Reduced intensity conditioning with thiotepa, fludarabine and melphalan for allogeneic transplantation in multiple myeloma

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In multiple myeloma (MM), high-dose therapy followed by single or autologous stem cell transplantation (auto-SCT) represents the treatment of choice for patients <60 years of age.[1,2] However, auto-SCT is not able to eradicate the disease. In a retrospective study of GITMO the event-free survival after auto-SCT failed to show a plateau. In practice, all patients relapsed within 3-5 years and later became resistant to any available treatment. In the meantime, molecular biology studies confirm that the myeloma cell clone seldom disappears after autologous transplantation.[3,4] The reason is the persistence of a sizeable number of neoplastic cells both in the patient and in the graft.

Allogeneic stem cell transplantation (alloSCT) is employed much less frequently than autologous transplantation, due in part to the limited availability of HLA-identical donors and in part to the higher transplant-related mortality (TRM).[5] Nonetheless, a retrospective study within the EBMT[6] has documented a TRM reduction over the last few years, as result of better selection of patients and improvements in technologies, as may be the preferential use of chemotherapy-based conditioning instead of total-body irradiation and the use of stem cells from the peripheral blood rather from bone marrow.[7]

The emerging concept is that suppression of the neoplastic clone may be obtained (in selected diseases) even without a mega-dose of chemo-radiotherapy as administered in the traditional transplantation regimens. An immunosuppressive protocol, in combination with the infusion of a large number of stem cells, will ensure stable engraftment and promote a graft-versus-tumor effect with little toxicity.[8] Such methodology is currently under evaluation in a variety of hematologic disorders, including MM.[9] MM is typically an immune-sensitive disease, as witnessed by the efficacy of donor-lymphocyte infusions (DLI) following allo-SCT and by the results of vaccination.[10] A rapid reduction of the M component, with disappearance of the marrow plasma-cell infiltration has been documented late after allo-SCT, at the time of chronic graft-versus-host disease (GVHD) onset.[7]

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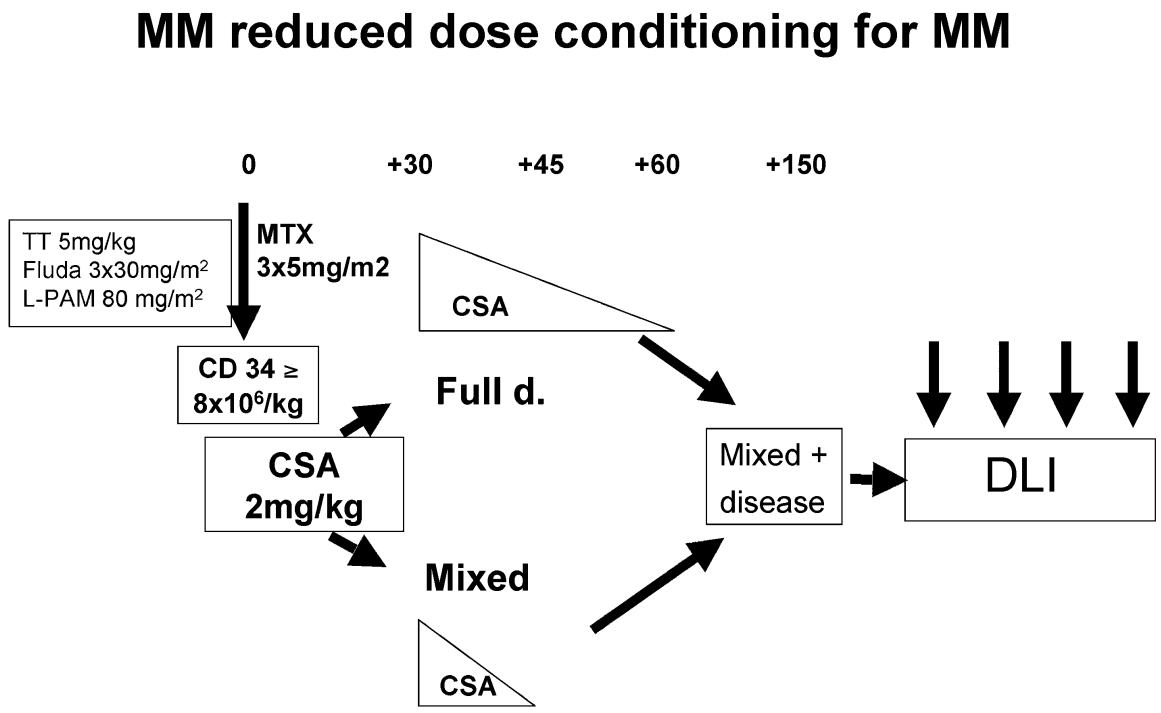
Design and methods

