Bone Marrow Transplantation (2001) 27, 1037–1043

www.nature.com/bmt

Graft outcome

Impact of complete remission with intensive therapy in patients with responsive multiple myeloma

R Alexanian, D Weber, S Giralt, M Dimopoulos, K Delasalle, T Smith and R Champlin

University of Texas MD Anderson Cancer Center, Houston, Texas, USA

Summary:

Clinical outcomes were assessed in 68 consecutive patients with multiple myeloma of high or intermediate tumor mass that had responded to VAD or dexamethasone-based therapy and were consolidated with early intensive therapy and autologous stem cell transplantation. Results were compared with those of 50 comparable patients who refused or were unable to receive intensive treatment for socioeconomic reasons. Following high-dose therapy, the rate of CR increased from 6 to 37%, with median survival prolonged by 10 months. Survival of 21 patients with disease converted from PR to CR (median 8.3 years) was significantly longer than that of similarly-treated patients who remained in PR (median 5.0 years). CR of myeloma represents the major surrogate marker of long survival and the primary goal of myeloablative treatment for patients in PR. Twelve of 18 patients with rapid reduction of myeloma protein ($T\frac{1}{2} < 0.5$ months), and myeloma protein reduction to <1.0 g/dl after primary therapy achieved CR (67%), identifying pretransplant features favorable to intensive therapy. Among 35 patients with slower reduction or higher residual myeloma protein, CR occurred in eight patients (23%) ($P < 0.01$), for whom other treatments should be considered. The kinetics of response to initial therapy should be considered in selecting patients more likely to achieve CR and consequent long survival after intensive treatment. *Bone Marrow Transplantation* (2001) **27,** 1037–1043.
Keywords: multiple myeloma; autologous cell transplantation; survival and remission times

Numerous studies have assessed the role of myeloablative therapy supported by autologous stem cell transplantation for patients with multiple myeloma.[1–8] Most reports have described a higher frequency of CR than that achieved with standard therapies, a potentially higher risk of morbidity or death among patients older than 65, and less benefit for patients in later phases of disease. One randomized comparison of standard *vs* intensive therapy in newly diagnosed patients confirmed a significantly higher frequency of PR, CR, and longer survival, for patients who received early myeloablative therapy.[5] We and Blade *et al* observed similar survivals among patients transplanted during remission in a retrospective comparison with matched controls, while Fermand *et al* observed similar outcomes in a prospective study among patients aged 55–65 assigned at random to intensive or standard treatments.[3,9,10] Several analyses of prognostic factors have revealed significantly shorter survivals for patients with more advanced disease, high serum B_2M or deletions of chromosome 13.[5,11] Thus, there is concern whether myeloablative treatment is useful for all patients or whether meaningful benefit is limited to subgroups yet to be identified. We analyzed the outcomes of consecutive patients with disease of high or intermediate tumor mass that had responded to primary treatment, and who then received early intensive therapy with autologous stem cell transplantation. In comparison with a matched control group treated concurrently, results showed longer survivals for all patients, and significantly longer survivals and relapse-free survivals for the higher percentage of patients with disease converted to CR. These findings confirm and extend those reported by Attal *et al*[5] and Lahuerta *et al*.[12] In addition, rapid and marked reduction of myeloma with initial chemotherapy were associated with more frequent CR after intensive treatment, adding factors that reflect tumor sensitivity in selection of patients for consolidation treatment.

