Primary treatment of multiple myeloma with thalidomide, vincristine, liposomal doxorubicin and dexamethasone (T-VAD doxil): a phase II multicenter study

On behalf of the Greek Myeloma Study Group

Greek Myeloma Study Group, Athens, Greece

Received 9 June 2003; revised 9 September 2003; accepted 17 September 2003

Background: High-dose chemotherapy with autologous stem cell transplantation after initial cytoreductive chemotherapy with the combination vincristine, doxorubicin and dexamethasone (VAD) is considered an effective therapy for many patients with newly diagnosed, symptomatic multiple myeloma. Response to initial cytoreductive chemotherapy is important for the long-term outcome of such patients. Thalidomide has recently shown significant antimyeloma activity. We studied the efficacy and toxicity of the combination of a liposomal doxorubicin-containing VAD regimen with thalidomide, administered on an outpatient basis, as initial cytoreductive treatment in previously untreated patients with symptomatic myeloma.

Patients and methods: Thirty-nine myeloma patients were treated with vincristine 2 mg intravenously (i.v.), liposomal doxorubicin 40 mg/m² i.v. administered as single dose on day 1, and dexamethasone 40 mg per os daily for 4 days. Dexamethasone was also given on days 15–18 of the first cycle of treatment. The regimen was administered every 4 weeks for four courses. Thalidomide was given daily at a dose of 200 mg at bedtime. Response to treatment was evaluated after four cycles of treatment. After completion of four cycles, the patients were allowed to proceed to high-dose chemotherapy or to receive two additional cycles of the same treatment.

Results: On an intention-to-treat basis, 29 of the 39 patients (74%) responded to treatment. Four patients (10%) achieved complete and 25 (64%) partial response. Three patients (8%) showed minor response and seven (18%) were rated as non-responders. Major grade 3 or 4 toxicities consisted of neutropenia (15%), thrombocytopenia (15%), deep vein thrombosis (10%), constipation (10%), skin rash (5%) and peripheral neuropathy (5%). Two patients (5%) experienced early death due to infection.

Conclusions: The combination of vincristine, liposomal doxorubicin, and dexamethasone (VAD doxil) with thalidomide is an effective and relatively well-tolerated initial cytoreductive treatment. Prospective randomized studies are required in order to assess the effect of this regimen on the long-term outcome of patients with multiple myeloma.

Key words: liposomal doxorubicin, multiple myeloma, thalidomide

Introduction

In multiple myeloma (MM) patients the 4-day continuous infusion of vincristine, doxorubicin and dexamethasone (VAD) is considered an effective initial treatment, especially if consolidation with high-dose chemotherapy and autologous stem cell rescue is planned. The VAD regimen induces early reduction of tumor burden and is less toxic to bone marrow stem cells than regimens that contain alkylating agents. The response rate after VAD ranges from 55 to 75% [1–3]. Increased cardiac toxicity and neurotoxicity due to doxorubicin and vincristine, respectively, may be limiting factors. In addition, the administration of VAD is cumbersome, requiring central venous access for continuous infusion chemotherapy. Recent studies have shown that the administration of VAD on an outpatient basis using 4 days of rapid intravenous (i.v.) infusion (VAD bolus) or the substitution of pegylated liposomal doxorubicin for doxorubicin in the VAD regimen (VAD doxil) are equally active to standard infusional VAD [4–6]. Liposomal doxorubicin has a prolonged half-life compared to standard doxorubicin, thus allowing increased exposure of the myeloma cells to the former agent [7]. Furthermore, in myeloma patients there is increased angiogenic activity in the bone marrow [8]. This may allow for higher concentration of the pegylated form where the tumor is concentrated.

Conventional chemotherapy followed by high-dose therapy and autologous stem cell transplantation is associated with improved
survival compared to conventional chemotherapy alone [9, 10]. Furthermore, response to initial cytoreductive treatment has significant impact on the results of subsequent high-dose chemotherapy [11]. Thus, rapid and profound reduction of myeloma load may be advantageous for newly diagnosed patients who require treatment. Singhal et al. first reported that thalidomide induced objective responses in one-third of patients with refractory myeloma, most of whom had also received one or two high-dose therapies [12]. Thalidomide has multiple mechanisms of antilymphoma activity which may differ from those of conventional chemotherapy and of corticosteroids [13]. Furthermore, single-agent thalidomide is active in at least one-third of patients with newly diagnosed myeloma [14]. Thus, we designed a multicenter phase II study in order to assess the efficacy and tolerability of the combination of VAD doxil, with thalidomide as an outpatient treatment for newly diagnosed patients with multiple myeloma who require therapy. The major benefits for the patients using the VAD doxil regimen could be the avoidance of a central venous line and the reduction of days of hospitalization or outpatient visits.

