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Allogeneic transplantation in multiple myeloma – How, when or at all?

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ABSTRACT

Allogeneic transplantation (allo) of patients with multiple myeloma is a controversial treatment due to high transplant related mortality (TRM) with myeloablative conditioning before the transplant. However, using reduced intensity conditioning (RIC) and previous autologous transplantation (auto) has dramatically reduced TRM. This, in combination with a lower relapse/progression rate, has in two out of six prospective studies resulted in prolongation of both progression free survival (PFS) and overall survival (OS) as compared to auto. No prospective study has proven auto – single or tandem – to be better than the auto/RICallo modality. The rapid development of relatively effective drugs in multiple myeloma has made most centers reluctant to use upfront RICallo. Considering the initial TRM of 12–16% with this treatment, it is now mainly used after progression-relapse following auto. New studies including more effective GVHD prevention and combination of allo with new drugs in the conditioning and as maintenance therapy are ongoing or in planning. Until clear advantageous results have been shown it seems reasonable to use the auto/RICallo procedure mainly in relapsed patients or upfront in patients with poor prognostic parameters such as del17p, del8p or gain 1q. The prospects for long-term survival or perhaps cure for a fraction of patients seem highest following some kind of allo.

Introduction

Based on a few initial promising case reports indicating possible cure with allogeneic transplantation (allo) of multiple myeloma the EBMT (the European Group for Blood and Marrow Transplantation) started to perform allo in the early 1980th, and results of the first large series of patients were published in 1987 [1] and 1991 [2]. A fraction of patients entered complete hematologic remission (CR) and CR was demonstrated to be the most important prognostic factor for long-term survival [3]. However, the high-dose myeloablative

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conditioning was associated with high transplant-related mortality (TRM) – up to 40% after upfront treatment [3]. In attempts to reduce the TRM the Seattle Group started a program using very low conditioning dosages – down to 200 cGy total body irradiation (TBI), the idea being to utilize the well documented graft-versus-myeloma (GVM) effect [4–6] for tumor cell killing. Recent prospective trials have mainly used variants of this nonmyeloablative, reduced intensity conditioning (RIC) approach, but preceded by an autologous transplant (auto) for tumor cell reduction. Until recently these studies used the VAD (vincristine + adriamycine + dexamethasone) or similar regimens for induction. Ongoing studies and those in planning are including novel drugs like thalidomide, bortezomib and lenalidomide in attempt to improve results.

How to perform an allogeneic transplantation in multiple myeloma

Myeloablative conditioning

Myeloablative conditioning has mainly been abandoned due to the high TRM. The primary goal of myeloablative conditioning is to eradicate the disease and rescue the patient with the normal cells in the allogeneic graft. However, in addition, a GVM effect is well documented [4–6]. The most common myeloablative conditioning regimens are TBI 10–12 Gray fractionated or unfractionated with lung shielding [2, 3]. Many other conditioning regimens including high dose melphalan, and cyclophosphamide have been used as well [7–9]. Myeloablative conditioning allo is associated with lower relapse rate as compared to both RICallo and high dose conditioning auto but the TRM is higher and amounted to of 30–40% in earlier studies, mainly due to severe graft-versus-host disease (GVHD). Despite the lower relapse rate the progression-free survival (PFS) and overall survival (OS) [3, 10] were therefore generally poorer with myeloablative conditioning allo. However, there were subgroups of patients who did better, e.g. females with a female donor [11, 12], but still the TRM was high. Thus, despite improvement in results with time due to better supportive treatment [13], high CR rate of 50–60% [3, 14], higher rates of molecular remissions than after auto [15] and comparatively low relapse/progression rate, the high TRM has discouraged from the use of myeloablative conditioning.

Reduced intensity (nonmyelablative) conditioning (RIC)

The idea of using nonmyeloablative reduced intensity conditioning (RIC) is to take advantage of the GVM effect for tumor killing and reduce TRM by lowering the irradiation and/or cytotoxic drug dose. Experimental canine transplant studies [16] by the Seattle Group showed that allogeneic engraftment [17] was possible with only 200 cGy irradiation and GVHD prophylaxis with mycophenylate moffetil and cyclosporine [18]. In a clinical study of 18 patients with refractory disease or failed prior autologous transplantation 2 entered CR and 3 further patients had a partial response with this approach. It was assumed that the response was mainly due to the GVM effect.

Since these crucial results appeared numerous phase I and II RICallo studies have been performed [7, 18–28]. In addition there are six prospective upfront studies with somewhat different design comparing the combination auto/RICallo to auto or auto/auto (Table I). All of them were based on the availability of an HLA matched sibling donor [29–37]. In four of the studies TBI 200 cGY was used for the RICallo conditioning as in the Seattle study. One – the EBMT study – used as well fludarabin 30 mg/m^2 × 3 before irradiation. The IFM study used a combination of fludarabine, low dose busulfan and ATG and the PETHEMA group Melphalan 140 mg/m^2 plus fludarabine. In five of the studies, the control group was tandem autologous transplantation in those patients who lacked a donor, while in one of the studies – the EBMT study – either single or tandem autologous transplantation was used. The induction treatment was VAD (vincristine + adriamycin + dexamethasone), thalidomide and dexamethasone, or similar combinations in all studies, and the conditioning for the initial autologous transplant was 200 mg/m^2 melphalan.

The IFM study [31, 32] included 219 patients without (tandem auto group) and 65 with an identical sibling donor (auto/RICallo group). All patients had high risk disease as defined by beta$_2$-microglobulin of more than 3 mg/L, and deletion of chromosome 13. On an intention to treat basis the median event-free survival was 19 versus 22 months and the OS 34 versus 48 months in the auto/RICallo and auto/auto groups respectively, i.e. a trend for inferior OS in the auto/RICallo group ($p = 0.07$). The use of antithymocyte globulin – Imtix Genzyme (2.5 mg/kg/day during 5 days) for GVHD prevention – and busulfan and fludarabine for conditioning might have played a role for the trend for poorer outcome with auto/RICallo.

The Italian study [33, 37] comprised 245 patients enrolled at time of diagnosis. Eighty out of 162 patients who underwent HLA typing had an HLA-identical sibling donor and 58 out of these 80 patients underwent the auto/RICallo procedure. They were compared to 46 patients without and HLA identical sibling who received auto/auto. On an intention to treat analysis the median event-free survival in the auto/RICallo group was 35 months, as compared to 29 months in the auto/auto group ($p = 0.02$). The median OS was 80 months versus 54 months, respectively ($p = 0.01$). Long-term intent to treat analysis with patients more than seven years from diagnosis continue to demonstrate an OS benefit for auto/RICallo with median survival not reached versus 4.2 years in the auto/auto arm ($p = 0.001$) [37].

The Spanish PETHEMA study [35] – was relatively small in that it included only 25 patients in the auto/RIC arm compared to 85 receiving auto/auto. Patients less than seventy who failed to achieve a CR or nCR after the initial autologous transplant were eligible for second transplant. The median time for PFS and OS had not been reached in the auto/RICallo group, while it was 31 months ($p = 0.08$) and 58 months ($p = 0.9$), respectively, in the auto/auto group. Thus, this study indicated a trend toward superior outcome with the auto/RICallo procedure in patients who did not reach CR after initial auto.