Targeted therapies in multiple myeloma: new antibodies and CAR-T cells

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SUMMARY

New therapeutic antibodies and T cells redirected to specific antigen targets with engineered chimeric antigen receptors (CARs) are emerging as powerful therapies in haematologic malignancies and multiple myeloma (MM). Various designs, manufacturing processes, and study populations, among other variables, have been tested and reported in clinical trials in MM. Here, we review and compare ongoing trials and the results of the reported clinical trials. We also discuss the outlook for CAR-T cell therapies, including managing toxicities and expanding the availability of personalized cell therapy as a promising approach to all haematologic malignancies.

INTRODUCTION

In 2015, the American Food and Drug Administration (FDA) and the European Medical Agency (EMA) approved 2 monoclonal antibodies (mAb) targeted against surface antigens on myeloma cells: daratumumab directed against CD38 and elotuzumab targeting SLAMF7. Based on their distinct mechanisms of action and their generally favourable toxicity profile, these mAbs were considered attractive partners in combination regimens and triggered the development of other therapeutic antibodies.[1]

Chimeric antigen receptor (CAR) T cell therapy is one kind of cancer immunotherapy that is rapidly evolving. It has been most successful in B cell malignancies with CD19 as most frequently targeted antigen, and there are numerous trials concerning various antigens in other hematological malignanciea.[2]

NEW THERAPEUTIC ANTIBODIES

ANTI-CD38 MAB

Isatuximab: A phase III combination trial comparing pomalidomide and dexamethasone with and without this new anti-CD38 mAb has an estimated completion date of 2021. Two additional phase III trials were launched in 2017. The IKEMA trial is comparing isatuximab in combination with carfilzomib and dexamethasone, compared to carfilzomib and dexamethasone alone in relapsed or refractory myeloma patients who have received 1 - 3 prior treatments. The IMROZ trial is studying the impact of adding isatuximab to bortezomib, lenalidomide and dexamethasone in newly diagnosed MM patients who are ineligible for a stem cell transplant (*Table 1*).[3,4]

MOR202: A phase I/IIa study of the human anti-CD38 moAb MOR202 as monotherapy and in combination with standard therapy in subjects with relapsed/refractory MM is running since 2011 (*Table 2*).[3,4]

CHECKPOINT INHIBITORS

The very first immune checkpoint called cytotoxic T-lymphocyte-associated protein (CTLA)-4 was discovered over 20 years ago and highlighted the body's ability to regulate the function of the immune system and illustrated the delicate balance in the recognition of self and non-self. The presence of CTLA-4 also appears to have a role in the bone marrow microenvironment for MM patients. The first inhibitor of this immune checkpoint that was used is ipilimumab and later on a second CTLA-4 inhibitor called tremelimumab was developed. Today there are no published clinical trials data with either of these inhibitors. Ipilimumab was studied in four patients in a post-allo setting where 6 out of 29 had MM. No responses were seen in the subgroup of MM patients. The more recent discovery of Programmed cell death protein (PD)-1 revealed that PD-1 was expressed on the surface of activated B cells and of natural killer cells. Researchers found that higher PD-1 expression is also associated with

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Conflict of interest: The authors have nothing to disclose and indicate no potential conflict of interest.

TABLE 1. Overview of ongoing clinical studies with isatuximab.

Study	Phase	Disease	Setting	Treatment
NCT01084252	1/2	CD38-positive hemato-logic malignancies	Relapsed/refractory	Isatuximab as single agent
NCT01749969	1b	MM	Relapsed/refractory	Isatuximab in combination with lenalidomide-dexamethasone
NCT02283775	1b	MM	Relapsed/refractory	Isatuximab in combination with pomalidomide-dexamethasone
NCT02513186	1	MM	Newly diagnosed, non-transplant eligible	Isatuximab in combination with CyBorD
NCT02332850	1b	MM	Relapsed/refractory	Isatuximab combined with carfilzomib

CyBorD: cyclophosphamide, bortezomib, and dexamethasone

higher myeloma proliferation, higher Bcl-2 levels and higher lactate dehydrogenase levels, all poor indicators of MM progression. Promising phase III studies were set up investigating the combination of pembrolizumab with either lenalidomide and dexamethasone, or pomalidomide and dexamethasone. Unfortunately, in July 2017 the FDA decided that all patients enrolled in KEYNOTE-183 and KEYNOTE-185 had to be discontinued from further examination as a result of toxicity concerns and the trials were halted prematurely. Interim results had shown an increased risk of death with pembrolizumab.

However, checkpoint inhibitors will not completely fade away from the myeloma landscape. They may be more effective and better tolerated in combination with an antibody like daratumumab and could also be used in combination with CAR-T cell therapy.[5]

ANTI-B-CELL ACTIVATING FACTOR (BAFF) ANTIBODY

Tabalumab, a human anti-B-cell activating factor (BAFF) antibody, is studied in combination with bortezomib and dexamethasone in patients with previously treated MM. There are no published data yet.

