

Early Results of Total Therapy II for Newly Diagnosed Multiple Myeloma

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INTRODUCTION

High-dose melphalan has finally become the mainstay of therapy for patients with new diagnoses of symptomatic multiple myeloma (MM). The Intergroupe Français du Myélome (IFM) can be credited with having performed the confirmatory trials that demonstrated the superiority of a single autotransplant with melphalan 140 mg/m² and total body irradiation (TBI) 800 cGy compared with standard-dose chemotherapy (IFM 90)¹ and, most recently, the superiority of tandem autotransplants (melphalan 140 mg/m² followed by melphalan 140 mg/m² and TBI 800 cGy vs. a single cycle of melphalan 140 mg/m² and TBI [IFM 94]).² Importantly, the differences between the two arms of both studies emerged only at 3 to 4 years, emphasizing the need for sufficiently long follow-up before reporting, perhaps prematurely, results from still ongoing randomized trials not showing the expected benefit from the intervention with the higher dose.

In this report, we provide an update on Total Therapy I (TT I), representing the first phase II pilot trial examining the feasibility and efficacy of a tandem autotransplant for patients up to the age of 70 years with new diagnoses. Between 1989 and 1994, 231 patients were enrolled, and the results of this study have previously been reported.³ TT II built on the success of TT I by intensifying remission induction with myelosuppressive doses of cytotoxic agents that required the support of granulocyte colony-stimulating factor. Induction was followed with the standard tandem autotransplant with melphalan 200 mg/m² 3 months apart, with a new concept of post-tandem autotransplant consolidation chemotherapy, and, finally, with interferon maintenance (Figure 1).⁴ Given our report of the marked activity of thalidomide in

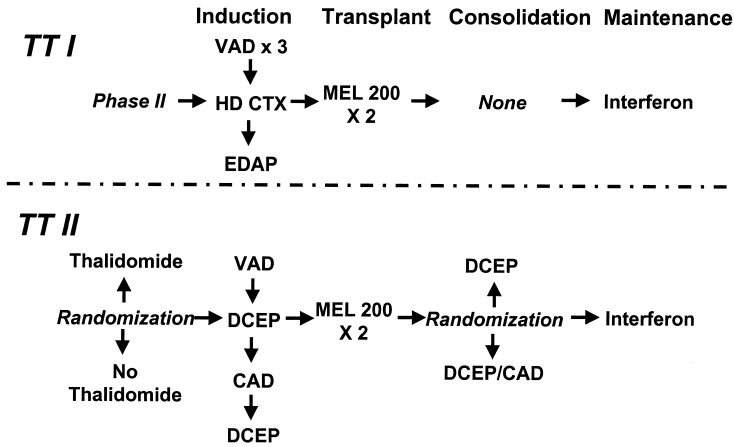


Figure 1. Treatment schema. *TT I*, total therapy I; *VAD*, chemotherapy regimen of vincristine, doxorubicin (Adriamycin), and dexamethasone; *HD CTX*, high-dose cyclophosphamide; *EDAP*, chemotherapy regimen of etoposide, dexamethasone, cytarabine (Ara-C), and cisplatin (Platinol); *MEL 200*, melphalan 200 mg/m²; *DCEP*, chemotherapy regimen of dexamethasone, cyclophosphamide, etoposide, and cisplatin (Platinol); *CAD*, chemotherapy regimen of cyclophosphamide, doxorubicin (Adriamycin), and dexamethasone.

treating MM patients who relapsed after prior autotransplants and who were typically refractory to dexamethasone pulsing and DCEP (dexamethasone, cyclophosphamide, etoposide, and cisplatin [Platinol]) chemotherapy,^{5,6} all patients were first randomly assigned to receive thalidomide 400 mg or no thalidomide, with dose reductions occurring during the consolidation and maintenance phases. This report summarizes the results of TT II for the first 231 patients of 520 currently enrolled patients and an anticipated total accrual of 660 patients. Results will then be compared with all 231 patients enrolled previously in TT I.

