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An Open-Label Study of Pegylated Liposomal Doxorubicin, Vincristine, and Reduced-Dose Dexamethasone Combination Therapy in Newly Diagnosed Multiple Myeloma Patients in the Chinese Population

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OBJECTIVE Though doxorubicin is highly active in the treatment of multiple myeloma, its toxicity profile limits its therapeutic index. We performed this study to evaluate the efficacy and safety of pegylated liposomal doxorubicin (PLD, Caelyx®), vincristine, and reduced-dose dexamethasone combination therapy in newly diagnosed multiple myeloma (MM) patients in a Chinese population.
METHODS This was an open-label, single-arm study in which newly diagnosed patients with MM received PLD 40 mg/m^2 intravenously on Day 1, vincristine 1.4 mg/m^2 intravenously (maximum 2 mg) on Day 1, and 40 mg of dexamethasone (intravenously or orally) from Day 1 to Day 4. Treatment was repeated every 28 days for at least 4 cycles.
RESULTS In the intent-to-treat (ITT) analysis, the overall response rate was 68.29%, and the complete remission rate was 10.98%. The incidence of all adverse events was 46.34%. The most common non-hematologic toxicities were palmar-plantar erythrodysesthesia (13.4%) and stomatitis (6.1%).
CONCLUSION PLD, vincristine, and a reduced-dose dexamethasone combination (DVd) is an effective and safe regimen in newly diagnosed MM patients in a Chinese population.

KEY WORDS: pegylated liposomal doxorubicin, multiple myeloma, chemotherapy.

Introduction

The estimated incidence of multiple myeloma (MM) is approximately 4 per 100,000 in western countries and 0.5-0.8 per 100,000 in China. This represents 1% of all malignant diseases and approximately 10% of hematologic malignancies[1]. Patients with MM typically respond to initial chemotherapy, but most of them have disease recurrence[1-3].

Favorable results have been obtained with doxorubicin-based combination regimens[4-10], such as VAD (vincristine, doxorubicin, and dexamethasone), which has response rates of 50%-80% in newly diagnosed patients and approximately 50% in patients with disease recurrence. The progression-free survival (PFS) for newly diagnosed patients treated with VAD is 9-12 months. However, toxicity of doxorubicin often precludes adequate dosing and limits the therapeutic activity of VAD[2,3]. The conventional formulation of doxorubicin is rapidly cleared from the bloodstream and has a very large volume of distribution (V_D)[11]. This large V_D may contribute to its toxicities, including cardiotoxicity and myelosuppression. A doxorubicin formulation with improved tolerability could increase the therapeutic window and thus enhance efficacy.

Pegylated liposomal doxorubicin (PLD) is a liposomal formulation of doxorubicin sterically stabilized by the grafting of segments of polyethylene glycol (PEG) onto the liposomal surface[12-14]. Liposomal encapsulation of doxorubicin may reduce the nonspecific drug delivery to normal tissues and the high peak plasma levels of free drug that are thought to be responsible for toxicity. At the same time, a liposomal formulation may deliver doxorubicin to tumors with improved specificity[12-15]. Patients with MM have increased angiogenesis in the bone marrow, and in addition, myeloma cells are known to have a low mitotic rate. Therefore, increased exposure of MM patients to doxorubicin might improve response rates. Given the demonstrated efficacy of VAD in MM patients[4-10] and the potential of PLD to extend the duration of bone marrow exposure to therapeutic levels of doxorubicin, a combination regimen of PLD, vincristine, and dexamethasone (DVd) could provide an advantage in the treatment of MM. We performed this study to evaluate the efficacy and safety of the DVd regimen in the treatment of newly diagnosed MM patients in a Chinese population.