ANTIBODY-DRUG CONJUGATES IN EARLY PHASE DEVELOPMENT

Milatuzumab doxorubicine utilises the first anti-CD74 humanized mAb that has entered into human testing. CD74 is an attractive target for a drug conjugate because of its rapid internalising property. Lorvotuzumab mertansine combines the CD56-binding mAb, lorvotuzumab, with the maytansinoid cell-killing agent DM1 via a disulfide linker. Finally, indatuximab ravtansine consists of the anti-CD138 chimerized moAb linked to the maytansinoid DM4. Other antibody drug conjugates in early phase development are GSK2857916 (anti-B-cell maturation antigen), ABBV-838 (anti-SLAMF7) and SGN-CD352A.

CAR-T CELLS

Chimeric antigen receptors, or CARs, are receptors that recognize tumour antigens independently from major histocompatibility complex (MHC) restriction.[6,7] Through the use of viral or non-viral vectors, T cells become adapted to express a chimeric antigen receptor.[6,8] The modified T cells that arise have cytotoxic activity towards tumour cells and are able to persist and self-amplify. They can be considered a kind of 'living drug' and can be used to target an antigen when mAbs are insufficient (e.g. when the density of the antigen is low).[9] With this treatment modality there is a possibility of treatment-free intervals with high quality of life, after a short period of treatment-related toxicity.[10]

In order to produce CAR-T cells, patients or donors are subjected to leukapheresis.[8] In some protocols a specific wash-out period for therapies such as immunomodulatory drugs or chemotherapy is respected before leukapheresis, in order to avoid impaired CAR-T cell proliferation.[11] The 'harvest' consists of a varying amount of memory T cells and a varying ratio of CD4:CD8 T cells. New techniques using magnetic bead isolation have been developed to increase the number of central memory T cell subsets and to standardise CD4:CD8 ratios.[7] Antibody bead conjugates or markers are used, in order to separate CD4 from CD8 counterparts.[8]

TABLE 2. Clinical study with MOR202.

Study	Phase	Disease	Setting	Treatment
NCT01421186	1/2	MM	Relapsed/refractory	MOR202 with or without dexamethasone (later stage MOR202 with lenalidomide-dexamethasone and MOR202 with pomalidomide-dexamethasone)

To get activated cells, they are cultured with autologous antigen-presenting cells (APC's), beads coated with anti-CD3 of anti-CD28 antibodies, or anti-CD3 antibodies with feeder cells and growth factors such as IL-2.[7,8]

Lentiviruses are generally used more often than retro-viruses, because of a safer profile. DNA minicircles, plasmid vectors, liposomes, polymerisers and molecular conjugates are examples of non-viral vectors, which have higher efficacy, specificity and carrier capacity and are non-infectious and safer. The use of DNA mini circles is associated with a higher gene transfer rate and cell viability than the use of plasmids, has a safer genomic integration than lentiviruses and is less expensive and less toxic than common techniques, and can become the preferred technique for the future.[12]

In *Table 3*, an overview of ongoing clinical trials with CAR-T cells in MM is provided.

SAFETY CONSIDERATIONS WITH CAR-T CELLS IN CLINICAL PRACTICE

Not only the conditioning lymphodepleting therapy prior to CAR-T cell therapy can have safety hazards, the genetically engineered T cells can have a toxicity of their own. Neutropenic infections, prolonged cytopaenias and tumour lysis syndrome are possible side-effects.[29-31]

Administering CAR-T cells to a patient, can give rise to a cytokine release syndrome (CRS). The severity of this phenomenon can vary from flu-like symptoms to severe hypotension requiring vasopressors, capillary leak, coagulopathy and organ dysfunction. It can have a biphasic course and severity can be related to tumor burden and therapeutic response to CAR T cell therapy. A uniform grading system is being developed to guide management of CRS according to severity. Besides supportive measures, an IL-6 receptor blocker, Tocilizumab, can be administered to reverse these systemic effects, without reducing efficiency of CAR T cell therapy. Corticosteroids can be reserved as a second line therapy for more severe cases. A second dose of Tocilizumab and the anti-IL-6 antibody Siltuximab, can be considered respectively for third and fourth line of therapy. Theoretically, other T cell directed therapies such as anti-thymocyte globulin, alemtuzumab or cyclophosphamide, can also be addressed in this context.

With this CRS, components of a macrophage-activation syndrome such as coagulopathy, cytopenias and liver dysfunction, can also be seen. In this case, frequent monitoring of fibrinogen levels and substituting with cryoprecipitate or fibrinogen is very important.

Another pitfall of CAR-T cell therapy, is the possibility of neurotoxicity. High cytokines and endothelial activation and disruption of the blood-brain barrier may contribute to the pathophysiology, though all aspects of this neurotoxicity are not yet disclosed. Usually the process is fully reversible. Encephalopathy can be mild with transient confusion, delirium, hallucinations, seizures and aphasia and it can be more severe with motor weakness, cerebral oedema, incontinence, somnolence, severe seizures, etc.

