Thalidomide in the Management of Multiple Myeloma

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Thalidomide has recently been shown to have significant activity in refractory multiple myeloma (MM). A follow-up of the original phase II trial, expanded to 169 patients, shows 2-year survival of 60%; patients receiving ≥42 g over 3 months had a higher response rate and superior survival than those receiving lower doses. The addition of thalidomide to dexamethasone and chemotherapy for the management of post-transplant relapses results in higher response rates. The early results of the Total Therapy II trial for newly diagnosed MM patients show an unprecedented complete remission (CR) and near-CR rate of 69% after two melphalan-based transplants (whether or not receiving thalidomide). In addition, available clinical trial information involving at least 20 patients confirms that thalidomide is active in one third of patients in single-agent trials for refractory disease, with response rates increasing to 50% to 60% in combination with dexamethasone and to as high as 80% in combination with dexamethasone and chemotherapy. When applied as primary therapy in smoldering myeloma, one third of patients experienced 50% paraprotein reduction (PPR); in combination with dexamethasone pulsing, 70% to 80% of symptomatic patients responded. Thus, thalidomide is a major new tool in the treatment armamentarium of MM. The virtual lack of myelosuppression makes it an ideal agent for combination with cytotoxic chemotherapy. Newer, more potent, and less toxic derivatives of thalidomide are being evaluated.

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ADVANCES IN THE management of multiple myeloma (MM) can be traced to two seminal observations. First, increasing dose intensity of glucocorticoids, mainly in the form of dexamethasone pulsing as realized in the vincristine, doxorubicin, and dexamethasone (VAD) regimen, was shown to overcome resistance to standard alkylating agent–prednisone combinations when applied in the setting of primary unresponsive and resistant relapse.[1,2] Similarly, dose escalation of the key alkylating agent melphalan to myeloablative intensity, facilitated by autologous hematopoietic stem cell support, was shown to overcome resistance to both alkylating agents in standard doses and high-dose glucocorticoid-containing regimens.[6,9,26] Historically controlled and subsequently randomized trials demonstrated that high-dose melphalan-based regimens, especially with peripheral blood stem cell (PBSC) support, when applied in the setting of newly diagnosed symptomatic MM, increased the incidence of true complete remission (CR) from 5% with standard regimens to 50% with high-dose therapy and markedly extended both event-free (EFS) and overall survival (OS).[1,2,10,11] This progress is closely linked to the recognition that mobilized PBSC, with the use of either stem cell–sparing chemotherapy (such as cyclophosphamide) or hematopoietic growth factors alone, facilitated brisker hematopoietic engraftment with earlier neutrophil and platelet recovery than had been the case with autologous bone marrow.[45] Thus, the duration at risk, especially in elderly and frail patients, could be reduced from 3 weeks to 7 days with a decrease in treatment-related mortality to 1% to 2%. An important consideration for successful high-dose therapy was the recognition that stem cell–toxic agents such as melphalan, nitrosoureas, and ionizing radiation to marrow-containing bone sites needed to be avoided in order to obtain hematopoietic stem cells of sufficient quantity and quality to facilitate rapid engraftment[17,44] and avoid secondary acute myelodysplasia syndrome (MDS)/acute myelogenous leukemia (AML).[22] Single-agent melphalan, usually at 200 mg/m^2, as conditioning results in superior outcome with less toxicity than regimens containing total-body irradiation.[1,19] With appropriate dose modifications of melphalan, such autotransplants can also be applied to the elderly (>65 and >70 years)[3,40] and in the setting of renal failure.[4,43] Post-transplantation management had relied mainly on interferon[33] and in recent years on consolidation chemotherapy with dexamethasone, cyclophosphamide, etoposide, and cisplatin (DCEP)[18] or glucocorticoids.[14]

