

# **Multiple Myeloma: Update on the Arkansas Experience—Year 2000**

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## **INTRODUCTION**

Autologous transplantation in multiple myeloma (MM) was introduced 15 years ago, initially as a palliative measure for patients who had failed multiple regimens of conventional therapy, but now applied with the intent to cure, especially in patients early after diagnosis. The mainstay of conventional therapy has been the melphalan and corticosteroids regimen. Our intensive treatment approach still has melphalan and corticosteroids as the backbone, but at maximally escalated doses. Analysis of our Total Therapy Program (1989–1994) indicates that cure is a realistic goal with autologous transplantation.

## **TOTAL THERAPY**

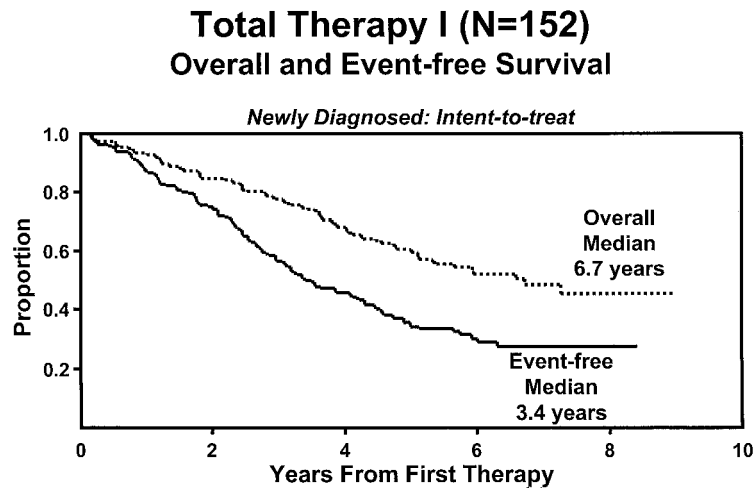
The intent of this program was to combine, in recently diagnosed MM patients (0 or 1 cycle of conventional chemotherapy), all active agents that were available at that time in a rapid sequence using non-cross-resistant drugs at maximally tolerated dose during induction and mobilization phases. This was followed by tandem transplants with melphalan 200 mg/m<sup>2</sup>. However, if less than a partial remission was attained after the first transplant, the preparative regimen for the second transplant consisted of melphalan 140 mg/m<sup>2</sup> with total body irradiation (TBI), or melphalan 200 mg/m<sup>2</sup> with cyclophosphamide 120 mg/kg for those in whom TBI was not feasible. This was followed by interferon maintenance. A total of 321 patients were enrolled; 152 of these patients had received no conventional treatment before enrollment. The characteristics are outlined in Table 1. The median follow-up is now >7 years. The median overall survival (OS) for these patients is 6.7 years, with 48% of the patients alive at 7 years; the median event-free survival (EFS) is 3.4 years, with 27% EFS at 7 years (Figure 1). The median complete remission (CR) duration was 3.9 years, with 44% still in CR at 7 years. The total CR rate was 41%. The transplant-related mortality was 1% with the first and 2% with the second transplant. In a multivariate analysis, the absence of a chromosome 13 abnormality and a C-reactive protein (CRP) level <4 mg/L at

**Table 1.** Total Therapy I: Characteristics of Untreated Patients (*N* = 152)\*

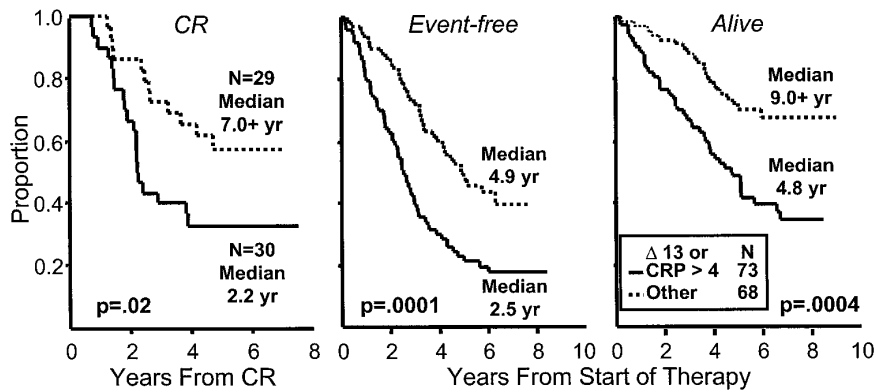
Parameter	%
-13/del 13	14
B2M >3.0 mg/L	51
CRP >4.0 mg/L	45
IgA isotype	17
Albumin <3.5 g/dL	30
Creatinine >2.0 mg/L	11
LDH >190 U/L	21
Hemoglobin <10 g/dL	33
Completed HDT-1	89
Completed HDT-2	77
Median follow-up, y	6