Patients and methods

Patients

Between 1986 and 1999, 68 patients with advanced multiple myeloma in partial or complete response received intensive, myeloablative therapy supported by autologous marrow or blood stem cells within 1 year of primary therapy. Patient characteristics are summarized in Table 1. The median age of the transplanted group was 49 (range 32–60), all had good performance, and adequate cardiac, pulmonary and renal function. Only patients with high or intermediate tumor mass and serum myeloma protein were considered in order to focus on a uniform group of patients with advanced disease who received early consolidation

Correspondence: Dr R Alexanian, Box 1, University of Texas MD Anderson Cancer Center, Houston, Texas, 77030, USA
Received 28 June 2000; accepted 1 February 2001

Table 1 Clinical features at diagnosis of patients who received intensive therapy during remission and of control patients

	Transplanted	*Control*
No. patients	68	50
Median age (range)	49 (32–60)	53 (25–60)
Pretreatment features		
Tumor mass (%)		
High	50	34
Intermediate	50	66
Hgb <10.5 g/dl (%)	74	66
Creatinine >2.0 mg/dl (%)	19	10
Serum B_2M (mg/l)	4.7	4.2
(median and range)	(2.0–14.8)	(1.9–14.4)
LDH >300 U/l (%)	12	6
Median months to:		
Remission	1.2	0.9
Ablative therapy	6.5	NA

NA = Not applicable.

treatment; the data of five patients with prior disappearance of only Bence Jones protein were excluded. All received intensive therapy after at least two courses of vincristine–doxorubucin by continuous infusion with pulse dexamethasone (VAD; 12 patients), pulse dexamethasone alone (30 patients), high-dose cyclophosphamide–etoposide with dexamethasone (18 patients) or a combination of fractionated high-dose cyclophosphamide with VAD (eight patients).[13–15] Because disease features, response rate and survival were similar among large series of patients who received each of these treatments, all patients were analyzed together.

Treatment

The median time between initial chemotherapy and intensive treatment was 6.5 months (range 2–12 months). Patients received one of two myeloablative regimens prior to autologous stem cell transplantation. Twenty-one patients received a combination of melphalan (140 mg/m^2) and TBI (850 cGy) from 1987 to 1991;[3] 40 received a combination of thiotepa (750 mg/m^2), busulfan (10 mg/kg) and cyclophosphamide (120 mg/kg) between 1991 and 1999;[16] since 1994, cyclosporine was added to the latter program for seven patients in an attempt to exploit a possible graft-versus-tumor effect.[17] Within 48 h after completion of therapy, patients received either ABMT ($>1.0 \times 10^4$ granulocyte–macrophage colony-forming units (CFU-GM)/kg) (1986–1991), or blood stem cells with $>2 \times 10^6$ CD34$^+$ mononuclear cells/kg (1992–1999). Because disease features and outcomes were similar for patients who received different intensive treatments or sources of stem cells, all patients were combined in the analysis of transplant-supported therapy.[16] Specifically, there was no effect of source of stem cells and time of study on frequency of early death, frequency of CR or survival.

Staging and response

Prior to initial therapy, tumor mass was defined in each patient as high or intermediate by standard criteria. High tumor mass required either Hb less than 8.5 g/dl or serum calcium greater than 11.5 mg/dl; intermediate tumor mass was defined by Hb between 8.5 and 10.5 g/dl or serum myeloma protein greater than 4.5 g/dl. Partial response was defined as >75% reduction of initial serum myeloma protein production, >95% reduction of Bence Jones protein, and reduction of marrow plasmacytosis to less than 5%; rapidity of response was assessed from the $T\frac{1}{2}$ of IgG or IgA myeloma protein reduction;[18] CR required disappearance of serum myeloma protein by immunofixation. All patients were maintained on IFN 1.5–3.0 MU s.c. 3 × weekly from time of hematologic recovery. Relapse was defined by earliest of either recurrent serum myeloma protein that had disappeared, doubling of myeloma protein, new lytic bone lesions or marrow plasmacytosis >10%.

Control patients

Fifty control patients were identified with the same clinical features who were responsive to the same primary therapies and met the eligibility criteria for myeloablative therapy, but did not receive such treatment. Patients either refused intensive treatment or were denied coverage of the procedure by their insurance company. As in patients who received intensive therapy, control patients were 60 years old or less, had myeloma of high or intermediate tumor mass at diagnosis, presented with serum myeloma protein, received the same therapies during the same time period, were free of serious cardiac, pulmonary, or renal dysfunction, and would have received myeloablative treatment if possible. Major prognostic factors were similar for patients who received a transplant-supported program or were continued on standard treatment (Table 1).

