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Stem Cell Transplantation

A reduced intensity conditioning regimen for allografting following autografting is feasible and has strong anti-myeloma activity

Sixteen patients with stage III multiple myeloma (MM) and a median age of 51 years were treated with autografting followed by reduced intensity conditioning allotransplantation (RICT). Nine patients are alive in remission at a median of 30 months after their transplants, one patient is alive in relapse and 6 patients died of progressive disease (5) or extensive chronic graft-versus-host disease, infections and progressive disease (1). We suggest that this two-step approach is feasible and it has strong anti-myeloma activity.

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The recent development of reduced intensity conditioning and allotransplantation (RICT) has opened a new way to assure engraftment of donor cells while reducing early transplant-related mortality (TRM). Taking advantage of this new approach we pionereed the combination of high-dose therapy and autologous stem cell transplantation (HDT/ASCT) followed by RICT to extend the benefit of allografting procedures.[1] Recently, we extended our experience to 16 patients with stage III multiple myeloma (MM) (Table 1). All patients received high dose melphalan (140 mg/m^2) followed by autologous peripheral blood progenitor cells previously collected after cyclophosphamide (3 g/m^2) and granulocyte colony-stimulating factor (G-CSF). At a median of 79 days after HTD/ASCT, the patients underwent RICT, consisting of fludarabine 30 mg/m^2 on days -4, -3, -2 and 2 Gy total body irradiation at 7cGy/min by a linear accelerator on day -1. Acute graft-versus-host disease (GVHD) prophylaxis consisted of mycophenolate mofetil (15 mg/Kg orally twice a day from day 0 until day +30) and cyclosporine 1 mg/kg i.v. from day -1 to day 35); subsequently, cyclosprorine A was administered at a dose of 5 mg/kg orally twice a day until day +90. Cytomegalovirus (CMV) reactivation was monitored and treated with ganciclovir. Donor chimerism was assessed on unfractionated bone marrow cells.[2] The evaluation of response was derived using ABMTR criteria.[3]

All patients were evaluated for response prior to and after transplants and then every 2-3 months (Table 2). Of 11 patients with responsive disease prior to HDT/ASCT, one patient maintained complete remission (CR) and one patient achieved CR from partial remission (PR) after ASCT; all other nine patients in PR maintained this state; 1/5 non-responsive patients achieved PR after ASCT. After RICT, 13 patients showed a complete donor chimerism at the time of engraftment; one patient with mixed chimerism received an infusion of donor lymphocytes (10^6 CD3$^+$ cells/kg) on day +60 and subsequently achieved full donor chimerism. Grade II-III acute GVHD occurred in 7 patients (43%) but no patient died of this complication. Six patients (37%) developed mild chronic GVHD and 3 patients (18%) developed an extensive form.

Three patients (18%) who were CMV seropositive or had CMV-seropositive donors developed CMV antigenemia and were treated with pre-emptively with ganciclovir.

Ten patients (1 after HDT/ASCT and 9 after RICT) (62%) of the 15 who were not in CR at our 2-step approach achieved CR and 1 (6%) achieved PR with an overall response rate of 68%. The patient who achieved CR after HDT/ASCT (patient #14 - Table 2) subsequently relapsed and died of MM 42 months after RICT. To date, nine patients are in continuing CR 11-36 months (median, 30) after RCT; 3 of them are still receiving immunosuppressive therapy for extensive chronic GVHD. In all patients the achievement of CR was gradual and a continued regression of monoclonal bands was observed with a median time to CR of 4 months. Eight out of 9 patients who developed acute/chronic GVHD achieved CR. Six patients did not achieve CR and died within 11 months: 5 patients of progressive disease and 1 patient of progressive disease, infections and extensive chronic GVHD. The overall survival and event-free survival following the 2-step procedure are shown in Figure 1.

Eight patients received a median number of 2 (range, 1-3) donor lymphocye infusions (DLI) with the median final dose infused being 2.4×10^7 CD3$^+$/Kg (range, 1×10^6-6×10^7). The median time from transplant to DLI was 80 days (range, 42-170). The indication for DLI was stable disease in 3 patients and mixed chimerism in 5 patients. None of 3 patients with

Table 1. Patients' charateristics at the time of autografting.

Patients	*16 (100%)*
Age, median (range)	51 (36-63)
Male/Female	11/5
Stage III	16 (100%)
β2 microglobulin >2.5 μg/mL	13 (81%)
Immunoglobulin class	
IgG	8(50%)
IgA	2 (12%)
Light chain	5 (31%)
Non-secretory	1 (6%)
Disease duration, months (range)	8 (5-40)
>12 months, n. (range)	4 (25%)
Prior chemotherapy	
VAD	16 (100%)
No cycles, median (range)	4 (3-9)
Response from last therapy before ASCT	
Complete remission	1 (6%)
Partial remission	10 (63%)
No response	5 (31%)

Table 2. Disease status and response during and after the 2-step approach.

