

Myeloma

Transplantation as salvage therapy for high-risk patients with myeloma in relapse

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Summary:

Patients with myeloma relapsing after tandem transplant have a poor survival and treatment options are limited. The role of additional salvage transplant procedures for these patients is unknown. To evaluate the benefit and identify prognostic factors, the outcome of 76 consecutive patients with recurrent myeloma after tandem transplant receiving salvage transplants (ST) was analyzed. Prior to ST, 23 patients (30%) had shown chemosensitive response to preceding salvage chemotherapy: two complete remissions (CR); eight near CRs (nCR: only immunofixation positive); 13 partial remissions (PR $\geq 75\%$ reduction in M protein). Fifty received an autologous transplant, 22 a sibling-matched allogeneic transplant, and four a matched-unrelated allogeneic transplant. Overall response after ST was 59%: eight CRs (11%); 14 nCRs (18%); 23 PRs (30%). Overall survival (OS) at 2 years was 19%; 2 year event-free survival rate (EFS) 7%. On univariate analysis for survival, only pre-transplant chemosensitive relapse ($P < 0.05$), serum albumin >3 g/dl ($P = 0.001$), normal LDH ($P = 0.04$), and long interval between the second transplant and relapse/progression were significant beneficial factors. In a Cox proportional hazard model, chemosensitive relapse, and albumin >3 g/dl were significant for better OS: hazard ratio (HR) 1.4, 1.7, respectively, while normal LDH, and absence of CA13 were significant for better EFS: HR 1.8, 1.7, respectively. Patients with albumin >3 g/dl who had chemosensitive disease before ST ($n = 16$) had a median survival of 16 months, compared to 7 months ($n = 34$) and 2 months ($n = 26$) for patients with only one ($n = 34$) or no favorable prognostic factors ($n = 28$), respectively ($P < 0.001$). Their survival at 2 years post-ST was 43%, 17% and 11%, respectively. Our study suggests further transplantation should only be considered in the setting of a clinical trial in patients with favorable prognostic factors.

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Long-term myeloma control has become possible since high-dose therapy (HDT) with melphalan was introduced in the mid-1980s.¹ Treatment-related mortality of HDT has decreased to less than 3% with autologous peripheral blood stem cell support and improved supportive care.^{2,3} In newly diagnosed myeloma, about 40% of patients achieve CR, resulting in a significant increase in EFS and OS when compared to conventional therapy.^{4–6} Further intensification of HDT by using tandem transplantation was apparently associated with progressive increase in CR rate and additional survival benefit.⁶ A recent randomized trial by IFM (IFM-94 02) showed significant improvement in both EFS and OS with tandem transplantation compared to a single transplant. This difference only became apparent after 42 months of follow-up.⁷

Despite these improvements, the frequency of disease progression or relapse remains high after transplantation, with a median EFS of approximately 4 years in newly diagnosed patients.⁸ Once relapse occurs or disease progresses, options for salvage therapy at present are limited.⁹ Thalidomide alone or in combination with dexamethasone has been shown to have excellent activity in a fraction of refractory myeloma patients.¹⁰ Combinations of chemotherapy with thalidomide have provided significant response rates in patients relapsing with a high tumor burden, high proliferative disease, or high risk cytogenetics.¹¹ Newer phase II agents, such as proteasome inhibitors or thalidomide derivatives, need to be studied further to define their role in salvage therapy.^{12,13} Allogeneic transplantation with a matched donor may be considered, exploiting a graft-versus-myeloma effect to overcome chemoresistance, but is associated with a substantial risk of life threatening graft-versus-host disease (GVHD). Although a repeat melphalan-based HDT with autologous transplantation remains an alternative option, if stem cells are still available, its role for patients in relapse after tandem transplant has been uncertain.^{9,14} The benefit of a repeat HDT should be carefully weighed against potential consequences of further

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damage to vital organs and chemoresistance of recurrent myeloma.

This retrospective study seeks to address the benefit of repeat HDT with either autologous or allogeneic transplantation as salvage therapy for patients with recurrent myeloma after tandem transplant. It also describes prognostic factors for outcome.

Materials and methods

Patients

Data were retrieved on all available patients ($n = 76$) with multiple myeloma, who received either a salvage autologous or allogeneic ST between January 1991 and December 1999 for disease progression or relapse after prior tandem transplant. The Institutional Review Board of the University of Arkansas for Medical Sciences and the Arkansas Cancer Research Center approved all treatment protocols and informed consent was obtained from all patients.