Patients and Methods

Study population

All patients provided written informed consent prior to enrollment. Patients were eligible if they met the following criteria: age ≥ 18; newly diagnosed multiple myeloma (Durie-Salmon stage II-III)[16,17]; Eastern Cooperative Group (ECOG) performance score of 0-2; life expectancy of 3 months or more; platelets ≥ 75,000/mm^3, neutrophil count ≥ 1.0 ×10^3/mm^3 and white blood cell count ≥ 2.5 × 10^3/mm^3 (unless cytopenias were related to MM, splenomegaly, or plasma cell leukemia); total serum bilirubin less than or equal to the institutional upper limit of normal and AST or ALT less than or equal to 2 times the institutional upper limit of normal; and able to provide written, informed consent. Patients were excluded if they were pregnant or breastfeeding; had a history of hypersensitivity to doxorubicin hydrochloride or to liposomal or pegylated drug formulations; had a history of cardiac disease (New York Heart Association Class II or greater) with congestive heart failure; or had active infections requiring intravenous antibiotics. Patients with solitary bone or extramedullary plasmacytoma or previous malignancies at other sites (with the exception of adequately treated cervical carcinoma in situ, basal or squamous cell carcinoma of the skin, or other cancer from which the patient had been disease free for 5 or more years) were also excluded. Patients could not receive any other chemotherapy during the study.

Study design

This was an open-label, single-arm study to determine the efficacy and safety of PLD as combination therapy with vincristine and reduced-dose dexamethasone (DVd) in newly diagnosed, Chinese MM patients.

Treatment consisted of 3 agents: PLD, vincristine, and dexamethasone and was repeated every 28 days for up to 4 cycles. On the first day of treatment (Day 1) PLD 40 mg/m^2 over 60 minutes via a peripheral or central line and vincristine 1.4 mg/m^2 (maximum 2.0 mg) were administered. From Day 1 to Day 4 of each cycle, dexamethasone 40 mg was given, either orally or intravenously. Response assessments were done prior to the start of each cycle and included a complete physical examination and serum β2 microglobulin, serum and urine M-protein content and a 24-hour urine light-chain protein quantitation. In addition, ECOG performance status was evaluated, and a CBC with differential and blood chemistries were obtained.

Bone marrow biopsy was re-performed after 4 cycles of therapy, or as soon as there was no peripheral evidence of disease, and was repeated every other cycle thereafter until the maximum response was achieved. All patients underwent a complete bone survey after 4 cycles of therapy or upon development of new symptoms. ECG (LVEF) was evaluated if patients received a total cumulative dose of 500 mg/m^2 pegylated liposomal doxorubicin or if it was clinically indicated. Therapy beyond 4 cycles was continued depending on the investigators' judgment of the potential benefit to the patient, and all patients were followed to disease progression.

Adverse events and concomitant treatments were recorded throughout the study. Intensity of adverse events was graded using the National Cancer Institute Common Toxicity Criteria (NCI-CTC) Version 3.0. In the event of grade III/IV non-hematologic toxicities, DVd was discontinued until the toxicity resolved. If a grade II non-hematologic adverse event was observed, the dose of PLD was reduced to 75%.

Statistical analysis

The primary efficacy variable was response rate, including complete remission, major response, and minor response. The secondary efficacy variable was progression-free survival (PFS). PFS/time to progression was defined as the time from the date on-study to the first date of documented disease progression or recurrence. Patients not known to have disease progression/recurrence were censored at their last clinical evaluation. The overall clinical response rate along with the two-sided 95% confidence interval was used. PFS was calculated using the Kaplan-Meier method.

Disease response was assessed as reported by Kyle et al.[18] and Alexanian et al.[19] Complete remission (CR) was defined as the complete disappearance of myeloma protein from the serum and urine, a bone marrow biopsy demonstrating less than 3% plasma cells, the absence of monoclonal plasma cells on 2 occasions 4 weeks apart, and no evidence of progressive disease by any other parameters. Partial response was defined as a greater than or equal to 50% decrease of myeloma protein from the serum and urine. Minimal response was defined as a decrease in bone pain, an improvement of performance status by one grade, and a reduction in serum myeloma protein of greater than or equal to 25%. Stable disease was defined as a less than 25% decrease in M-protein, and if any of the criteria for response or progression were not met.

