

# DTPACE: An Effective, Novel Combination Chemotherapy With Thalidomide for Previously Treated Patients With Myeloma

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**Purpose:** To improve outcome in previously treated patients (at least two cycles of standard therapy) with multiple myeloma, thalidomide was combined with cytotoxic chemotherapy as induction therapy.

**Patients and Methods:** The regimen consisted of 4-days of oral dexamethasone, daily thalidomide, and 4 days of continuous-infusion cisplatin, doxorubicin, cyclophosphamide, and etoposide (DTPACE). Response to two cycles of DTPACE for induction was evaluated in 236 patients. Before being treated with DTPACE, 148 patients (63%) had shown progressive disease while receiving standard chemotherapy, and 55 patients (23%) had chromosome 13 abnormalities.

**Results:** The partial remission rate (PR) after two cycles of DTPACE was 32%, with 16% attaining a complete remission (CR) or near-CR (nCR; defined as only immunofixation electrophoresis-positive). Patients with high lactate

dehydrogenase (LDH;  $n = 98$ ) showed a better response than those with normal LDH ( $n = 138$ ): PR or better, 43% v 27% ( $P = .01$ ); CR + nCR, 25% v 11% ( $P = .01$ ). Patients with chromosome 13 abnormalities ( $n = 55$ ) responded equally well as the other patients ( $n = 181$ ): PR or better, 35% v 33% ( $P = .84$ ); CR + nCR, 17% v 15% ( $P = .73$ ). Patients who received 100% dose of DTPACE for two cycles ( $n = 115$ ) achieved higher response rates than those with less than 100% dose ( $n = 121$ ): PR or better, 49% v 17% ( $P < .0001$ ); CR + nCR, 27% v 6% ( $P < .0001$ ).

**Conclusion:** Combination therapy of oral dexamethasone and thalidomide with infusional chemotherapy is effective as induction therapy before autotransplantation, especially in patients with high-risk features.

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FEWER THAN 5% of patients with symptomatic multiple myeloma (MM) treated with melphalan-prednisone achieve a strictly defined complete remission (CR), and the median survival duration generally does not exceed 3 years.<sup>1</sup> Combination chemotherapy with additional alkylating agents and anthracyclines has not improved survival beyond results obtained with standard melphalan-based therapy. In contrast, the introduction of high-dose melphalan and autologous stem-cell support has significantly increased CR rates (up to 50%) and doubled the overall survival benefit.<sup>2-6</sup>

Thalidomide represents the first new class of active agents in the treatment of MM since the introduction of melphalan and glucocorticoids more than 3 decades ago. In a phase II trial at our institution, thalidomide induced a 50% reduction in paraprotein levels in 30% of 169 heavily pretreated patients with advanced MM, including 14% CRs and near-CRs (nCRs).<sup>7</sup> The lack of myelosuppression and the presumed multiple potential mechanisms of action, including induction of apoptosis, inhibition of

vascular endothelial growth factor and basic fibroblast growth factor production, modulation of immune surveillance, and decreased adherence of myeloma cells to bone marrow stromal cells, make it ideal to test the efficacy of thalidomide in combination with cytotoxic agents earlier in the disease course.<sup>8-10</sup>

In this study, thalidomide was combined with high-dose dexamethasone and a 4-day continuous infusion of cisplatin, doxorubicin, cyclophosphamide, and etoposide (DTPACE). Infusional doxorubicin has been shown to induce a marked response in patients with advanced MM, in combination with dexamethasone.<sup>11</sup> Likewise, a combination of high-dose dexamethasone with 4-day continuous infusion of cyclophosphamide, etoposide, and cisplatin has been found to be effective for patients with relapsing myeloma after tandem transplantation, including those presenting with unfavorable cytogenetics.<sup>12</sup> This report focuses on the response rates and toxicities of the first two cycles of DTPACE administered as induction therapy before autotransplantation with high-dose melphalan or continuation of additional cycles of DTPACE.

