Multiple Myeloma

The role of second autografts in the management of myeloma at first relapse

We report an analysis of the value of a second high-dose melphalan autograft, performed at relapse, on a series of newly diagnosed myeloma patients entered into the high-dose program at our center. We conclude that relapse-free survival after the first autograft is a major prognostic factor in determining outcome.

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Prolonged progression-free survival following a high-dose melphalan autograft (HDM) for myeloma is uncommon.[1,2] To clarify the role of a second autograft (HDM2) in the context of relapsed myeloma, we performed an intention-to-treat analysis on 383 newly diagnosed patients. The diagnosis of myeloma was made according to standard criteria.[3] CVAMP therapy (0.4 mg vincristine and doxorubicin 9 mg/m^2 by iv infusion for 4 days, methylprednisolone 1.5 g iv/po for 5 days and cyclophosphamide 500mg iv on days 1, 8, and 15) was delivered to maximum response. Patients received HDM based on an ECOG score <2 and adequate stem cell collection. Non-responders with ECOG<2 received HDM (200 mg/m^2) if stem cell collection was adequate or melphalan 140 mg/m^2 if this was not possible. Responses to induction protocols at the time of maximum response and at three months following high-dose treatment were recorded. At relapse, all patients were reinduced with CVAMP. The type of salvage therapy given subsequently was based on adequacy of stem cell collection, performance status and the patients' consent. In the absence of an adequate stem cell harvest, patients were treated with CVAMP to maximum response and alternative post induction regimens were used (Table 1). Patients were identified as non-responders if they did not meet the criteria for complete response or partial response[4] after at least two cycles of treatment.

The median follow-up of patients receiving a first HDM (HDM1) was 8 years.

At presentation hemoglobin, creatinine, albumin and β_2-microglobulin concentrations were significantly predictive of outcome as we have described previously.[5] Following HDM1, 172 patients relapsed with a median time to relapse of 2.6 years; 83 patients subsequently received a HDM2 and 83 received an alternative post-induction regime (Table 1). The six patients who were allografted were excluded from the analysis. In total, 118 patients received CVAMP at first relapse and 54 received alternative induction chemotherapy because of lack of consent, poor performance status or non-compliance (Figure 1).

There was no significant difference in event-free survival or overall survival for patients receiving HDM2 or alternative therapy at first relapse (median event-free survival 1.3 years versus 0.9 years, respectively p=0.73; median overall survival 2.9 years versus 1.7 years, respectively, p=0.07). The difference in OS of 1.2 years may be explained by a poorer performance status in the latter group. There was no association between achievement of a complete response and outcome.

Using a relapse-free survival cut-off of 18 months from HDM1, two groups of patients with highly significant differences in overall survival could be identified. Patients with a relapse-free survival of <18 months had a median survival of <6 months whereas those with a RFS of ≥18 months had a median survival approaching 3 years (p<0.00001) (Figure 2A). A similar result was observed in the group receiving alternative therapy (median overall survival of 1 year for relapse <18 months versus 2.9 years for relapse ≥18 months, p=0.004). The type of therapy received at relapse for those with an relapse-free survival ≥18 months did not influence outcome (p=0.33, median overall survival 4.6 years for HDM2 versus 2.9 years for alternative therapy) (Figure 2B). β_2 microglobulin concentration at relapse was highly significant in predicting overall survival (p=0.0007 at a cut-off of 3.1 mg/L). The hemoglobin, creatinine, albumin and β_2 microglobulin concentration at relapse were not significantly different between the two treatment groups using a p<0.05 cut-off and age was the only variable that differed (p=0.026).

In our study approximately 50% of patients were eligible for HDM2 at relapse and of this group, 25% will have relapsed within 18 months following HDM1. For this 25% of patients with a short relapse-free survival, the overall survival is poor in both treatment arms and our data do not support the use of HDM2. This group of patients may benefit from novel drug combination regimes.[6,7] Our study shows that the 75% of patients with

Table 1. Alternative post-induction regimes received by relapsed myeloma patients. Patients who died or were lost to follow-up or who could not tolerate further therapy are included in the no post-induction treatment category.