Disease progression was defined as a greater than 50% increase in serum or urine myeloma protein above the lowest remission level, a greater than 50% increase in soft tissue plasmacytoma, the appearance of new lytic bone lesions or an increase of greater than 50% in the size of existing lesions, or unequivocal new bone lysis requiring palliative radiation. Disease was also considered to have progressed if there was a 25% to less than 50% increase in myeloma protein, a calcium level greater than 12 mg/dL, or a decrease of 2 g/dL in hemoglobin level (due to progressive bone marrow replacement with plasma cells, not to bleeding or chemotherapy-induced bone marrow suppression).

The safety analyses were based on the safety population, which included all enrolled patients who received at least one dose of study medication. The efficacy analyses were based on the intent-to-treat (ITT) population, which included all safety patients who provided at least one post-baseline assessment. All the patients were followed after the treatment.

Results

Patients

Eighty-two patients at 15 centers were enrolled in this study from January 2006 through February 2007. Ten patients (12.2%) received 1 cycle of treatment; 9 patients (11.0%) received 2 cycles of treatment; 10 patients (12.2%) received 3 cycles of treatment; and 53 patients (64.6%) completed 4 scheduled cycles of treatment. In total, 52 patients completed all 4 cycles of the treatment and were evaluable for efficacy.

The ITT population consisted of 82 patients: 64% were male, the median age was 58 years, and the mean body weight was 61.86 kg (Table 1). Baseline echocardiography assessment was normal in 62% of patients, and most presented with normal neutrophil and platelet counts, 62% and 66%, respectively. As expected, the majority of patients (90%) presented with anemia.

Thirty-five patients (42.68%) received concurrent medications. Fifteen patients (18%) received bisphosphonates for the treatment of bone pain and hypercalcemia. Six patients (7.32%) received vitamin B_6 for management of palmar-plantar erythrodysesthesias (PPE).

Primary efficacy variables

In the ITT analysis, the overall response rate, defined as complete + major + minor response, was 68.29% (95% CI: 58%-78%). The rate of complete remission was 10.98%, partial response was 40.24%, and minimal

response was 17.07%. Stable disease and progressive disease was observed in 14.63% (12/82) and 12.20% (10/82) of patients, respectively.

In the age-adjusted efficacy evaluation, there was no statistically significant difference between the age groups in the ITT analysis. The response rates of younger patients (< 60 years) and elderly patients (≥ 60 years) were 68.09% and 68.57% (P = 0.965), respectively (Table 2). In an ISS-adjusted efficacy evaluation[20,21], there was no significant difference in the response rate between different stages of disease (P = 0.2063). The response rate of the patients in stage I, II, and III disease in the ITT analysis was 63.64% (95% CI: 35.21%-92.06%), 63.89% (95% CI: 48.20%-79.58%) and 70.37% (95% CI: 53.15%-87.59%), respectively. There was no significant difference between subtypes of MM (P = 0.2996).

Secondary efficacy variables

The cumulative 4-month progression free survival was 88.37% in the ITT analysis (Fig.1).

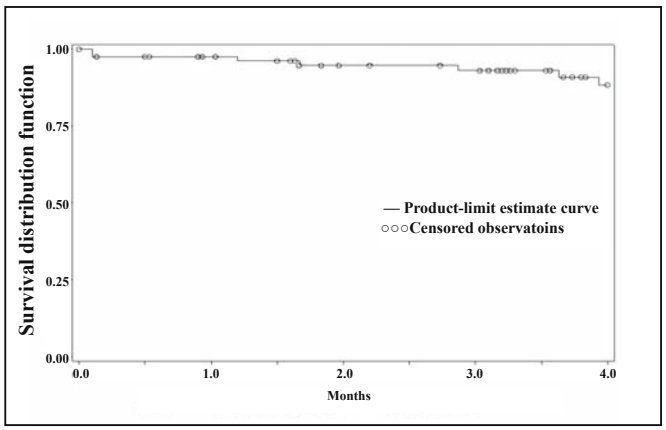

Fig.1. Cumulative progression-free survival (ITT population).

