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Peripheral blood progenitor cells

Dexamethasone, paclitaxel, etoposide, cyclophosphamide (d-TEC) and G-CSF for stem cell mobilisation in multiple myeloma

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Summary:

Forty-one patients with multiple myeloma were treated with a novel stem cell mobilisation regimen. The primary end points were adequate stem cell mobilising ability (>1% circulating CD34-positive cells) and collection (≥4 × 10^6 CD34-positive cells/kg), and safety. The secondary end point was activity against myeloma. The regimen (d-TEC) consisted of dexamethasone, paclitaxel 200 mg/m^2 i.v., etoposide 60 mg/kg i.v., cyclophosphamide 3 g/m^2 i.v., and G-CSF 5–10 μg/kg/day i.v. A total of 84 cycles were administered to these 41 individuals. Patient characteristics included a median age of 53 years, a median of five prior chemotherapy cycles, and a median interval of 10 months from diagnosis of myeloma to first cycle of d-TEC. Seventy-five percent of the patients had stage II or III disease, 50% had received carmustine and/or melphalan previously, and 25% had received prior radiation therapy. Eighty-eight percent of patients mobilised adequately after the first cycle of d-TEC and 91% mobilized adequately after the second cycle. An adequate number of stem cells were collected in 32 patients. Of the remaining nine patients, three mobilised, but stem cells were not collected, two mobilised but stem cell collection was <4 × 10^6 CD34-positive cells/kg, three did not mobilise, and one died of disease progression. Major toxicities included pancytopenia, alopecia, fever and stomatitis. One patient died from multi-organ failure and progressive disease. Fifty percent of evaluable patients demonstrated a partial response and 28.6% of patients had a minor response. This novel dose-intense regimen was safe, capable of stem cell mobilisation and collection, even in heavily pre-treated patients, and active against the underlying myeloma. *Bone Marrow Transplantation* (2001) **28,** 137–143.

Keywords: dexamethasone; paclitaxel; etoposide; cyclophosphamide; stem cell mobilisation; multiple myeloma

High-dose chemotherapy (HDC) followed by autologous haemopoietic stem cell transplantation has become an accepted modality of treatment for patients with multiple myeloma.[1,2] A randomised study has demonstrated the superiority of HDC over conventional chemotherapy.[3] The use of autologous peripheral blood stem cell transplantation (PBSCT) has potential advantages compared to autologous bone marrow transplantation including earlier engraftment and, possibly, reduced tumor cell contamination of the stem cell product. Numerous regimens have been utilized for the purpose of stem cell mobilisation for patients with multiple myeloma.[1,4–38] Repeated courses of dose-intense chemotherapy may also result in sufficient tumor cytoreduction to allow a decrease in plasma cell contamination in peripheral blood progenitor cell collections.[15,39] Individuals who have been treated previously with stem cell toxic agents such as melphalan and carmustine may experience difficulty mobilising an adequate number of stem cells for subsequent transplantation. An ideal stem cell mobilising regimen should enhance the yield of peripheral blood stem cells and produce optimal tumour cytoreduction. We utilised a novel regimen consisting of dexamethasone, paclitaxel (Taxol), etoposide and cyclophosphamide (d-TEC) supported by granulocyte colony-stimulating factor (G-CSF). The primary end points of this study were to determine the stem cell mobilising and collecting ability, and safety of this regimen. The secondary end point was to ascertain the response of the underlying multiple myeloma.

Patients and methods

Patients

Patients with multiple myeloma were referred to the University of Connecticut Health Center, Farmington, CT, for HDC/PBSCT. Informed consent was obtained prior to the administration of stem cell mobilisation chemotherapy, and collection of PBSC. Between May 1994 and July 2000, 41 patients with multiple myeloma received a dose-intense chemotherapy regimen with the aim of collecting PBSC. The protocol was approved by the institutional review board of the University of Connecticut Health Center. Eligibility criteria included stage II or III disease as well as those individuals with stage I myeloma who required treatment

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for the management of disease manifestations, an age <70 years, an ECOG performance status of 0, 1, 2 or 3, an absolute neutrophil count (ANC) >1.5 × 10^9/l, a platelet count >100 × 10^9/l, a creatinine clearance of >50 ml/min, a left ventricular ejection fraction of >50%, and a diffusion lung capacity of >50% of the predicted value.