Unfortunately, once disease progression occurred, especially within the first year after single or tandem autotransplants, few treatment options were available. In search of an antiangiogenic agent to target the increased microvessel density noted in the bone marrow of patients with active MM,[29,35] thalidomide was evaluated because of its multiple, including antiangiogenic, antitumor mechanisms.[16,41]

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Table 1. Phase II Study of Thalidomide

Regimen		Parameter	%
200 mg		Age > 60 yr	44
↓		β2M > 6 mg/L	22
400 mg		Abnormal cytogenetics	67
↓	Every 2 weeks	Deletion 13	37
600 mg		Prior therapy > 60 mo	20
↓		Prior high-dose therapy	76
800 mg		>1 cycle	53

The Arkansas Experience

Single-Agent Thalidomide in Post-transplant Refractory Myeloma[7,13]

Between December 1997 and December 1998, 169 consecutive eligible patients with extensively pretreated and progressive MM were enrolled in a phase II trial that called for a dose-escalating schedule of thalidomide of 200 mg daily with 200-mg increments every 2 weeks to a maximum of 800 mg, according to tolerance. Study endpoints included paraprotein reduction (PPR) in serum or urine of at least 25%, 50%, 75%, or 90%; CR was defined by the absence of monoclonal protein on immunofixation analysis. Patients who achieved a PPR less than 25% or who discontinued treatment before response could be assessed (minimum of 4 weeks of therapy) were considered treatment failures. All results are presented on an intent-to-treat basis; relapse criteria have been previously reported.

Table 1 summarizes patient characteristics. Importantly, 67% had cytogenetic abnormalities, including 37% who presented with chromosome 13 deletion. More than two thirds had at least one and more than 50% had two or more cycles of prior high-dose therapy with autologous stem cell support. Dose escalation of thalidomide to 400 mg was possible in almost 90% and to 800 mg in more than 50% of patients. Treatment-related mortality was not observed. Grade ≥ 3 toxicities included sedation/somnolence in 25%, constipation in 16%, and mainly sensory neuropathy in 9% (Table 2). These toxicities were related to both intensity and cumulative dose of thalidomide administered. Deep vein thrombosis (DVT) or cytopenia was encountered in fewer than 5% of patients.

Table 2. Responses to Phase II Study of Thalidomide

Response	%	Toxicity ≥ Grade 3	%
CR	2	Treatment-related mortality	0
≥90% PPR	12	Sedation	25
≥75% PRR	6	Constipation	16
≥50% PPR	10	Neuropathy	9
≥25% PPR	7	Deep vein thrombosis	2
Total	37		

PPR ≥ 25% was observed in 37%; 30% achieved PPR ≥ 50%; and CR or near-CR (>90% PPR) was obtained in 14% (Table 2). Response kinetics were such that 90% had achieved PPR ≥ 25% within 4.5 months. PPR ≥ 25% was more common when cytogenetics were normal (52% *v* 28%, $P = .003$) and when the plasma cell labeling index (PCLI) was less than the median of ≤ 0.5% (44% *v* 10%, $P < .001$). Responses were associated with significant reductions in marrow plasmacytosis and β_2-microglobulin (β2M), as well as improvement in hemoglobin and levels of IgM as an indicator of recovery of normal B-cell function (Table 3).

With a median follow-up of 22 months among 84 alive and refractory patients, 2-year EFS and OS estimates are, respectively, 20% ± 6% and 48% ± 6% (Fig 1). On multivariate analysis, EFS and OS were longer in the presence of normal cytogenetics, low PCLI, and low β2M (≤3 mg/L), so that four distinct risk groups could be identified (Fig 2). As cytogenetic and cytokinetic data are not commonly available, the analysis was performed in the absence of these two variables and demonstrated that three risk groups could be readily discerned on the basis of β2M and C-reactive protein (CRP) levels (Fig 2). Prognosis was not superior in patients who had not received prior high-dose therapy or in those with a longer time lapse since the last transplant.