## PATIENTS AND METHODS

### Patients

Two hundred thirty-six patients between 31 and 84 years of age with previously treated MM were prospectively enrolled at the Myeloma Institute for Research and Therapy of the University of Arkansas for Medical Sciences (Little Rock, AR) between September 1998 and April 2001, onto trial UARK-98035. The major aim of the study was to evaluate whether DTPACE might be equivalent or even superior to tandem transplantation with high-dose melphalan. Patient characteristics are described in Table 1. The outcome of these patients was analyzed on September 31, 2002. The Institutional Review Board of the University of Arkansas for Medical

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Table 1. Patients Characteristics

Parameter	Median	Range	Cut-Off	No. of Patients (N = 236)	%
Age, years	60	31-84	> 60	130	55
Male/female				151:85	
Beta <sub>2</sub> -microglobulin, mg/L	3.5	0.1-40.5	> 2.5	156	66
CRP, mg/L	0.8	0.1-22.1	> 2.0	55	23
Labeling index	0.4	0-5.8	> 0.4	107	45
LDH, U/L	168	42-723	> Normal	98	42
Serum creatinine, mg/dL	1	0.5-14.7	> 2	37	16
Zubrod performance score	1	0-4	> 1	58	25
Albumin, g/dL	4	1.6-5.3	< 3.5	50	21
Chromosome 13 deletion				55	23
Prior therapy duration, months	6	1-101	> 12	58	25
Prior therapy					
VAD				121	51
Melphalan-based*				44	19
VAD and MP				33	14
Dexamethasone-based†				38	16
Response to prior therapy					
Progressive disease				148	63
Improvement				68	29
Partial remission				15	6
Near-complete remission				5	2
IgA MM				45	19
IgG MM				131	56
Light-chain MM				49	21
Nonsecretory MM				5	2
IgD MM				3	1
IgM MM				3	1

Abbreviations: VAD, vincristine, doxorubicin, dexamethasone; VMBCP, vincristine, carmustine, cyclophosphamide, melphalan and prednisone; MP, melphalan and prednisone; CRP, C-reactive protein; LDH, lactate dehydrogenase; IgA, immunoglobulin A; IgG, immunoglobulin G; IgD, immunoglobulin D; IgM, immunoglobulin M; MM, multiple myeloma.

\*Melphalan and prednisone (n = 32); VMBCP (n = 12).

†Dexamethasone alone (n = 30) or dexamethasone and thalidomide (n = 8).

Sciences approved the treatment protocol and an informed consent was signed by all patients.

### Eligibility

Eligible patients were previously treated (with at least two cycles of prior therapy) and had active MM that was measurable (defined as serum monoclonal protein  $\geq$  1.0 g/dL, 24-hour urine monoclonal protein  $\geq$  1.0 g, or  $\geq$  20% bone marrow plasmacytosis). Patients had adequate spirometric values of pulmonary function test at least 50% of predicted, carbon monoxide diffusion capacity at least 50% of predicted, and left ventricular ejection fraction more than 45%. Patients with the following conditions were ineligible: serious uncontrolled infection; a poor performance status of Zubrod 3 to 4 except if caused by bone pain; a platelet count less than 100,000/ $\mu$ L except if caused by extensive marrow plasmacytosis; a recent ( $\leq$  6 months) history of myocardial infarction, unstable angina, uncontrolled symptomatic congestive heart failure, hypertension, or cardiac arrhythmias; or a history of chronic obstructive or restrictive pulmonary disease. Prior malignancy was acceptable, provided there had been no evidence of disease recurrence during the 3 years before entry onto the study and there had been no prior therapy with cytotoxic drugs. Pregnant or nursing women and those who had undergone a prior auto- or allotransplantation were not eligible.