Chemotherapy

Patients received combination chemotherapy supported by granulocyte colony-stimulating factor (G-CSF) to facilitate PBSC mobilisation and harvesting. The regimen (d-TEC) is presented in Table 1. G-CSF was initiated at a dose of 5–10 μg/kg/day intravenously from hour 60 until an ANC >5 × 10^9/l was reached or until completion of PBSC collection. Patients were hospitalised for 72 h during the administration of chemotherapy. Cycles of chemotherapy were repeated at 4-week intervals.

Supportive care

Supportive measures included an intensive anti-emetic regimen consisting of lorazepam 0.5–1.0 mg intravenously every 6 h with dexamethasone and ondansetron 0.15 mg/kg intravenously every 6 h. Diphenhydramine 50 mg intravenously and ranitidine 50 mg intravenously were administered 30 min prior to the commencement of the paclitaxel infusion. Antibiotic prophylaxis and treatment, and transfusion criteria have been outlined previously.[40] Each individual was seen in the outpatient clinic on alternate days from day 6 until recovery of the WBC count. Toxicity was graded in accordance with the World Health Organization (WHO) criteria.[41]

Definitions

Adequate mobilisation of peripheral blood stem cells (PBSC) was defined by a peripheral blood CD34-positive cell count of >1% when the total white blood cell (WBC) count exceeded 1 × 10^9/l. Adequate PBSC harvesting was defined as the collection of ⩾4 × 10^6 CD34-positive cells/kg in the harvest product. Efficient PBSC harvesting was defined as the collection of ⩾3 × 10^6 CD34-positive cells/kg/leukapheresis, because it identified individuals in whom adequate collection was likely to be achieved after one or two leukapheresis.

Table 1 Chemotherapy regimen

Hour	*Therapy*
0–18	Etoposide 60 mg/kg ideal body weight by continuous i.v. infusion
24–25 and 30–31	Cyclophosphamide 1.5 g/m^2 (actual body weight) in 250 ml of 5% dextrose i.v.
24, 27, 30, 33, 36, 39 and 42	Mesna 12 mg/kg actual body weight i.v.
48–51	Paclitaxel 200 mg/m^2 (actual body weight) by continuous i.v. infusion
60	Granulocyte colony-stimulating factor 5–10 μg/kg actual body weight i.v.

Peripheral blood stem cell collection

The CD34-positive cell count was determined from a whole blood specimen prior to leukapheresis and from the leukapheresis product by a method described previously.[42] The number of colony-forming units granulocyte–macrophage (CFU-GM) after 14 days of culture of the PBSC product was determined by modification of a previously described method.[43] If the circulating CD34-positive cell count was greater than 1%, stem cell leukapheresis was conducted with a continuous flow cell separator (Cobe Spectra; Cobe CBT, Lakewood, CO, USA) processing 10–20 l of blood per day at flow rates of 50–80 ml/min. Stem cell leukapheresis was attempted following both the first, as well as the second cycle of chemotherapy in the initial group of patients. If an adequate number of stem cells was harvested after the second cycle of d-TEC, they were utilised for the PBSCT. Patients who mobilised well (>5% CD34-positive cells in the circulation) following the first cycle of chemotherapy usually mobilised adequately (>1%) after the second course. In subsequent patients, stem cell collection was deferred to the second cycle of chemotherapy if mobilisation of CD34-positive cells exceeded 5% following the first cycle of d-TEC. The level of contamination of the leukapheresis products with malignant plasma cells was not evaluated in this study. Whenever possible, we attempted to re-infuse only those stem cells that had been collected after the second course of chemotherapy. To that end, stem cell collection was performed daily until a target of ⩾4.0 × 10^6/l CD34-positive cells/kg body weight was achieved, if possible.