RESULTS

Total Therapy II

Figure 2 shows that the accrual to TT II is exactly on time, with a completion of accrual scheduled for March 2004. Extensive laboratory tests are carried out both at prestudy and during specific follow-up time points to investigate specifically whether myeloma genetics allows the distinction of separate disease entities with traditional cytogenetics, interphase fluorescence in situ hybridization (FISH), and, more recently, gene expression profiling by microarray. We hope that magnetic resonance imaging (MRI) studies performed at diagnosis, prior to and after 2 transplants, and at the end of consolidation therapy will reveal the incidence

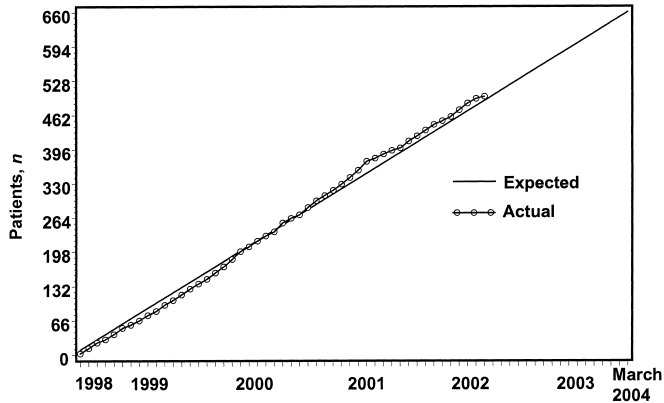


Figure 2. Protocol accrual to Total Therapy II.

of MRI-defined complete remission and will determine whether such radiologic response has additional prognostic implications (Table 1). Table 2 summarizes the frequencies of completion for important protocol steps, treatment-related mortality (TRM), complete remission (CR), and near-CR (n-CR) (immunofixation positive). On an intent-to-treat basis, 80% have achieved CR/n-CR by the time of the second high-dose therapy cycle (HDT-2). Remarkably, the cumulative TRM is only 5%. In part because of insurance issues among patients aged 65 years and older, only 74% of patients have completed HDT-2, compared with the 83% of patients who

Table 1. Laboratory Tests and Scans with Total Therapy II*

Test	Prestudy, n	Total, n
Cytogenetics	450	1687
FISH	351	585
Gene expression	207	235
Serum banking	354	918
Telomere length	257	725
MRI	447	2130

*FISH, fluorescence in situ hybridization; MRI, magnetic resonance imaging.

Table 2. Total Therapy II: Patient Outcome—Initial 231 Patients*

	Induction	HDT-1	HDT-2
Completed protocol step	92%	83%	74%
Cumulative TRM	3%	4%	5%
CR and near-CR	41%	60%	80%

*HDT-1, high-dose therapy cycle 1; HDT-2, HDT cycle 2; TRM, treatment-related mortality; CR, complete remission.

Table 3. Superior Survival with Complete Remission and 2 Transplants—Initial 231 Patients

	Alive		Event Free	
	Hazard Ratio	P	Hazard Ratio	P
Time-dependent complete remission	0.40	.024	0.51	.041
Time-dependent 2 transplants	0.43	.039	0.34	.002
CA 13*	2.81	.010	2.76	.001

*CA 13, cytogenetic abnormality on chromosome 13.

completed a single autotransplant (HDT-1). Taking into account nearly 20 different variables at baseline, as well as posttransplant events such as CR and a second autotransplant, multivariate analysis revealed that chromosome abnormalities (CA) of chromosome 13 (CA 13) recognized on metaphase karyotyping were the only significant laboratory features associated with both short survival time and event-free survival. Favorable features included achievement of CR and timely administration of HDT-2 (Table 3). These data are graphically depicted in Figure 3, which reveals superior 3-year estimates for both survival and event-free survival in most patients achieving CR who received a second autotransplant. A progressively worse outcome was observed of 49% event-free survival and 58% overall survival at 3 years when CR was not achieved and no second transplant was performed. We also had the opportunity to compare directly the implications of interphase FISH-defined deletion of chromosome 13 (FISH 13), which was present in 50% of patients, vis-à-vis the presence of CA 13 (14%). Importantly, event-free survival (and overall survival; data not shown) were similar among the 3 subgroups exhibiting no FISH 13 with no CA or any CA or FISH 13 without CA; by contrast,

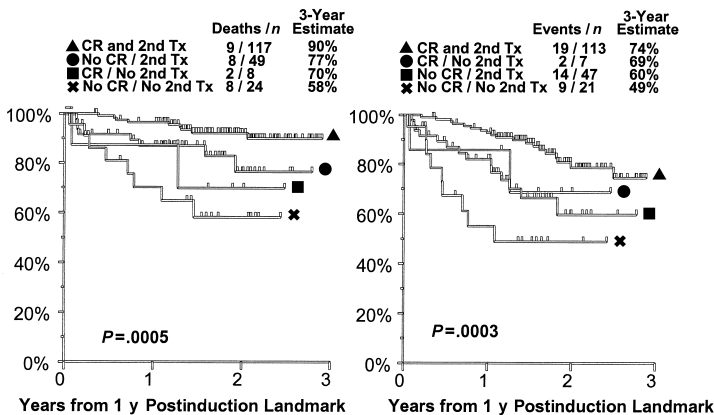


Figure 3. Superior survival and event-free survival of patients with both two transplants (Tx) and complete remission (CR).