Patients were treated with two cycles of DTPACE as induction therapy (Table 2), followed by a random assignment to either tandem autotransplantation with high-dose melphalan or continuation of up to four more cycles of DTPACE (Fig 1). After two cycles of DTPACE, eligibility for random assignment to treatment required a reduction in paraprotein levels of more than 50% or reduction in marrow plasmacytosis of more than 50% for those with nonsecretory myeloma. Patients who achieved less than 50% reduction

in these indices were offered tandem autotransplantation after high-dose melphalan, without random assignment to treatment. It was planned to collect at least  $15 \times 10^6$  CD34<sup>+</sup> cells/kg from all patients after the first cycle of DTPACE, in preparation for future autotransplantations. Maintenance therapy consisted of dexamethasone 20 mg/d for 4 days every 4 weeks and daily thalidomide 50 to 200 mg.

### DTPACE

DTPACE consisted of high-dose dexamethasone 40 mg orally daily for 4 days; thalidomide 400 mg PO at night; 4-day continuous infusion of cisplatin 10 mg/m<sup>2</sup>/day (total dose per cycle 40 mg/m<sup>2</sup>), doxorubicin 10 mg/m<sup>2</sup>/day (total dose per cycle 40 mg/m<sup>2</sup>), cyclophosphamide 400 mg/m<sup>2</sup>/day (total dose per cycle 1,600 mg/m<sup>2</sup>), and etoposide 40 mg/m<sup>2</sup>/day (total dose per

Table 2. DTPACE Regimen

Drugs	Dose
Dexamethasone	40 mg PO daily $\times$ 4 days
Thalidomide	400 mg PO at night
Cisplatin	10 mg/m <sup>2</sup> /d $\times$ 4 days, CIV
Doxorubicin	10 mg/m <sup>2</sup> /d $\times$ 4 days, CIV
Cyclophosphamide	400 mg/m <sup>2</sup> /d $\times$ 4 days, CIV
Etoposide	40 mg/m <sup>2</sup> /d $\times$ 4 days, CIV

Abbreviations: DTPACE, dexamethasone, thalidomide, cisplatin, doxorubicin, cyclophosphamide, and etoposide; CIV, continuous intravenous infusion.



test. Cumulative incidence curves were generated to calculate the probability of responses, using the NCSS statistical software, version 2001 (Kaysville, UT).<sup>14,15</sup> For the cumulative incidence of response, death before response assessment was a competing risk for response.

## RESULTS

### Patient Characteristics

Of the 236 patients, 148 patients (63%) had shown progressive disease after the preceding standard chemotherapy, 107 patients (45%) had PCLI  $\geq$  0.4%, 98 patients (42%) had high LDH levels (greater than normal), and 55 patients (23%) had chromosome 13 abnormalities at the time of study enrollment (Table 1). Of the 148 patients with progressive disease, 34 patients had primary refractory myeloma, 83 patients had refractory relapse, and 31 patients experienced relapse while not receiving therapy. Two hundred twelve (90%) patients had at least one of these poor prognostic factors. One hundred fifty-four (65%) patients had received doxorubicin-based regimens before study entry. The median interval was 210 days (range, 13 to 5,430 days) between the last cycle of preceding therapy and DTPACE; 166 days (range, 35 to 5,430 days) for patients with progressive disease, and 416 days (range, 13 to 3,409 days) for those who showed a reduction of at least 50% in paraprotein levels after the preceding chemotherapy.