All patients had symptomatic multiple myeloma. Patients up to the age of 70 years were eligible, although one patient of 71 years of age underwent autologous transplantation based on adequate physiological function. For autologous transplantation, patient eligibility was based on cardiopulmonary function including left ventricular ejection fraction $\geq 45\%$, corrected diffusion capacity of the lungs (DLCO) $\geq 45\%$, and adequate hepatic function (bilirubin, AST, ALT ≤ 2 times upper normal). Patients could have renal dysfunction (serum creatinine > 2 mg/dl) or poor performance status if the latter was related to multiple myeloma. For allogeneic transplantation, patients had to have a Zubrod performance ≥ 2 (Karnofsky performance $\geq 60\%$), adequate hepatic (bilirubin, AST, ALT ≤ 2 times upper normal) and renal function (serum creatinine ≤ 2 mg/dl). Family donors were acceptable if genotypically or phenotypically identical for human leukocyte antigens (HLA) A, B, DR or DRB1 by serologic testing. For unrelated transplantation, HLA match in A and B by serology, and in DRB1 by low-resolution molecular typing was required.

Transplant procedures

Marrow or blood stem cells had been collected before their initial autologous transplant in all patients. Seven patients received both autologous marrow and blood stem cells, and the remaining 44 only peripheral blood stem cells. The median number of autologous CD34 cells/kg for the 50 patients was 5.74×10^6 (range 1.5×10^6 to 47.92×10^6). Four patients received matched unrelated marrow, whereas six patients had a related marrow graft and 16 patients received peripheral blood stem cells from a matched sibling donor. Preliminary outcome data have been published on four of the 16 patients with a matched sibling donor who received a non-myeloablative allotransplant.¹⁵ Median number of allogeneic CD34 cells/kg was 4.1×10^6 (range 0.9–8.8). Median number of marrow mononuclear cells/kg was 1.8×10^8 (range 0.8–5.2).

BEAM (BCNU $300 \text{ mg/m}^2 \times 1$, etoposide $200 \text{ mg/m}^2 \times 4$, Ara-C $400 \text{ mg/m}^2 \times 4$, melphalan $140 \text{ mg/m}^2 \times 1$),

BuCy (busulfan 16 mg/kg , cyclophosphamide 120 mg/kg) or a melphalan-based myeloablative regimen was administered prior to autologous transplantation, whereas a melphalan-based regimen or fractionated total body irradiation (fTBI) regimen (1375 cGy) with thiotepa 5 mg/kg , and cyclophosphamide 120 mg/kg was given prior to a sibling or unrelated donor transplant, respectively. Melphalan was given as single agent at 200 mg/m^2 , or in combinations with fTBI at a lower dose (melphalan 140 mg/m^2 , fTBI 1000 cGy) or with cyclophosphamide (melphalan $140\text{--}200 \text{ mg/m}^2$, cyclophosphamide 120 mg/m^2). For non-myeloablative allotransplants, melphalan 100 mg/m^2 was given as single agent. Standard supportive care included antibacterial, antifungal and antiviral prophylaxis. Hemoglobin and platelet levels were maintained at $\geq 10 \text{ g/dl}$ and $\geq 20 \times 10^9/l$, respectively. For patients receiving an allogeneic transplant, GVHD prophylaxis consisted of a standard cyclosporine-based regimen. Patients who did not develop GVHD or whose GVHD became well controlled received tapering doses of cyclosporine over 3–4 months. Corticosteroids were administered as initial therapy of acute GVHD of grade $\geq \text{II}$ or chronic GVHD.

Statistical analysis

Patients were studied for response, OS and EFS. Cumulative incidence was used for response, TRM, and relapse.¹⁶ CR required the disappearance of monoclonal gammopathy in serum and urine on immunofixation analysis and attainment of normal bone marrow aspirate and biopsy with $< 1\%$ light chain-restricted plasma cells on flow cytometry, on at least two successive occasions at least 2 months apart.⁶ Cases were considered as near CR (nCR) if positive immunofixation analysis of serum or urine was the only evidence of disease, with normal bone marrow findings. PR implied 75% reduction from baseline serum M protein including a normal marrow aspirate and biopsy and/or, in case of Bence-Jones proteinuria, reduction to $< 100 \text{ mg/day}$. Chemosensitive response at disease relapse was defined as CR + nCR + PR by conventional-dose chemotherapy. For computation of PR and CR rates after ST, all patients were eligible (intent-to-treat); those dying early before antitumor effect could be established were considered treatment failures. Treatment-related mortality included any death within 100 days post ST. Events included disease progression/relapse or death from any cause. Relapse was defined as recurrence of monoclonal protein or bone marrow plasmacytosis or evidence of extramedullary disease in case of CR or nCR or any new disease manifestation, including hypercalcemia. Disease progression for non-CR patients implied at least a 25% increase in tumor mass or any new disease manifestation, including hypercalcemia. Pre-transplant variables analyzed were β_2 microglobulin, C-reactive protein, LDH, albumin, marrow plasmacytosis, cytogenetic findings, duration between the second transplant of the tandem transplant and relapse/progression, and response to salvage chemotherapy. Variables related to transplantation included type of transplant (allogeneic vs autologous), and response to ST. Survival analyses were performed using the product limit estimate of Kaplan–Meier method. Day +100 post transplant