Safety assessment

Adverse events

The overall incidence of reported adverse events was 46.34%, with 39.02% related to DVd. The most common drug-related adverse events were PPE (13.41%) and stomatitis (6.10%).The most commonly reported adverse events are shown in Table 3. Eight patients experienced serious adverse events, and 3 patients died. A 66-year-old male died from heart failure; a 69-year-old male presented with change of awareness and death due to leukoaraiosis; and a 56-year-old female died from an intracranial hemorrhage. None of the deaths were considered treatment-related by the investigators.

The major impact of DVd on laboratory findings was hematologic events, including neutropenia and thrombocytopenia. Grade 1 and 2 neutropenia was experienced by 26.92% and 19.23% of patients, respectively, with 33.3% and 1.28% reporting grade 1 and 2 thrombocytopenia, respectively. The incidence of grade 3-4 neutropenia and thrombocytopenia was low, 8.97% and 1.28%, respectively (Table 4).

Dose modification

Ten patients (12.2%) had their dose modified during treatment. Five patients received a reduced dose of dexamethasone, and 2 patients received a reduced dose of vincristine. In 3 patients (3.7%), the dose of PLD was adjusted. The first patient had PLD reduced from 40 mg/m^2 to 26.7 mg/m^2 in the second cycle of treatment, and 33.3 mg/m^2 and 36.7 mg/m^2 in the third and fourth cycles, respectively. Two patients had the dose modified from the pre-planned dose of 40 mg/m^2 to 26.7 mg^2 in the fourth cycle. PLD had an acceptable toxicity profile and was tolerated well overall.

Table 1. Baseline demographics of the ITT population.

Variables	No. of Patients (%)
Age (years)	
< 60	47 (57.32)
≥ 60	35 (42.68)
Gender	
Male	53 (64.63)
Female	29 (35.37)
ECOG score	
0	17 (20.73)
1	48 (58.54)
2	16 (19.51)
3	1 (1.22)
Serum β2-MG	
Normal	10 (13.51)
Elevated	64 (86.49)
Clinical stage (D-Stage)	
IA	1 (1.22)
IIA	10 (12.21)
IIB	2 (2.40)
IIIA	51 (62.20)
IIIB	16 (19.52)
Plasma cell leukemia	2 (2.45)
Subtypes of MM	
IgG	33 (40.24)
IgA	20 (24.39)
IgD	6 (7.32)
Light chain	17 (20.73)
Plasma cell leukemia	2 (2.44)
Non-secreted	1 (1.22)
Non-classified	3 (3.66)

Table 2. Efficacy evaluation stratified by age (ITT).

Efficacy evaluation	< 60 years (%)	≥ 60 years (%)	*P*
n	47	35	0.9653
Complete remission	5 (10.64)	4 (11.43)	
Major response	18 (38.30)	15 (42.86)	
Minor response	9 (19.15)	5 (14.29)	
Stable disease	6 (12.77)	6 (17.14)	
Progressive disease	6 (12.77)	4 (11.43)	
Not evaluated	3 (6.38)	1 (2.86)	
Response rate (complete + major + minor) 95% confidence interval (CI)	32 (68.09) 54.76%-81.41%	24 (68.57) 953.19%-83.95%	

Table 3. Incidences of the adverse events of the investigational drug.

	Total patients (*n*)	No. of patients (*n*)	Incidence (%)
All adverse events	82	38	46.34
Palmar-plantar erythrodysesthesia	82	11	13.41
Pulmonary infection	82	8	9.76
Stomatitis	82	5	6.10
Fever	82	4	4.88
Septicemia	82	3	3.66
Nausea	82	3	3.66
Hypertension	82	4	4.88
Anemia	82	3	3.66

Table 4. Hematological toxicities of the investigational drug.