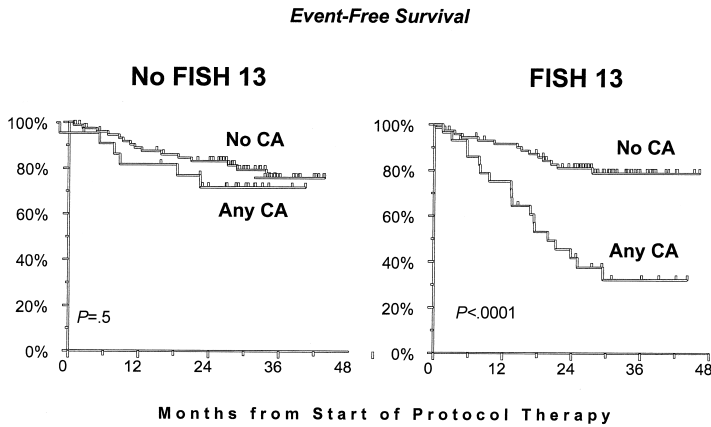


Figure 4. Total Therapy II: cytogenetic abnormality (CA) imparts poor risk in the presence of fluorescence in situ hybridization detection of cytogenetic abnormalities on chromosome 13 (FISH 13).

a FISH 13–defined deletion had adverse consequences only when corresponding metaphase abnormalities were also present (Figure 4).

The data are still blinded with regard to the impact of the addition of thalidomide on response, response duration, and survival. An analysis was conducted separately of the 123 patients receiving no thalidomide and of the 108 patients on the thalidomide arm to determine whether comparable baseline and time-dependent covariate parameters affected outcome (Table 4). Remarkably, CA 13 remained a very strong adverse variable in the no-thalidomide arm, whereas the timely application of a second transplant was the key feature in the thalidomide group. Thalidomide does produce considerable side effects, consisting of sedation, constipation, and, importantly, acute and cumulative dose-dependent peripheral neuropathy. A further complication was the significantly higher incidence of deep venous thrombosis (DVT) of almost 40% in the thalidomide arm vs. 15% in the no-thalidomide arm

Table 4. Multivariate Analysis of Total Therapy II Arms*

	<u>Overall Survival</u>		<u>Event-Free Survival</u>	
	Hazard Ratio	P	Hazard Ratio	P
No thalidomide (n = 123)				
Time-dependent 2 transplants		NS	0.32	.007
CA 13	6.28	.001	3.61	<.001
Age ≥65 y	2.81	.034	2.82	.004
Thalidomide (n = 108)				
Time-dependent 2 transplants	0.13	<.001	0.21	.004

*NS, not significant; CA 13, cytogenetic abnormality on chromosome 13.

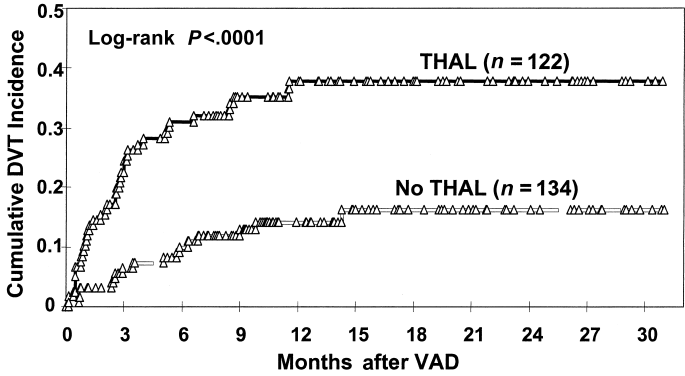
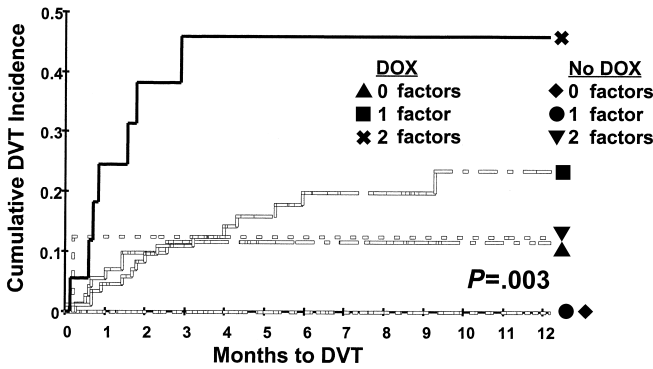