\*B2M, B-2 microglobulin; CRP, C-reactive protein; HDT, high-dose therapy; Ig, immunoglobulin; LDH, lactate dehydrogenase.

diagnosis were the most important factors associated with a good outcome. Of the total group, 68 patients had both favorable variables; 73 had either one or no favorable variables. In the good-prognosis group, the median CR duration was >7 years, with a 7-year CR rate of 60%, the median EFS was 4.9 years, and the median OS was 9 years, with 70% of these patients still alive at 7 years (Figure 2). Figure 3 compares survival with tandem transplants for good- and poor-prognosis patients with that of 723 myeloma patients under the age of 70 years treated with conven-

**Figure 1.** Overall and event-free survival for Total Therapy I (*n* = 152).

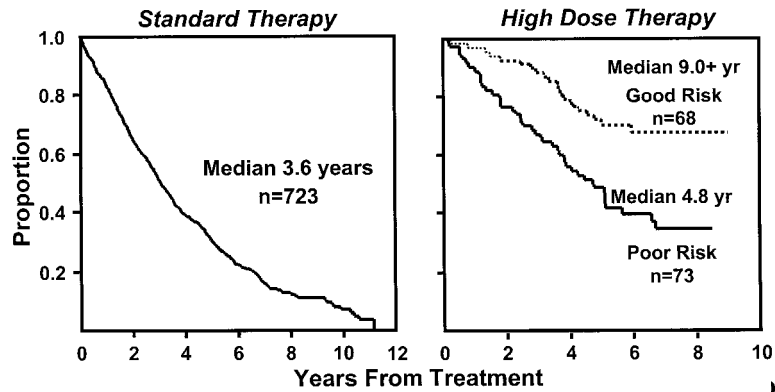
**Superior Prognosis in Absence of  $\Delta 13$  and with Low CRP**



**Figure 2.** Duration of complete remission (CR), event-free and overall survival in newly diagnosed patients treated on Total Therapy I. CRP, C-reactive protein.

tional therapy on 4 consecutive SWOG studies. Even the poor-prognosis patients fared much better than the whole group of conventionally treated patients, irrespective of prognostic factors. When we compare our results with tandem transplants to those published by the Intergroupe Français du Myelome (IFM)

**Survival in Myeloma**



**Figure 3.** Comparison of overall survival with standard therapy in 4 consecutive SWOG studies versus tandem transplants in newly diagnosed patients on Total Therapy I.

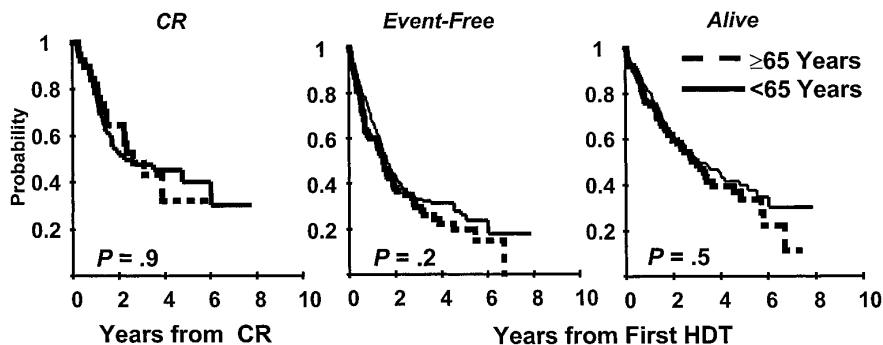
**Table 2.** Single vs. Tandem Transplant\*

	HDT		
	Attal Single	Powles Single	Barlogie Tandem
<i>n</i>	100	195	152
CR rate, %	22	53	41
EFS, mo	27	25	41
EFS at 5 years, %	24	NA	34
OS, mo	57	54	80
OS at 5 years, %	47	NA	60

\*CR, complete remission; EFS, event-free survival; HDT, high-dose therapy; OS, overall survival.

