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New opportunities in immunotherapy in multiple myeloma

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Abstract

Immunotherapy is a rapidly developing field of multiple myeloma, a disease which despite the development of new drugs remains incurable. There are several antigens that are being assessed in preclinical and clinical settings, but the most studied of all is B-cell maturation antigen (BCMA). BCMA is a target for antibody conjugated with toxins (ADCs), bispecific engagers (BITEs), and modified autologous lymphocytes (CAR-T, chimeric antigen receptor T cells). Belantamab mafodotin (ADC, registered in the European Union), teclistamab (BITE) and two CAR-Ts: ide-cel (Food and Drug Administation-approved) and cilta-cel are the most studied therapies in myeloma. Immunotherapy will definitely change the treatment strategy of multiple myeloma and accelerate the fight against myeloma.

Key words: immunotherapy, CAR-T, bispecific antibodies

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Mutliple myeloma, despite the introduction of new drugs, remains incurable mostly due to its acquired resistance to all existing therapies. The mechanism of resistance is multifactorial and still not fully understood, but one major factor is immunological escape. Such escape is related to genetic alterations leading to loss of antigens and the development of resistance to immune effector responses. The immunosuppression seen in myeloma is a result of T cell exhaustion, tolerance by tumor-associated antigen-presenting cells, alterations in cytokine production, and accumulation of myeloid-derived suppressor cells and suppressive tumor-associated macrophages [1, 2]. Therefore, the search for therapies that are focused on activation of the immune system seems a promising direction for improvements in treatment.

Immunotherapy is currently the most promising area of the development of myeloma therapy. There are several different approaches to activating the immune system in the fight against myeloma, including immunomodulatory drugs (IMiDs).

IMiDs act not only by direct myeloma cell killing, but also by stimulation of T and NK cells which is an effect of increased production of IL (interleukin)-2 and IFNγ and reduction of IL-10 production in both CD4+ and CD8+ T [3]. IMiDs, due to their good toxicity profile, can be combined with other immunostimulatory drugs such as elotuzumab, an IgG monoclonal antibody against SMALF7 (previously CCS1). The cumulative immunostimulatory effect was very visible in the Eloquent 2 and 3 studies, where elotuzumab was added to either lenalidomide (Eloquent 2) or pomalidomide (Eloquent 3) and dexamethasone for patients with refractory myeloma. Elotuzumab has a weak direct impact on myeloma cells (no significant responses were seen when used as a single agent), but by activation of NK cells through both CD16-mediated antibody dependent cellular cytotoxicity (ADCC) and direct co-stimulation via engagement with SLAMF7 and promoting antibody dependent cellular phagocytosis (ADCP) by macrophages, it engages the immune system against myeloma. In Eloquent 2, the addition of elotuzumab to lenalidomide

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results in a 30% reduction of progression or death compared to lenalidomide and dexamethasone, with a median progression-free survival (PFS) of 19.4 months compared to 14.9 months in the control arm [4]. In Eloquent 3, the effect was even more visible: a combination of elotuzumab and pomalidomide resulted in a 47% reduction in risk of death or progression compared to pomalidomide, with median PFS of 10.9 and 4.7 months respectively [5]. Both combinations are already registered by the European Medicines Agency (EMA).

However, the most widely studied antigen in myeloma is B cell maturation antigen (BCMA). BCMA is present only in late memory B cells and plasma cells, and is more expressed on myeloma cells compared to healthy plasma cells. The development of immunotherapy that is focused on BCMA includes monoclonal antibodies conjugated with cellular toxins (ADCs), bispecific T cell engagers (BiTEs), and therapy with modified human lymphocytes (CAR-T, chimeric antigen receptor T cells).