Statistical analysis

Chi-square tests were used to compare complete remission rates. The Kaplan–Meier method was used to calculate survival and progression-free survival times, and differences were compared by the log rank test. Survival was measured from initial therapy for all patients; progression-free survival was calculated from onset of partial response to first objective sign of relapse or death from unrelated disease.

Results

Complete remission

CR had occurred with initial therapy in four responding patients who received later myeloablative treatment (6%) and in five control patients who received standard VAD or dexamethasone-based therapy (10%), similar to our previous experiences.[13,14] After intensive treatment, CR was induced in 21 additional patients so that the total frequency of CR among transplanted patients of 37% was significantly higher than that of control patients ($P < 0.01$). Conversion of PR to CR was recognized by a median 5.3 months after high-dose treatment (range, 1–12 months).

Early death

Treatment-related death occurred in five patients who received intensive treatment (7%), namely in two of 53 patients less than 55 years old (4%) and in three of 15 patients aged 55–60 (20%) ($P = 0.03$). Causes of death were multiorgan failure (three patients), respiratory syncytial viral pneumonia (one patient) and failure of bone marrow engraftment (one patient). Transplant-related deaths occurred at a median 10 months after primary therapy (range 4–15 months) and 1.9 months after transplantation (range 1.1–3.1 months). No other factors were associated with early death, such as source of stem cells or pre-1990 *vs* later transplant.

Survival and remission

Deaths have occurred in 57% of all patients. The median survival was 10 months longer for transplanted patients in comparison with control patients (Figure 1, left panel) ($P = 0.12$). In order to focus on the role of intensive therapy in converting PR to CR, we excluded from subgroup analyses the four patients with CR prior to intensive therapy. Median survival of 21 patients with disease converted from PR to CR after intensive therapy (8.3 years) was more than 3 years longer than those of 43 patients who remained in PR (5.0 years), or of 45 patients with persistent PR after standard therapy (4.4 years) ($P = 0.03$) (Figure 1, right panel).

Relapse-free survival was longer for patients converted to CR when relapse-free survival was defined by the earliest of either disease relapse or death from any cause. The median relapse-free survival of 21 patients with CR induced by ablative therapy was 4.1 years, approximately 2 years longer than the progression-free survival of 43 similar patients who remained in PR after intensive therapy (median 2.3 years), or of 45 patients with persistent PR after standard therapy (median 2.1 years) ($P = 0.26$). CR has been sustained for more than 8 years in two patients who received intensive treatment and in two patients given standard therapy.

Complete remission with standard therapy

Survival and remission were assessed in 13 similar patients with CR only to standard therapy. These included the five control patients included here, as well as five patients $\leqslant$ age 60 treated earlier from 1975 to 1986 and three patients aged 61–67 treated from 1987 to 1999, all with similar high or intermediate tumor mass and serum myeloma protein at diagnosis (both older age and treatments prior to 1986 have been associated with shorter survival than those observed with more recent treatments in younger patients[9]). Figure 2 shows similar survival and myeloma-specific survival for 13 patients in CR with standard therapy and 21 patients converted from PR to CR by intensive therapy; median relapse-free survival times were also similar at approximately 4 years when relapse was censored at death from causes other than myeloma.

Prognostic factors

Multiple factors were assessed in order to identify those that might be associated with conversion of PR to CR after intensive treatment. These included age, protein type, tumor mass, serum B_2M, level of myeloma protein at diagnosis and prior to intensive treatment, prior speed of myeloma protein reduction and months to partial remission. The only suggestive factors are shown in Table 2 with combinations of features assessed in Figure 3. CR occurred in 12 of 18 patients with rapid reduction of serum myeloma protein to initial therapy ($T\frac{1}{2} < 0.5$ months) and serum myeloma protein <1.0 g/dl prior to transplant, in eight of 20 patients