Post-induction regime	*Number of patients*
Interferon	18
Thalidomide regime	8
Cyclophosphamide regime	8
Melphalan	8
Velcade	2
Local radiotherapy	9
No post-induction treatment	30

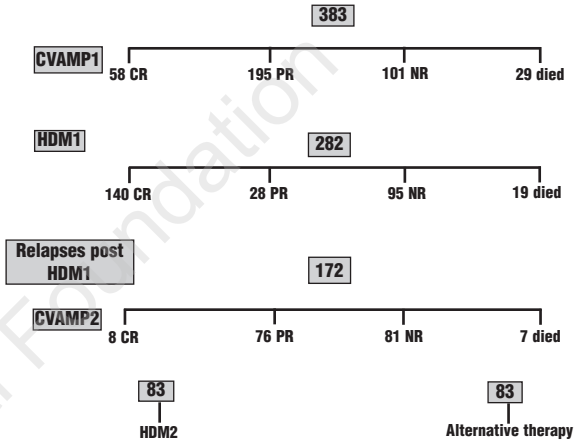

Figure 1. Flow chart of myeloma patients through the autograft program and responses at each stage.

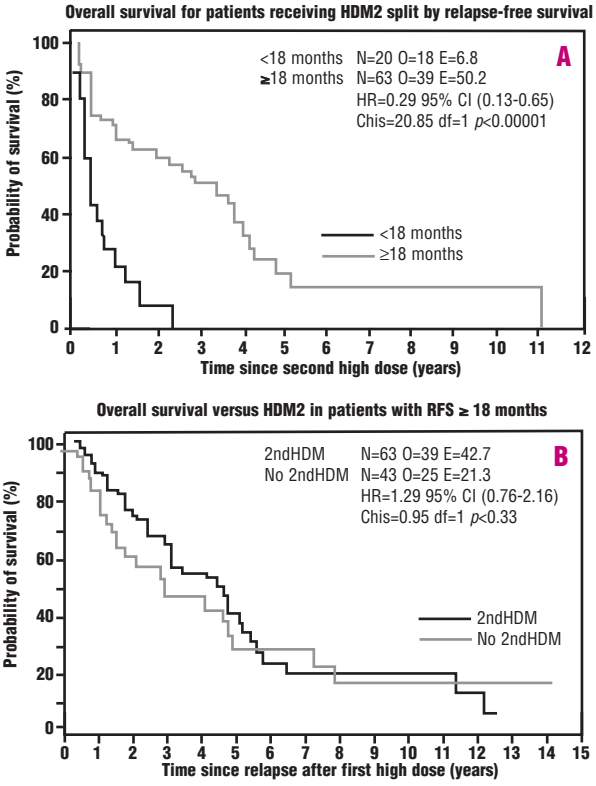

Figure 2. A. Relapse-free survival of≥18 months following the first HDM is an important predictor of overall survival (data for patients receiving a second HDM are shown). **B.** For patients with a relapse-free survival ≥18 months, the type of salvage therapy received (HDM2 or not) does not influence overall survival.

an relapse-free survival ≥18 months are in a good prognostic category. The type of salvage therapy delivered to this group does not significantly influence their overall survival. Our findings concur with those of Tricot *et al.*[8,9] who used a 12-month relapse-free survival cut-off and we have shown that this can be extended to 18 months. The Little Rock group recently published data showing that a survival of 3 years after a second autograft, given in a tandem setting, can predict outcome after a third autograft.[10]

We conclude that relapse-free survival is an important prognostic factor determining outcome and should be incorporated in therapeutic decisions for patients at first relapse. These findings need to be confirmed in larger series in the context of randomized trials and the UK Myeloma Forum is planning such a study.

Caroline L. Alvares, Faith E. Davies, Clive Horton, Gita Patel, Ray Powles, Gareth J. Morgan

Royal Marsden Hospital, Haemato-oncology Unit, Downs Road, SM2 5PT Sutton, UK

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Correspondence: Professor Gareth J. Morgan, Haemato-oncology Unit, Royal Marsden Hospital, Downs Road Sutton, Surrey SM2 5PT, United Kingdom.
E-mail: gareth.morgan@rmh.nthames.nhs.uk

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