As this phase II study was not designed to determine whether a dose-response effect existed, a 3-month landmark analysis was performed to determine whether patients tolerating dose escalation had better disease control. Indeed, 54% of those receiving greater than 42 g of thalidomide over a period of 3 months (median cumulative dose) responded (PPR ≥ 25%), compared to 21% in the lower-dose group ($P < .001$). Similarly, the 2-year survival estimate was higher in the high-dose group (63% ± 8% *v* 45% ± 13%; $P < .001$) (Fig 3). Table 4 examines whether such dose escalation benefited a particular subgroup defined on the basis of cytogenetics, β2M, and PCLI; 2-year survival rates were superior among high-risk patients receiving the higher thalidomide dose.

Table 3. Myeloma Protein Response and Associated Laboratory Changes

	M-Protein Response				
Parameter	N	≥ 50%	N	< 50%	*P*
Bone marrow plasma cells	41	−20* (75)†	78	+13 (183)	<.0001
β2M	42	−7 (35)	86	+22 (55)	<.0001
IgM	29	+58 (107)	56	−9 (48)	.002
Hemoglobin	44	+9 (15)	89	0 (24)	.003

* Median % change.

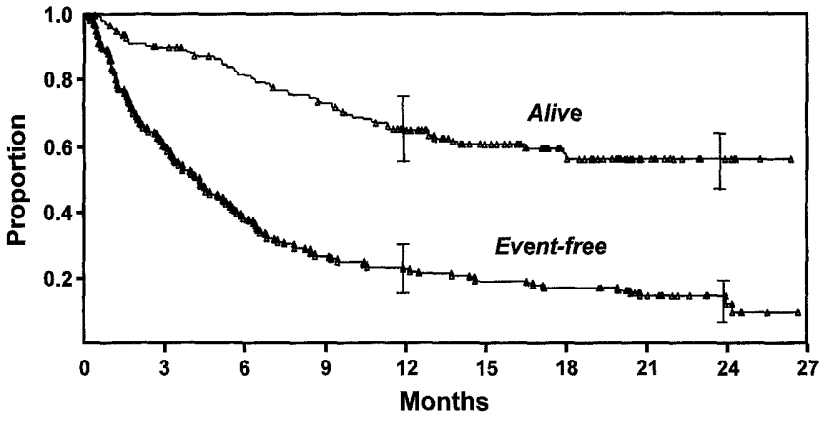

Figure 1. EFS and OS survival after single-agent thalidomide for 169 patients with advanced and refractory myeloma.

Combination Trials

Post-transplant relapse. Clinical trials in progress will determine the role of thalidomide in the management of both refractory and newly diagnosed patients in combination with glucocorticoids and, because of its virtual lack of myelosuppression, cytotoxic chemotherapy (Table 5). At our center, post-transplant relapses are categorized in terms of cytogenetics and PCLI.

Patients with low tumor burden or at low risk of relapse post-transplantation are randomized to dexamethasone with or without thalidomide. To date, 25 patients have been enrolled and their characteristics are listed in Table 6. Responses graded by tumor cytoreduction and survival are depicted in Fig 4. With a median follow-up of 23 months, 2-year EFS and OS rates for the entire population are 40% and 80%, respectively. The incidence

