and refractory MM.

Immune effector cell (IEC) therapy comprises novel therapies that involve using the body's own immune system to treat cancer. Chimeric antigen receptor (CAR) T-cell therapy is an example of IEC therapy.

CAR T-cell therapy is a novel approach to cancer treatment in which a patient's own T cells are harvested and genetically modified to recognize specific antigens on the surface of the cancer cells.[5] Currently CAR T- cell therapy is indicated and funded in Canada for third-line treatment for large B-cell lymphoma, B-acute lymphoblastic leukemia and mantle cell lymphoma. Funding and access for two CAR T-cell therapy products for myeloma, idecabtagene vicleucel (ide-cel) (Abecma® [Bristol-Myers Squibb, New York, NY]) and ciltacabtagene autoleucel (cilta-cel) (Carvykti® [Janssen Oncology, Titusville, NJ]) is available in the United States and Europe for those with MM post four lines of therapy. **Table 1** summarizes landmark studies evaluating ide-cel and cilta-cel in RRMM. CAR T-cell therapy for MM will likely soon be available in Canada for similar indications.

The purpose of this review is to explore the evidence for CAR T-cell therapy in MM.

A Closer Look at Ide-cel:

Idecabtagene vicleucel (ide-cel) is a B-cell maturation antigen (BCMA) CAR T-cell therapy for MM. Ide-cel was examined in the Phase II KarMMa trial. Patients with RRMM whose disease had relapsed after at least three prior regimens, including a proteasome inhibitor, immunomodulatory agent and an anti-CD38 antibody, were included.[7] One hundred and fifty-eight patients were

	Ide-cel KarMMa n=158	Ide-cel Real-world Evidence (RWE) n=196	Cilta-cel CARTITUDE-1 n=97
Phase	II	RWE	Ib/II
Target	BCMA	BCMA	BCMA
scFv	Chimeric mouse	Chimeric mouse	Chimeric llama
Co-stimulatory	4-1BB	4-1BB	4-1BB
Specificity	Autologous	Autologous	Autologous
Median Age (range)	61 (33-78)	64 (36-83)	61 (43-78)
Median Prior lines	6	4	5
HR Cytogenetics %	35	38	27
Extramedullary disease %	39	47	10
Triple refractory %	84	83	86
Overall Response Rates (ORR)	73%	84%	97.9%
Complete Response Rates (CR)	33%	42%	82.5% (stringent CR)
Grade 3+ CRS	5%	3%	4%
Grade 3+ Neurotoxicity	3%	6%	9%
Median PFS	8.8 months	8.5 months	Not yet reached; 27 month PFS 54.9%
Median OS	Estimated 19.4 months	12.5 months	Not yet reached; 27 month OS 70.4%

Table 1. *Landmark studies evaluating ide-cel and cilta-cel in RRMM.*[6-9]
BCMA: *B-cell maturation antigen;* ***HR:*** *high risk;* ***scFV:*** *Single-chain variable fragments;* ***OS:*** *overall survial;* ***PFS:*** *progression free survival;* ***CRS:*** *cytokine release syndrome.*

enrolled, 140 of whom were leukapheresed. One hundred and twenty-eight of these patients received ide-cel infusions. The median follow up was 13.3 months. Ninety-three out of 128 patients (73%) had a response and 42 out of 128 patients (33%) had a CR or better. MRD negative status was confirmed in 33 patients. The median PFS was 8.8 months.

Common toxicities post-ide-cel infusion included cytopenias. Neutropenia occurred in 91% of patients; anemia occurred in 70% of patients; and thrombocytopenia occurred in 63% of patients. Cytokine release syndrome post CAR T-cell therapy occurred in 84% of patients and Grade 3 or higher cytokine release syndrome (CRS) occurred in 5% of patients. Neurotoxicity occurred in 18% of patients and Grade 3 or higher neurotoxicity occurred in 3% of patients.[7]