**Patients and methods**

**Eligibility**

Newly diagnosed patients with symptomatic myeloma and age ≤75 years were included in the study. Eligible patients were required to have Eastern Cooperative Oncology Group (ECOG) performance status ≤3, life expectancy >3 months, left ventricular ejection fraction (LVEF) ≥50% and adequate liver function. Patients with renal failure not requiring hemodialysis were also eligible. All patients provided informed consent according to institutional guidelines.

**Study design**

This was a prospective multicenter phase II study with primary end point objective response rate (i.e. complete plus partial response) of the combination of VAD doxil with thalidomide (T-VAD doxil). Based on previous reports on the activity of VAD doxil and of thalidomide in previously untreated patients with multiple myeloma, we considered that an objective response rate of 70% ± 15% with a 95% confidence interval would be acceptable. Thus, 37 patients were required. All patients were scheduled to receive four courses of T-VAD doxil before final assessment of response. Subsequently, patients <70 years with responding disease were allowed to proceed to blood stem cell mobilization with intermediate dose cyclophosphamide (4 g/m² i.v.) followed by high-dose melphalan (200 mg/m² i.v.) and autologous stem cell rescue, or to receive two additional cycles of T-VAD doxil with or without subsequent maintenance. The decision of high-dose therapy was left to the patient and his primary physician. Complete clinical and laboratory evaluation was performed in all patients before treatment, including X-ray skeletal survey, serum protein electrophoresis and 24-h urine protein quantitation and electrophoresis, immunofixation, determination of serum immunoglobulins, β₂ microglobulin (β₂M) and C-reactive protein (CRP), LVEF, as well as bone marrow aspiration and biopsy. Baseline assessments, except X-ray skeletal survey, were repeated before each cycle of treatment. Bone marrow aspiration, biopsy and X-ray skeletal survey were repeated 4 weeks after administration of the fourth cycle of treatment. The monoclonal immunoglobulin response was assessed before each cycle of treatment for determination of time to response. Toxicity was also evaluated before each cycle of treatment. The National Cancer Institute common toxicity criteria (version 2) were used to grade adverse effects.

Patients who discontinued treatment at any time because of death, toxicity or patient’s refusal to continue were rated as non-responders. The event-free survival was estimated from the date of diagnosis to the date of disease progression or death from any cause. Overall survival was defined from the date of diagnosis to the date of death from any cause.

**Treatment and response criteria**

The VAD doxil regimen consisted of vincristine 2 mg in 100 ml NaCl0.9% on day 1, liposomal doxorubicin 40 mg/m² in 500 ml DSW i.v. over 1 h on day 1 and dexamethasone 40 mg per os daily for 4 days. Dexamethasone was also given in the first cycle of treatment on days 15–18. Thalidomide was given daily at bedtime and at a dose of 200 mg continuously. The regimen was administered every 4 weeks for four cycles and subsequently patients underwent final assessment.

The response criteria used in this study were complete response (CR): disappearance of serum and/or urine monoclonal component (MC) in immunofixation, bone marrow plasma cells ≤5% with no evidence of clonality with immunohistochemistry; partial response (PR): ≥50% decrease of serum MC levels and/or ≥25% decrease of Bence Jones proteinuria, ≥50% decrease in transverse diameter of existing plasmacytomas; minor response (MR): ≤50% but ≥25% decrease of serum MC, improvement of performance status by one grade; stable disease (SD): no fulfilling criteria for CR, PR or PD; progressive disease (PD): ≥50% increase in serum and/or urine MC above the response level, ≥50% increase in transverse diameter of soft tissue plasmacytomas, progression of lytic bone lesions. Also, increase ≥25% but ≤50% of MC in conjunction of hypercalcemia (Ca >11mg/dl) or disease-related hemoglobin decrease of 2 g/dl was considered as PD. Criteria for CR and PR must persist in two evaluations 4 weeks apart.