was used as landmark point for analysis of outcome according to response post transplant. For multivariate analyses, variables with a *P* of <0.1 in univariate analysis were entered into a stepwise multivariate regression by the Cox proportional hazard model.

Results

Patient and disease characteristics

Demographic data are described in Table 1. At time of initial transplant, 23 patients (30%) had high risk disease defined as either β_2 microglobulin >2.5 mg/l, or unfavorable karyotypes (chromosome 13 abnormalities) or >12 months of preceding standard therapy.¹⁷ Twenty-four patients (32%) had achieved CR after one and 42 patients (55%) after their second transplant. Median duration between the second transplant and relapse/disease progression was 18 months (range 3–61 months). At the time of relapse, 53 patients (70%) had cytogenetic abnormalities with 30 patients (39%) showing chromosome 13 abnormalities. Nine patients (12%) had β_2 microglobulin >6 mg/l, 13 (17%) had C-reactive protein >4 mg/l, 38 (50%) had LDH >200 IU/l (normal 100–190 IU/l), 14 (18%) had albumin <3.0 g/dl and six (8%) had calcium >12 mg/dl, reflecting aggressive disease features. Of the 76 patients, 61 (80%) had at least one of these poor prognostic features.

Pre-ST therapy and response (Figure 1)

Twenty-two patients received DCEP (dexamethasone, cyclophosphamide, etoposide, cisplatin) or a variant (\pm doxorubicin \pm thalidomide) as initial salvage therapy. Sixteen additional patients received DCEP after initial salvage therapy with dexamethasone. Nine patients received combination chemotherapy with EDAP (etoposide, dexamethasone, doxorubicin, cisplatin). Of these 47 patients (62%) receiving salvage combination chemotherapy (median number of cycle: 2, range 1–5), two achieved CR; five nCR; five PR; 13 had no response (NR); progressive disease (PD) was seen in 22 patients. The 35 patients with NR or PD received ≥ 1 salvage chemotherapy after failing initial chemotherapy, resulting in four additional PRs. Eighteen patients (23%) received initial salvage therapy with C \pm VAD (cyclophosphamide, vincristine, doxorubicin, dexamethasone), resulting in one nCR, two PR, nine NR and six PD. One additional PR occurred on further salvage

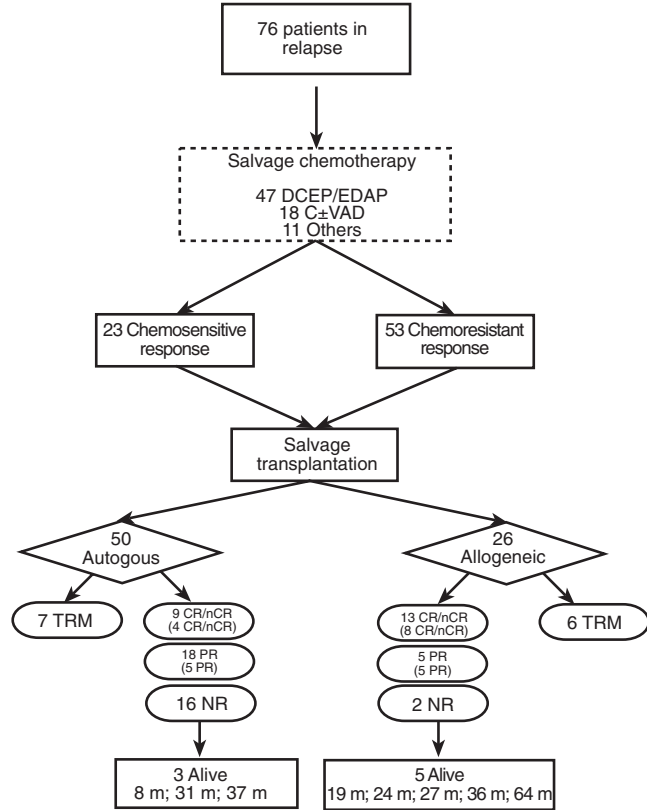


Figure 1 Flowchart of 76 patients. In the response sections, () denotes the number of additional responses after ST.