Figure 5. Total Therapy II: higher rate of deep venous thrombosis (DVT) with thalidomide (THAL). VAD, chemotherapy regimen of vincristine, doxorubicin (Adriamycin), and dexamethasone.

(Figure 5).⁷ Most DVTs occurred in the first 3 to 4 months on both arms when the tumor burden was high and tumor cytoreduction was proceeding, perhaps with the elaboration of procoagulant cytokines. We had the opportunity to compare a posttransplant salvage regimen of DCEP plus thalidomide with DT PACE (dexamethasone, thalidomide, cisplatin [Platinol], doxorubicin [Adriamycin], cyclophosphamide, and etoposide) for previously treated MM, the latter differing only by the additional presence of doxorubicin (Figure 6). It is readily apparent that doxorubicin played a major role, with additional aggravating features such as age >60 years and abnormalities of chromosome 11 (mainly trisomy 11).⁸ The



Other Risk Factors: Age >60 y, Chromosome 11 Abnormalities

Figure 6. Deep venous thrombosis (DVT) risk traced to doxorubicin (DOX) in thalidomide combinations.

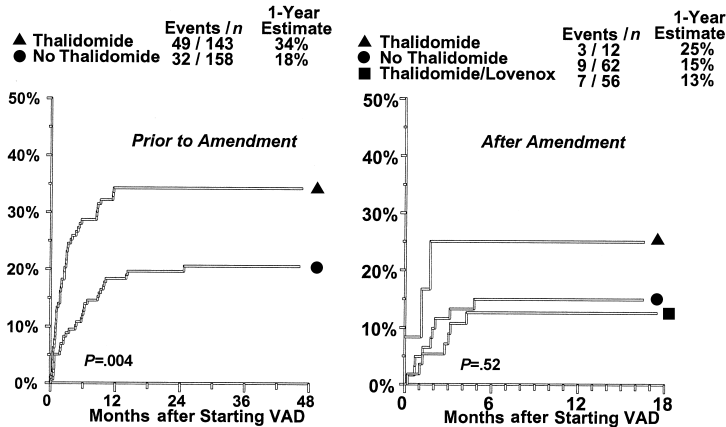


Figure 7. Deep vein thrombosis reduced with enoxaparin (Lovenox). VAD, chemotherapy regimen of vincristine, doxorubicin (Adriamycin), and dexamethasone.

subsequent introduction of therapeutic anticoagulation therapy with enoxaparin (Lovenox) eliminated this complication (Figure 7).⁹

Total Therapy II vs. Total Therapy I

The characteristics of the 462 patients are summarized separately for TT I and TT II in Table 5. A significantly higher proportion of patients aged 60 years and older occurred in the TT II study, whereas all other prognostically relevant features were entirely comparable. Table 6 summarizes protocol completion, TRM, and CR/n-CR for the 2 studies. Importantly, despite the greater dose intensity with TT II, more of the older patients completed the second transplant, and the group experienced less TRM. In addition, the TT II patient group had higher CR/n-CR rates regardless of age. A multivariate analysis including treatment as a variable revealed that, in

Table 5. Total Therapy I vs. Total Therapy II

Parameter	Total Therapy I (n = 231)	Total Therapy II (n = 231)*
Age ≥60 y†	24%	39%
β ₂ -microglobulin >4.0 mg/L	30%	28%
C-reactive protein >4.0 mg/L	47%	55%
Lactate dehydrogenase >190 U/L	21%	22%
Any cytogenetic abnormality	27%	28%
CA 13‡	12%	14%

*First 231 of 490 current patients. †P<.05. ‡CA 13, cytogenetic abnormality on chromosome 13.