Study Group (IFM-90) and Royal Marsden (Powles et al.), the EFS and OS as well as EFS and OS at 5 years appear much better with tandem transplants (Table 2). The high CR rate in the Powles series is due to the use of nonstrict CR criteria. In addition, application of a second transplant increased the CR rate for our total therapy patients on an intent-to-treat basis from 26% to 41%. The IFM 94 study comparing single vs. tandem transplants showed higher CR and VGPR (very good partial remission) rates ( $P=.6$ ) and EFS at 4 years ( $P=.07$ ) in the tandem transplant group. It is very likely that with longer follow-up the EFS will become significantly different. A higher CR rate and better EFS for tandem transplants was also reported by an Italian group.<sup>1</sup> Taking all these data together, there is strong evidence that tandem transplants are superior to a single transplant. The next SWOG myeloma

### Comparable Survival in Young & Old Pair Mates after High-Dose Therapy



**Figure 4.** Absence of difference in complete remission (CR) duration, event-free and overall survival in patients  $\geq 65$  years versus younger patients.

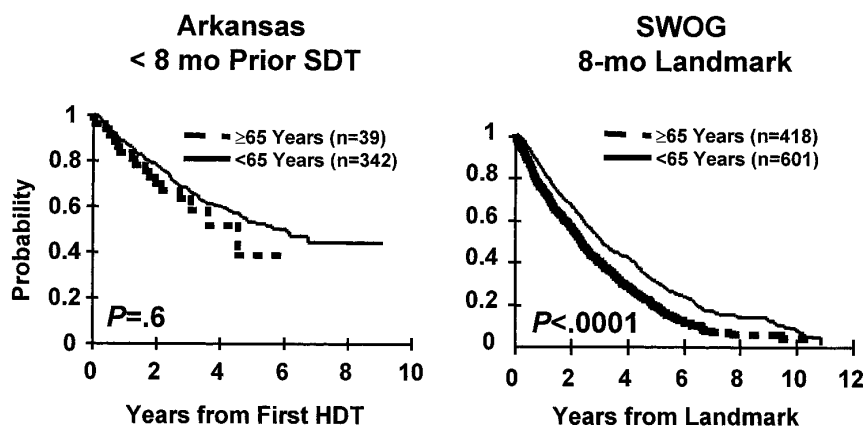
**Table 3.** Multivariate Analysis of Prognostic Variables\*

Favorable Variable	CR		CR Duration		EFS		OS	
	OR	P	OR	P	OR	P	OR	P
Age <65 y	—	NS	—	NS	—	NS	—	NS
No del 13	2.1	.0003	0.7	.03	0.5	<.0001	0.4	<.0001
B2M <2.5	1.5	.006	—	NS	0.7	<.0001	0.6	<.0001
Sensitive	3.2	<.0001	—	NS	0.7	<.0001	0.7	.0005
CRP <4	—	NS	0.7	.01	0.8	.04	0.7	.0004
Non-IgA	0.6	.002	0.6	.003	0.8	.004	0.7	.002
SDT <12 mo†	2.0	<.0001	0.6	<.0001	0.6	<.0001	0.7	<.0001
Timeliness of second HDT cycle†					0.7	.001	0.5	<.0001

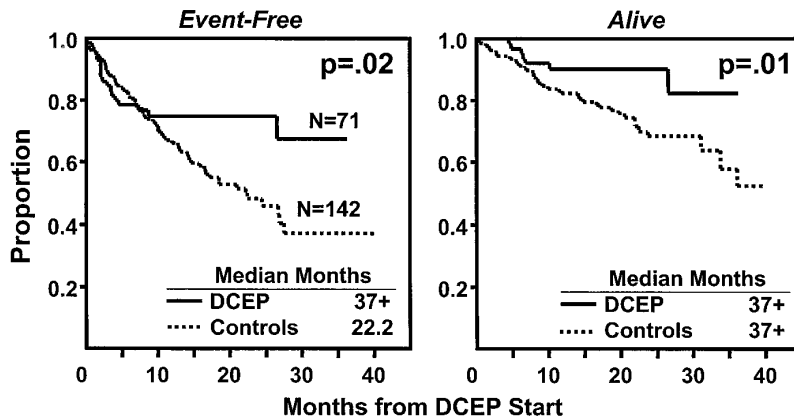
\*B2M, B-2 microglobulin; CR, complete remission; CRP, C-reactive protein; EFS, event-free survival; HDT, high-dose therapy; Ig, immunoglobulin; NS, not significant; OR, odds ratio; OS, overall survival; SDT, standard dose therapy. †Variables that can be controlled through medical intervention.