Hansen et al examined the outcomes of ide-cel in a real-world data set.[6] This data set examined outcomes of patients receiving ide-cel from 10 academic centres in the United States. One hundred and ninety-six patients with MM who received ide-cel were included in this analysis. Seventy-seven percent of these patients would have been ineligible for the KarMMa trial. Twenty percent had an

ECOG performance status of two or higher. Toxicities were similar to those in the trial and Hansen et al demonstrated that 82% of infused patients developed CRS. Three percent of patients developed Grade 3 or higher CRS. Neurotoxicity was observed in 18% and 6% experienced Grade 3 or higher neurotoxicity. The six-month OS was 84%. Similar safety and efficacy to the trial were seen in the real-world setting, despite the fact that patients treated in the real world were often less fit and were more often penta-refractory.

A Closer Look at Cilta-cel:

CARTITUDE-1 is a single arm, open-label Phase Ib/II study that examined the use of ciltacabtagene autoleucel (cilta-cel) for RRMM at 16 centres in the United States. Eligible patients were those with RRMM per the IMWG criteria who had received at least three prior regimens or were double refractory to an immunomodulatory drug and a proteasome inhibitor, and had received an immunomodulatory drug, a proteasome inhibitor and an antiCD38 monoclonal antibody.[9] One hundred and thirteen patients were enrolled in this study and 101 underwent lymphodepletion chemotherapy. Ninety-seven patients were infused with cilta-cel. The baseline characteristics of this patient population demonstrated that 23.7% had high risk cytogenetics. Extra medullary disease was seen in 13.4% of patients. The median number of prior therapies was six (3-18). A total of 87.6% were triple refractory. The ORR to cilta-cel was 97%. Sixty-five percent of those infused had achieved stringent CR. The time to first response was one month and the median duration of response was not reached. The twelve-month PFS was 77%. Grade 3–4 hematologic adverse events were common with neutropenia occurring in 95% of patients; anemia in 68% of patients; leukopenia in 61% of patients; and thrombocytopenia in 60% of patients. CRS was common, occurring in 95% of patients; however, only 4% had Grade 3 or higher CRS. The median time to onset of CRS was seven days, with a median duration of four days. Neurotoxicity occurred in 21%, with 9% of patients experiencing Grade 3 or higher neurotoxicity.

Comparing cilta-cel and ide-cel is challenging

Both ide-cel and cilta-cel are autologous products made from patients' own T cells and both are BCMA antigen-directed CAR T-cell products. BCMA is an antigen expressed in malignant plasma cells with a role in the differentiation and proliferation of plasma cells. It is difficult to state whether ide-cel or cilta-cel is superior in the management of RRMM in the absence of a randomized controlled trial comparing the two.[10] Limited data exists on long-term side effects with these agents.

Structurally, there are differences between the agents. Ide-cel has a single murine scFV binding domain for the BCMA antigen while cilta-cel has two camelid VH binding domains conferring higher activity and less immunogenicity.[10] It is unclear whether or not this led to better depth or duration of remission with cilta-cel, as the patients in the landmark trial with ide-cel had a higher percentage of extra-medullary disease and high risk cytogenetic abnormalities.

With respect to toxicity between the two agents, later onset of CRS was seen with cilta-cel. This may be due to a lower median CAR T-cell dose in the CARTITUDE-1 trial.[10] The late onset of CRS may make cilta-cel more amendable to outpatient administration for the first several days. The patient can be admitted at the first signs of CRS leading to decreased overall length of stay. Late-onset neurotoxicity was seen in 10% of patients receiving cilta-cel in the CARTITUDE-1 trial and it lasted for more than three months. It was not reversible in all cases. Ide-cel may be preferred in patients with underlying neurologic disease. The choice between the products is difficult in the absence of a randomized prospective clinical trial as both are effective with tolerable safety profiles.

