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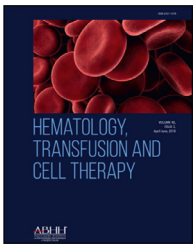

Special article

Associação Brasileira de Hematologia, Hemoterapia e Terapia Celular Consensus on genetically modified cells. IV: CAR-T cell therapy for multiple myeloma patients

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ABSTRACT

Extraordinary progress has been made over the last decade in the treatment of multiple myeloma with the incorporation of new drugs, particularly proteasome inhibitors, immunomodulators, and monoclonal antibodies.

The combined use of innovative drugs, already in the first lines of treatment, has led to an expressive increase in the survival of these patients. However, the approach to relapse remains a great challenge, and the disease continues to be incurable. In this scenario, modern immunotherapy has gained the limelight, especially with its recent use of CAR-T cells in clinical trials, as in the case of multiple myeloma, having the BCMA as the primary target.

The results are impactful in the treatment of multiple myeloma patients who have had multiple relapses and are triple- and penta-refractory. In this Consensus, we have

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brought together a group of experts in multiple myeloma to discuss and forward their recommendations for the future, which we hope is very near, incorporating the CAR-T in our country.

Introduction

Among all hematological neoplasias, multiple myeloma (MM) stands out as being the condition in which the greatest number of therapeutic classes has been incorporated in the last two decades, including some absolutely innovating strategies.[1] This has reflected in therapeutic success for the patients, with an increase in the overall survival from 3 to 5 years in the decades between the 70s and the 90s to the current 7–11 years.[2]

The basis of MM treatment is anchored in three main therapeutic classes: the proteasome inhibitors (PIs) (bortezomib, carfilzomib and ixazomib), the immunomodulators (IMs) (thalidomide, lenalidomide and pomalidomide) and the monoclonal antibodies (daratumumab, isatuximab and elotuzumab).[3]

The majority of these therapeutic agents have already been approved for use in Brazil, the exception being pomalidomide, which to date has the regulatory agency approval with the condition that it be used only in combination with isatuximab and dexamethasone

Even considering the success those therapeutic agents have shown, used in combination in the very first lines of treatment, the autologous hematopoietic stem cell transplantation (ASCT) remains an important therapeutic strategy for MM patients diagnosed under the age of 70 years. Studies have shown that the use of ASCT immediately after 3–4 cycles of induction, compared with strategies without transplantation, were favorable for the ASCT upfront,[4,5] at least in terms of progression-free survival.

Today, it is possible to obtain deep responses for patients who are eligible and ineligible for ASCT, but the emergence of resistant subclones makes the approach to the MM patient, in early or late relapse, a challenge to be overcome. It is becoming more and more frequent the necessity to treat patients who have been exposed and become refractory to all classes of approved medications (triple-, quadruple- or penta-refractory), and this situation can possibly occur after the 1st or 2nd line of treatment.[6]

A retrospective study performed at 14 academic centers in USA evaluated 275 MM patient's refractory to the antibody anti-CD38. The median overall survival (OS) for the whole group was 8.6 months, range from 11.2 months for patients who were non-refractory to simultaneous immunomodulator agent and proteasome inhibitor and 5.6 months for "penta-refractory" patients (refractory to anti-CD38, two proteasome inhibitors and two immunomodulators). These data make it clear that there is an unattended necessity for this ever more frequent patient group.[7]

New therapeutic agents have been tested in this scenario, such as selinexor, an exportin 1 (XPO1) inhibitor; iberdomide (CC- 220), which represents a new generation of immunomodulators (CELMoD); melflufen, the first peptide-conjugated drug, a conjugate targeting intracellular aminopeptidases and venetoclax, an agent targeting BCL-2 which has an anti-tumor activity in MM patients with t (4;11).[8–11] Both selinexor and melflufen have already been approved by the FDA.

Despite the efficacy of the new drugs and the perspectives of other approvals, there is a frequent and pertinent global discussion about access to new drugs, mainly due to their high cost. In Brazil, one must add to this fact, the disparity access between the private and public health systems in which, no less importantly, we additionally have the limitation of the access to ASCT.[12] Due to such challenges, we identified that implementing a new cell therapy can be even more difficult in Brazil, thus justifying this consensus.

Our objective is to identify, within the current MM reality, the unattended necessities and to list the precise indications for the use of CAR-T cells in this scenario, assisting in the implementation of this new therapy in our country.