therapy in the 15 NR or PD patients. Thalidomide alone or in combination with dexamethasone was administered to seven patients who failed salvage chemotherapy. Two achieved nCR, one PR and four NR. The 11 remaining patients (15%) received interferon- α (*n* = 3), cis-retinoic acid (*n* = 3), gemcitabine (*n* = 1) or fludarabine + taxol (*n* = 2). After all reinduction treatments, two achieved complete CR, eight nCR, and 13 PR, resulting in 30% of patients having chemosensitive relapse.

Transplant therapy

Table 2 describes the different transplant regimens, which varied as a result of our effort to reduce toxicity over the

Table 1 Patient and disease characteristics in relapse

Parameter	Median	Range	Cut-off	%
Age (years)	52	31–71	(>50)	61
β_2 M (mg/l)	3.2	0.97–60	(>4.0)	31
CRP (mg/l)	2.8	0.2–13.8	(>4.0)	17
Creatinine (mg/dl)	1.2	0.5–4.7	(>2.0)	13
Hemoglobin (mg/dl)	9.3	6.7–15.9	(\leq 10.0)	48
Albumin (gm/dl)	3.7	2.1–4.9	(\leq 3.5)	26
LDH (IU/l)	376	34–1033	(>200)	49
Marrow plasmacytosis (%)	40	5–95	(>40)	39

Table 2 Transplant regimens

Regimen	Autologous <i>n</i> = 50	Allogeneic <i>n</i> = 26
BEAM	10	0
BuCy	4	0
Mel 200	17	0
Mel 100	0	4
Mel 200-Cy 120	0	4
Mel 140-Cy 120	3	0
Mel 140-ftBI	13	10
Mel 110-ftBI	3	2
ftBI-Thio-Cy	0	6

9-year period. Thirteen patients died ≤ 100 days post ST. In 50 patients who received autotransplants, nine patients (18%) achieved a CR ($n = 4$) or nCR ($n = 5$), 18 patients (36%) had a PR, and 16 patients (32%) had NR. The number of additional improvement in disease status by salvage autotransplant was two CR, two nCR and five PR.

Thirteen of 26 patients (50%) receiving an allogeneic transplant attained a CR ($n = 4$) or nCR ($n = 9$) and five patients (19%) a PR. The number of additional responses to allotransplant were four CR, four nCR and five PR.

Therefore, the overall response rate (\geq PR) was 22 of 76 (29%) to the salvage transplant and 45 of 76 patients (59%) to both salvage pre-transplant therapy and transplant. Eight of 23 patients (35%) who had chemosensitive response to pre-transplant salvage therapy obtained a CR ($n = 3$) or nCR ($n = 5$) after ST, compared to two CR and two nCR of 53 patients (8%) with no response to pre-transplant salvage ($P = 0.005$).

Transplant-related mortality (TRM) and engraftment after ST (Figure 1)

Seven (14%) autologous transplant patients died before 100 days post transplant (median 10 days, range 0–52 days), compared with six patients (23%) receiving an allogeneic transplant (median 38 days, range 11–82 days), with an overall TRM rate of 17%. Of the autologous transplants, three died of sepsis and four of multi-organ failure. In the allogeneic transplant group, three died of organ failure (one veno-occlusive disorder, one idiopathic pneumonia syndrome, one multi-organ failure), and three of acute GVHD or its complications. Except for the four patients who died before day 28 post transplant, all patients showed myeloid engraftment (absolute neutrophil count $>1000/\mu\text{l} \times 2$ days) at a median of 18 days (range, 9–43 days). One-year TRM was 34%, including 14 of toxicity, nine of infections, and three of GVHD.