Of the total number of 236 patients enrolled onto trial UARK-98035, 156 patients received the first cycle at 100% dose. Seven patients who were enrolled never started treatment. Six patients with renal failure who were dependent on dialysis received 100% dose dexamethasone, thalidomide, doxorubicin, cyclophosphamide, and etoposide without cisplatin for two cycles. The remaining 67 patients received the first cycle at  $\leq$  50% dose either because of comorbidity ( $n = 49$ ) or advanced age ( $> 75$  years;  $n = 18$ ). Twenty-four patients received  $\leq$  50% dose of cisplatin, doxorubicin, cyclophosphamide, and etoposide (PACE) but full-dose dexamethasone and thalidomide either because of advanced age ( $n = 18$ ) or combined hepatic and renal dysfunction ( $n = 6$ ); 23 patients received  $\leq$  50% dose of cisplatin because of renal dysfunction (serum creatinine  $> 2.0$  mg/dL); four patients received  $\leq$  50% dose of doxorubicin because of significant prior irradiation to the chest region adjacent to the heart; and 16 patients received  $\leq$  50% dose of thalidomide because of significant peripheral neuropathy of prior vincristine. After the first cycle, five patients died as a result of treatment-related causes and one patient died as a result of progressive disease; nine patients were taken off study (patient's decision [ $n = 5$ ], physician's decision [ $n = 2$ ], and denial of insurance coverage [ $n = 2$ ]); two patients were lost to follow-up; and six patients had progressive disease that was treated with other regimens. Of the available 206 patients for the second cycle, 115 received full-dose DTPACE. Eighty-five patients received the second cycle at reduced doses because of grade 3 to 4 toxicities, including 13 patients at 75% dose of PACE, 22 patients at  $\leq$  50% dose of PACE, 13 patients at  $\leq$  50% dose of cisplatin, 13 patients at  $\leq$  50% dose of doxorubicin, and 24 patients at  $\leq$  50% dose of thalidomide. Six patients who were receiving dialysis also received dexamethasone, thalidomide,

**Table 3. Distribution of the 236 Patients During Two Cycles of DTPACE**

	First Cycle	Second Cycle
100%	156*	115
75% of PACE*	0	13
$\leq$ 50% of PACE*	24	22
$\leq$ 50% Cisplatin	23	13
$\leq$ 50% Doxorubicin	4	13
$\leq$ 50% Thalidomide	16	24
100% of DTACE	6	6
Never started treatment	7	7
Death after first cycle		6
Lost to follow-up		2
Off study		9
Progressive disease		6

Abbreviations: DTACE, dexamethasone, thalidomide, doxorubicin, cyclophosphamide, and etoposide; PACE, cisplatin, doxorubicin, cyclophosphamide, and etoposide; DTPACE, dexamethasone, thalidomide, cisplatin, doxorubicin, cyclophosphamide, and etoposide.

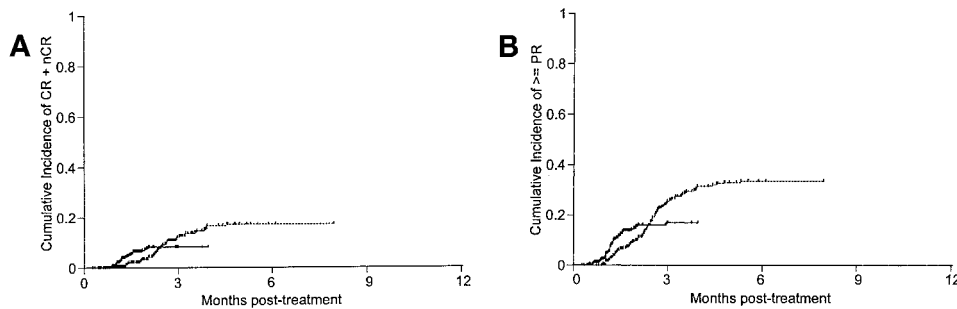
\*PACE, but with 100% dose dexamethasone and thalidomide.

doxorubicin, cyclophosphamide, and etoposide at 100% dose. The median interval between the first and second DTPACE treatment was 40 days (range, 16 to 138 days). One hundred fifty-two patients received at least one autotransplantation, including 110 patients after two cycles and 42 patients after more than two cycles of DTPACE, at a median interval of 68 days from the last DTPACE (range, 27 to 288 days). Distribution of the patients for two cycles is listed in Table 3.

