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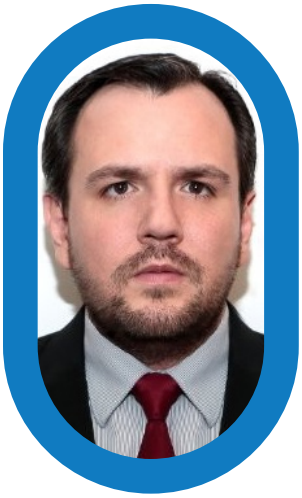

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EVOLVING ROLE OF NOVEL THERAPIES IN MYELOMA: T-CELL ENGAGERS AND ANTIBODY DRUG CONJUGATES

Introduction

Multiple myeloma (MM) is a hematologic malignancy characterized by the proliferation of abnormal clonal plasma cells. This population of neoplastic plasma cells can subsequently cause damaging lytic lesions to the bones, kidney dysfunction, high levels of calcium in the blood, and anemia.[1] MM is more prevalent in individuals over age 65 than in younger individuals; the median age at diagnosis is 69 years old. This malignancy is generally considered incurable. The five-year overall survival (OS) is estimated to be as high as 82% with the Revised International Staging System (R-ISS) for Stage I of the disease, and 40% with R-ISS Stage III of the disease.[2] A large proportion of patients in the relapsed/refractory (R/R) setting are unable to achieve durable responses to treatment. There remains an unmet need for novel, highly effective and well-tolerated therapies in this patient population.[3]

Treatment of myeloma patients has evolved in the past two decades with the introduction of novel therapies:[4] the proteasome inhibitors (PIs) bortezomib, carfilzomib and ixazomib; the immunomodulatory imide drugs (IMiDs) thalidomide, lenalidomide and pomalidomide; and the anti-CD38 monoclonal antibodies (MoAb's) daratumumab and isatuximab. All of these therapeutic agents have demonstrated improved outcomes in myeloma patients.[3,5] Survival of myeloma patients continues to improve over time, particularly with the combination of novel first-line and subsequent agents, resulting in median OS of 8 to 12 years.[6] Survival data in Canada is very similar with median OS of >10 years.[7]

Outcomes of patients with R/R myeloma continues to be an additional important area of unmet need. Clinical data have reported poor outcomes for patients who have become refractory to PIs, IMiDs and MoAb's, with progression-free survival (PFS) of 3.4 months and OS of 9.3 months.[8] This has been confirmed, as well, by real-world data from Canadian patients, with reported PFS of 4.4 months and OS of 10.5 months in triple-class refractory patients.[9]

BCMA as a Therapeutic Target

B-cell maturation antigen (BCMA) is a cell surface protein expressed on late-stage B-cells and plasma cells. It is virtually absent on naïve and memory cells and highly expressed on malignant plasma cells in all patients with myeloma. It is essential for the proliferation and survival of malignant plasma cells.[10-12] In myeloma, BCMA has been targeted as a major area of T-cell engager and antibody-drug conjugate (ADC) research.[12,13]

T-cell Engagers

T-cell engagers are unique constructs that simultaneously bind two antigens, usually engaging an antigen on the tumor and a molecule on an immune cell; this results in immune cell activation and tumor lysis. T-cell engagers teclistamab and elranatamab (both of which target BCMA) recently received FDA approval for use in relapsed myeloma with at least three prior lines of therapy.

Teclistamab is a T-cell engager (BCMAxCD3). The Phase 1-2 Majes TEC-1 clinical study involved 165 patients with

relapsed myeloma with at least 3 prior lines of therapy, and prior use of PI/IMiD and anti-CD38 antibody therapy. At baseline, 77.6% of the subjects were triple-class refractory and had a median of five prior lines of therapy. They demonstrated a 63% OR (39.4% complete response [CR]), with a median PFS of 11.3 months. Cytokine release syndrome (CRS) was present in 72.1% of patients, the majority of which were Grade 1/2; cytopenias (70.9% neutropenia) and infections (76.4%) were common, and 14.5% of patients had some grade of neurological toxicity.[14]

Elranatamab is a bispecific T-cell engager. MagnetisMM-3 was a Phase 2 clinical trial involving 123 relapsed myeloma patients who had received at least 3 prior lines of therapy, all of whom were refractory to a PI, an IMID and anti-CD38 antibody. They had all received a median of five prior lines of therapy; the overall response rate (ORR) was 61%; the median PFS had not been reached; CRS was 57.7%; anemia occurred in 45.5% of patients; neutropenia occurred in 43.1% of patients; infections were common and were reported in 61.8% of patients; and neurological toxicity was reported in 3.4% of patients.[15]

Target	Product	n	ORR	CR
BCMA	Teclistamab	165	63%	39.40%
BCMA	Elranatamab	123	61%	NA
BCMA	CC-93269	30	43%	17%
BCMA	AMG-701	85	26%	10%
BCMA	REGN5458	49	39%	16%
BCMA	TNB-383B	58	47%	14%

Table 1 *T-cell engagers currently being studied*[13]

Additional BCMA T-cell engager agents (engaging BCMAxCD3) for the treatment of R/R myeloma are currently under investigation **(Table 1).**
Aside from BCMA, other antigen targets under investigation for T-cell engagers in R/R myeloma include FcRH5 and GPRC5D, both of which have demonstrated initial results that are encouraging.