	Grade	After the end of 1st cycle (%)	After the end of 2nd cycle (%)	After the end of 3rd cycle (%)	After the end of 4th cycle (%)	Total (%)
Neutropenia	I	8 (10.67)	11 (16.67)	11 (20.37)	11 (22.00)	21 (26.92)
	II	12 (16.00)	9 (13.64)	3 (5.56)	2 (4.00)	15 (19.23)
	III	0 (0.00)	1 (1.52)	3 (5.56)	3 (6.00)	6 (7.69)
	IV	0 (0.00)	1 (1.52)	0 (0.00)	0 (0.00)	1 (1.28)
Thrombocytopenia	I	17 (21.79)	0 (0.00)	10 (16.95)	10 (19.61)	26 (33.33)
	II	1 (1.28)	0 (0.00)	0 (0.00)	0 (0.00)	1 (1.28)
	III	1 (1.28)	0 (0.00)	0 (0.00)	0 (0.00)	1 (1.28)
	IV	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)

Discussion

MM is an incurable disease with recurrent relapses and multi-drug resistance, which is observed in the later stages of the disease. MM is associated with a median overall survival of 2-3 years[1,2,18,19]. VAD or melphalan plus prednisone are 2 of the standard first-line treatments for MM,[1,18,19] and they are associated with response rates of 50%-70% and very few complete remissions. Toxicity, especially cardiotoxicity and myelosuppression, is an important consideration, given the older median age of MM patients. New formulations of doxorubicin have been developed in an attempt to maintain the antitumor activity of doxorubicin and to reduce its toxicity[22-25]. PLD is a doxorubicin formulation in which the drug is encapsulated in liposomes (STEALTH® liposomes) that can avoid uptake by the reticuloendothelial system. As a result, the formulation has a long circulation time, and the liposomes can eventually become extravasated through the abnormally permeable vessels characteristic of many tumors[12-14]. Once concentrated in tumors, the liposomes of PLD can deliver high levels of doxorubicin to destroy malignant cells without affecting normal tissue. The circulation half-life in humans

is about 40 h, approximately a 100-fold prolongation when compared to standard doxorubicin[12-14]. Moreover, following PLD administration, the time to absolute neutrophil count (ANC) nadir is also extended relative to standard doxorubicin (approximately 21 days for PLD *vs.* 10-14 days for doxorubicin). Prolonged residence in the circulation permits greater uptake of the PLD by the tumor[12-14]. Clinically, PLD has less cardiotoxicity than conventional doxorubicin and results in less nausea and vomiting, alopecia, and less severe granulocytopenia[26]. This represents a more favorable toxicity profile that could be especially beneficial in an elderly population.

PLD in combination with vincristine and reduced-dose dexamethasone was reported effective and safe in newly-diagnosed MM in previous studies. In a phase II trial, Hussein et al.[22,23] reported a response rate of 88% in newly-diagnosed MM patients receiving PLD, vincristine, and reduced-dose dexamethasone (DVd). In patients who responded to the regimen, 12% achieved complete remission; 55% achieved partial remission; and 21% achieved minimal response. Rifkin et al.[24] reported the results of a phase III randomized trial, comparing DVd combination therapy with conventional VAD. The overall response rate was 44% in the DVd group compared with 41% in the VAD group. In addition, 3 patients (1.5%) in the DVd arm achieved a CR, compared with no patients receiving VAD. The safety and efficacy of DVd may be different in a Chinese population because of possible metabolic differences. This study was performed to evaluate DVd in newly diagnosed Chinese MM patients.