### Response

After the first cycle of DTPACE ( $n = 229$ ), 19 patients (8%) achieved either CR ( $n = 6$ ) or nCR ( $n = 13$ ), 20 patients (9%) achieved PR, and 124 patients (53%) achieved improvement at a median of 37 days (range, 13 to 120 days). After the second cycle, the response rate increased to 16 patients (7%) with CR, 22 patients (9%) with nCR, 37 patients (16%) with PR, and 127 patients (54%) who showed improvement (Fig 2). Additional response was seen in the 63 patients who received more than two cycles of DTPACE, including five patients (2%) with CR, seven patients (3%) with nCR, seven patients (3%) with PR, and nine patients (4%) who showed improvement, with the overall response rate of 40% ( $n = 94$ ) of  $\geq$  PR and 21% ( $n = 50$ ) of CR ( $n = 21$ ) + nCR ( $n = 29$ ).

The response rate was not affected by chemosensitivity to preceding standard chemotherapy, prior exposure to doxorubicin, beta<sub>2</sub>-microglobulin level, or PCLI (Table 4). Patients with high LDH ( $n = 98$ ) showed a better response than those with normal LDH ( $n = 138$ ):  $\geq$  PR, 43%  $\nu$  27% ( $P = .01$ ); CR + nCR, 25%  $\nu$  11% ( $P = .01$ ). Patients with chromosome 13 abnormalities ( $n = 55$ ) responded equally well as the others ( $n = 181$ ):  $\geq$  PR, 35%  $\nu$  33% ( $P = .84$ ); CR + nCR, 17%  $\nu$  15% ( $P = .73$ ). Patients who received 100% dose DTPACE for two cycles ( $n = 115$ ) achieved higher response rates than those with less than 100% dose ( $n = 121$ ):  $\geq$  PR, 49%  $\nu$  17% ( $P < .0001$ ); CR + nCR, 27%  $\nu$  6% ( $P < .0001$ ).



**Fig 2.** Cumulative incidence of response. (—) First cycle; (- - -) second cycle. (A) Complete response (CR) + near-CR (nCR); (B)  $\geq$  partial remission (PR).

### Toxicity

Toxicity was monitored up to 3 months after each of the two induction cycles of DTPACE (number of cycles, 435; Table 5). Grades  $\geq 2$  neutropenia occurred in 65% of cycles, with a median onset of 7 days (range, 5 to 12 days) to an ANC less than  $0.5 \times 10^9/L$ . Neutropenic fever was observed in 12% of cycles and lasted a median of 5 days (range, 1 to 24 days). Grades  $\geq 2$  thrombocytopenia occurred less frequently (11%) and were associated with 22 episodes of hemorrhage (eight episodes of gastrointestinal mucosal bleeding, eight episodes of hematuria, two episodes of significant epistaxis, and five episodes of catheter site bleeding).

The most common nonhematologic toxicities were nausea and vomiting (21%), followed by mucositis (19%) and hypophosphatemia (17%). Although gastrointestinal toxicity was frequent, it was not associated with serious complications, such as typhlitis or bowel perforation. A number of cardiovascular toxicities occurred, including thromboembolism and arrhythmias. Before routine thrombosis prophylaxis (n = 242 cycles), thromboem-

bolic events occurred after 37 cycles (15%), including deep vein thrombosis of extremities (n = 25) and at the site of the central venous line (n = 12). Three of these patients developed a nonfatal pulmonary embolism. Except for the episode of pulmonary embolism, all events were mild and limited to grade 3 toxicity. All episodes of cardiovascular toxicity resolved at a median of 8 days (range, 1 to 61 days) and included sinus bradycardia (n = 6) and supraventricular arrhythmia (n = 7), which improved after discontinuation of thalidomide. Five episodes of sinus bradycardia were associated with symptomatic syncopal episodes.

Pulmonary and renal toxicities and metabolic abnormalities were brief, usually lasting less than a week after completion of 4-day chemotherapy; these toxicities responded well to fluid and electrolyte management. Patients with renal failure (n = 6) who were receiving maintenance dialysis during therapy tolerated the regimen well without cisplatin and had no significant metabolic complications, but grade 3 mucositis occurred. Of note, there was no occurrence of acute tumor lysis syndrome even in patients with high baseline LDH levels.