Response to chemotherapy

Response was assessed by bone marrow aspirate and biopsy, serum immunofixation electrophoresis and quantification of Bence-Jones protein in the urine over 24 h. Evaluation of disease status was conducted prior to the initiation of d-TEC and approximately 3 weeks following the completion of the last course of d-TEC. Response was defined using the common criteria of the EBMT, IBMTR and ABMTR.[44]

Statistical analysis

Several variables were examined as potential determinants of adequate PBSC mobilisation (total collection of ⩾4 × 10^6 CD34-positive cells/kg *vs* <4 × 10^6 CD34-positive cells/kg) and mobilisation per leukapheresis (⩾3 × 10^6 CD34-positive cells/kg/leukapheresis *vs* <3 × 10^6 CD34-positive cells/kg/leukapheresis). These included age <53 years *vs* ⩾53 years, male *vs* female sex, stage 1 *vs* stages 2 and 3, IgG myeloma *vs* other subtypes, κ *vs* λ light chains, prior radiation therapy *vs* no prior radiation, prior use of interferon-α *vs* no prior interferon-α, prior use of stem cell toxic agents such as melphalan or carmustine *vs* no previous stem cell toxic chemotherapy, one or no pre-

vious chemotherapy regimen *vs* ⩾2 prior regimens, <5 prior cycles of chemotherapy *vs* ⩾5 prior cycles, interval from diagnosis of myeloma to first cycle of d-TEC of <10 months *vs* ⩾10 months, use of d-TEC at initial remission *vs* use of d-TEC at relapse or second or greater remission, ECOG performance status of 0 and 1 *vs* 2 and 3, and interval from last cycle of standard chemotherapy to first cycle of d-TEC <6 weeks *vs* ⩾6 weeks. The same variables were also examined as potential determinants of partial response *vs* less than a partial response. Contingency table (χ^2) analyses were utilised to estimate the statistical significance of each discrete variable. Continuous variables were compared using the median test. Finally, the joint effect of a combination of variables as a set of 'risk factors' for not mobilising an adequate number of PBSC following d-TEC was determined using a logistic regression model.

Results

Patient characteristics

Forty-one patients with multiple myeloma received a total of 84 cycles of d-TEC. Twenty-seven individuals were given two cycles of d-TEC, six received one cycle only and eight received three cycles. The third cycle of d-TEC was administered for further tumor cytoreduction rather than for the purpose of PBSC mobilisation. Patient characteristics are outlined in Table 2. Thirty-nine individuals had received a median of five cycles (range 2 to 48 cycles) of chemotherapy previously. Moreover, 21 patients had been administered a median of six cycles (range 3 to 22 cycles) of regimens containing stem cell toxic agents, such as melphalan or carmustine. Two patients did not receive any prior chemotherapy. One of these two patients had received radiation therapy for relief of symptoms. The other patient was given d-TEC as initial treatment of symptomatic myeloma. Twenty-one patients were treated with d-TEC for refractory or relapsed disease.

Stem cell mobilisation and collection

Thirty-six (88%) out of the 41 patients who received a first cycle of d-TEC mobilised an adequate number of PBSC (Table 3). The median peripheral blood CD34-positive cell count was 7.8% (range 0% to 69.1%). Stem cell leukapheresis was conducted in 23 patients and yielded a median of

Table 3 Mobilisation and collection of peripheral blood stem cells

	d-TEC cycle 1	*d-TEC cycle 2*
Number of patients	41	35
Number of patients who mobilised adequately (>1% $CD34^+$ cells in the peripheral blood)	36	32
Number of patients in whom collection was attempted	23	33
Median number of leukapheresis/cycle of d-TEC (range)	1 (1–3)	1 (1–5)
Median peripheral blood $CD34^+$ cell % (range)	7.8 (0–69.1)	3.4 (0–31.8)
Median number of $CD34^+$ cells collected $\times 10^6$/kg (range)	7.1 (0.1–61.6)	6.6 (0.3–29.8)
Median CFU-GM colony count/10^5 cells plated (range)	66 (8-TNTC)	68.7 (13.3-TNTC)

d-TEC = dexamethasone, paclitaxel, etoposide and cyclophosphamide; CFU-GM = colony-forming units granulocyte–macrophage; TNTC = too numerous to count.