MM immunotherapy – novel anti-BCMA agents

Among the new strategies in MM immunotherapy, the anti-BCMA agents stand out. The B-cell maturation antigen (BCMA) is the most tested target in MM immunotherapy due to its important functions in the development of plasma cells. The BCMA is a transmembrane glycoprotein, a member of the superfamily of the tumor necrosis factor (TNF) receptor, being highly expressed in neoplastic plasma cells and absent in memory B-lymphocytes, T-cells and other non-lymphoid tissues.[13]

The anti-BCMA antibodies are capable of inducing clinical response by means of multiple mechanisms: inducing direct apoptosis and also by immune responses which lead to the cellular death of neoplastic plasmacytes that express the BCMA.[14]

Three different classes of anti-BCMA agentes have also been evaluated in clinical studies.

Belantamab – mafodotin, an antibody conjugate drug with promising results, particularly when used in combination with other agents, is at an advanced developmental stage and already approved for use in the USA and Europe.[15]

The bispecific antibodies are in an earlier stage of development, still without regulatory approvals and in ongoing phase 2 studies.[16]

The focus of our revision and this consensus is the CAR-T cell therapy in the MM scenario, in which the development of this treatment strategy is in its most advanced stage of clinical trials.

Cellular CAR-T immunotherapy and MM

Various CAR-T cells constructs have been evaluated in clinical trials on MM. At the most advanced stage are the autologous CAR-T cells targeting anti-BCMA (the patient own cells are collected for subsequent reinfusion). Other studies are under way, as allogeneic CAR-T cells and T-cell receptor (TCR) engineering. In this revision and consensus, we will focus the autologous anti-BCMA CAR-T cells which had a profound progress, more advanced and positive results, and with the closest perspective of approval by the regulatory agencies.

Idecabtagene vicleucel (Ide-Cel)

This construct was the first to obtain regulatory approval by the Food and Drug Administration FDA, in March 2021, for patients with four previous lines, including PI, IM and anti-CD38, based on the phase II study KarMMa. Included in this study were 140 patients, 128 of whom were effectively treated with CAR-T cells. These patients had received multiple lines of treatment (a median of 6 lines), 84% of them classified as triple-refractory. The CAR-T cell doses varied from 150 to 450 $\times 10^6$. The overall response rate (ORR) was 73%, with 33% reaching a complete response (CR). The median progression-free survival (PFS) was 8.8 months. The patients who received the higher cell dose, of 450 $\times 10^6$ CAR-T cells, obtained the best results, with an 82% ORR, 65% with a very good partial remission (VGPR) or better. The measurable minimum residual disease (MRD) rate was at 79% among the 42 patients who had a CR or better. The clinical benefit was observed in all patient subgroups, including those with high-risk cytogenetics and extramedullary disease and penta-refractory patients (refractory to two PIs, two IMiDs and anti-CD38 antibodies).

Concerning the adverse events, the most common among the 128 patients treated were neutropenia in 117 (91%), anemia in 89 (70%) and thrombocytopenia in 81 (63%). The cytokine release syndrome (CRS) was observed in 107 patients (84%), including 7 (5%) who had grade 3 events or higher. Neurotoxicity was observed in 23 patients (18%), with only 3% of the patients being considered grades 3. No neurotoxic effect over grade 3 occurred. It is important to note that the results of the efficacy among patients aged ≥ 65 and ≥ 70 years were comparable, with no difference in the safety profile.[17]

Ciltacabtagene autoleucel (Cilta-Cel, JNJ-4528)

Cilta-Cel is a CAR-T cell construct characterized by two single-domain antibodies directed at the BCMA, the CD3ζ activation domains and the 4-1BB co-stimulator domain. The phase I study LEGEND-2 was developed in China and included 57 patients with a median of three previous therapies. The ORR was 88%, with a median PFS of 19.9 months and a median OS of 36.1 months.

This same construct was tested in sequence in the Cartitude 1 Study. This phase 1b / 2 study included MM patients who had received three or more prior lines of therapy, or were double refractory to a proteasome inhibitor, and an immunomodulatory, and who had been treated with a proteasome inhibitor, an immunomodulatory, and anti-CD38 antibody. The single infusion of cilta-cel was administered 5–7 days after the initiation of lymphodepletion.

A total of 113 patients were included in the study, 97 (29 in phase 1b and 68 in phase 2) of whom received an infusion of cilta-cel in the phase 2 recommended dose of 0.75 $\times 10^6$/kg. The median of treatment lines was six. In a median follow-up of 12.4 months, the ORR was 97%, 65 patients (67%) achieved a sCR; the median time to the first response was one month. The PFS at 12 months was 77% and the OS was 89%. The grades 3 and 4 hematological adverse events were frequent; neutropenia in 95%, anemia in 68% and thrombocytopenia in 60% of the patients. CRS occurred in 95% of the patients, however, grades 3 or 4 were reported in only 4%, with a (median) time of initiation at 7 days and a median duration of 4 days. Neurotoxicity occurred in 21% of the patients, with grades 3 and 4 only in 9%. Fourteen deaths were reported in the study, six due to adverse events related to the treatment, five due to progressive disease and three due to adverse events not related to the treatment.[18]

Despite the relatively short follow-up, the Cartitude 1 results, in terms of efficacy and safety, are very positive, considering the patient population of refractory MM and multiple lines of treatment.

