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WHAT IS THE ROLE OF AUTOLOGOUS HEMATOPOIETIC STEM CELL TRANSPLANTATION (AHSCT) IN THE SCENARIO OF NEW DRUGS FOR MULTIPLE MYELOMA (MM)

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Patients with multiple myeloma (MM) in clinical conditions to be referred to autologous hematopoietic stem cell transplantation (AHSCT) generally start therapy with an induction chemotherapy followed by high-dose alkylating and AHSCT (1). The ideal regimen and the number of pre-AHSCT induction is still a controversial subject, however, opting for at least three to four cycles of chemotherapy including a drug with immunomodulatory action, a proteasome inhibitor, with a corticosteroid, are advised as the first line before AHSCT [3].

It was defined that triple therapies are preferred as induction before transplantation [2,4], and with a better understanding of the pathophysiology of MM new therapies with agents that overcome the responses of established therapies, such as pomalidomide and the new proteasome inhibitors (carfilzomib and ixazomib), has emerged [5].

The current scenario of treatment of MM patients who are candidates for AHSCT includes new agents with many studies, such as the one that assesses the use of daratumumab (Dara) in association with bortezomib, lenalidomide and dexamethasone (Dara-VRd) in the induction and consolidation after TACTH [6]. This study has demonstrated the safety and efficacy of this association, as well as in the CASSIOPEIA clinical trial, which evidenced the benefit of the association of Daratumumab, with the classic VTD (bortezomib, thalidomide and dexamethasone) scheme, increasing the depth of the therapeutic response after TACTH [7].

First-line AHSCT has been questioned, several studies assessed the role of AHSCT in this scenario comparing to its use in first relapse [8,9,10,11]. The EMN02/HO95 study, patients were randomly to receive four cycles of bortezomib, melphalan and prednisone (VMP) or AHSCT after high-dose melphalan, 1197 patients were eligible for the randomization, of whom 702 were assigned to AHSCT and 495 to VMP. The median progression-free survival (PFS) was significantly improved with AHSCT compared with VMP [10].

The IFM trial used induction therapy based on VRd with initial or delayed consolidation with AHSCT. A total of 700 patients radomized for VRd 8 cycles, with lenalidomide maintenance and AHSCT only in relapse, and VRd 3 cycles with AHSCT in the first line, with consolidation of 2 VRd cycles and lenalidomide maintenance. An increase in PFS survival was observed, in addition to deeper responses, with the transplant done early, but with no difference in overall survival (OS). However, 79% of patients who had disease progression in the non-AHSCT arm were submitted to a rescue AHSCT, which may justify the similarities in the OS [11].

In the IFM/DFCI 2009 trial, patients with negative minimal residual disease (MRD) pre-maintenance showed an improvement in PFS (> 80% in 3 years) compared to patients with positive MRD [12]. The impact of negative MRD on OS can also be seen with this scheme, being more frequent in those undergoing first-line AHSCT than in patients who received only 8 cycles of VRd [11]. These findings confirm that the absence of minimal residual disease is an important treatment target for myeloma [13,14] and suggest that the use of high-dose chemotherapy and transplantation after induction therapy with VRd may help to this goal.

The use of other proteasome inhibitors such as carfilzomib has also been tested in a randomized study comparing: carfilzomib, lenalidomide and dexamethasone (KRd) followed by AHSCT plus consolidation with KRd (KRd-AHSCT-KRd) versus KRd 12 Cycles versus carfilzomib, cyclophosphamide and dexamethasone (KCd). The rates of MRD negativity, sCR, ≥CR, ≥VGPR were significantly higher with KRd-AHSCT-KRd and KRd12 vs KCd. No differences were observed in MRD and in the best overall response (sCR, ≥CR, ≥VGPR) between KRd-ASCT-KRd and KRd12, requiring longer follow-up to assess survival [15].

Several other alternatives to avoid AHSCT in the first line have been proposed using different strategies such as MRD and cytogenetic risk stratification, despite these attempts, most studies have shown an increase in PFS and a consequent improvement in response with the consolidation with TACTH despite the scheme used and the consolidation [16].

Although most intense therapies have been suggested with the association of 4 drugs from different classes [6, 7], and some studies try to remove AHSCT in an initial moment [8,9,10,11], none has been able to demonstrate its "uselessness". Thus, in a phase when the therapy with four drugs starts to appear as "gold standard" in the treatment of the newly diagnosed patient, the IMWG recommendation remains up to date regarding the use of ASCTH in the first line and today the main objective is to achieve a sustained MRD negative in order to "cure" these patients.

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