Overall and event-free survival after ST (Figure 2a)

Median survival of all patients from ST was $8\frac{1}{2}$ months and 2-year overall survival was 19%. The projected 5 year survival is 6% (CI 2–10%). Median survival from ST for patients with autologous transplant was 9 months, compared with 2 months for patients with allogeneic transplant ($P = 0.54$). Survival at 2 years was 19% for the autologous vs 26% for allogeneic ST ($P = 0.52$). Patients with chemosensitive relapse had a median survival of 12 months (2 year survival 30%; 5 year survival 3%) vs 4 months (2 year survival 13%; 5 year survival 0%) for chemoresistant patients ($p < 0.05$). Using a 100 day landmark, the patients in CR + nCR ($n = 22$) after ST survived a median of 13 months (2 year survival 36%; 5-year survival 15%), compared with $4\frac{1}{2}$ months in patients ($n = 41$) with less than CR + nCR (2 year survival 16%; 5 year survival 0%) ($P < 0.05$).

Median EFS was $3\frac{1}{2}$ months for all patients, with a 2 year EFS rate of 7%. The projected 5 year EFS is 5% (CI: 2–8%). Eight patients are alive and event free from 8 months to 5 years. Median EFS for autologous and allogeneic transplants was 4 months (2 year EFS 10%; 5 year

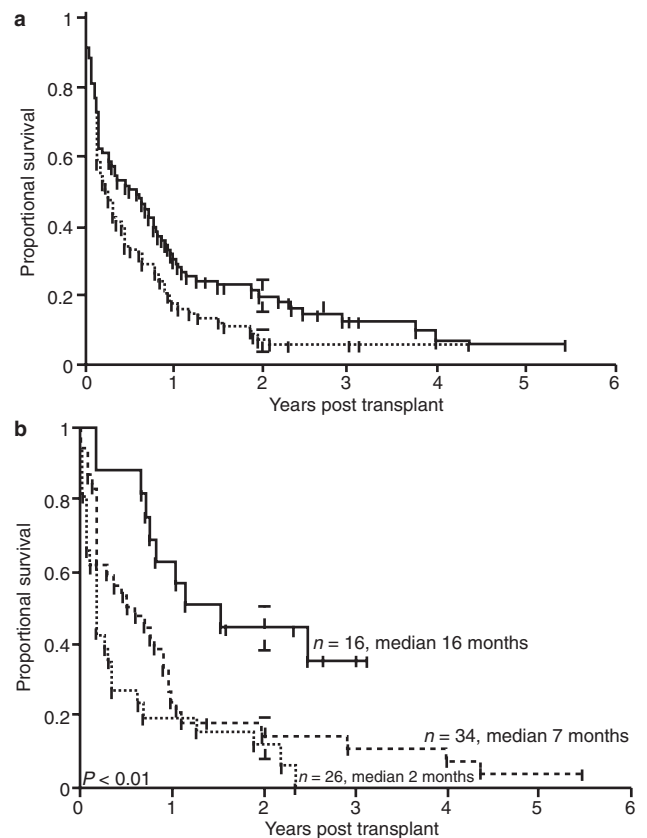


Figure 2 (a) Overall survival (—) and event-free survival (---) of all 76 patients; (b) two good prognostic factors (—), one good prognostic factor (---) and no good prognostic factors (----).

survival 0%) and 2 months (2 year EFS 15%; 5 year survival 11%), respectively ($P = 0.79$). Using a 100 day landmark, patients achieving CR or nCR post ST had a median EFS of 8 months (2 year EFS 18%; 5 year survival 13%), compared with 3 months for those attaining $<$ nCR (2 year EFS 9%; 5 year survival 0%) ($P = 0.06$).

Univariate and multivariate analyses

Table 3 shows factors affecting survival. Through bivariate regression analysis for survival, albumin >3 g/dl, normal LDH (≤ 190 units/l), marrow plasmacytosis $<40\%$, and ≥ 18 months of interval between the second transplant and relapse/disease progression were selected as significant dichotomous values for categorical designation. On multivariate analysis shown in Table 4, albumin >3 g/dl, and chemosensitive relapse were good prognostic factors for overall survival, whereas normal LDH, and absence of CA13 were favorable for EFS. When combining albumin >3 g/dl and chemosensitive response the median survival was 16 months (2 year survival 43%; 5 year survival 8%) for the 16 patients with two favorable prognostic factors, compared to 7 months (2 year survival 17%; 5 year survival 0%) and 2 months (2 year survival 11%; 5 year survival 0%) for those with 1 ($n = 34$) and no favorable prognostic factors ($n = 26$) ($P < 0.001$) (Figure 2b).