Table 2 Patient characteristics

Number of patients	41
Median age in years (range)	53 (39–65)
Cycles of d-TEC	84
Median number of cycles of d-TEC/patient (range)	2 (1–3)
Male:Female ratio	23:18
Type of multiple myeloma	IgGκ (n = 20); IgGλ (n = 6); IgAκ (n = 2); IgAλ (n = 6); κLCM (n = 5); λLCM (n = 1); non-secretory (n = 1)
Stage	I (n = 9); II (n = 22); III (n = 10)
Prior radiation therapy	11 patients
Prior interferon-α therapy	6 patients
Median number of prior chemotherapy cycles	5 (range 0–48)
Median number of prior chemotherapy regimens	1 (range 0–5)
Prior stem cell toxic chemotherapy	21 patients
ECOG performance status	0 (n = 10); 1 (n = 17); 2 (n = 9); 3 (n = 5)
Disease status at first d-TEC	Initial treatment or remission (n = 20); relapsed or refractory disease (n = 21)
Interval from diagnosis of myeloma to first cycle of d-TEC	Median 10 months (range 2–156 months)
Interval from last cycle of standard chemotherapy to first cycle of d-TEC	Median 6 weeks (range 0 weeks to 5 years)

d-TEC = dexamethasone, paclitaxel, etoposide and cyclophosphamide; n = number; LCM = light chain myeloma.

7.1 × 10^6 CD34-positive cells/kg (range 0.1–61.6 × 10^6 CD34-positive cells/kg) after a median of 1 (range 1–3) leukapheresis. The median CFU-GM colony count was 66 colonies/10^5 cells plated (range, eight colonies to too many colonies to count/10^5 cells plated).

Thirty-five individuals received a second cycle of d-TEC. Three of these 35 patients failed to mobilise an adequate number of PBSC. Patients who failed to mobilise adequately with the first cycle of d-TEC were also unsuccessful in mobilising PBSC with the second course. The median peripheral blood CD34-positive cell count was 3.4% (range 0 to 31.8%). Stem cell leukapheresis was attempted in 33 patients including one individual with inadequate mobilisation. A median of 6.6 × 10^6 CD34-positive cells/kg (range 0.3–29.8 × 10^6 CD34-positive cells/kg) was collected with a median of one leukapheresis (range 1–5 leukaphereses). The median CFU-GM colony count was 68.7 colonies/10^5 cells plated (range 13.3 colonies to too many colonies to count/10^5 cells plated).

Stem cell leukapheresis was conducted after both first and second cycles of d-TEC in 21 patients, after the second cycle only in 12 patients, and following the first cycle only in three individuals. Two of these 36 patients underwent an unsuccessful attempt at PBSC harvesting even though they had failed to demonstrate adequate mobilisation of stem cells in the peripheral blood. Five patients did not undergo leukapheresis following d-TEC. One of these patients had failed to mobilise PBSC and an additional patient died of progressive myeloma following d-TEC. The three remaining individuals, all of whom mobilised an adequate number of PBSC after the first cycle of d-TEC, but did not undergo stem cell collection, developed side-effects which precluded a second cycle of d-TEC. Two of these three patients underwent successful PBSC harvesting utilising alternate regimens. Furthermore, 17 out of 20 evaluable patients (85%) who had received prior melphalan or carmustine mobilised adequately with d-TEC.

Thirty-two (78%) of 41 individuals underwent successful collection of an adequate number of PBSC. One of these patients was not transplanted because of chronic sinusitis secondary to aspergillosis. She continues to do well at the time of this report. The remaining 31 patients proceeded to HDC-PBSCT. Two other individuals (4.9%) in whom an adequate number of stem cells could not be collected (2.6 × 10^6 CD34-positive cells/kg and 3 × 10^6 CD34-positive cells/kg, respectively) were also transplanted. Therefore, 33 patients underwent HDC-PBSCT utilising stem cells collected after d-TEC. The myelo-ablative regimen consisted of busulfan 16 mg/kg orally (day −7 to −4 in 16 divided doses), etoposide 60 mg/kg i.v. (day −3), cyclophosphamide 90 mg/kg i.v. (day −2 in two divided doses), and G-CSF 5 μg/kg/day i.v. from day +1 until recovery of the neutrophil count. The median duration of neutropenia following transplantation was 6 days (range 3–12 days). The median day of engraftment (ANC >1 × 10^9/l) post transplantation was day +9 (range day +8 to day +13). Major toxicities included pancytopenia, fever, stomatitis and alopecia. Transplant-related mortality was limited to one patient who died at day +48 as a result of cytomegalovirus–interstitial pneumonitis. The product collected after the second cycle of d-TEC was utilized in 31 individuals whereas the two remaining patients received PBSC that had been harvested after the first cycle. Neither of the two patients who received less than 4 × 10^6 CD34-positive cells/kg demonstrated any delay in engraftment. Two additional patients underwent successful PBSC harvesting utilising alternate regimens (cyclophosphamide and G-CSF, and cyclophosphamide, etoposide and G-CSF, respectively) followed by autologous PBSCT. Both patients had mobilised previously with an initial cycle of d-TEC, and were in the process of PBSC harvesting as part of the initial treatment of myeloma. Neither had received stem cell toxic agents previously. Two non-mobilisers underwent autologous bone marrow transplantation. One additional patient died following d-TEC. Another individual who mobilised PBSC was not collected or transplanted, and one non-mobiliser was also not transplanted.

