Modifications to Therapy for Multiple Myeloma: Pegylated Liposomal Doxorubicin in Combination With Vincristine, Reduced-Dose Dexamethasone, and Thalidomide

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ABSTRACT

The combination of vincristine, doxorubicin, and dexamethasone is an effective treatment for multiple myeloma that produces a more rapid response than other regimens, probably a function of the high-dose, intense steroid schedule. However, vincristine/doxorubicin/dexamethasone administration requires a 96-hour continuous infusion delivered via a central venous catheter, which necessitates hospitalization in a large number of patients and may increase the risk for infection. Moreover, the high dosages of corticosteroids required with this regimen can cause substantial toxicity. Therefore, a number of modifications to the regimen have been evaluated in an effort to improve its tolerability and efficacy. These include replacing doxorubicin with pegylated liposomal doxorubicin and using a reduced frequency of dexamethasone, and, later, the addition of thalidomide. The results of an ongoing study demonstrated that this latest regimen (including thalidomide) is associated with an improved response rate and a higher quality of response compared with previous regimens in patients with relapsed/refractory multiple myeloma. This modified regimen is well tolerated when prophylactic and supportive measures are incorporated. Although additional follow-up is required to determine the effect on survival, this modified regimen has significant potential in the management of advanced myeloma. The Oncologist 2003;8(suppl 3):39-45

INTRODUCTION

A number of effective chemotherapy agents and regimens are available for the treatment of multiple myeloma [1]. Some of the more frequently used chemotherapy agents include vincristine (V), cyclophosphamide (C), carmustine (BCNU [B]), melphalan (M), doxorubicin (A), dexamethasone (D), and...
orubicin/vincristine/reduced-dose dexamethasone (DVd), the success of the original regimen, pegylated liposomal doxorubicin, permitting a shorter treatment time, longer exposure to VAD, increasing quality of response. Modifications include the substitution of pegylated liposomal doxorubicin (Doxil®; marketed and distributed in the U.S. by Ortho Biotech Products, L.P.; Bridgewater, NJ) for conventional doxorubicin. Pegylated liposomal doxorubicin is associated with rapid responses, the responses are not durable. The addition of other chemotherapeutic agents is generally required to produce a durable response. In a study by Facon et al., single-agent dexamethasone produced response rates similar to those of melphalan or interferon monotherapy; however, patients treated with dexamethasone had a significantly shorter duration of response than patients given the other treatment regimens. Despite its demonstrated efficacy, VAD has a number of disadvantages that limit its use. The regimen requires vincristine and doxorubicin to be administered as a continuous infusion for 96 hours each cycle [1, 2], necessitating the insertion of a central venous catheter and hospitalization of the patient in the majority of cases. The VAD regimen is associated with cardiotoxicity related to the doxorubicin therapy [6]. The first- and second-phase half-lives of pegylated liposomal doxorubicin are approximately 5 hours and 55 hours, respectively, compared with approximately 10 minutes and 30 hours, respectively, for conventional doxorubicin [7, 10]. As a result, pegylated liposomal doxorubicin may be administered at a lower dose than the conventional formulation, potentially reducing the incidence of anthracycline-induced toxicities such as nausea, vomiting, alopecia, myelosuppression, and cardiac toxicity [7]. The lower toxicity is also related to the encapsulation of doxorubicin into microscopic liposomes, which preferentially penetrate and accumulate in tumor vasculature [10]. This provides the compound with an advantage in that the liposomes accumulate preferentially in tissues with increased microvascular permeability. Because increased angiogenic activity occurs in the bone marrow of patients with multiple myeloma, this pegylated formulation can enhance the delivery of doxorubicin to the tumor site [11]. In addition, because myeloma cells divide slowly [7, 12], the increased exposure of these cells to doxorubicin has the potential of overcoming resistance and increasing tumor cell killing capacity, theoretically resulting in improved response rates. The longer half-life of the compound also allows for shorter infusion times, compared with the lengthy infusion times associated with conventional doxorubicin [7]. Finally, pegylated liposomal doxorubicin has been reported to have significantly less cardiotoxicity than conventional doxorubicin [13-15].

A number of preliminary studies have evaluated the incorporation of pegylated liposomal doxorubicin into VAD regimens [16-19]. Overall, these studies demonstrated that this regimen had activity in newly diagnosed or relapsed/refractory multiple myeloma patients who had an acceptable tolerability profile [16-19]. These studies, which used a dose and schedule of dexamethasone similar to those of the VAD regimen, have...
suggested that pegylated liposomal doxorubicin is an acceptable alternative to conventional doxorubicin in combination chemotherapy regimens for the treatment of multiple myeloma.