Finally, using viral vectors and genetic engineering, has led to concerns about oncogenicity and infectivity of this therapy. Further investigation is required, but at this moment there is no hard evidence for such complications.[32]

CONCLUSIONS

Immunotherapy that uses monoclonal antibodies and genetically engineered immune cells can be highly effective in patients with newly diagnosed and advanced MM. Although most patients in early phase clinical trials had good responses to the treatment, including many who experienced complete remissions, the length of time that most patients have been followed after receiving the treatment is still limited. Serious side effects, including immune-related effects seen in other CAR T-cell trials, have been limited in myeloma patients treated to date. We need to validate these early findings and to see if we can make this type of therapy accessible to more patients.

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TABLE 3. Web of Science published results of CAR-T cell clinical trials for multiple myeloma.

	Expansion method	Transfer method	Antigen	Signaling domains
n=5 [13]	aCD3 IFN-γ/IL-2	Lentiviral	CD138	4-1BB/CD3ζ
n=1 [14]	ND	ND	CD138	ND
n=12 [15]	aCD3	Retroviral	BCMA	CD28/CD3ζ
n=16 [10]	aCD3	Retroviral	BCMA	CD28/CD3ζ
n=21 [16,17]	aCD3/CD28	Lentiviral	BCMA	4-1BB/CD3ζ
n=5 [18]	ND	ND	BCMA	ND
n=21 [19]	ND	Lentiviral	BCMA	4-1BB/CD3ζ
n=22/35 [20,21]	ND	Lentiviral	BCMA	4-1BB/CD3ζ
n=6 [22]	ND	Retroviral	BCMA	4-1BB/CD3ζ + EGFRt
n=10 [23]	ND	Retroviral	BCMA	4-1BB/CD3ζ + EGFRt
n=8 [24]	aCD3	Lentiviral	BCMA/CD19	OX40/CD28/CD3ζ
n=10 [25,26]	aCD3/CD28	Lentiviral	CD19	4-1BB/CD3ζ
n=5 [27]	OKT3 IL-2	Retroviral	NKG2D	CD3ζ
n=7 [28]	OKT3 or aCD3/CD28 IL-2 or IL-7+IL-15	Retroviral	κLC	CD28/CD3ζ

n: number of patients; aCD3/CD28, anti-CD3 or CD28 monoclonal antibody; IFN: interferon; IL: interleukin-; ND: no data; BCMA: B-cell maturation agent; κLC: kappa light chain; EGFRt: truncated epidermal growth-factor receptor; PCD: pomalidomide-cyclophosphamide-dexamethasone; CP: cyclophosphamide; VAD: vincristine-doxorubicin-dexamethasone; Flu: fludarabine; Mel: melphalan;

T-cell dosage	Conditioning	Therapy-related side effects	Clinical effects
0.756×10^{7}/kg	PCD, CP or VAD	• Infusion-related fever (4)	• SD >3m (4) • ↓ circulating PCL cells (1)
1.5×10^{8}/kg	CP/Flu	CRS	PR
0.3-1-3-9×10^{6}/kg	CP/Flu	• Prolonged cytopenias (2) • CRS (5, dose-related)	• CR (1) • VGPR/PR (3) • SD (8)
9×10^{6}/kg	CP/Flu	• CRS (severe but reversible)	• CR/VGPR 63% • ORR 83% • Median EFS 31 wks
1-5×10$^{7-8}$/kg	CP or none	• CRS (8) • CRES (2)	• CR (2) • VGPR (3) / PR (6) • MR (5) / SD (5)
0.17-1.05×10^{6}/kg	CP/Flu	• CRS (5)	• CR (1) • VGPR (3) / PR (1)
50-800×10^{6}/kg	CP/Flu	• Grade 1 or 2 CRS (13) • Grade 3 CRS (2)	• sCR (3/18) / CR (1/18) • VGPR (7/18) / PR (5/18) • SD (1/18)
1.5-7×10^{6}/kg	CP	Grade 3 or 4 CRS (3)	• CR (6) • VGPR (14) / PR (1) • Transient PR (1)
72-137×10^{6}/kg	CP or CP/Flu	• Grade 1 or 2 CRS (3)	• VGPR (2/4) / PR (1/4) • SD (1/4)
9×10^{6}/kg	CP/Flu	• No greater than grade 1 toxicity	• CR (2/7) • VGPR (2/7)
2.5-8.2×10^{7}/kg	CP/Flu	• CRS (8)	• sCR (1/5) • VGPR (1/5) / PR (2/5) • SD (1/5)
1-5×10^{7}/kg	Mel/ASCT	• GvHD (1, probable) • Mucositis (1, possible)	• VGPR (6) at d100 post-ASCT • PR (2) at d100 post-ASCT • ↑ PFS (2)
1-3×10$^{7-8}$/kg	None	• None	• None
1-2×10^{8}/m^{2}	CP (4) or none (3)	Lymphopenia (1, possible)	SD 6wk-24m (4)

ASCT: autologous stem cell transplant; CRS: cytokine release syndrome; CRES: CAR-T cell-related encephalopathy syndrome; GvHD: graft-versus-host disease; SD: stable disease; PCL: plasma cell leukemia; (s)CR: (sustained) complete response; (VG)PR: (very good) partial response; ORR: objective response rate; EFS/PFS: event-free survival or progression-free survival; d: days; wk: weeks; m: months.

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