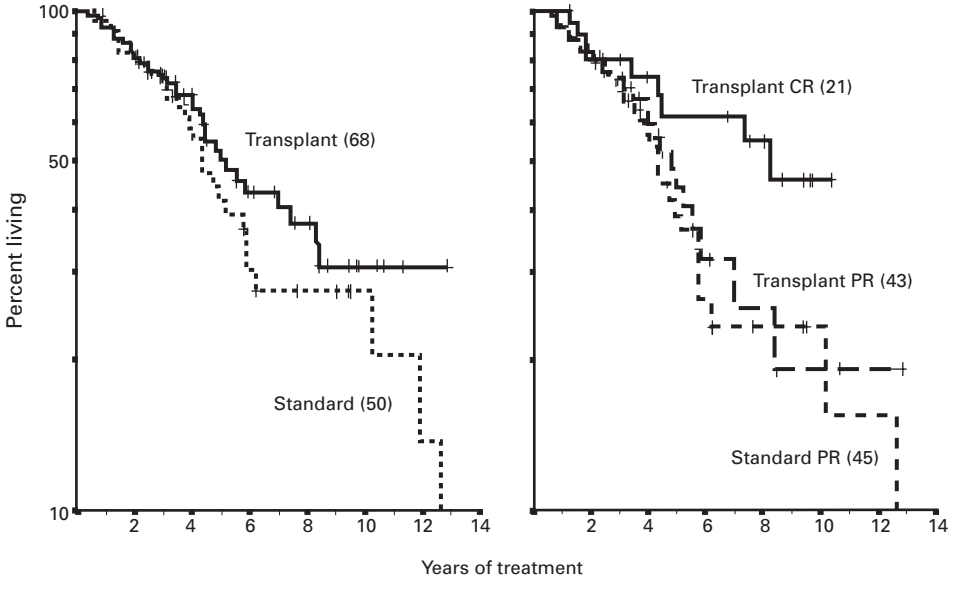

Figure 1 Left panel. Survival from primary treatment of 68 responding patients intensified during remission in comparison with 50 control patients continued on standard treatment. Right panel. Survival of 21 patients with disease converted from PR to CR, 43 patients with persistent PR despite intensive treatment, and 45 patients with disease in PR after standard therapy ($P = 0.03$).

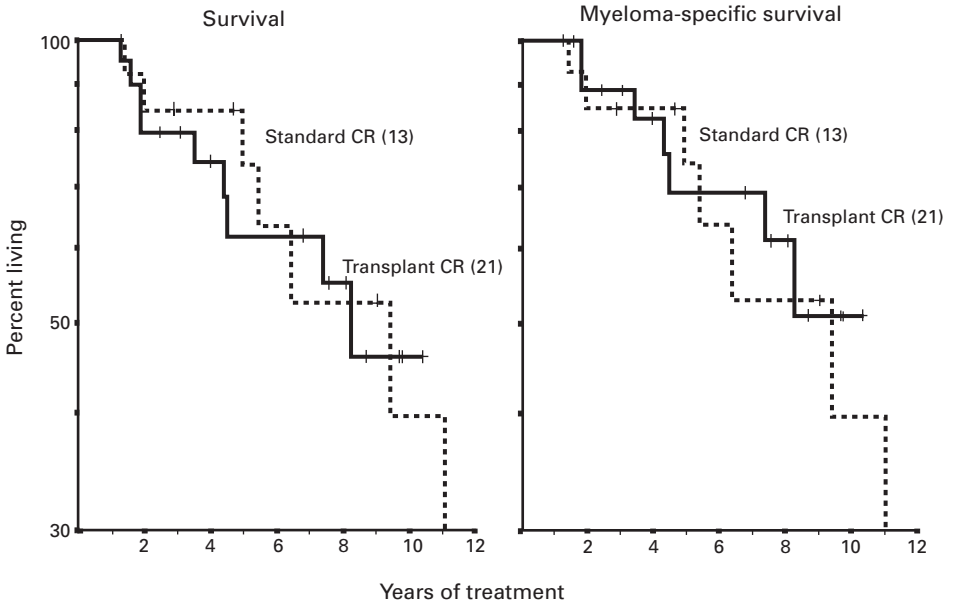

Figure 2 Left panel. Survival from primary therapy of similar responding patients in complete remission who had received intensive or standard treatment. Right panel. Myeloma-specific survival of same patients with lifespan censored at death from unrelated disease.