None of the variables studied, including prior use of melphalan or carmustine, predicted failure to achieve the goal of adequate PBSC collection (≥4 × 10^6 CD34-positive cells/kg). However, collection of ≥3 × 10^6 CD34-positive cells/kg/leukapheresis was significantly associated with an age equal to or less than 53 years (P = 0.034), fewer than five prior cycles of chemotherapy (P = 0.005), and avoidance of melphalan/carmustine in prior chemotherapy regimens (P = 0.005). Successful collection of ≥3 × 10^6 CD34-positive cells/kg/leukapheresis was also analyzed using a logistic regression model. Candidate predictors included younger age, fewer prior cycles of chemotherapy, and avoidance of prior melphalan or carmustine. The final model included avoidance of prior treatment with melphalan or carmustine (P = 0.0095; odds ratio 0.1; and confidence interval 0.018–0.569).

Response rates

No patient was in complete remission at the time of initiation of d-TEC. However, 13 individuals could not be evaluated for response to d-TEC because their serum immunoglobulin levels were within normal limits following standard chemotherapy. The remaining 28 patients were evaluable for response to d-TEC. Upon completion of d-TEC chemotherapy, there were 14 partial responders (50%), eight minor responders (28.6%), four non-responders (14.2%), and two patients with progressive disease (7.1%). A median 48.5% decline in serum paraprotein level was evident in evaluable patients following completion of d-TEC. The serum and/or urine immunoglobin level was within normal limits upon completion of d-TEC in 12 of 28 evaluable patients. Among 15 evaluable patients with relapsed or refractory multiple myeloma, there were five partial responders (33%), six minor responders (40%), two non-responders (13%), and two individuals with progressive disease (13%). None of the variables studied were predictive of a partial response. However, earlier treatment with d-TEC (P = 0.058) and fewer than five prior cycles of conventional chemotherapy (P = 0.053) demonstrated an increased probability of attaining a partial response although this trend did not achieve statistical significance with either of the two variables.

Toxicity

The World Health Organization (WHO) toxicity grading is outlined in Table 4. The median duration of neutropenia was 7 days (range 4–17 days). The maximum depth of neutropenia was an ANC of $<0.1 \times 10^9$/l in all patients. The ANC recovered at a median of 14 days (range 11–20 days) following the initiation of chemotherapy. There were 23 (27%) readmissions for fever during neutropenia. However, only six patients developed bacteremia (three staphylococcus species; three viridans streptococcal species). Alopecia was universal. A median of one PRBC transfusion (range 0–5) was administered during each cycle of d-TEC. A median of one platelet product (range 0–6) was transfused during each cycle of d-TEC. Two individuals were unable to receive a second cycle of d-TEC because of severe generalised skeletal pain at the time of recovery of blood counts following the first cycle. An additional patient died 27 days after the initiation of chemotherapy from sepsis and progressive disease.