DTPACE produced infrequent but diverse neurologic toxicities. One of the most common neurologic complaints was paresthesias and numbness in hands and feet, which tended to worsen with continuation of thalidomide but improved with dose reduction of thalidomide. Weakness caused by motor neuropathy was most prominent during the first 2 weeks of each chemotherapy cycle. Increase in the level of thyroid-stimulating hormone or decrease in thyroxine was noted after 17 (4%) cycles. Of these, only six episodes were associated with clinical hypothyroidism, which required treatment with levothyroxine. After the first cycle of DTPACE, six patients (3%) died as a result of treatment-related causes, including bacterial sepsis (n = 2), invasive aspergillosis (n = 2), respiratory failure caused by bacterial pneumonia (n = 1), and intracerebral hemorrhage while receiving coumadin (n = 1); one patient died as a result of progressive disease. Three additional patients died of sepsis (n = 2) and cytomegalovirus pneumonia (n = 1) after the second cycle, with a 4% incidence of treatment-related mortality at 3 months after the second cycle.

### DISCUSSION

The combination of thalidomide with chemotherapeutic agents shows outstanding response rates in patients with myeloma who experience relapse after or are completely or partially

**Table 4.** Pretreatment Factors Affecting the Incidence of Response (N = 236)

Factors	CR + nCR (%)	P	$\geq$ PR (%)	P
Response to prior therapy				
Chemotherapy-sensitive	20	.37	36	.52
Chemotherapy-resistant	15		32	
Prior doxorubicin exposure				
Yes	19	.22	32	.4
No	13		32	
Beta <sub>2</sub> -microglobulin, mg/dL				
> 2.5	20	.35	29	.29
$\leq$ 2.5	17		36	
PCLI, %				
> 0.4	18	.84	34	.83
$\leq$ 0.4	17		35	
CA-13				
Yes	17	.73	35	.84
No	15		33	
LDH				
> Normal	25	.01	43	.01
Normal	11		27	
Dose-intensity, %				
100	27	< .0001	49	< .0001
< 100	6		17	

Abbreviations: CR, complete remission; nCR, near-complete remission; PR, partial remission rate; PCLI, plasma cell labeling index; CA-13, chromosome 13 abnormalities; LDH, lactate dehydrogenase.

Table 5. Toxicity of DTPACE Chemotherapy

Event (N = 435)	Overall Incidence		Grades 3 to 4		Median Duration (days)	
	No. of Patients	%	No. of Patients	%	No.	Range
ANC < 1.5 × 10 <sup>9</sup> /L	282	65			4	2-24
ANC < 0.5 × 10 <sup>9</sup> /L	168	39			4	2-21
Platelets < 75 × 10 <sup>9</sup> /L	161	37			5	1-27
Platelets < 10 × 10 <sup>9</sup> /L	48	11			3	1-11
Gastrointestinal						
Nausea or vomiting	91	21	26	6	3	1-7
Stomatitis or pharyngitis	83	19	17	4	8	1-45
Esophagitis or gastritis	23	5	9	2	4	1-16
Colitis	21	5	11	3	4	1-8
Diarrhea	35	8	7	2	5	1-11
Constipation	76	18	0	0	14	1-60
Hepatobiliary						
Elevation of hepatic enzymes	12	3	0	0	3	2-9
Hyperbilirubinemia	11	3	2	1	6	2-18
Hypoalbuminemia	54	13	9	2	5	2-16
Cardiovascular						
Sinus bradycardia	6	1	6	1	7	2-22
Supraventricular arrhythmia	7	2	7	2	6	2-8
Hypertension	12	3	0	0	16	2-28
Hypotension	6	1	6	1	2	1-6
Congestive heart failure	3	1	3	1	12	8-32
Thromboembolism	37	15	22	5	38	7-61
Edema	24	6	0	0	7	1-18
Pulmonary						
Dyspnea	21	5	5	1	5	1-21
Pulmonary infiltrates	7	2	0	0	6	3-25
Pulmonary edema	5	1	3	1	2	1-5
Genitourinary						
Renal insufficiency	15	3	0	0	8	2-24
Neurologic						
Confusion	19	4	0	0	2	1-11
Somnolence	12	3	0	0	3	1-8
Tremor	30	7	0	0	6	1-24
Seizure	2	1	2	1	1	1
Syncope	9	2	9	2	NA	
Motor neuropathy	39	9	0	0	16	1-60
Ataxia	11	2	11	2	2	1-7
Agitation	32	7	0	0	3	1-13
Sensory neuropathy	56	13	16	4	27	3-120
Dizziness	19	4	0	0	5	1-11
Hearing loss	4	1	0	0	30	20-396
Infection						
Documented infection (ANC < 1.0 × 10 <sup>9</sup> /L)	17	4	17	4	12	4-18
Neutropenic fever	54	12	24	9	3	1-18
Erythema or rash	22	5	6	1	16	2-60
Metabolic						
Hypocalcemia	57	13	13	3	5	1-14
Hypophosphatemia	74	17	17	4	8	1-42
Hypomagnesemia	23	5	6	1	9	2-38
Hypokalemia	26	6	8	2	5	1-22
Hyponatremia	19	4	5	1	4	1-16
Decrease in bicarbonate	16	4	6	1	8	2-24
Endocrine						
Increase in TSH and/or decrease in T4	17	4	0	0	60	48-98