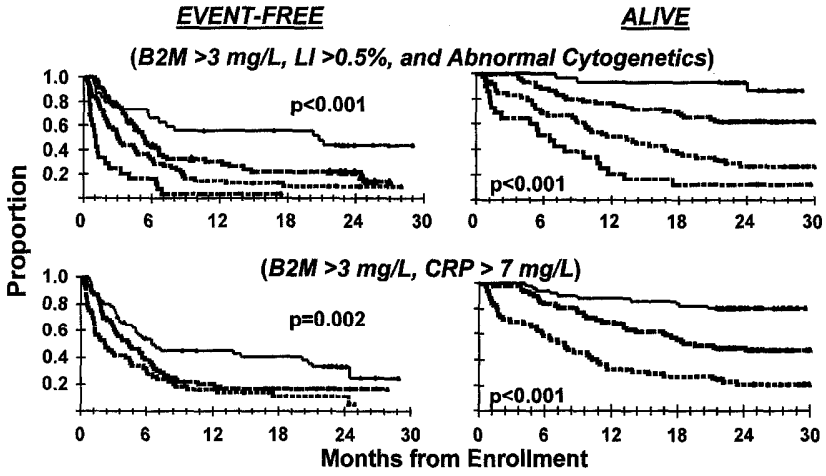

Figure 2. EFS (left) and OS (right) according to the number of unfavorable prognostic factors present prior to thalidomide. Top: Risk discrimination on the basis of abnormal cytogenetics (EFS HR 2.15, $P < .001$; OS HR 2.53, $P = .002$), PCLI > 0.5% (EFS HR 1.86, $P = .002$; OS HR 1.82, $P = .009$) and β2M > 3 mg/L (EFS HR 1.54, $P = .016$; OS HR .99, $P < .001$). Number of risk factors represented by solid lines 0, dashed 1, dotted 2, dash-dotted 3. Bottom: Risk discrimination on the basis of standard variabls β2M > 3 mg/L (EFS HR 1.61, $P = .009$, OS HR 3.33, $P > .001$) and CRP > 7 mg/L (EFS HR 1.37, $P = .08$; OS HR 1.92, $P = .005$). Number of risk factors represented by solid lines 0, dashed 1, dotted 2.

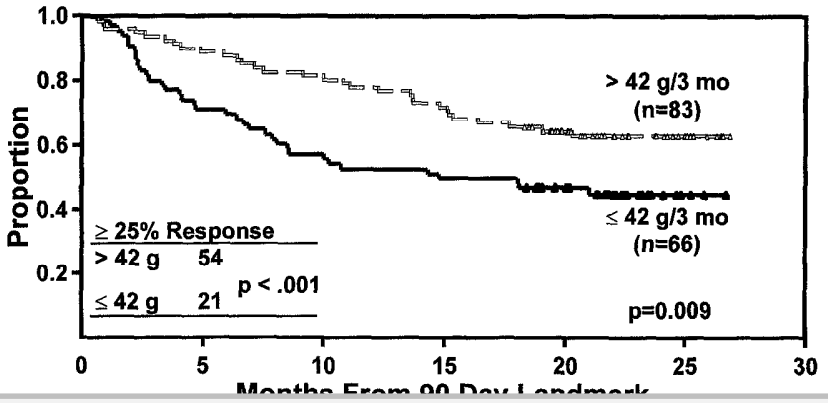

Figure 3. Higher response rate and longer survival with higher dose tha-

Table 4. Higher Thalidomide Dose Benefits High-Risk Disease

No. of Risk Factors*	Thalidomide Dose > 42 g/3 mo	N	Response ≥ 25%	P	% Alive at 2 yr	P
≤1	Yes	55	45	.01	74	NS
	No	36	19		66	
>1	Yes	28	43	.02	42	.01
	No	30	13		20	

* β2M > 3 mg/L; PCLI > 0.5%; abnormal cytogenetics.
Abbreviation: NS, not significant.

of ≥50% PPR was 57% among 14 patients on dexamethasone plus thalidomide versus 27% on dexamethasone alone; 29% on the combination but none of 11 patients on dexamethasone alone achieved CR ($P = .04$).

DCEP plus thalidomide was offered to patients relapsing with high tumor burden, high proliferative disease, or high-risk cytogenetics (Table 7). With a median follow-up of 17 months, response could be assessed in 80 patients. After three cycles (intent-to-treat), 27% achieved ≥50% myeloma protein reduction including 18% with CR or near-CR. Added thalidomide doubled the response rate (36% *v* 18%), including ≥90% PPR in 25% versus 10% ($P = .07$). At 2 years, 38% are event-free and 48% are alive; no difference is yet apparent between the two treatment arms (data not shown).

