HemaSphere

EHA EUROPEAN HEMATOLOGY ASSOCIATION

Editorial
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Anti-BCMA CAR T-cell Therapy: Changing the Natural History of Multiple Myeloma

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The treatment of multiple myeloma (MM) is in necessary evolution to overcome the refractoriness and the mechanisms of tumor escape from immune surveillance to improve survival. One of the big challenges is to offer new therapeutic alternatives to patients who have already been exposed to immunomodulatory drugs (IMiDs), proteosome inhibitors (PIs), and antiCD38 antibodies (MoAbs), called as triple-exposed MM patients. These patients have poor prognosis, especially when they become refractory to IMiDs, PIs, and CD38 MoAbs, as shown in recent studies. The MAMMOTH retrospective study included 275 MM patients refractory to CD38 MoAbs and showed that the median overall survival (OS) for this group was only 11 months. Moreover, when patients were triple refractory, median OS was 9 months, and only 6 months if they were also pentarefractory (bortezomib, carfilzomib, lenalidomide, pomalidomide, and CD38 MoAb refractory).[1] Interesting conclusions can also be drawn from the LocoMMotion trial, the first prospective, noninterventional, multinational study of real-life current standards of care in relapsed/refractory multiple myeloma (RRMM) patients who have received ≥3 prior lines of therapy. All of these MM patients were triple-class exposed and 70% were triple refractory with an overall response ratio (ORR) of 20.1% and only 5% of patients achieving very good partial response (VGPR) or better.[2,3] Moreover, the response rate, depth of response, and time to disease progression of MM patients decreases with each subsequent line of therapy, making late-stage MM difficult to treat.[4] In this regard, novel therapies targeting B-cell maturation antigen (BCMA), and especially, chimeric antigen receptor (CAR) T-cell therapy against BCMA might be promising approaches. These therapies could change the natural history of the disease, as shown by recent results published and reported in last ASH, EHA, and ASCO meetings.

The results of the KarMMa and CARTITUDE-1 studies demonstrate how effective and safe BCMA CAR T-cell therapy can be in RRMM patients, especially in the triple refractory group. The KarMMa study enrolled RRMM patients who had received ≥3 prior lines of therapy (median, 6 previous regimens).[5] In this study, 84% and 26% of patients were triple or pentarefractory, respectively.[5] The results of the study have been recently updated with a follow up of 24.8 months and are showing that 73% (94 of 128) of patients treated with Idecabtagene Vicleucel (ide-cel) achieved VGPR, 33% (42 of 128) stringent complete response or complete response (CR), and 26% (33 of 128) minimal residual disease negative status. The median duration of response was 10.9 months, median progression free survival (PFS) was 8.6 months, with an impressive median OS of 24.8 months. The median duration of response increased with depth of response, being 21.5 months for patients who achieve CR or better.[6,7] Therefore, these data display that ide-cel is an effective disruptive therapy regardless of the number or prior lines of treatment. Recently, ide-cel received a positive opinion by EMA and the approval is expected for RRMM after at least 3 prior therapies including PI, IMiD, and antiCD38 and refractory to the last line. Interestingly, in the CARTITUDE-1 trial, a very similar group of patients was included (≥3 prior lines of therapy, median was 6) with 88% (85 to 97) of patients being triple refractory and 42% (41 of 97) being pentarefractory. Very encouraging results have been presented in the update of the study, with a median follow up of 18 months. Here, the ORR was 98% (95 of 97), with 80% (78 of 97) of patients achieving stringent CR and 58% (56 to 97) had negative minimal residual disease. This high proportion of rapid and deep responses translated into a remarkable 18-month PFS rate of 66% as well as OS rate of 81%.[8,9]

