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EDITORIAL
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CAR T-cells in patients with multiple myeloma

Linfocitos T-CAR en pacientes con mieloma múltiple

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With an incidence of 4-5 new cases per 100,000 inhabitants, multiple myeloma (MM) is the second most frequent malignant hematological condition after non-Hodgkin lymphoma. Mean age at diagnosis exceeds 65 years of age[1].

Although MM remains an incurable disease, a better understanding of the condition's biological underpinnings together with the introduction of new drugs has resulted in a significant improvement in overall survival (OS).

Proteasome inhibitors (PIs) such as bortezomib, carfilzomib and ixazomib, as well as immunomodulatory drugs (IMiDs) such as thalidomide, lenalidomide and pomalidomide, together with monoclonal antibodies, particularly those targeted against CD38, have played a key role, moving from the later lines of treatment to the frontline, either on their own or in triple or quadruple combinations. Mention should also be made for autologous stem cell transplant as a consolidation strategy in amenable patients. As a result of these strategies, median progression-free survival (PFS) of MM patients following first-line treatment has increased to 5-6 years. Nevertheless, the majority of MM patients sooner or later will experience a relapse, with second-generation PIs and IMIDs currently being used for relapsing patients, combined with monoclonal antibodies especially if they are naïve for this drug class. This means that MM patients are typically administered three main kinds of drugs between the first and the third line. The fact that many of them are refractory to those drugs results in the emergence of an unmet medical need[2].

LocoMMotion is a prospective observational study that was carried out in 226 MM patients triple exposed and most of them three drug class refractory to determine the salvage treatments for this patient population in the real life outside of clinical trials. The study identified over 80 different regimens with an overall response rate of 20%. This and other retrospective studies have confirmed that there is no gold standard for MM patients triple exposed/refractory and that these patients therefore need different treatment strategies[3].

New drugs have emerged such as melflufen or selinexor and new IMIDs, among others, that have a different mechanism of action but in spite of these agents, there is still need for new approaches and B-cell maturation agent (BCMA) emerged as a very promising target in MM. BCMA is universally and specifically expressed in plasma cells, which makes it an optimal target for different approaches and one of the most promising-one is the use of chimeric antigen receptor T-cells (CAR-T) against it[4].

Idecabtagene vicleucel, also known as ide-cel, is the first CAR-T to be approved by the European Medicines Agency for relapsing MM patients who have been exposed to at least three different treatments including PIs, IMIDs and antiCD38s and who have been shown to be refractory to the last line of treatment. The efficacy of the new drug has been demonstrated by the results of KarMMa, a pivotal study including 128 MM patients, most of them (84%) triple refractory who, following a median of six previous lines of treatment, and treated with between 150 and 450 million CAR T-cells[5]. Seventy-three percent of patients responded to the treatment and 33% achieved complete response that persisted a median of 10.9 months (21.5 months in patients with complete response). OS was 24.8 months and was maintained regardless of the presence of some specific features like to be older than 65 years or presenting with high risk features. In addition, the efficacy was comparable in patients who had received at least four prior lines or more than four. Ciltacabtagene, also known as cilta-cel, will be the second CAR T to be approved, following the CARTITUDE-1 trial where 97 patients of similar characteristics as those of patients in the KarMMa trial received a fixed 0.72 x 10^6/Kg dose of the drug. Ninety-eight percent of patients in this trial responded and 80% achieved a complete response. At 18 months' follow-up, 81% of patients were alive, and 66% were both alive and progression-free[6].

These results indicate that these drugs are likely to be able to cover the unmet needs of MM patients exposed to the three conventional drug classes, i.e. PIs, IMIDs and anti-CD38s. Their use therefore seems warranted.

Although the drugs' toxicity profile is not negligible, side effects can be managed with an appropriate learning process and close supervision by specialized pharmacists within the context of a multidisciplinary team. Most patients are apt to develop cytokine release syndrome (CRS) one day after administration of ide-cel and seven days after administration of cilta-cel, but most of them will only present with grade 1-2, which tends to resolve with appropriate support treatment (tocilizumab and corticosteroids, as needed). Neurotoxicity, which is less frequent than CRS, tends to manifest itself

after the appearance of CRS and also resolves uneventfully with support treatment. Cytopenias are also quite common, as well as infections and they should be managed with adequate prophylaxis.

The above-mentioned studies have kickstarted the use of CAR T-cell therapy in MM patients and, even if survival curves have not yet shown signs of plateauing, the results achieved so far are much better than those obtained with any other MM treatment strategy.

Are all relapsing MM patients already exposed to PIs, IMIDs and anti-CD38s amenable to CAR T-cell therapy? Patient selection criteria should include not only previous exposure to conventional treatments, but also other factors such as the patients' general health status, comorbidities, bone marrow reserve status and heart, respiratory, renal and neurologic function, which require for the patient to be evaluated by a multidisciplinary team, who should also consider the family and social support required.

Can the treatment be administered at any clinic? In Spain, the Ministry of Health is responsible for designating the centers that can apply this treatment, with eight or nine centers having been appointed so far. This restriction is sensible for the short-to-medium term as it ensures patient safety, all designated centers being required to undergo an appropriate learning process. In the future, the number of eligible centers is likely to be expanded.

Can the results of CAR T-cell therapy be improved in MM patients? Multiple research projects are underway to improve the efficacy of CAR T-cell therapy[7]. These seek to: a) optimize the apheresis product to be manipulated by selecting T-cells capable of increasing their expansion and persistence; b) utilize CAR T-cells devoid of any so-called "fully human" murine residues to minimize immunogenicity and enhance patient safety; c) create dual CAR T-cells to increase specificity; d) use viral-free platforms to optimize and shorten the manufacturing process; e) generate allogenic CAR T-cells from healthy donors.

What are the therapeutic alternatives? Effective anti-BCMA monoclonal antibodies have been developed either conjugated with cytotoxic agents, such as the recently approved belantamab mafodotin[8], or in bispecific form. The latter, still under investigation, are intended to redirect T-cells to the tumor niche where they are activated to unleash their anti-tumor effect[9]. Although all three anti-BCMA agents have shown themselves to be effective, the final choice will depend on the patients' characteristics, the type of disease they have and their family and social circumstances. In principle, patients with fast developing conditions who cannot wait for the manufacturing process to be completed would be better suited to a conjugated or a bispecific antibody, which would help control their disease. In the future, the three strategies could become complementary, which should open new research avenues directed at looking into the mechanisms that drive resistance to T-cell therapy, focusing both on the target and on the potential exhaustion of T-cells. Luckily, new targets have been identified, apart from BCMA, such as GPRC5d, FCRH5, CD38, SLAMF7, which are currently under investigation.

CAR T-cell therapy holds huge promise for MM patients and, as such, is here to stay. There are several clinical trials ongoing in which CAR-T are being evaluated in first relapses and even in the setting of newly diagnosed patients.

Making this ground-breaking therapy available to MM patients requires a multidisciplinary team, where hospital pharmacists should play an essential role. Indeed, hospital pharmacists should be active across all the different stages of the process, including selecting the best bridging therapy during product manufacturing and patient lymphodepletion, instituting support treatment and, of course, ensuring traceability of CAR T-cells from harvest to administration. In summary, hospital pharmacists are key players in the multidisciplinary team through the journey the patients have to follow for the CAR-T administration.

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