For patients with MM we have recently designed a program of reduced-intensity conditioning transplant from HLA-identical sibling donors. The conditioning combines fludarabine, thiotepa and melphalan (Figure 1). GVHD prophylaxis is based on methotrexate-cyclosporine, but the latter is rapidly tapered following transplantation to favor the emergence of an immune-mediated suppression of tumor. DLI are employed in those patients who remain GVHD-free but still harbor detectable tumor following cyclosporine tapering. The study is supported by a molecular analysis of bone marrow cells to detect IgH gene mutation as a marker of miminal residual disease.[4]

Results

Twenty patients have been enrolled so far. We have data on 18 of them. Their characteristics are reported in Table 1. Seven were transplanted early in the course of their disease, while 11 had the allograft as treatment for disease progression or relapse. As transplant, they received a median of 5.1×10^6/Kg $CD34^+$ cells (range 0.2-10.2), and 3.0×10^8/Kg $CD3^+$ cells (range 0.4- 4.2) from bone marrow or granulocyte colony-stimulating factor (G-CSF)-primed peripheral blood. Full engraftment occurred in all, with 14 days to recover $>0.5\times10^9$/L granulocytes (range 10-18) and 12 days to recover $>20\times10^9$/L platelets (range 4-22). Acute GVHD is evaluable in 16. Grade 1 GVHD developed in 4, grade 2 in 3 (18%). None developed grade >2 acute GVHD. Of the 11 patients evaluable, 6 (54%) developed chronic GVHD. Clinical results are summarized in Table 2. Thirteen patients are evaluable for transplant response. Three of them were already in complete remission (CR) at the time of transplantation. Another 2 achieved CR after the allograft, while 6 reached only a partial remission and 2 were refractory. Twelve patients are currently in follow-up, since 1 died of disease progression soon after transplantation. Until now there has been a single relapse. Four patients remain in CR at a median of 12 months follow-up (range 5-15 months).



Design of the protocol.

Table 1. Patients' characteristics.

Patients (No.)	18
Age (years)	median 53 (21-64)
Disease phase	
early	7
advanced	11
Previous autotransplant (No.)	10
Time from diagnosis to allo (months)	median 8 (3-66)

Table 2. Clinical results.

	No. patients
Evaluable	13
In CR at transplantation	3
Evaluable for response to transplant	10
CR	2
PR	6
NR	2
In CR following transplantation	5 (38.4%)
In follow-up	12
Continuous CR	4
Relapse	1
Death	1

Conclusions and comments

The preliminary results of the present protocol show that reduced-intensity conditioning with fludarabine, thiotepa and melphalan is well tolerated even in patients who have a long disease history or who have had previous autograft(s). In fact, no patient died of transplant-related complications. For this reason this scheme seems to be applicable also in elderly patients, or when comorbidities would discourage the use of transplantation.

In terms of GVHD, our experience is encouraging. Acute GVHD ≥ grade 2 occurred in less than 20% of patients and we did not observe grade 3 or 4. Chronic GVHD is expected to occur in

over 50% of cases, but this is not to be envisaged as a negative factor in a disease that is known to be sensitive to immune aggression.

Our protocol is able to induce a response in a sizeable proportion of patients. Eighty percent showed a response, with over 30% CR. Of the 5 patients in CR after transplantation only one has relapsed. The follow-up is, however, too short to draw any conclusions on remission duration. Data on IgH-gene rearrangement will be available in the next months, and will probably shed more light on the significance of CR after this treatment program.

In conclusion, the reduced-intensity conditioning transplant presented here is considerably less toxic than conventional conditioning. The incidence of acute GVHD is limited, and clinical results appear to be encouraging, as nearly 30% of patients achieve a complete remission and the majority maintain this status, at least in the short-term. We currently offer this program to patients with an HLA-identical sibling donor at the time of induction, after 3-4 courses of VAD.

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