More evidence supporting that BCMA CAR T-cell therapy is changing the natural history of the disease is the KarMMa-RW study. In this retrospective study, outcomes of KarMMa patients were compared with outcomes of a comparable real-world cohort of triple-class exposed MM patients, showing that ORR, CR, PFS, and OS were better with ide-cel than with currents standards of therapy for this population.[10] In the case of patients treated with ide-cel, ORR and the achievement of VGPR or better was 76.4% and 57.9%, respectively, versus 32.2% and 13.7% in the real-world cohort of triple exposed. Similar studies were developed with CARTITUDE-1. The treatment with cilta-cel provided superior outcomes in comparison with real-word clinical practice regimens. Weisel and colleagues presented at the EHA 2021 congress the different outcomes between triple-exposed patients that received cilta-cel and SOC based in clinical trials with daratumuab (POLLUX, CASTOR, and

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HemaSphere (2022) 6:3(e691).
http://dx.doi.org/10.1097/HS9.0000000000000691.

EQUULEUS).[11] Cilta-cel had better results, with ORR of 97.9% and CR or better of 80.4% compared with 33.6% and 0.7% with SOC. In the absence of head-to-head comparison between ide-cel or cilta-cel and treatments of real-world clinical practice, these studies suggest that treatment with anti-BCMA CAR T-cell therapy offers substantially more clinical benefit than current real-world regimens for triple-exposed patients with RRMM.

Furthermore, if heavily pretreated patients can achieve a deep and durable response with BCMA CAR T-cell therapy, we could infer that the response to the BCMA CAR T-cell therapy in prior lines would be even more effective and more sustained. Indeed, there are ongoing clinical trials, such as CARTITUDE-2, to test this hypothesis, with already interesting preliminary results with cilta-cel in RRMM after 1 to 3 prior lines of therapy. The results of CARTITUDE-2 were presented at the recent ASCO and EHA conferences, with an ORR of 95% and 85% of patients achieved VGPR or better.[12]

However, this novel therapy has also a number of disadvantages. Regarding safety, early complications are very common, occurring within the first weeks after infusion.[13] The most frequent adverse event is cytokine releasing syndrome (CRS), although severe or life-threatening CRS (grade 3 or 4) is uncommon (<5%). Other toxicities to be aware of are immune effector cell associated syndrome (known as ICANS), cytopenias, or hypogammaglobulinemia due to B-cell aplasia. Nevertheless, the initial severe adverse events reported in the pivotal trials are decreasing with closer monitoring and aggressive management by clinicians. In addition, a logistic support and production time, usually taking 3 to 4 weeks to manufacture, is needed. Some patients with aggressive disease cannot wait that long and can already progress with fatal outcome, while the CAR T-cell manufacturing is ongoing. For this reason, the patient selection should be careful and accurate, as well as the selection of bridging therapy. As well as to consider using so called *off-the-shelf* BCMA targeting therapies such as belantamab, conjugated-drug antibody,[14] or clinical trials with bispecific antibodies. However, there is a lack of trials comparing these strategies to conclude which one is more effective and safer. In addition, further research is required to address other concerns such as prevention of T-cell exhaustion, the potential acquisition of resistance to BCMA CAR T-cell therapy,[15] information about efficacy of rescue treatments and development of new rescue drugs after BCMA CART therapy.

In summary, the results of long-term follow up of MM patients treated with BCMA CAR T-cell therapies ide-cel and cilta-cel in KarMMa and CARTITUDE-1 trials have demonstrated that CAR T-cell therapies can improve outcomes in a poor prognosis population such as the triple-refractory MM patients. This is providing a unique opportunity to change the natural history of myeloma once these strategies will be approved. Many questions remain open about whether these CAR T-cell therapies will replace the conventional treatments in early phases of the disease or complement the current standards of care. Several clinical trials are ongoing to address these uncertainties.

SOURCE OF FUNDING

This work was supported by "Fundación para el Desarrollo de la Hematología y Hemoterapia en Salamanca."

DISCLOSURES

MVM has received honoraria derived from lectures and advisory boards from Janssen, BMS-Celgene, Amgen, Takeda, Abbvie, Sanofi, Oncopeptides, Adaptive, Roche, Pfizer, Regeneron, GSK, Bluebird Bio, Sea-Gen. VGC has received honoraria from Janssen and Celgene, research funding from Janssen; consulting or advisory role for Prothena and Janssen. BPM has received honoraria from Janssen.

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