Table 5. Thalidomide Alone and in Combination for Multiple Myeloma (as of April 1, 2001)

Study	Phase	N	Eligibility
Thalidomide	II	169	Advanced, refractory
Dex ± Thalidomide	III	25	Post-HDT relapse, low risk
DCEP ± Thalidomide	III	80	Post-HDT relapse, high risk
DT PACE	III	229	Prior therapy
Total Therapy II	III	309	Untreated

Abbreviations: Dex, dexamethasone; DCEP, dexamethasone, cyclophosphamide, etoposide, cisplatin; HDT, high-dose therapy.

Table 6. Patient Characteristics for Dexamethasone ± Thalidomide Study

Parameter	Dex Alone (n = 11), %	Dex + Thal (n = 14), %	P
Age > 60 yr	36	57	.4
Male	73	64	1.0
β2M > 2.5 mg/L	45	43	1.0
CRP > 4.0 mg/L	27	43	.7
IgG	45	43	1.0
IgA	9	36	.2
−13/13q−	18	14	1.0
Prior HDT	82	93	.6

DT PACE salvage therapy without prior transplant. The combination DT PACE regimen consists of dexamethasone, thalidomide, and 4-day continuous infusions of cisplatin 40 mg/m^2, doxorubicin 40 mg/m^2, cyclophosphamide 1,600 mg/m^2, and etoposide 160 mg/m^2. A previous pilot trial in 12 high-risk patients with high lactate dehydrogenase (LDH) levels and proliferative disease demonstrated a first-cycle CR rate of greater than 50%.[8] Hence, patients not qualifying for Total Therapy II (those with more than one cycle of prior therapy) are eligible for two induction cycles with PBSC collection. Responders (≥50% PPR) with a CD34 yield large enough for two autotransplants (>12 × 10^6 CD34/kg) are randomized to continuation of DT PACE versus the standard melphalan (200 mg/m^2)-based tandem transplant program. For maintenance, patients are again randomized to dexamethasone plus thalidomide at 200 versus 50 mg daily. Another question examines the CD34 dose administered with the second transplant and its impact on the subsequent development of MDS/AML.

As of March 1, 2001, 229 patients have been enrolled. Patient characteristics are depicted in Table 8, and the flow through the program is shown in Fig 6. The median

% Responding After 3rd Cycle	Thalidomide +	Thalidomide -
CR*	29	0
≥ 90%*	7	0
≥ 75%	14	18
≥ 50%	7	9
Total	57	27

*p=0.04

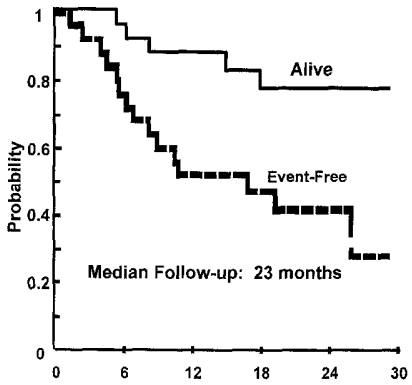

Figure 4. Results of randomized trial of dexamethasone ± thalidomide for post-transplant relapse (low risk). Significantly higher response rate with dexamethasone + thalidomide. No apparent difference in EFS or OS yet

Table 7. Patient Characteristics for DCEP ± Thalidomide Study

Parameter	DCEP Alone (n = 42), %	DCEP + Thal (n = 38), %	P
Age > 60 yr	38	39	1.0
Male	71	55	.2
β2M > 2.5 mg/L	71	74	1.0
CRP > 4.0 mg/L	55	75	.1
IgG	60	47	.4
IgA	19	24	.8
−13/13q−	45	32	.2
Prior HDT	98	89	.2