Orvacabtagene autoleucel

The CAR-T cell construct, denominated Orva-Cel, was evaluated in the phase I/II study EVOLVE. Three different doses, varying from 300, 450, and 600 $\times 10^6$/Kg and manufactured with the same process, were used in this study. It included 62 patients with a median of 6 (3–18) previous lines of treatment, 92% of whom had been penta-exposed (2 IMiDs, 2 PIs and an mAb). The ORR rate was 92% for all the dose groups and 68% of the patients achived at least a VGPR. Of all the assessable patients, 84% reached a negative MRD three months after the infusion. The most common adverse events were hematological toxicities and CRS, which occurred in 89% of the patients, only 3% of whom were grades 3 and 4. Neurotoxicity was reported in 13% of the patients and grades 3 and 4, only in 3% of them.[19]

The summary of the studies on the three constructs can be seen in Table 1.

Points of consensus

Based on the clinical studies results, we were able to select points directed to the autologous CAR-T cells therapy in the current scenario:

1. Recommendation: It is suggested that patients with good performance undergo the proposed therapy. The overall clinical condition, ECOG or Karnosfky and fragility grade should be evaluated, and the age should not be considered a limiting factor. Its use is recommended for relapsed/refractory MM patients who have been exposed to at least 4 previous lines, identifying at least the use of a proteasome inhibitor, an immunomodulator and an anti-CD38. It is important to highlight in this point that the use of these classes of drugs has been approved in combination, as

Table 1 – Summary of principal studies with CAR-T anti-BCMA in relapsed/refractory multiple myeloma.

Dose CAR-T cells	KarMMa: Idecabtagene Vicleucel (n = 128)	CARTITUDE 1: Ciltacabtagene Autoleucel n = 97)	EVOLVE: Orvacabtagene Autoleucel (n = 62)
Dose CAR T cells	150×10^6 - 450×10^6	0.75×10^6/Kg	$300 - 600 \times 10^6$
ORR, %	73	97	92
CR, %	33	67	39
PFS, median months	8.8	Not reached	Not reached
Total neutropenia/≥ 3, %	91/89	96/95	-/90
Total anemia/≥ 3, %	70/60	81/68	-/-
Total thrombocytopenia total/≥ 3, %	63/52	79/60	-/47
Total CRS /≥ 3, %	84/5	95/4	89/3
Total neurotoxicity total/ ≥ 3	18/3	20/9	13/3
Tocilizumabe total CRS, %	52	69	76
Tocilizumabe total neurotoxicity, %	-	4	-

ORR: overall response rate; CR: complete remission; PFS: progression-free survival; MRD: measurable minimum residual disease; CRS: cytokine release syndrome.

early as in the first lines of treatment. In this manner, we should consider soon the triple exposure, without taking the number of lines into account.

2. Cellular process: The collection and infusion of cells in the patient should be performed preferentially at centers that have already performed these procedures. The previous qualification of the multidisciplinar team, continuous training and data collection on efficacy and safety are of fundamental importance.
3. Support therapy: The CAR-T treatment centers must have access to support therapy due to the new toxicities identified. The access to interleukin-6 (IL-6) (tocilizumabe) inhibitors and trained neurology and intensive care teams must be also available.
4. Bridge therapy: Based on published studies, the bridge therapy should be strongly considered during the waiting period of the construct processing and preparation. Approximately 80% of the myeloma cases in the studies needed this procedure.

Conclusion

Therapies with CAR-T cells are establishing themselves as a new and important tool in the treatment of hematological neoplasia's, including MM. The initial recommendations will be for the patients triple exposed to proteasome inhibitors, immunomodulators and anti-CD38.

Other anti-BCMA constructs, as well as those against other targets, are in full clinical development.[20]

Sequencing strategies and combined immunotherapy with antibodies and bispecifics may be adopted in the future to prolong the response duration and in post-CART-T relapse treatments. The earliest possible use of CAR-T, even in the first line for high-risk MM patients, is being investigated in clinical studies.[21]

An important challenge in Brazil will be the access issue, both in the Public Healthcare System and in the Supplementary Healthcare. The use of CAR-T cells, as well as that of other innovative treatments has a very expressive aggregated cost, which should be considered and balanced with their promising clinical benefit. Adequate patient selection, attently observing eligibility criteria, previous therapies and future planning are fundamental to the success of the treatment.

Conflicts of interest

The authors declare no conflicts of interest.

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