The overall response rate for DVd was 68.29% in our study in a Chinese population. Complete remission, partial remission, and minimal response rates were 10.98%, 40.24%, and 17.07%, respectively, which is consistent with previous reports[22-24] of this combination and equivalent to or better than the reported efficacy of VAD[4-10]. Only 53 patients received the pre-planned 4 cycles of treatment, and 10 patients received only 1 cycle of the regimen. The per-protocol (PP) analysis (not shown) indicated that the overall response rate was 80.77%, and the complete remission rate could be as high as 15.38%. The subgroup analysis classified by age, ISS stage, and subtypes of multiple myeloma did not show any statistical significance. A relatively small sample of enrolled patients and short follow-up may have affected the results. The cumulative 4-month PFS is 88.37%. This result needs to be confirmed with a longer follow-up.

In other reported trials, the incidence of grade 3/4 hematologic toxicities was much lower in the DVd group than in the VAD group. Hussein et al.[22,23] reported that 10% of patients in the DVd group experienced grade III/IV neutropenia compared with 24% in the VAD group. Furthermore, the incidence of related septicemia and antibiotics usage was much lower in the DVd group. The most frequent adverse effect of the DVd regimen was PPE, accounting for 25% of all adverse events. Most of the reported PPE events were grade I and II. These results are quite similar to those of the phase III study conducted by Rifkin[24], in which the most frequent grade 3 or 4 adverse events were peripheral neuritis (22%), PPE (8%), neutropenia (14%), and thrombocytopenia (5%). In the same trial, (24) cardiac toxicities were also compared between 2 different regimens. Two patients developed grade 3 and 4 congestive heart failure in the VAD group compared to no patients on the DVd arm. In our study, the incidence of all adverse events was 46.34%, with 39% thought to be treatment-related. The most common non-hematologic toxicities were PPE (13.41%) and stomatitis (6.10%). The reported hematologic toxicities were mostly grade 1 and 2, with 8.97% and 1.28% grade 3/4 neutropenia and thrombocytopenia, respectively. Only 3 patients developed abnormal echocardiography during the treatment.

The combination of PLD, vincristine, and reduced-dose dexamethasone (DVd) is an effective and safe regimen in newly diagnosed MM patients in a Chinese population. The efficacy of the DVd regimen is equivalent to traditional VAD, with reduced toxicities, especially cardiac and grade 3 or 4 hematologic adverse events. A randomized study in a Chinese population is needed to confirm these results.

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References

1 Munshi NC, Tricot G, Barlogie B. Plasma cell neoplasms. In: DeVita VT Jr, Hellman S, Rosenberg SA, eds. Cancer: Principles & Practice of Oncology; Vol 2. 6th ed. Philadelphia, Pa: Lippincott Williams & Wilkins; 2005.
2 Terpos E, Rahemtulla A, Dimopoulus MA. Current treatment options for myeloma. Expert Opin Pharmacother 2005; 6: 1127-1142.
3 Hussein MA. Thalidomide: present and future in multiple myeloma. Expert Rev Anticancer Ther 2005; 5: 25-31.
4 Samson D, Gaminara E, Newland A, et al. Infusion of vincristine and doxorubicin with oral dexamethasone as first-line therapy for multiple myeloma. Lancet 1989; 14: 882-885.
5 Alexanian R, Barlogie B, Tucker S. VAD-based regimens as primary treatment for multiple myeloma. Am J Hematol 1990; 33: 86-89.
6 Dimopoulos MA, Kastritis E. Is there still place for VAD as primary treatment for patients with multiple myeloma who are candidates for high-dose therapy? Leuk Lymphoma 2006; 47: 2271-2272.
7 Wu P, Davies FE, Horton C, et al. The combination of cyclophosphomide, thalidomide and dexamethasone is an effective alternative to cyclophosphamide-vincristine-doxorubicin- methylprednisolone as induction chemotherapy prior to autologous transplantation for multiple myeloma: a case-matched analysis. Leuk