Table 8. Patient Characteristics (N = 229) for DT PACE Study

Parameter	%
Age > 60 yr	53
Male	64
β2M > 6 mg/L	25
CRP > 4 mg/L	13
Deletion 13	21
Months of prior therapy	
≤12	75
12-24	15
>24	12

age is 60 years with an upper age of 89 years. Twenty-seven percent had greater than 12 months of prior therapy, and 20% had chromosome 13 abnormalities. A full-dose first cycle was given to 73% of the patients. Among the 179 enrolled at least 15 weeks prior to analysis, and hence reaching the first randomization stage, only 45% rather than the expected 80% were randomized, mainly due to a lower than expected response rate to the induction regimen. Thus, only 26% achieved ≥75% tumor mass reduction, indicating that only a small percentage indeed of cases is exquisitely sensitive to DT PACE. Among the first 80 patients randomized and actually treated according to the randomization arm, 26 of 39 on the tandem transplant arm and only 11 of 41 on the DT PACE continuation arm achieved CR (P = .0005). In addition, by protocol design, 40% of patients on the DT PACE arm crossed over to the tandem transplant arm because of failure to show ongoing response and especially to acheive CR. Importantly, however, the 2-year EFS of 73% ± 20% was identical between the two arms. In addition, 33 patients failing two cycles of DT PACE received tandem transplant as a rescue regimen with a 2-year EFS rate of 70% ± 27% (Fig 7). A multivariate prognostic factor analysis was performed to determine features associated with at least a partial response (PR) (PPR ≥ 75%) after two induction cycles. Higher PR rates were noted with the application of full doses of DT PACE (odds ratio [OR], 19.4; P = .005) and, surprisingly, in the presence of cytogenetic abnormalities, including those involving chromosome 13 (OR, 2.9; P = .05), whereas a level of marrow plasmacytosis greater than 30% was an unfavorable feature (OR, 0.2; P = .002). Thus, for the first time, we have identified an active regimen for high-risk chromosome 13 disease, as observed in the initial pilot trial.

On the basis of these results, the trial has been modified to call for one cycle of DT PACE with PBSC collection and immediate randomization to tandem transplants with melphalan 200 mg/m^2, or the use of a recently developed hybrid regimen employing DT PACE (with whole doses given in 48 rather than 96 hours) combined with melphalan 100 mg/m^2 and PBSC support. The latter regimen, when tested in the third and fourth transplant salvage setting, had a high incidence of CR and considerably less stomatitis than standard melphalan 200 mg/m^2. Three hundred patients will be enrolled to determine whether EFS increases from 25% to 35% at the end of 5 years.

Total Therapy II as front-line therapy for newly diagnosed patients (≤1 cycle prior standard therapy). The trial design (Fig 8) consists of four phases: (1) induction chemotherapy with VAD, DCEP, and cyclophosphamide, doxorubicin, and dexamethasone (CAD) with subsequent PBSC collection followed by a further cycle of DCEP; (2) tandem autotransplants with two cycles of melphalan 200 mg/m^2; (3) consolidation chemotherapy with either DCEP every 3 months for four cycles or DCEP alternating with CAD every 6 weeks for 1 year; and (4) interferon

% Responding After 3rd Cycle	Thalidomide +	Thalidomide -
CR *	8	5
≥ 90% *	17	5
≥ 75%	3	0
≥ 50%	8	8
Total	36	18

* p=0.07

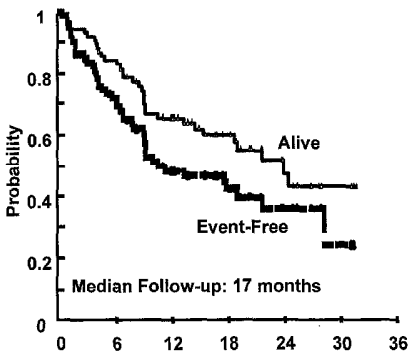

Figure 5. Results of randomized trial of combination chemotherapy with DCEP ± thalidomide; no apparent difference yet in EFS or OS (data

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