Table 2 Clinical features associated with complete remission after myeloablative therapy

	No. CR/Total (%)	*P*
Before primary treatment		
All patients	21/64 (33)[a]	
LDH (U/L) (normal <225 U/l)		
<300	15/34 (44)	0.06
>300	0/5 (0)	
Missing data	6/25 (24)	
B_2M (mg/l)		
<5.0	14/30 (47)	0.10
⩾5.0	6/24 (25)	
Missing data	1/10 (10)	
After primary treatment		
Myeloma protein halving (months)		
<0.5	17/28 (61)	<0.01
⩾0.5	3/25 (12)	
Missing data	1/11 (9)	
Months to remission		
<1.0	13/26 (50)	0.02
⩾1.0	8/36 (22)	
Missing data	0/2	
Pretransplant myeloma protein (g/dl)		
<1.0	16/31 (52)	<0.01
⩾1.0	5/33 (15)	

[a]Four patients in complete remission prior to intensive therapy were excluded from this analysis.

with either finding, and in none of 15 patients with neither feature ($P < 0.01$). A similar relation was found when short time to PR (<1.0 month) was substituted for rapid myeloma protein halving time.

Discussion

During the past 10 years, there have been many studies of myeloablative therapy supported by autologous stem cell transplantation for patients with multiple myeloma.[1–8] Most centers have agreed on the potentially higher risk for older patients so that few patients older than 65 have received such treatment. Yet, a recent report has described similar outcomes among 49 selected patients older than 65 (representing 9% of treated patients) who received high-dose melphalan alone supported by autologous stem cell transplantation, in comparison with 49 matched, younger patients.[19] Patients treated later in their course, such as during resistant relapse or with more than 1 year of primary resistant disease, have also benefitted less than those treated earlier.[3,11] One controlled study has described significantly longer progression-free survival and survival among patients randomized to myeloablative treatment in comparison with continued standard treatment,[5] while a similar randomized study among patients aged 55–65 found less difference.[10] Two retrospective studies have described similar outcomes with intensive *vs* standard therapies for patients with responsive disease of comparable age and disease stage,[3,9] while other retrospective comparisons showed longer survival for all transplanted patients *vs* matched controls.[7,20]

Because of the high morbidity, occasional mortality, expense and social dislocation associated with intensive treatment supported by autologous stem cell transplantation, we defined the efficacy of this procedure in a retrospective analysis of consecutive patients with advanced disease that had responded to VAD or similar programs with high-dose dexamethasone. Results were compared with those of control patients who were matched for major prognostic variables and qualified for transplantation in all respects but either refused or were denied treatment for