Cevostamab, a FcRH5xCD3 construct, was investigated in a Phase I trial involving 160 patients with myeloma who had received a median of six prior lines of therapy. The study results demonstrated an ORR ranging from 53% to 61% at higher doses, with manageable CRS.[16] Long-term data suggest that patients can maintain durable therapeutic response.[17]

Talquetamab, a GPRC5DxCD3 construct, was investigated in MonumenTAL-1, a Phase 1-2 trial involving 288 patients who had received a median of five prior lines of therapy, with two different dosing regimens of 0.4 mg/kg weekly or 0.8 mg/kg q2 weeks. The study results reported an ORR of 74.1 to 73.1%, with median PFS of 7.5 to 11.9 months. CRS was 72.1% to 79%, primarily Grade 1/2. Adverse events were common and the following were observed with the 0.4 mg/kg QW dosing regimen: Anemia occurred in 44.8% of patients; neutropenia occurred in 34.3% of patients; Infections were common: (57.3%); skin-related AEs (55.9%); and nail disorders (51.7%). Rash occurred in 39.2% of patients; dysgeusia occurred in 48.3% of patients. Neurological toxicity was reported at 10.7%. All of these adverse events were managed with supportive care.[18]

A pooled analysis of 11 studies involving 1,185 patients treated with bispecific T cell engager, 71.6% of them targeting BCMA, showed that those targeting BCMA resulted in 34.8% grade 3/4 neutropenia, and 24.5% grade 3/4 infections including 10% grade 3/4 pneumonia and 11.4% grade 3/4 COVID-19 infections. Non-BCMA bispecific T cell engager were associated with lower risk for neutropenia and infections. This pooled analysis also showed a prevalence of 75.3% of hypogammaglobulinemia. Typical and opportunistic infections including cytomegalovirus, candida, herpes virus, pneumocystis were reported with the use of these agents.[19]

Antibody Drug Conjugates
ADCs are MoAb's that contain a cytotoxic drug linked as a payload that releases upon internalization on the antibody. Combinations of a MoAB and a cytotoxic drug are not new. This strategy has been used previously to treat Hodgkin's lymphoma (brentuximab vedotin); and in acute myeloid leukemia (gemtuzumab ozogamicin). Several ADCs have been studied in relapsed myeloma, in most cases as an antibody targeting BCMA, with various cytotoxic drugs used as payloads **(Table 2)**.[13]

Belantamab mafodotin is a humanized afucosylated, IgG1 BCMA-targeted ADC that neutralizes soluble BCMA, with monomethyl auristatin F (MMAF) as its cytotoxic payload. It has four mechanisms of action: antibody-dependent cellular cytotoxicity, immunogenic cell death, BCMA receptor signaling inhibition, and ADC. It was approved in August of 2020 for patients with R/R myeloma who have received >4 lines of therapy including a PI, an IMiD and an anti-CD38 antibody.[12,20,21]

The Phase 1 DREAMM-1 trial involving 35 patients with refractory myeloma showed an ORR of 60%.[22] Phase 2 data from the DREAMM-2 trial involving 196 patients comparing two doses, 2.5mg/kg q3 week and 3.4 mg/kg q3 week, reported an ORR of 30-34% with a median PFS of 2.9 to 4.9 months.[23] The Phase 3 DREAMM-3 trial involving 325 patients, comparing belantamab mafodotin 2.5 mg/kg q3 week to pomalidomide plus dexamethasone in R/R myeloma

Name	Target	Cytotoxic agent	Combination	Phase (number of patients)	Response
Belantamab mafodotin	BCMA	MMAF	Monotherapy	1; n=35	ORR 60%
			Monotherapy	2; n=96	ORR 30-34%
			B vs Pd	3; n=325	ORR 41%
			B-Pd	1/2; n=96	ORR 88.9%
			B-Pd vs V-Pd	3; n=450	N/A
MEDI2228	BCMA	PBD	Monotherapy	1; n=82	ORR 66%
CC 99712	BCMA	Maytansinoid-like	Monotherapy	1; n=160	N/A
AMG 224	BCMA	Mertansine	Monotherapy	1; n=42	ORR 27%

Table 2. *ADCs currently being studied in relapsed myeloma*[13]

did not meet its primary endpoint of PFS (11.2 vs 7 months; HR 1.03; 95% CI, 0.72-1.47). It reported an ORR of 41% vs 36%.[24,25]

Common adverse events with belantamab mafodotin include keratopathy, thrombocytopenia, and anemia. Corneal toxicity was associated with the MMAF cytotoxic payload; most ocular toxicity was reversible when holding treatment. In certain subsequent trials of combination therapy, the incidence of keratopathy was as high as 81%.[23,24]

MEDI2228 is a fully humanized anti-BCMA antibody conjugated with pyrrolobenzodiazepine (a DNA cross-linking agent), which binds to membrane bound BCMA. A Phase 1 dose finding and toxicity study is ongoing.[26]

Conclusion

In the past 20 years, the advent of novel agents for the treatment of MM has definitely led to a notable improvement in survival, from 3-4 years in the 1990s to close to 8-12 years, according to the most recent data.[6,7]

Immunotherapies such as T-cell engagers and ADC-targeting novel antigens such as BCMA in myeloma are promising therapeutic options. Early clinical trial results show median PFS (11.3 months) that is significantly greater than that of standard of care options for heavily pretreated R/R myeloma (4.4 months).[9]

The advantage of ADCs and T-cell engagers is that they are readily available compared to that of other novel approaches such as CAR T-cell therapy which may require a lengthy manufacturing process and may result in delays in some cases due to supply chain issues. However, these agents also have disadvantages such as the need for ongoing treatment, especially when compared to a single dose of CAR T-cell therapy. Furthermore, in some cases, these novel agents are associated with new toxicities, such as ocular toxicity (keratopathy) which may limit their use or lead to dosing delays.

The future for myeloma patients appears promising, with a growing number of therapeutic options. These include non-BCMA antigen targeted therapy and CAR T-cell therapy, which have shown anti-myeloma activity in R/R myeloma, and the use of more active triplet and quadruplet regimens in a first-line setting.

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