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Allogeneic transplantation for multiple myeloma

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In multiple myeloma (MM), the standard of treatment for patients < 65 years is high-dose chemotherapy followed by autologous stem cell transplantation. However, following either a single or a tandem autograft MM invariably recurs due to the persistence of tumor cells either in the host and/or in the graft.[1-5] Purification procedures have generally proved unsuccessful.[6,7] Allogeneic transplantation not only skips graft tumor contamination, but also exerts an immune effect against the myeloma clone.[8-11] This effect is also displayed by donor lymphocytes when infused to the recipient in adeguate amounts.[11-13] Despite these biological advantages, the precinse role of allograft in MM remains controversial. In fact, when a standard, high dose conditioning regimen is employed for allogeneic graft the better antineoplastic potential is counteracted by a transplant-related mortality (TRM) ranging from 30 to 50%.[10,14,15]

We have previously used a protocol with allogeneic peripheral blood stem cells and high-dose busulphan and melphalan as conditioning for advanced MM, attaining over 70% complete remission.16 With that program half the CR patients also obtained a molecular, IgH-negative remission, but the TRM was still 30%. More recently, the so-called reduced-intensity conditioning (RIC), has contributed to reduce the TRM in allogeneic transplantation.[17-19] To improve the overall results in MM we designed a RIC protocol with thioteopa 5 mg/kg, fludarabine 90 mg/m^2 and melphalan 80 mg/m^2 and a GVHD prophylaxis with CSA plus low-dose MTX. This scheme was applied within the GITMO to 53 patients with MM undergoing an allogeneic stem cell transplant (HSCT) from their HLA identical siblings. Their median age was 52 years (range 38-68) and the median interval from diagnosis 12 months. Forty-three patients (82%) had advanced disease and 33 had previously been treated with high-dose therapy with one (N=21), or more (N=12) autologus transplants. Ten (18%) had their allograft programmed after induction chemotherapy. The majority (n=44) received peripheral blood as stem cell source. Acute GVHD grade II-IV developed in 45%, but grade III-IV in only 5%. Cumulative incidence of chronic GVHD was 64%. Sixty-two percent were in complete remission (CR, EBMT criteria)[23] following transplantation. Transplant-related mortality was 12%.

Twenty-six (49%) of the 53 patients had a PCR study for IgH rearrangement[21,22] and showed a molecular marker. A PCR monitoring of MRD was available in 15 of the 28 CR patients. Only 4 showed at least a PCR-negative sample. In two cases at least 2 consecutive samples proved PCR-negative, while in the other two PCR-negative results occurred in single scattered samples. With a median follow-up of 22 months, 3-year overall survival is 45% and progression free survival (PFS) 37%. In multivariate analysis, front-line allograft, CR after transplant and chronic GVHD were significant factors for OS, while CR after transplant was the only significant factor for PFS.

The combination of thiotepa, fludarabine and melphalan at reduced doses has not been used previously, although the single components are widely used in the transplant community.[24-30] In our study, despite the poor prognostic features, the TRM was low with no toxic deaths in the group transplanted early after diagnosis, confirming the relevance for TRM of time to transplant and previous therapy. With 62% complete response rate our results show a powerful anti-myeloma activity of our regimen. The shortened CsA course may account for the high incidence. Of chronic GVHD. In fact cGVHD was diagnosed at a median of 191 days from transplant, and was coincidental with CSA withdrawl. Our patients had a relatively long duration of CR (median two years). As expected with advanced disease, the PFS curve shows no plateau. cGVHD did not influence PFS, though the patients sample is too limited to draw a conclusion. In heavily pre-treated patients response may be less influenced by cGVHD due to

the rapid kinetics of disease.

In conclusion, we show that the combination of thiotepa, fludarabine and melphalan can induce a complete remission in the majority of patients with myeloma without the significant toxicity observed with other regimens. This combination is safe and can be used even in patients after several lines of treatment. We presently ignore whether RIC is superior to double autograft[31,32] to the tandem auto-allo and to conventional allograft in terms of final outcome, and only a randomized study could address this important question. The role of graft-vs-myeloma is also a key issue that needs to be clarified. [33-36]

New drugs as bortezomib[37] and thalidomide analogs show an impact on response in relapsed and refractory MM and a possible advantage in early stage disease. In the near future they may be integrated in autologous and allogeneic transplantation for MM patients.

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