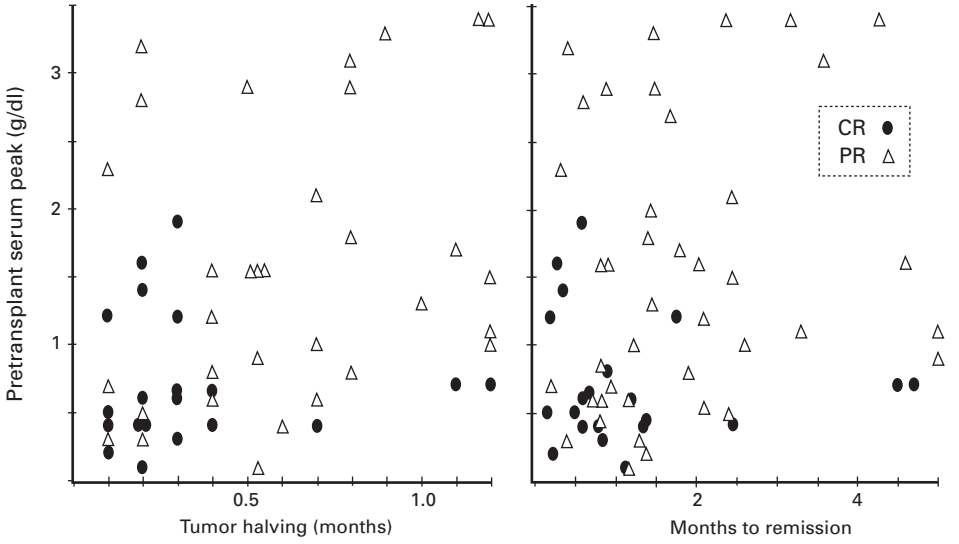

Figure 3 Left panel. Occurrence of CR or PR after intensive therapy in relation to pretransplant level of serum myeloma protein and rapidity of prior reduction. Right panel. Similar correlation of CR or PR with time to remission substituted for myeloma protein halving.

socioeconomic reasons. Undetected selection factors may have excluded some patients from either group, perhaps biasing the outcomes, but such effects would have been small. Our patients were homogeneous in terms of their advanced disease at diagnosis, that was responsive to programs with repeated dexamethasone, consolidated with myeloablative treatment during the first year, and with outcomes compared with those of a matched control group. One shortcoming was the absence of consistent studies of special biologic features such as plasma cell labeling index or cytogenetics.

Among patients with responsive disease, the overall frequency of CR (as defined by disappearance of serum myeloma protein by immunofixation) increased with intensive treatment from 6 to 37%. Similar high frequencies of CR have been described by others.[2,4–8] Some of the slight differences in various studies could be due to the inclusion of patients with nonsecretory disease or only Bence Jones protein that had disappeared prior to treatment, where criteria for CR are less clear. The role of interferon in contributing to conversion of PR to CR after transplant was also uncertain, but probably had less impact on reduction of myeloma than the prior intensive therapy.

Patients who developed CR after intensive therapy experienced longer survival and relapse-free survival than comparable patients with persistent PR. The median gains of approximately 3 years of survival and 2 years of relapse-free survival represent important indices of the potential magnitude of benefit to weigh against the medical risks, expense, and social adjustments. Since durations of disease stability and survival were similar for patients with disease in persistent PR after intensive or standard therapies, induction of CR represents the primary goal of consolidation treatment for patients in PR after initial therapy. These conclusions confirm those reached in larger series by Attal *et al* and Lahuerta *et al*, who have emphasized the importance of CR as a major factor for long survival.

The similarly long survival of approximately 8 years for patients in CR after either standard or transplant-supported therapy indicated that achievement of CR as a surrogate marker of long survival was more important than the method used in reaching this goal. Not clear is whether patients already in CR with initial therapy gain further with intensification. While further studies are needed, the burden of proof appears to rest with those who favor intensive therapy for all patients in CR, especially older patients and others at high risk for serious complications.

Treatment-related deaths were usually due to multiorgan failure and/or opportunistic infection attributed to the toxic effects of intense chemotherapy, especially in patients older than 55. Less intensive therapies, such as melphalan (200 mg/m^2) given once or melphalan (140 mg/m^2) given twice, have induced similar high frequencies of complete remission with less early mortality of $<5\%$.[2,7] In fact, a recent randomized comparison showed superior results with high dose melphalan alone (200 mg/m^2) than with a lower dose of melphalan and total body irradiation.[21] In addition, the substitution of blood stem cells for marrow as a source of transplanted cells has been associated with earlier and consistent engraftment.[8,16] Thus, some of our treatment-related mortality should be avoided with less intensive therapy supported by autologous blood stem cells and should permit treatment of more older patients as proposed by the Arkansas group.[19]