Lymphoma 2006; 47: 2335–2338.
8 Jimenez-Zepeda VH, Dominguez-Martinez VJ. Vincristine, doxorubicin, and dexamethasone or thalidomide plus dexamethasone for newly diagnosed patients with multiple myeloma? Eur J Haematol 2006; 77: 239–244.
9 Alexnanian R, Dimopoulos M. Management of multiple myeloma. Semin Hematol 1995; 32: 20.
10 Lane SW, Gill D, Mollee PN, et al. Role of VAD in the initial treatment of multiple myeloma. Blood 2005; 106: 3674.
11 Doxorubicin package insert. Ben Venue Laboratories, Bedford, OH. October 2006.
12 Drummond DC, Meyer O, Hong K, Kirpotin DB, et al. Optimizing liposomes for delivery of chemotherapeutic agents to solid tumors. Pharmacol Rev 1999; 51: 691–743.
13 Gabizon A, Catane R, Uziely B, et al. Prolonged circulation time and enhanced accumulation in malignant exudates of doxorubicin encapsulated in polyethylene-glycol coated liposomes. Cancer Res 1994; 54: 987–992.
14 Vail DM, Amantea MA, Colbern GT, et al, Hilger RA, Working PK. Pegylated liposomal doxorubicin: proof of principle using preclinical animal models and pharmacokinetic studies. Semin Oncol 2004; 31 (6 Suppl 13): 16–35.
15 Garcia-Sanz R, Hernandez JM, Sureda A, et al. Pegylated liposomal doxorubicin, melphalan and prednisone therapy for elderly patients with multiple myeloma. Hematol Oncol 2006; 24: 205–211.
16 Durie BG, Salmon SE. A clinical staging system for multiple myeloma. Cancer 1975; 36: 832.
17 Durie BG, Jacobson J, Barlogie B, et al. Magnitude of response with myeloma frontline therapy does not predict outcome: importance of time to progression in southwest oncology group chemotherapy trials. J Clin Oncol 2004; 22: 1857–1863.
18 Kyle RA, Rajkumar SV. Multiple myeloma. N Engl J Med 2004; 351: 1860–1873.
19 Alexanian R, Bonnet J, Gehan E, et al. Combination chemotherapy for multiple myeloma. Cancer 1972; 30: 382–389.
20 Kim H, Sohn HJ, Kim S, et al. New staging systems can predict prognosis of multiple myeloma patients undergoing autologous peripheral blood stem cell transplantation as first-line therapy. Biol Blood Marrow Transplant 2006; 12: 837–844.
21 Kyle RA. Diagnostic criteria of multiple myeloma. Hematol Oncol Clin North Am 1992; 6: 347.
22 Hussein MA, Baz R, Srkalovic G, et al. Phase 2 study of pegylated liposomal doxorubicin, vincristine, decreased-frequency dexamethasone, and thalidomide in newly diagnosed and relapsed-refractory multiple myeloma. Mayo Clin Proc 2006; 81: 889–895.
23 Hussein MA, Wood L, Hsi E, et al. A phase II trial of pegylated liposomal doxorubicin, vincristine, and reduced-dose dexamethasone combination therapy in newly diagnosed multiple myeloma patients. Cancer 2002; 95: 2160–2168.
24 Rifkin RM, Gregory SA, Mohrbacher A, et al. Pegylated liposomal doxorubicin, vincristine, and dexamethasone provide significant reduction in toxicity compared with doxorubicin, vincristine, and dexamethasone in patients with newly diagnosed multiple myeloma. Cancer 2006; 106: 848–858.
25 Honemann D, Prince HM, Seymour JF, et al. A phase II study of liposomal doxorubicin, vincristine and dexamethasone in multiple myeloma. Leuk Lymphoma 2005; 46: 945–947.
26 O'Brien ME, Wigler N, Inbar M, et al. Reduced cardiotoxicity and comparable efficacy in a phase III trial of pegylated liposomal doxorubicin HCl (Caelyxtm/DoxilR) versus conventional doxorubicin for first-line treatment of metastatic breast cancer. Ann Oncol 2004; 15: 440–449.