Table 6. Protocol Completion, Treatment-Related Mortality, and Complete Remission*

	<i>Induction</i>		<i>MEL 200 No. 1</i>		<i>MEL 200 No. 2</i>	
	<i>TT I</i>	<i>TT II</i>	<i>TT I</i>	<i>TT II</i>	<i>TT I</i>	<i>TT II</i>
Completed protocol						
<65 y	92%	92%	87%	87%	74%	77%
≥65 y	67%†	89%†	62%	68%	48%†	62%†
Treatment-related mortality (cumulative)						
<65 y	2%	2%	3%	3%	8%	4%
≥65 y	9%	6%	11%†	6%†	14%†	9%†
Complete remission and near-complete remission						
<65 y	21%†	44%†	36%†	62%†	48%†	80%†
≥65 y	15%†	29%†	34%†	53%†	42%†	79%†

**MEL 200, melphalan 200 mg/m²; TT I, Total Therapy I. †P<.05.*

addition to the adverse consequences of CA 13 still observed in the entire population of 462 patients, TT I was an independent adverse feature for both event-free and overall survival; conversely, TT II provided a significantly superior outcome (not analyzed by thalidomide arm) (Table 7). In addition, elevations in C-reactive protein and lactate dehydrogenase levels were independent adverse parameters. The superior outcome with TT II vs. TT I is summarized in Figure 8 for those patients without CA.

SUMMARY AND CONCLUSION

The pursuit of dose intensity, especially with the hematopoietic stem cell–toxic drug melphalan, which exhibits a dose-response effect on MM but requires stem cell support for prompt hematopoietic recovery, has paid off. The results of our phase II studies employing tandem transplants have been confirmed by the IFM in prospective randomized trials.² The TT II program appears safe and, at this early

Table 7. Total Therapy II Appears Superior to Total Therapy I*

	<i>Overall Survival</i>		<i>Event-Free Survival</i>	
	<i>Hazard Ratio</i>	<i>P</i>	<i>Hazard Ratio</i>	<i>P</i>
Total Therapy I	1.61	.021	2.26	<.001
CA 13	2.33	<.001	1.83	<.001
Age ≥65 y	1.72	.011	1.54	.020
C-reactive protein ≥4 mg/L	1.56	.005	1.53	.002
Lactate dehydrogenase ≥190 U/L	1.67	.003	1.38	.044
β ₂ -microglobulin ≥4 mg/L		NS	1.43	.012

**Multivariate regression results for Total Therapy I (n = 231) and first 231 patients on Total Therapy II. CA 13, cytogenetic abnormality on chromosome 13; NS, not significant.*

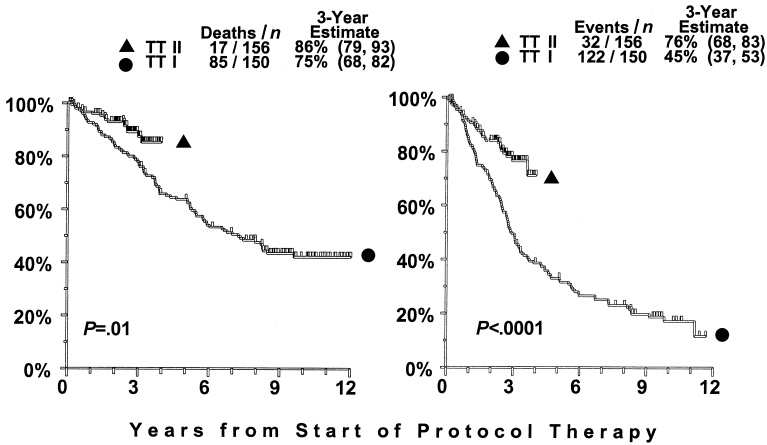


Figure 8. Total Therapy I (TT I) vs. Total Therapy II (TT II) comparison for survival and event-free survival of the first 231 patients: no cytogenetic abnormalities.

stage of analysis, seems to be superior to TT I in terms of CR/n-CR as well as event-free and overall survival. Post-tandem autotransplant consolidation chemotherapy was likewise feasible, and thalidomide-associated aggravation of DVT could be eliminated by effective anticoagulation therapy. Using appropriate statistical methods, we determined that both CR and timely application of the second transplant were favorable features with TT II and that CA 13 remained an adverse variable, particularly in the no-thalidomide arm. The presence of CA 13 as an adverse feature only pertained to standard metaphase karyotyping and not to interphase FISH analysis, a finding attesting to the clinical relevance of in vitro cell division required for metaphase detection and perhaps reflecting MM growth independent of the bone marrow microenvironment that is present in vivo.⁴ Extensive laboratory investigations pertinent to cellular and molecular genetics and to radioimaging for baseline and response staging will make TT II a uniquely important trial for the dissection of discrete molecular entities.

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