The occurrence of CR after ablative therapy was more likely among patients with a high degree of myeloma sensitivity to initial therapy. Provided a VAD or dexamethasone-based primary therapy had been given, criteria were defined that were associated with a CR rate in the 67% range in comparison with a much lower frequency for other patients. Such kinetic considerations of primary tumor sensitivity should be considered with other factors, such as age, performance and major organ functions in balancing the overall benefit and risk of intensive treatment, especially for older patients. Our model should also permit more rapid assessment of innovative intensive treatments, by focusing on the frequency of CR for subgroups of patients with favorable or unfavorable kinetic features. The previously

observed relation between rapid disease response and early relapse of myeloma has not been observed with recent VAD and high-dose dexamethasone regimens for reasons not clear. One factor may be the much more rapid onset of remission with repeated dexamethasone regimens in contrast to previous programs.

Alternative strategies should be considered for responding patients with disease unlikely to meet the criteria for CR. These include experimental therapies that add ^{166}holmium DOTMP (a bone-seeking radioisotope without extramedullary toxicity) to established ablative therapies, or that exploit a graft-versus-tumor effect with less intensive treatment supported by HLA-matched allogeneic transplantation.[22,23] Attempts to purge tumor cells by stem cell selection have not been useful presumably because of the large tumor burden that remains in most patients despite intensive treatment.[24] Prolongation of remission by other techniques, such as with idiotypic or dendritic cell vaccination, or with thalidomide maintenance, are also worthy of study especially in attempts to convert PR to CR.[25,26]

For our patients whose disease relapsed on interferon, several programs of therapy were given in sequential phases, such as an alkylating agent-glucocorticoid combination, a VAD-based regimen and in recent years a thalidomide–dexamethasone combination. Most patients achieved multiple remissions or prolonged stabilization of the myeloma. Such treatments were undoubtedly useful in prolonging lifespan for both transplanted and control patients after initial relapse. The systematic application of effective salvage therapies may well narrow current survival differences between transplanted and control patients.

Acknowledgements

We thank Rose Guevara for the careful preparation of the manuscript. This work was supported by the Lucille Murchison and Kay Laro research funds.