**Reduced Corticosteroid Dosage**

Reducing the dose or the frequency of dexamethasone has the potential of making the regimen more tolerable. The risk of lowering the overall dose of corticosteroid is the potential decrease in response rate. This was demonstrated in a study by Brownman et al., who reported that a modified VAD regimen that used bolus doses of doxorubicin and vincristine and the omission of one cycle of dexamethasone (VAd) was associated with a low response rate (27%) and a short duration of response (4 months) [20]. However, the results of a phase II trial with DVd have been promising [7].

In that phase II study, the efficacy and safety of a DVd regimen were evaluated in 33 newly diagnosed symptomatic multiple myeloma patients requiring active therapy. Patients were required to have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 3; a life expectancy ≥3 months; and acceptable hematologic, renal, and hepatic functions [7]. The DVd regimen comprised pegylated liposomal doxorubicin at a dose of 40 mg/m²/day once every 4 weeks, vincristine at a dose of 2 mg/day i.v. once every 4 weeks, and dexamethasone at a dose of 40 mg/day for 4 days per 4-week cycle. A major response was defined as a ≥50% decrease in myeloma protein levels in the serum and urine [7]. A complete response was defined as the complete disappearance of myeloma protein, a bone biopsy demonstrating <3% plasma cells, the absence of monoclonal plasma cells by immune staining of the bone marrow on two occasions 4 weeks apart, and no evidence of progressive disease by any other parameter [7]. Patients who required stem cell harvesting and/or autologous bone marrow transplantation were considered to be treatment failures for the purpose of not influencing the progression-free and overall survival times [7].

Overall, the regimen was effective and well tolerated. A major response was achieved in 77% of patients and the progression-free survival time was 24.1 months. After 5 years of follow-up, the median overall survival time had not been reached. Analysis of pretreatment and posttreatment bone marrow biopsies revealed significant reductions in microvesSEL density posttreatment, indicating that the DVd regimen reduced angiogenesis [7]. The DVd regimen was generally well tolerated, with no patients requiring treatment discontinuation. The most common grade 3/4 toxicities were palmar-planter erythrodysesthesia (PPE), neutropenia, and mucositis [7]. The incidence of PPE was significantly reduced with patient education.

In patients with relapsed/refractory disease, the response to DVd was less consistent. A major response was achieved in only 25% of patients. Notably, a correlation was seen between the degree and durability of response. Patients who did not achieve a near-complete response (defined as a >80% decrease in monoclonal protein) failed within 6 months of discontinuing therapy. However, those with a near-complete response had more durable responses, with a progression-free survival time of approximately 2 years.

Preliminary results have been reported from two prospective, randomized, phase III clinical trials of the DVd regimen in the U.S. and Europe [16, 21]. Both studies compared DVd ( pegylated liposomal doxorubicin, 40 mg/m²/day i.v. over 1 hour once every 4 weeks; vincristine, up to 2 mg/day i.v. once every 4 weeks; and dexamethasone, 40 mg/day orally for 4 days per 4-week cycle in the U.S. trial and a modified version of high-dose dexamethasone in the European trial) with VAd (vincristine, 0.4 mg i.v.; doxorubicin, 9 mg/m² i.v.; and dexamethasone, 40 mg/day orally; all administered daily for 4 days in the U.S. trial and a modified version of high-dose dexamethasone in the European trial) in patients with newly diagnosed multiple myeloma. Each regimen was administered every 28 days for four cycles. In one study, in which 230 of 272 patients were evaluable for response, DVd was as effective as VAd, with objective responses reported in 55% and 57% of patients, respectively [16]. The tolerability of the regimens was generally similar; DVd was associated with significantly more hand-foot syndrome, whereas VAd was associated with significantly more alopecia [16]. Although both regimens could be administered in the outpatient setting, the DVd regimen required fewer hospital visits for treatment administration [16].

Efficacy data are not yet available for the second study, which is ongoing. However, fewer treatment cycles were administered by central line to patients receiving DVd (35%) compared with those receiving VAd (88%) [21]. Adverse-event-related hospitalizations and study terminations were similar between treatment groups [21].