**Results**

**Patient characteristics**

Since March 2001, 39 previously untreated patients (20 males and 19 females), with a median age of 68 years (range 43–75 years) were entered into the study. Patient characteristics are listed in Table 1. Eight of 39 patients had stage IIIb disease, 16 had serum β₂ microglobulin >4 mg/l, 14 had serum C-reactive protein >6 mg/l and 12 patients had serum albumin <3 g/dl.

**Response to therapy**

Overall, 29 of the 39 patients (74%) achieved a significant response. Four patients (10%) achieved CR and 25 (64%) PR. Three patients (8%) showed MR. Inclusion of these minor responses increases the overall response rate to 82%. The time to response was short and at least 50% reduction of monoclonal protein was noted within 2 months of treatment in 80% of responding patients. In all these patients the monoclonal protein response was confirmed by bone marrow examination after four cycles of treatment. Seven patients (18%) were characterized as non-responders. Six of them experienced early death during the first 3 months of treatment, due to disease progression (four patients) or neutropenic infection (two patients). Of the 32 patients who showed response after four cycles of treatment, 15 (47%) proceeded to blood stem cell collection and subsequent high-dose melphalan. The median number of apheresis was two (range one to three). The median number of CD34+ cells that were collected was 4 × 10⁶ cells/kg (range 2.5–8.5 × 10⁶ cells/kg). The remaining 17 patients
completed six cycles of treatment. Eleven of these patients (65%) continued with maintenance treatment with dexamethasone (40 mg per os 4 days every month) and six (35%) received no further treatment. Median follow-up was 10 months (range 2–22 months).

During follow-up two patients, with initial partial response, progressed 15 and 19 months from diagnosis. Of the 39 patients, eight died (20.5%). Two responders died; one after disease progression and the other during autologous stem cell transplantation because of aspergillosis. Event-free survival and overall survival at 22 months were 55% and 74%, respectively (Figure 1).

Toxicity

The most common toxicities recorded during the four cycles of treatment are shown in Table 2. Treatment was generally well tolerated and no patient discontinued therapy because of toxicity. Five patients developed neutropenic infections; in two patients these were associated with pneumonia and in three patients no focus of infection or positive culture was found. Two patients died within the first 2 months of treatment of infectious complications. Most patients experienced mild somnolence, constipation, dizziness and tremor. Grade 1 or 2 peripheral neuropathy was noted in 46% of patients, whereas one patient developed grade 3 neuropathic pain. Palmar–plantar erythrodysesthesia, grade 2, was observed in four patients (10%). Four patients (10%) developed uncomplicated deep vein thrombosis (DVT) requiring anticoagulant therapy. Severe, grade 3, hematological toxicity was observed in six patients (15%).

Discussion

To the best of our knowledge we report the first completed study which combined thalidomide with a VAD-like regimen for the primary treatment of patients with multiple myeloma. The anti-myeloma activity of thalidomide was first reported by Singhal et al. and subsequently several independent studies confirmed the activity of this agent in relapsed and refractory myeloma [12, 13, 15–18]. It appears that thalidomide has multiple mechanisms of action including inhibition of angiogenesis, downregulation of tumor necrosis factor, inhibition of myeloma cell adhesion to the
bone marrow stroma, and stimulation of natural killer cells and T-lymphocytes [19]. The combination of thalidomide with dexamethasone showed synergism in vitro [20] and demonstrated activity in at least 50% of patients with refractory multiple myeloma [21, 22]. Moreover, two recent studies assessed the efficacy of this combination in previously untreated patients and reported objective responses in 64% and 72% of patients, respectively, but patients with high tumor mass were excluded from the latter study [23, 24]. We have recently reported a prospective randomized trial for previously untreated patients with multiple myeloma and we observed that VAD doxil was active in 61% of patients. In our current study we added thalidomide to this regimen and we documented an objective response in 74% of patients, including complete responses in 10% of patients. These data appear encouraging since our study was conducted in several hospitals and since the median age of our patients was 68 years. The median time to response was rapid, consistent with previous experience with VAD-like regimens [2, 6]. Monoclonal protein response was associated with clearing of bone marrow plasmacytosis in all patients. Approximately one-half of the responding patients underwent blood stem cell collection in order to support the administration of high-dose i.v. melphalan. Despite the small number of patients there was no evidence that prior treatment with T-VAD doxil affected the collection of blood stem cells. A preliminary analysis from Cleveland Clinic indicated that the administration of T-VAD doxil to previously untreated patients induced objective responses in 88% of patients including complete responses in 24% [25]. Thalidomide was started at 50 mg/day and increased by 50 mg/day each week to a maximum tolerated dose up to 400 mg/day. This study was performed in a single institution and the median age of its patients was 7 years younger than that of our patients [25]. We used an intermediate dose of thalidomide at 200 mg per os daily despite the fact that we were aware that some studies have indicated that the cumulative 3-month dose of single-agent thalidomide in resistant patients is a prognostic factor for response [15, 17]. However, such a dose–response effect has not been reported when thalidomide is combined with dexamethasone or with chemotherapy. Furthermore, in our phase II study we were concerned about the possibility of increased neurotoxicity with the combination of high-dose thalidomide and vincristine. However, it is possible that a higher dose of thalidomide might have increased the response rate of our T-VAD regimen.

