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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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