Abbreviations: DTPACE, dexamethasone, thalidomide, cisplatin, doxorubicin, cyclophosphamide, and etoposide; ANC, absolute neutrophil count; TSH, thyroid-stimulating hormone; T4, thyroxine; NA, not applicable.

refractory to standard chemotherapy. Patients who had experienced treatment failure after high-dose dexamethasone and doxorubicin-based regimens, or who had high LDH levels, chromosome 13 changes, or hypodiploid karyotypes, achieved similar response rates as the others. More importantly, two cycles of DTPACE resulted in an excellent tumor reduction

before autotransplantation in a group of patients, of whom 90% had at least one poor prognostic factor. The CR and nCR rate (16%) was considerably higher than with conventional chemotherapy, and the rate after two cycles of full-dose DTPACE compares favorably with that achieved with a single autotransplantation in primary refractory or relapsed myeloma.<sup>16,17,18</sup>

Long-term disease control of myeloma has become possible since high-dose therapy with melphalan was introduced in the mid 1980s, with attainment of CR as a primary goal of therapy. Randomized and historically controlled studies have shown that high-dose therapy combined with autologous stem-cell transplantation produces up to 50% CRs and significantly improves survival in newly diagnosed, symptomatic patients with myeloma.<sup>2-5</sup> In contrast, in patients who experience relapse after or are refractory to standard-dose chemotherapy, lower CR rates and shorter overall and event-free survival are observed after autotransplantation.<sup>16,17-19</sup> In one multi-institutional study of autotransplantation for patients with refractory myeloma, 27% of patients achieved CR and median overall survival was 19 months.<sup>16</sup> Similar observations were made in a study of patients who experienced relapse or were refractory, with a 34% CR rate and a median overall survival of 20 months after transplantation.<sup>17</sup>

Survival of relapsing or refractory MM patients may improve if more effective cytoreduction can be achieved before autotransplantation, similar to that achieved in newly diagnosed patients.<sup>6,19</sup> Although the relative contribution of induction chemotherapy to survival after transplantation requires more randomized trials, in general, better response rates are observed with more intensive chemotherapy before high-dose therapy.<sup>19,20</sup> Most conventional pretransplantation induction regimens attain no more than 5% CR (patients are immunofixation-negative) even after multiple cycles of either vincristine, doxorubicin, and dexamethasone or alkylator-based therapy, and the CR rate typically does not increase when such therapy is continued.<sup>4,18,21</sup> Improvements in at least PR (as defined) before autotransplantation may not be observed with conventional chemotherapy in patients who experience relapse or are refractory.<sup>22</sup> In this context, the response rate of our patients after two induction cycles of DTPACE was quite remarkable, and comparable with those seen with multiple cycles of chemotherapy in newly

diagnosed patients who received the total therapy I.<sup>6</sup> The excellent response rates in patients with prior doxorubicin or progressive disease, those with a high proliferative disease reflected by high LDH levels and high PCLI, and those with deletion of chromosome 13 indicate that a combination of thalidomide with chemotherapeutic agents and dexamethasone can overcome multidrug resistance induced by either epigenetic or genetic alterations.<sup>9,10</sup>