Table 3 Univariate pre-transplant factors affecting 2 year survival (Kaplan–Meier)

Factors	OS (P)	EFS (P)
Response to pre-transplant salvage ≥PR vs <PR	30% vs 13% (0.03)	13% vs 9% (0.04)
Albumin >3 g/dl vs ≤3 g/dl	26% vs 9% (0.001)	10% vs 0% (0.02)
LDH Normal vs > Normal (≤190 IU/l)	24% vs 19% (0.04)	18% vs 3% (0.008)
Chromosome 13 abnormality Absent vs present	24% vs 17% (NS)	15% vs 4% (0.01)
2nd transplant-relapse interval >18 vs ≤18 months	29% vs 17% (0.06)	23% vs 4% (0.03)
Response to the salvage transplant CR/nCR vs <nCR	36% vs 16% (0.048)	18% vs 9% (0.06)
Type of transplant Auto vs allo	19% vs 26% (NS)	10% vs 15% (NS)
Regimen BEAM vs melphalan-based	28% vs 14% (0.07)	10% vs 11% (NS)

NS = not significant ($P > 0.1$).**Table 4** Multivariate analysis of variables with each hazard ratio (HR) and P value

Variables	HR for OS (P value)	HR for EFS (P value)
Response to the salvage transplant	1.4 (0.005)	NS
Albumin ≤3 g/dl	1.7 (0.001)	NS
LDH ≤190 U/l	NS	1.8 (0.002)
CA13 absent	NS	1.7 (0.006)
2nd transplant-relapse interval >18 months	NS	NS
Auto vs allo	NS	NS

NS = not significant ($P > 0.1$).

Discussion

Significant progress has been made in long-term disease control of myeloma by high-dose therapy and autologous transplantation. Nevertheless, the rate of relapse and progression is high, reaching more than 70%, with the majority of relapses seen during the first 3 years, then a slower relapse rate up to 7 years and an apparent plateau thereafter.¹⁷ In a recent European Bone Marrow Transplant report on long-term follow-up of more than 12 years of patients treated with autologous transplantation,¹⁸ similar to what we have observed in our program, actuarial OS and PFS at 10 years post transplant were 30% and 16%, indicating that a small proportion of patients remain alive and disease-free for up to 14 years. The most likely explanation of the high incidence of relapse after autotransplantation is persistence of residual clonal myeloma cells that can be detected by polymerase chain reaction-based tests in 80% to 90% of patients in CR.^{19,20}

The present study tries to define the role of further salvage transplantation for patients who relapse after tandem autologous transplantation. The response rate of 59% in patients alive >100 days post ST including CR and nCR (29%) was high but unfortunately not maintained long-term

in the majority of patients, resulting in a 2 year overall survival rate of only 19%. Event-free interval was likewise short, with more than 80% of events occurring in the first year post transplant. The patient population, however, was heavily pre-treated and the majority (80%) had high risk disease. Fifty-four patients (71%) had unfavorable karyotypes, and 36 (47%) had received more than one line of salvage chemotherapy prior to ST. Patients with serum albumin >3 g/dl who achieved CR or nCR ($n = 13$) prior to salvage transplantation had a 2 year survival of 43% and median survival of 16 months. Patients with chemosensitive relapse also had a higher incidence (55%) of CR and nCR post transplant. It is difficult to ascertain the contribution of the transplant to the relatively good 2 year survival of patients with high-grade responses and an albumin >3 g/dl, as these patients would be expected to have a better outcome anyway. In patients undergoing allogeneic transplantation, TRM was prohibitively high, similar to the experience with second allogeneic transplantation in patients with leukemia relapse after a first allotransplant,²¹ but resulted in a better 2 year progression-free survival (27%) than autologous ST (16%) ($P = 0.006$). However, unless TRM decreases, which may be accomplished by using non-myeloablative therapy, salvage allogeneic transplantation remains a challenging treatment approach in patients relapsing after autotransplantation. Thalidomide alone or in combination with other agents has shown an encouraging EFS of 20% at 2 years in the cohort of heavily pre-treated patients.¹⁰ Our study suggests that unless prospective clinical trials that compare salvage autotransplant with other non-transplant therapy, such as thalidomide-based therapy, show a clear survival benefit, it is premature to recommend a further autotransplant for relapse after tandem transplant. If an allogeneic donor is available, a clinical trial with a non-myeloablative approach should be considered in patients with chemosensitive disease. Obviously, additional efforts are necessary to prevent relapse after initial transplantation. We are exploring immunotherapeutic approaches either with adoptive immunotherapy in patients with a sibling donor by administration of an autologous transplant followed by a non-myeloablative allo-transplant, or with tandem autologous transplantation plus vaccination with dendritic cells pulsed with either idiotype, tumor cell lysate or cancer/testis antigen-derived peptides.

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