There are several ADCs under development in the treatment of multiple myeloma: belantamab mafodotin, CC-99712 and MEDI2228. Belantamab mafodotin (Blenrep) is the most advanced of these. It is an IgG kappa monoclonal antibody directed against BCMA antigen conjugated with the cellular toxin auristatin F. There have been promising results in the DREAMM1 study, where clinical efficacy [at least a partial response (PR)] was demonstrated in 60% of patients, paving the way towards the phase II study DREAMM2, which assessed the efficacy and safety of two doses of belantamab: 2.5 and 3.4 mg/kg. That study included patients with very advanced disease (median number of lines of therapy for dose of 2.5 mg/kg was 7, and for dose of 3.4 mg/kg was 6). The vast majority of patients were refractory to daratumumab (92–100%), pomalidomide (78–87%) and carfilzomib (58–65%). The study showed a median PFS of 2.9 months for the lower dose and 4.9 months for the higher dose.

Among adverse events that are seen in patients in such advanced myeloma, one is new and definitely will impact patients treated with belantamab. Keratopathy, an effect of auristatin F, was seen in more than 70% of patients in DREAMM2. Keratopathy grade 3 or higher was observed in 46% treated with the lower dose and in 42% of those treated with the higher dose. This complication is temporary and usually resolves after dose modification and symptomatic treatment. However, it is very troublesome due to its affecting vision. In subsequent studies, the percentage of these side effects was slightly lower, which results from procedures being developed which more carefully qualify patients for belantamab therapy, introducing prophylactic masks to cool the eye area to reduce perfusion in the eyeball, a routine ophthalmological assessment, and the use of protective, moisturizing and anti-inflammatory drops. Belantamab is currently being explored in different phases of myeloma and will surely soon complement the drugs available to combat myeloma. This drug was approved in 2020 by the EMA for patients with refractory multiple myeloma who had received at least four lines of treatment including an immunomodulatory drug, a proteasome inhibitor, and a monoclonal antibody [6].

Bispecific antibodies that bridge T cells (typically via CD3) and tumor-specific antigens (in myeloma mostly BCMA) are more advanced forms of immunotherapy. The most common formulations are bispecific T cell engagers (BiTEs), which only comprise the variable heavy and light chain regions. This allows for T cell engagement and activation after tumor antigen recognition that is independent of T cell receptor (TCR) specificity. It is important to note that BiTEs rely on the presence of a functional T cell response, and this therapy is likely to be most efficacious early in the disease course. Several molecules are currently being investigated in different phases of clinical trials, including AMG 420, teclistamab, AMG 701, CC-93269, PF-06863135, and REGN5458. One of the first molecules used in humans was AMG 420, a bispecific antibody against CD3 antigen and BCMA. This molecule is composed of two light chains, which is associated with a very short half-life and the use of continuous, multi-day intravenous infusion. A study that enrolled 42 patients with very advanced disease (median number of previous treatment lines 7) showed very promising efficacy with an overall response rate reaching 70% depending on the dose of the drug with a good toxicity profile: no severe symptoms of cytokine release syndrome (CRS) and no neurological complications (ICANS, immune effector cell-associated neurotoxicity syndrome) were observed. The most important issue was infections, which occurred in 20/42 patients and resulted in the death of two of them. Despite quite optimistic results, this drug is no longer being developed due to the serious logistical difficulties resulting from the need to hospitalize patients for many weeks to allow continuous drug infusion [7].

A molecule with a similar concept of action against myeloma is teclistamab. This is an antibody similarly to AMG 420 directed against CD3 and BCMA antigens. It has been constructed as a complete immunoglobulin, which gives it a much longer half-life and the possibility of subcutaneous administration once a week. This drug is currently being evaluated at varying levels in clinical trials with very promising results. Efficacy was demonstrated in a phase I study involving 72 patients. The best results were achieved at a dose of 270 μg/kg: overall response rate (ORR) was 67% including very good partial response (VGPR) in 50%, although the number of patients was very small at 12. Importantly, the treatment was well tolerated except for hematological and infectious complications observed at a similar percentage and severity as in other studies

enrolling patients with very advanced myeloma; 44 patients had cytokine release syndrome, although no grade 3 or higher was found [8]. In the context of cell therapies and related logistic complications, teclistamab will clearly become an attractive alternative to CAR-T.