**Thalidomide in the Treatment of Multiple Myeloma**

Interest in manipulating the immune system as a treatment modality for the management of multiple myeloma has stimulated basic and clinical research with immunomodulators, such as thalidomide, for the treatment of multiple myeloma and other cancers [22]. Thalidomide is a biologic response modifier with a number of properties that may contribute to its antimyeloma activity (Fig. 1) [22, 23]. These include the direct inhibition of myeloma and/or bone marrow stromal cells and modulation of the profile of adhesion molecules; this latter effect results in
reduction of the secretion and biologic activity of cytokines, inhibition of angiogenesis, and modulation of cellular immunity [22, 23]. One of the most important actions of thalidomide is probably related to its ability to interrupt the interaction between the myeloma cell and the bone marrow stroma and, subsequently, downregulate the supportive cytokine environment [8, 23]. This activity results in the myeloma cell becoming more vulnerable to cytotoxic chemotherapy [23].

Thalidomide therapy has been evaluated in several studies for the treatment of multiple myeloma. In newly diagnosed and relapsed/refractory myeloma patients, the response rates with and without dexamethasone pulses were approximately 50%-70% and 25%-30%, respectively [24, 25].

Combination regimens appear to increase the response rate in patients receiving thalidomide. For example, in newly diagnosed multiple myeloma patients, the response rate was higher for combination therapy with thalidomide and dexamethasone (72%) than for thalidomide monotherapy (36%) [24]. The combination of thalidomide (200-800 mg/day), oral cyclophosphamide (50 mg/day), and pulsed dexamethasone (40 mg/day × 4 days, every 3 weeks) elicited a 53% response rate in patients with relapsed/refractory disease [26].

Thalidomide is associated with significant toxicity (e.g., neurologic, hematologic) when initiated at a high dose. Therefore, The Cleveland Clinic Myeloma Research Group has adopted a low-dose, slow titration and the use of adjuvant supportive therapy to ensure treatment compliance and receipt of an adequate therapeutic regimen. This slow incremental dosing of thalidomide has been shown to improve the tolerability and duration of therapy in patients with multiple myeloma [27]. In a recent study, patients with multiple myeloma began therapy with thalidomide at a dose of 50 mg/day, with dose increases in 50-mg increments each week up to 400 mg/day or the individual’s maximum-tolerated dose (iMTD) [27]. This schedule allowed more than 90% of patients to remain on therapy for an average of approximately 16 months.

Adjuvant supportive care is also necessary to improve the tolerability of thalidomide-based regimens. Measuring and correcting vitamin B₁₂ and folate deficiencies can prevent the development of neurotoxicity. The use of epoetin alfa to correct disease- or chemotherapy-induced anemia among patients with multiple myeloma is critical in allowing patients to better tolerate therapy, both in the short term and in the long term [28]. Epoetin alfa also appears to have neuroprotective properties that are unrelated to erythropoiesis [28-30].

PEGYLATED LIPOSOMAL DOXORUBICIN, VINCristine, DEXAMETHasONE, AND Thalidomide

Rationale and Objective

Based on the efficacy of the DVd and thalidomide-based regimens, a pilot study was designed to determine whether the addition of thalidomide to DVd (DVd-T) increases the rate and quality of response to treatment in patients with relapsed/refractory multiple myeloma [8]. Since the antiangiogenic effect of thalidomide prevents the formation of new blood vessels (rather than reversing angiogenesis), it was hypothesized that thalidomide may be able to maintain the antiangiogenic responses produced by DVd [8]. In addition, it was hypothesized that the addition of thalidomide may increase the sensitivity of myeloma cells to chemotherapy,
thus increasing response rate and quality of response.

Study Design
The treatment regimen for this study is illustrated in Figure 2. On the first day of each cycle, patients received pegylated liposomal doxorubicin at a dose of 40 mg/m² i.v. over 2-3 hours and vincristine, 2 mg i.v. [8]. Dexamethasone, 40 mg/day, was administered on days 1-4 of each cycle. Thalidomide was initiated at 50 mg/day and was increased by 50 mg/day every week to the iMTD, not to exceed 400 mg/day [8]. The regimen was repeated every 4 weeks for a minimum of six cycles, and for two cycles after the best response. After completion of chemotherapy, patients were maintained on prednisone, 50 mg every other day, plus the iMTD of thalidomide until the onset of disease progression or toxicity [8]. Based on the experience of other investigators [31], an algorithm to monitor for the development of deep vein thrombosis (DVT) and to allow for dose reductions for those experiencing neuropathy was included. The protocol was also amended after higher incidences of neutropenia, infection, oral herpes simplex activation, and DVT developed among the first 20 patients enrolled in the relapsed/refractory arm of the study. A prophylactic regimen consisting of amoxicillin, 250 mg twice daily, and acyclovir, 400 mg twice daily, until the completion of chemotherapy, was included to prevent infectious complications. Patients also received GM-CSF or G-CSF for WBCs <5,000/µl on day 1 of therapy and acetylsalicylic acid, 81 mg/day, for antiplatelet activity [8]. Patients with hemoglobin levels <10 g/dl were started on epoetin alfa at a dose of 40,000-80,000 U administered s.c. once weekly until hemoglobin increased by at least 2 g/dl, at which time the dosing frequency was reduced to maintain hemoglobin between 12 and 14 g/dl.