The combination of thalidomide and VAD doxil was relatively well tolerated. Two patients died due to infectious complications and five developed neutropenic infections necessitating hospitalization and i.v. antibiotics. Primary treatment with thalidomide and dexamethasone has also induced treatment-related deaths in 5% and in 6% of patients, respectively [23, 24]. A recent report with a regimen similar to our T-VAD doxil regimen indicated that with prophylactic amoxycillin 250 mg twice daily, acyclovir 400 mg twice daily and granulocyte colony-stimulating factor for white blood cell counts <5000/ml, there was reduction of infectious episodes [25]. Side-effects due to thalidomide, such as constipation, somnolence, tremor edema and skin rash, occurred in several of our patients. The incidence of palmar–plantar erythrodysesthesia associated with liposomal doxorubicin was relatively low, probably due to the concomitant administration of dexamethasone. Nevertheless, grade 3 and 4 skin toxicity, neuropathy and constipation were rarely seen in this study, probably as a result of the short duration of treatment, for most of the patients, and because of the lower dose of thalidomide used in our study. There are data showing that the combination of thalidomide with doxorubicin-containing chemotherapy is associated with an increased risk of DVT, especially in newly diagnosed patients [26, 27]. Recent in vitro data suggest that thalidomide may be procoagulant through stimulation of thrombin receptors of doxorubicin-injured endothelium [28]. Higher incidence of DVT was also reported when the combination of thalidomide and dexamethasone was administered to previously untreated patients [23, 24]. In our study, 10% of the patients developed DVT which is similar to that reported with combination of thalidomide and dexamethasone. Compared to the incidence reported with the combination of thalidomide and doxorubicin-containing chemotherapy, the incidence of DVT in our study appeared lower. This difference could be attributed to the low dose of thalidomide and/or to the liposomal formulation of doxorubicin that we used. Nevertheless, the number of patients in our study is too small to draw any definitive conclusions regarding the incidence of DVT. This complication remains an important issue when thalidomide is combined with chemotherapy in previously untreated patients. The optimal prophylaxis for DVT after thalidomide has not been clearly established [13]. The benefits of anticoagulant therapy should be balanced against the risks. Until then we advocate prophylactic treatment either with low molecular weight heparin or with coumadin for newly diagnosed patients treated with T-VAD doxil.

From our study, no conclusions can be drawn regarding time to progression and overall survival, since we treated a mixture of younger patients who could undergo autologous stem cell transplantation (ASCT) after induction treatment with T-VAD doxil and of older patients who continued the same treatment. The interest of T-VAD doxil is different in the two populations. In younger patients the main interest is to obtain a more profound tumor burden reduction prior to ASCT without reducing the hematopoietic quality of the graft. In older patients the main goals are to increase response rate and time to progression. We conclude that the combination of thalidomide with VAD doxil may represent an effective cytoreductive regimen for previously untreated patients with multiple myeloma. In order to fully assess the impact of thalidomide on the activity of VAD doxil we are currently conducting a prospective randomized trial, which compares VAD doxil with or without thalidomide.

Acknowledgements
We are grateful to Asimina Petropoulou for editing and typing the manuscript.

References