The therapy with the most spectacular results, and so the one with which the greatest hopes are associated, is therapy with modified human lymphocytes. CAR-T cells have been revolutionary in the treatment of patients with B cell malignancies, in which CD19 serves as an ideal target. There are several constructs of CAR-T currently under development in clinical and preclinical settings in myeloma that are directed against BCMA: ide-cel (called Abecma in the USA), cilta-cel, ALLO-715, bb21217, LCAR-B38M, orvacabtagene autoleucel, and P-BCMA-101. The first two are the closest to achieving EMA registration. Ide-cel, previously named bb2121, was registered by the Food and Drug Administation (FDA) based on the KarMMA study in March 2021. In the study, three different doses of 'the drug' were evaluated: 150 $\times 10^6$, 300 $\times 10^6$, and 450 $\times 10^6$ cells per kg. The study was performed on 128 patients with refractory and relapsed multiple myeloma with a median number of treatment lines of 6. The study showed an ORR of 73% in the entire population, including complete response (CR) of 31%. In the group of patients treated with the highest dose this was 82% and 35%, respectively. The median PFS of the whole population of the study was 10.6 months, while for the more effective higher dose it was 11.3 months. Severe neurological complications and CRS were observed only in 5% and 3%, respectively.

Based on the KarMMA study, ide-cel has been approved in the USA for patients previously treated with at least four lines of therapy including an immunomodulatory drug, a proteasome inhibitor, and an anti-CD38 monoclonal antibody [9]. This CAR-T construct is also being developed with a manufacturing modification (bb21217) which involves incubation of the cells with a phosphatidylinositol 3-kinase (PI3K) inhibitor. That process aims to increase the subpopulation of memory cells and eventually prolong the period of CAR-T anti-myeloma activity. In a phase I study which included 69 patients, very high efficacy was demonstrated: ORR reached 83% and CR 42%, with median PFS of 17 months. As in the KarMMa study, only isolated cases of severe CRS and ICANS syndromes were observed.

The second very advanced CAR-T construct studied in multiple myeloma is cilta-cel. This drug, like ide-cel, targets the BCMA antigen, although each receptor has two recognition domains, whereas ide-cel has only one. The Cartitude 1 study results, presented at American Society of Hematology (ASH) 2020, were very promising: in 97 patients with a similar population of myeloma patients as in the KarMMa study (median number of treatment lines of 6), 97% of patients achieved at least PR, including VGPR in 92.8% and CR in 67%.

Considering the challenging patient population that was included in Cartitude 1, these results are spectacular. Symptoms of cytokine release syndrome of at least grade 3 were found in 4% of patients, and ICANS in 2%. One patient died of hemophagocytic syndrome as a consequence of the CRS. Interestingly, late neurological complications other than ICANS of at least grade 3 were observed in 12% of patients [10].

CAR-T therapy based on the modification of autologous lymphocytes, despite its undeniable effectiveness, is associated with a number of logistical issues. CAR-Ts need to be produced and transported; this requires time and is very expensive and the process is not always successful. Modified allogeneic lymphocytes are an extremely attractive alternative, which as universal cells can wait for the patient, just like an ordinary medicine in a pharmacy. Research on such a design of allogeneic CAR-T 'off-shelf' is already underway and the results are very promising. The construction of ALLO715, where, in addition to the modified anti-BCMA receptor, lymphocytes lacked the TCR, was evaluated in a phase I study involving 36 patients with refractory multiple myeloma. ORR was observed in 30% of patients, but a much more important observation was the virtual absence of severe forms of CRS, ICANS and, above all, graft-versus-host disease (GvHD) [11].

BCMA is only one of a number of targets being explored as immunotherapeutic targets. An example is talquetamab, a BiTe specific to CD3 and GPRC5D. This antibody was successfully assessed in a phase I study, and is now being studied in a phase II [12].

Immunotherapy is a vigorous and dynamically developing field of oncology which we have high hopes for, and likewise in multiple myeloma. Advanced antibodies and cell therapies are becoming vital tools in the fight against cancer, and will remodel the treatment strategy of multiple myeloma over the next few years.

Author's contributions

DD — sole author.

Conflict of interest

None.

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Ethics

The work described in this article has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans; EU Directive 2010/63/EU for animal experiments; Uniform requirements for manuscripts submitted to biomedical journals.

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