RESULTS
Currently, 40 patients with relapsed/refractory multiple myeloma have been enrolled in the trial, with a median age of 63.5 years and a median performance status of ≤3 [8]. Median β₂-microglobulin and albumin values were 4.6 mg/dl and 3.2 mg/dl, respectively [8]. Of the 40 patients enrolled to date, 35 were assessable for efficacy and toxicity. Response rates are summarized in Table 1. Overall, 26 of 35 patients (74%) achieved a response to therapy according to Southwest Oncology Group (SWOG) criteria (≥50% decrease in myeloma protein). Notably, three patients (9%) achieved complete responses and another 13 patients (37%) achieved near-complete responses. The median time to initial response was 1.0 months (range, 0.7-5.6 months) and the median time to best response was 2.7 months (range, 0.9-6.3 months) [8].

Prior to the institution of preventive measures, hematologic toxicities were frequent; 18 of 20 patients had grade 3/4 neutropenia, and 10 of 20 patients had thrombocytopeenia. There were four cases of pneumonia, one case of septic arthritis, two episodes of gastrointestinal bleeding, and five instances of DVT [8]. After the institution of precautionary measures, grade 3 cytopenia-related complications occurred in only one of 15 patients. DVT was noted in only two of 15 patients and, in one of those patients, the DVT was located below the knee and required no specific therapy or treatment discontinuation. Patients who developed DVT on therapy received anticoagulation therapy and continued their treatment regimen. Grade 3 paresthesia requiring dose reductions or discontinuation of vincristine therapy was observed in 20% of patients [8].

CONCLUSIONS
The preliminary results of this study suggest that DVd-T is an effective regimen for the treatment of relapsed/refractory multiple myeloma and has an acceptable toxicity profile.

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<th>Table 1. Efficacy of DVd-T in patients with relapsed/refractory multiple myeloma [8]</th>
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<td><strong>Response</strong> (decline in myeloma protein)</td>
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<tr>
<td>Complete remission*</td>
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<td>≥90% to complete remission</td>
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*Disappearance of myeloma protein by immune fixation and presence of polyclonal plasma cells in the bone marrow by immune staining.
The rate and quality of response observed in this trial are higher than those seen in previous studies evaluating DVd or thalidomide/dexamethasone. In particular, the quality of response produced by DVd-T was impressive. Almost half the patients evaluated achieved near-complete responses or complete remissions, a rate substantially higher than that reported with DVd. These data suggest that the addition of thalidomide to DVd improves the response rate and quality of response, possibly by reversing resistance to chemotherapy.

SUMMARY
Combination VAD chemotherapy is effective in the treatment of patients with multiple myeloma, producing a more rapid response than other combination chemotherapy regimens [1]. A simplified and well-tolerated regimen was developed by the substitution of pegylated liposomal doxorubicin for conventional doxorubicin, a reduction in the corticosteroid dosage, and the addition of the immune modulator thalidomide. The inclusion of pegylated liposomal doxorubicin enhances the delivery of active agent to the target site, decreases the risk for cardiotoxicity, and obviates the need for prolonged inpatient drug administration via a central venous catheter. Properties of thalidomide that support its inclusion in chemotherapy regimens include its antiangiogenic activity, its direct inhibitory effect on myeloma cells, and its ability to increase the susceptibility of myeloma cells to chemotherapy.

DVd-T chemotherapy has produced promising results in patients with relapsed/refractory multiple myeloma, producing a higher rate of response and a better quality of response than other versions of this regimen. A major advantage of DVd-T is that a much lower dosage of dexamethasone is required than in the more conventional VAD and thalidomide/dexamethasone regimens, with what appears to be a better overall response.

Although promising, further evaluation of the DVd-T regimen is required to determine its role in the treatment of patients with multiple myeloma. Most importantly, additional follow-up is required to determine whether DVd-T improves progression-free or overall survival times. The results of these studies are awaited. Utilizing the ability of the DVd regimen to reduce the abnormal angiogenic process in the bone marrow with the immunomodulatory features of agents such as thalidomide and CC-5013 (Revimid®; Celgene Corporation, Warren, NJ) is currently being investigated.

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