study will have a tandem transplant incorporated for all patients. The new IFM study also provides for tandem transplants in all patients with good prognostic factors and in those with poor prognosis without a matching sibling donor.

## Overall Survival: Arkansas High-Dose Therapy and SWOG Standard-Dose Therapy

**Figure 5.** HDT, high-dose therapy; SDT, standard dose therapy.

## Superior Outcome with DCEP Maintenance Pair-mate Analysis



**Figure 6.** DCEP, dexamethasone, cyclophosphamide, etoposide, and cisplatin.

### AGE AND TRANSPLANTATION

Age has independent adverse prognostic implications with standard therapy, with patients between 65 and 74 years of age faring significantly worse than those <65 years of age after adjusting for B-2 microglobulin, creatinine, and calcium. We compared in our database the outcome of 102 patients over the age of 65 years who had received high-dose therapy to that of 204 control subjects under the age of 65 years matched for cytogenetics, B-2 microglobulin, duration of prior therapy, C-reactive protein levels, and presence of resistant disease. CR duration, EFS, and OS were comparable in the 2 groups (Figure 4). In multivariate analysis, age was not a significant factor for CR rate, CR duration, EFS, or OS (Table 3). Because 90% of patients entered on transplant protocols have received their first transplant within 8 months after enrollment on study, an 8-month landmark analysis was performed on patients treated on 4 consecutive SWOG protocols. Figure 5 shows that age was not important for patients' outcome with high-dose therapy, while patients over the age of 65 years fared significantly worse with standard therapy ( $P<.0001$ ). There is no scientific reason to systemically exclude myeloma patients from transplantation based on only age. It should be the preferred therapy for older patients who do not have severe comorbid conditions.

## POSTTRANSPLANT CHEMOTHERAPY

In patients with limited prior treatment with standard therapy (<12 months), most of the relapses posttransplantation occur late (>24 months). In an attempt to reduce the late relapse rate, we explored the concept of posttransplantation chemotherapy given at regular intervals (3 months) for 1 year. The chemotherapy employed was DCEP (dexamethasone, cyclophosphamide, etoposide, and cisplatin), which was found to be effective in patients who had relapsed after autotransplant, with 40% of these patients reducing their abnormal protein by >75% and their bone marrow plasmacytosis to <5%; 13% attained a CR. This regimen was well tolerated. The major toxicities were hematologic (neutropenia and thrombocytopenia). Patients eligible for this study had to have good hematologic recovery posttransplantation and a creatinine level <2 mg/dL. The outcome of 71 patients receiving DCEP posttransplant was compared with that of 142 previously transplanted patients who had not received DCEP. The 2 groups were matched for all important prognostic variables. Figure 6 shows the superior EFS and OS for patients who received posttransplantation consolidation. Superior EFS and OS rates were observed for good- as well as poor-prognosis patients. Posttransplantation chemotherapy has now become an integral part of our transplant program.

## FUTURE DIRECTIONS

Our aims for the treatment of myeloma have shifted from palliative to curative in the last decade. Cure can be obtained only by prolonged treatment with cytotoxic therapy given at maximal doses in a dose-dense schedule.

In newly diagnosed patients, we are currently evaluating whether the combination of thalidomide with intense therapy is better than intensive therapy alone. It is possible that posttransplant chemotherapy with DCEP is still not intensive enough for patients with poor prognosis and that further transplants will be necessary to ultimately improve EFS significantly. This approach, as well as dendritic cell vaccination, will be explored in poor-prognosis patients.

## REFERENCES

1. Lemoli RM, Martinelli G, Zamagni E, et al. Engraftment, clinical, and molecular follow-up of patients with multiple myeloma who were reinfused with highly purified CD34<sup>+</sup> cells to support single or tandem high-dose chemotherapy. *Blood* 95:2234–2239, 2000.