DTPACE was well tolerated and given on an outpatient basis in most cases, with a low treatment-related mortality. The regimen caused a wide range of toxicities (although they were infrequent), especially those related to the cardiovascular and neurologic system. Some of these toxicities, such as thromboembolism, sinus bradycardia, supraventricular arrhythmia, somnolence, syncope, and sensory neuropathy, are unique and not usually seen in the context of conventional chemotherapy or high-dose dexamethasone. Thalidomide has been shown to be associated with an increased risk of thromboembolism, especially when combined with doxorubicin.<sup>23</sup> Thalidomide appeared to be etiologically related to arrhythmia and syncope because these conditions improved when the dose was reduced or temporarily discontinued.<sup>24</sup> Sensory neuropathy was common in the present study, presumably because of a large number of elderly patients, the majority of whom had received prior vincristine therapy.<sup>25</sup> At present, patients are routinely given daily low molecular weight heparin 40 to 80 mg to prevent thromboembolism, except when the platelet count is reduced to less than 30,000/ $\mu$ L. Doses of thalidomide are reduced to a range of 100 to 200 mg a day or temporarily withheld if either cardiovascular or neurologic toxicities of grades 3 to 4 occur, until patient's condition is stabilized and allows re-treatment at a lower dose.

This study shows a significant therapeutic potential of the DTPACE regimen and reveals a novel way of managing patients with myeloma, especially those with high-risk features. On the basis of the promising activity of DTPACE, we are currently investigating its role in posttransplantation consolidation therapy and salvage therapy for patients experiencing relapse after autotransplantation. The combination of infusional chemotherapy with PS-341, which induces responses irrespective of presenting disease features, also is planned.

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## ERRATA

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The July 15, 2003, article by Lee et al entitled, “DTPACE: An Effective, Novel Combination Chemotherapy With Thalidomide for Previously Treated Patients With Myeloma” (J Clin Oncol 21:2732-2739, 2003) contained errors.

In the Patients and Methods section, under DTPACE, the fifth from last sentence indicated that patients were given fluconazole 200 mg PO qid and levofloxacin 250 mg PO qid, whereas it should have indicated that both drugs be given daily, as follows:

“With each cycle, patients were started on a prophylactic regimen of fluconazole 200 mg PO **daily**, levofloxacin 250 mg PO **daily**, and acyclovir 400 mg PO bid from the first day of chemotherapy, which was continued until the ANC reached more than 1,000/ $\mu$ L for 2 consecutive days.”

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The January 10, 2008, correspondence by Zhang et al entitled, “Clinically Relevant QTc Prolongation Is Not Associated With Current Dose Schedules of LBH589 (panobinostat)” (J Clin Oncol 26:332-333, 2008) contained an error.

In the second paragraph, the second to last sentence referred to patients with nonleukemic hematological malignancies, whereas it should have included patients with all hematological malignancies, as follows:

“Alternative dose schedules have been developed for both IV and oral panobinostat, which minimize cardiac adverse events (Table 1) while still maintaining activity in patients with a variety of solid tumors and hematological malignancies.”

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The February 20, 2008, Diagnosis in Oncology article by Sosvińska-Mielcarek et al entitled, “Cardiac Involvement at Presentation of Non-Small-Cell Lung Cancer” (J Clin Oncol 26:1010-1011, 2008) contained an error in the spelling of Katarzyna Sosińska-Mielcarek. It was originally published as Katarzyna Sosvińska-Mielcarek and should have been Katarzyna Sosińska-Mielcarek.

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