Future Directions

Multiple trials are examining the use of ide-cel and cilta-cel earlier in the disease course of MM. **Table 2** outlines upcoming trials involving ide-cel and cilta-cel. Many of these trials are still ongoing. CARTITUDE-4 was recently published. It is a randomized trial comparing patients with lenalidomide-refractory MM to receive cilta-cel or the physician's choice of effective standard of care. All of the patients had received one to three lines of prior therapy. This trial demonstrated that a single cilta-cel infusion resulted in a lower risk of disease progression or death vs standard of care treatment in lenalidomide-refractory patients with MM who had received one to three previous therapies. PFS at one year was 75.9% in the cohort receiving cilta-cel vs 48.6% in the cohort receiving standard therapy.[11] CAR T-cell therapy will be likely be indicated in the future in earlier lines of therapy.

One of the challenges with CAR T-cell therapy in MM is limited manufacturing capacity. The manufacturing time of ide-cel and cilta-cel is approximately 28 days. There is currently a bottleneck in manufacturing capabilities related to limited lentivirus vectors and this has led to limited slot availability and delayed onboarding of new centres.[12] Other challenges include risk of manufacturing failure and unequal access to care due to a limited number of centres providing CAR T-cell therapy. The cost of CAR T-cell therapy ranges from $419,500 U.S. (ide-cel) to $465,000 U.S. (cilta-cel) for one infusion, not including the cost of an inpatient stay which may be prolonged. This has significant implications for provincial health care budgets.

Additionally, other CAR T-cell agents are under development. The UNIVERSAL study is examining the feasibility of an allogeneic anti-BCMA CAR T-cell for RRMM. It is a Phase I study enrolling patients with RRMM who have received three or more therapies and were refractory to their last therapy. This is a dose-expansion study. The advantage of allogeneic CAR T-cell therapy is that it can be administered quickly.

In this study, the median time from enrolment to start of lymphodepletion was five days.[13] Non-BCMA CAR T-cell agents are also under development such as MCARH109 targeting GPRC5D.[14]

Trial	Description
Ide-cel	
KarMMa-2 Cohort 2a	RRMM with early relapse (PD <18 months) since starting induction, ASCT, and lenalidomide maintenance
KarMMa-2 Cohort 2b	RRMM with 1 prior therapy not including ASCT and with early relapse
KarMMa-2 Cohort 2c	NDMM, received 3 or more cycles of induction therapy (PI, IMiD and dexamethasone), inadequate response (<VGPR) to ASCT
KarMMa-3	Ide-cel v. SoC in patients with 2-4 lines of therapy
KarMMa-4	High-risk, newly diagnosed MM
Cilta-cel	
CARTITUDE-2	Multiple cohorts including early relapse
CARTITUDE-4	Cilta-cel v. SoC in patients with 1-3 prior lines
CARTITUDE-5	VRd->cilta-cel v. VRd -> Rd in newly diagnosed, transplant ineligible patients
CARTITUDE-6	Trial of DVRd-> cilta-cel v. DVRd -> ASCT in newly diagnosed MM

Table 2. *Upcoming trials involving ide-cel and cilta-cel.*[15-20]
ASCT: *autologous stem cell transplantation;* ***IMiD:*** *immunomodulatar agent;* ***PI:*** *proteasome inhibitor;* ***PD:*** *progressive disease;* ***VGPR:*** *very good partial response.*

Conclusion

CAR T-cell therapy will soon be available in Canada to treat RRMM. Determining the optimal sequencing of CAR T-cell therapy in relation to other therapies is critical and there is emerging data suggesting that CAR T-cell therapy can be utilized in earlier lines of therapy. Improving access to CAR T-cell therapy and immune effector cell therapy in Canada is critical to ensure equitable care for all Canadians with MM. As this is an emerging therapy, monitoring for long-term side effects such as opportunistic infections and late neurotoxicity is important. Early referral to a CAR T-cell therapy centre is essential in order to expedite the time to treatment, due to the current manufacturing times. The addition of CAR T-cell therapy to the Canadian treatment algorithms will help improve PFS and OS in MM. The rapid development of new therapies in MM is promising.

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Financial Disclosures:

Consulting/Honoraria: Novartis, Gilead, Sanofi
Grants/Research Support: Canadian Immunization Task Force (CITF), Princess Margaret Cancer Centre Foundation

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ISSUE 3
2023

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