Patient No.	HDT/ASCT Prior	HDT/ASCT After	Best Response after RICT	GVHD Acute	GVHD Chronic	Outcome (months)
1	PR	PR	CR	I		Alive CCR (+36)
2	PR	PR	CR	II	mild	Alive CCR (+35)
3	PR	PR	CR	I	mild	Alive CCR (+34)
4	PR	PR	CR	–	mild	Alive CCR (+33)
5	NR	NR	SD	III	extensive	Died ext. cGVHD, PD (6)
6	PR	PR	CR	III	mild	Alive CCR (+30)
7	NR	PR	SD	–	–	Died PD (6)
8	PR	PR	CR	II	mild	Alive CCR (+28)
9	PR	PR	CR	II	mild	Alive CCR (+26)
10	PR	PR	CR	III	extensive	Alive CCR (+23)
11	PR	PR	PD	–	–	Died PD (6)
12	NR	NR	PR	–	–	Alive PR (+43)
13	CR	CR	PD	–	–	Died PD (52)
14	PR	CR	PD	–	–	Died PD (42)
15	NR	NR	SD	–	–	Died PD (42)
16	NR	NR	CR	II	extensive	Alive CCR (+11)

NR: no response; PD: progressive disease; CR: complete remission; SD: stable disease; PR: partial remission; CCR: continuous CR.

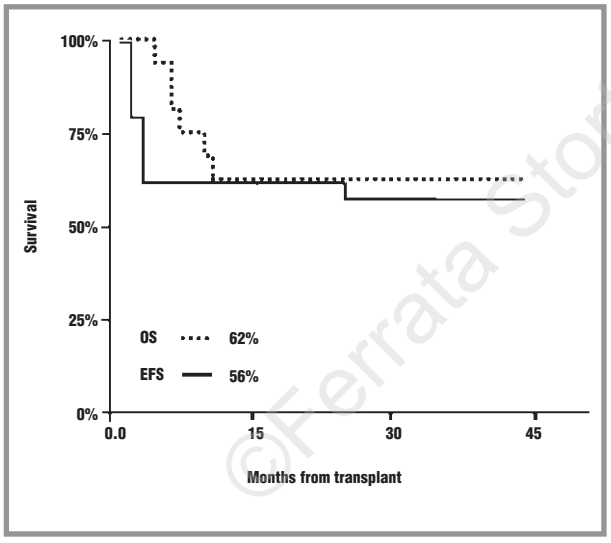

Figure 1. Overall survival and event-free survival (n=16).

stable disease attained CR and 1 patient only converted from mixed to complete chimerism. Our experience of HDT/ASCT - RICT in MM can be summarized by the following observations. No patient died after HDT/ASCT or in the first 100 days after RICT. One patient died of extensive chronic GVHD and infections in progressive disease 6 months after RICT. Pancytopenia after RICT was minimal and sustained allogenic stem cell engraftment occurred in 87% of patients. These results are particularly important if we consider that 15/16 (93%) had never achieved CR before the tandem transplants and 5 patients (31%) had resistant disease after conventional chemotherapy. A good correlation between GVHD, full chimerism and remission was found. Eight of 9 patients (88%) who developed acute/chronic GVHD achieved CR. However, Maloney *et al.* also demonstrated that 5 patients achieved CR after 9 months from RICT without any GVHD suggesting that subclinical GVHD or another antitumor effect of this approach may control multiple myeloma.[4] Badros *et al.* treated 31 patients who had had 1 or 2 prior autografts with transplants from identical sibling donors (25 patients) or unrelated donors (6 patients).[5] More than half of the patients developed acute GVHD and 61% achieved CR or a good PR. The median overall survival was 15 months and it was better in patients who received the RICT as planned consolidation of a single autograft. The 2-step approach was also employed with success by Kroger *et al.* in 42 patients with related or unrelated/mismatched donors.[6,7]

In conclusion, all the published studies confirm that the HDT/ASCT-RICT procedure is associated with lower TRM than myeloablative allografting alone, even in older patients. We and others have confirmed the feasibility of the sequential combination of HDT/ASCT and RICT; therefore this 2-step approach deserves further investigation, i.e. by comparing this approach with tandem autografting as recently proposed by the Bone Marrow Transplant-Clinical Trials Network (BMT-CTN).

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