Discussion

Numerous strategies have been devised to optimise PBSC mobilisation among patients with multiple myeloma. High-dose cyclophosphamide with growth factor support, or use of growth factors alone, are utilised most frequently.[1,4–38] On an average, three or more leukapheresis procedures are required with these regimens in order to attain the targeted stem cell yield. In this study, we combined cyclophosphamide with paclitaxel and etoposide because all three agents are capable of PBSC mobilisation. G-CSF was administered on a daily basis following the completion of chemotherapy until recovery of the WBC count and/or collection of PBSC. It is noteworthy that the targeted stem cell yield was attained with a median of one leukapheresis procedure in our patients which compares favorably with the results of most other regimens.

Factors predicting a poor yield of PBSC include duration of prior treatment with alkylating agents such as melphalan, number of prior cycles of chemotherapy, interval from diagnosis to stem cell mobilising chemotherapy, prior radiation therapy, response to treatment before stem cell mobilising chemotherapy, extensive infiltration of the bone marrow with plasma cells, and lack of growth factor support.[8,10,14,18,45] Mobilisation may be improved in patients with multiple myeloma if a growth factor is added to high-dose cyclophosphamide.[4,13,18] Moreover, both G-CSF and GM-CSF appear to be equivalent when added to cyclophosphamide.[19] It has also been suggested that a combination of cyclophosphamide, etoposide and G-CSF is superior to either cyclophosphamide plus growth factor or G-CSF alone in patients with multiple myeloma.[10] We combined cyclophosphamide with etoposide and G-CSF and added paclitaxel because of its ability to mobilise PBSC in other malignancies.[46] Despite heavy pretreatment, a long interval from diagnosis, and use of prior alkylator therapy in many of our patients, mobilisation was more than adequate in 90% of cases. Even though the number of PBSC harvested/leukapheresis was reduced, statistical analysis failed to demonstrate a significant negative impact of prior therapy with melphalan or carmustine on subsequent collection of an optimal number of stem cells.

Cyclophosphamide, etoposide,[47] and paclitaxel[45] have limited single agent activity in multiple myeloma. Dexamethasone, paclitaxel, etoposide and cyclophosphamide were combined primarily for PBSC mobilisation in the current study. It is noteworthy that only between one and three cycles of this combination yielded a partial response rate of 50% in evaluable patients utilizing the strict EBMT, IBMTR and ABMTR criteria for response. It must also be mentioned that evaluation of response to d-TEC excluded a favorable group of 13 individuals in whom standard chemotherapy had already resulted in normalisation of serum and urinary immunoglobulin levels. Furthermore, a partial response rate of 33% and a minor response rate of 40% in relapsed or refractory patients was not significantly inferior to most standard salvage chemotherapy regimens. It is possible that further cycles of d-TEC may have resulted in a greater number of partial responders. It is also possible that longer follow-up after completion of d-TEC may have demonstrated an even greater decline of the paraprotein level. Therefore, it appears that d-TEC results in more cytoreduction than is observed with any of its chemotherapeutic components used alone. Although not evaluated in the current study, this anti-tumor activity may be potentially advantageous because it is possible that *in vivo* cytoduction may decrease contamination of the PBSC product with malignant plasma cells especially following two or more cycles of the regimen. In fact, two other groups of investigators have reported reduced plasma cell contamination of the PBSC product by adding cyclophosphamide to G-CSF *vs* G-CSF alone,[39] and following repeated cycles of high-dose chemotherapy.[15]

An ideal regimen for PBSC mobilisation in individuals with multiple myeloma should not only be efficient (fewer leukapheresis to collect adequate stem cells) even in heavily pre-treated patients, but should also be capable of tumor cytoreduction. The regimen described in the current report, d-TEC, appears to fulfill these criteria. Furthermore, adverse reactions and cumulative toxicity is manageable

Table 4 Major toxicities (n = 84 cycles)

Clinical features	*Grade*				
	0	*1*	*2*	*3*	*4*
Neutrophils	0	0	0	0	84
Hemoglobin	9	26	33	16	0
Platelets	0	0	1	10	73
Stomatitis	36	29	14	4	1
Liver	59	14	7	3	1
Lungs	62	11	8	2	1
Heart	78	4	2	0	0
Kidneys	82	2	0	0	0
Peripheral neuropathy	27	57	0	0	0
Rash	74	9	1	0	0
Nausea/Emesis	51	20	8	5	0
Diarrhea	66	13	4	1	0
Skeletal pain	35	35	7	7	0

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