References

1 Barlogie B, Alexanian R, Dicke K *et al*. High dose chemoradiotherapy and autologous bone marrow transplantation for resistant multiple myeloma. *Blood* 1987; **70**: 868–872.
2 Cunningham D, Pazares L, Gore M *et al*. High-dose melphalan and autologous bone marrow transplantation as consolidation in previously untreated multiple myeloma. *J Clin Oncol* 1994; **12**: 759–763.
3 Alexanian R, Dimopoulos M, Hester J *et al*. Early myeloablative therapy for multiple myeloma. *Blood* 1994; **84**: 4278–4282.
4 Harousseau J, Attal M, Divine M *et al*. Autologous stem cell transplantation after first remission induction treatment in multiple myeloma. *Blood* 1995; **85**: 3077–3085.
5 Attal M, Harousseau J, Stoppa J *et al*. Autologous bone marrow transplantation versus conventional chemotherapy in multiple myeloma. *New Engl J Med* 1996; **335**: 91–97.
6 Bensinger W, Rowley S, Demirer T *et al*. High-dose therapy followed by autologous hematopoietic stem-cell infusion for patients with multiple myeloma. *J Clin Oncol* 1996; **14**: 1447–1456.
7 Barlogie B, Jagannath S, Vesole D *et al*. Superiority of tandem autologous transplantation over standard therapy for previously untreated multiple myeloma. *Blood* 1997; **89**: 789–793.
8 Fermand J-P, Chevret S, Ravaud P *et al*. High dose therapy and autologous blood stem cell transplantation in multiple myeloma. *Blood* 1998; **92**: 3191–3196.
9 Blade J, San Miguel J, Fontanillas M *et al*. Survival of multiple myeloma patients who are potential candidates for early high-dose therapy intensification/autotransplantation who were conventionally treated. *J Clin Oncol* 1996; **14**: 2167–2173.
10 Fermand J-P, Ravaud P, Katsahian S *et al*. High dose therapy and autologous blood stem cell transplantation versus conventional treatment in multiple myeloma. *Blood* 1999; **94**: 396a (Abstr. 1754).
11 Tricot G, Barlogie B, Jagannath S *et al*. Poor prognosis in multiple myeloma is associated only with partial or complete deletions of chromosome 13 and not with other karyotype abnormalities. *Blood* 1995; **86**: 4250–4256.
12 Lahuerta J, Martinez-Lopez J, de la Serna J *et al*. Remission status defined by immunofixation vs electrophoresis after autologous transplantation has a major impact on the outcome of multiple myeloma patients. *Br J Haematol* 2000; **109**: 438–446.
13 Alexanian R, Barlogie B, Tucker S. VAD-based regimens as primary treatment for multiple myeloma. *Am J Hematol* 1990; **33**: 86–89.
14 Alexanian R, Dimopoulos M, Delasalle K, Barlogie B. Primary dexamethasone treatment of multiple myeloma. *Blood* 1992; **80**: 887–890.
15 Dimopoulos M, Weber D, Kantarjian H *et al*. HyperCVAD for VAD-resistant multiple myeloma. *Am J Hematol* 1996; **52**: 77–81.
16 Dimopoulos M, Alexanian R, Przepiorka D *et al*. A new preparative regimen for autologous marrow or blood stem cell transplantation in high-risk multiple myeloma. *Blood* 1993; **82**: 2324–2328.
17 Giralt S, Weber D, Colome M *et al*. Phase I trial of cyclosporine-induced graft-versus-host disease in patients with multiple myeloma undergoing high-dose chemotherapy with autologous stem cell rescue. *J Clin Oncol* 1997; **15**: 667–673.
18 McLaughlin P, Alexanian R. Myeloma protein kinetics following chemotherapy. *Blood* 1982; **60**: 851–855.
19 Siegel D, Desikan K, Mehta J *et al*. Age is not a prognostic variable with autotransplants for multiple myeloma. *Blood* 1999; **93**: 51–54.
20 Lenhoff S, Hjorth M, Holmberg E *et al*. Impact on survival of high-dose therapy with autologous stem cell support in patients younger than 60 years with newly diagnosed multiple myeloma. *Blood* 2000; **95**: 7–11.
21 Harousseau J, Facon T, Moreau P *et al*. Comparison of high-dose melphalan 140 mg/m^2 plus total body irradiation and high-dose melphalan 200 mg/m^2 as conditioning regimen for peripheral blood progenitor cell autotransplantation in patients with newly diagnosed multiple myeloma. *Blood* 1999; **94**: 713a (Abstr. 3150).
22 Champlin R, Giralt S, Eary J *et al*. ^{166}Holmium-DOTMP in combination with melphalan with or without total body irradiation as a preparative regimen for autologous stem cell transplant for patients with multiple myeloma. *Blood* 1999; **94**: 709a (Abstr. 3133).
23 Giralt S, Weber D, Aleman A *et al*. Non myeloablative conditioning with fludarabine/melphalan for patients with multiple myeloma. *Blood* 1999; **94**: 347a (Abstr. 1549).
24 Stewart A, Schiller G, Vescio R *et al*. CD34 selection does not prolong disease free or overall survival in myeloma patients

undergoing autologous stem cell transplant. *Blood* 1999; **94**: 714a (Abstr. 3151).
25 Osterborg A, Yi Q, Henriksson L *et al*. Idiotype immunization combined with granulocyte–macrophage colony-stimulating factor in myeloma patients induced type 1, major histocompatibility complex-restricted, CD8- and CD4-specific T-cell responses. *Blood* 1998; **91**: 2459–2464.
26 Singhal S, Mehta J, Desikan R *et al*. Antitumor activity of thalidomide in refractory multiple myeloma. *New Engl J Med* 1999; **341**: 1565–1571.