Superiority of thalidomide and dexamethasone over vincristine-doxorubicin-dexamethasone (VAD) as primary therapy in preparation for autologous transplantation for multiple myeloma

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The aim of the present study was to compare thalidomide-dexamethasone (Thal-Dex) and vincristine-doxorubicin-dexamethasone (VAD) as primary therapy in preparation for autologous peripheral blood stem-cell (PBSC) transplantation for multiple myeloma (MM). For this purpose, we performed a retrospective matched case-control analysis of 200 patients who entered 2 consecutive studies from 1996 to 2004 and received Thal-Dex (n = 100) or VAD (n = 100) administered for 4 months before collection of PBSCs.

Introduction

Over the last decade, major advances in the treatment of multiple myeloma (MM) have been reported with the use of autologous stem-cell transplantation and, more recently, of novel agents targeting the tumor clone and the bone marrow microenvironment. In this setting, thalidomide represents a new treatment paradigm because of its alternative mechanisms of action that include disruption of myeloma–bone marrow stromal cell interactions, inhibition of cytokine secretion, and immunomodulatory effects. The observation that increased bone marrow angiogenesis correlates with advanced phases of MM, along with the well-documented in vitro antiangiogenic activity of thalidomide, led to the investigational use of this agent in patients with advanced and refractory MM. Response rates in the 30% range initially reported by Singhal et al were extended and confirmed by other groups (for a review, see Cavenagh and Oakervee and Dimopoulos et al). Subsequent combination of thalidomide with dexamethasone increased the rate of response up to 50% to 55%, suggesting a synergism between these agents and providing the rationale for their use as primary therapy for patients with symptomatic MM. Results of 3 phase-2 studies with thalidomide-dexamethasone (Thal-Dex) in preparation for subsequent autologous transplantation and a randomized comparison of Thal-Dex with dexamethasone alone were promising in terms of response rate and collection of adequate quantities of peripheral blood stem cells (PBSCs). Based on these data, Thal-Dex has been proposed, and is currently accepted at many centers, as a front-line treatment option for patients with symptomatic MM, particularly if it is planned to offer subsequent high-dose therapy with autologous transplantation. However, no comparative study of Thal-Dex with vincristine-doxorubicin-dexamethasone (VAD), the reference treatment used so far to reduce tumor cell mass before autologous transplantation, has been reported. To address this issue, we performed a retrospective matched case-control analysis of 200 patients with symptomatic MM who were primarily treated with Thal-Dex (n = 100) or VAD (n = 100) in preparation for autologous stem-cell transplantation as part of 2 consecutive studies conducted from 1996 to 2004.

Patients, materials, and methods

Patients and criteria of matching

A series of 100 consecutive patients with symptomatic MM who were enrolled onto the Bologna 2002 clinical study from January 2002 to January 2004 and were treated with Thal-Dex as first-line therapy in...
preparation for double autologous transplantation was analyzed. For comparison of their outcome, an equal number of pair mates were selected among patients who entered the Bologna 96 study from March 1996 to November 2000 and received primary therapy with VAD before assignment to either single or double autologous transplantation. Case matching was performed with respect to age (± 2 years), clinical stage at diagnosis (same stage, according to the Durie and Salmon system), and serum β2-microglobulin levels (± 1 mg/L). Data on baseline patient characteristics are summarized in Table 1; the 2 groups were comparable with respect to the major presenting variables known to potentially affect clinical outcome. Both studies were approved by local ethical committees of participating centers. Informed consent was provided according to the Declaration of Helsinki.

Response to therapy

On an intent-to-treat basis, response (at least PR) was documented in 76 patients of 100 who were treated with Thal-Dex (Table 2). The corresponding figure among patients who received VAD was 52 of 100. The difference between the 2 groups (76% vs 52%, respectively; 95% CI, 11%-37%) was statistically significant (P < .001). Analysis by major response categories (CR, nCR, and VGPR) revealed that both treatment groups had the same probability of attaining at least nCR or VGPR (Table 2). At the opposite, the percentage of patients who failed to attain at least a partial remission on VAD was twice that observed in the Thal-Dex group (48% versus 24%, respectively).

Response to primary therapy with Thal-Dex or VAD was generally rapid. Among responders, a decrease in M protein concentration of at least 50% above pretreatment values was seen at the end of the first 2 months of therapy in 71% of patients who received Thal-Dex and in 59% of those treated with VAD; the difference between the 2 groups did not reach the level of statistical significance. The magnitude of tumor reduction effected by Thal-Dex or VAD was also evaluated by comparing the pretreatment and posttreatment levels of monoclonal immunoglobulins. In comparison with VAD, Thal-Dex was found to induce more profound reduction in tumor cell mass, as reflected by significantly lower levels of residual IgG (P = .02) and IgA (P = .03) M proteins.

Toxicity

Toxicities registered during therapy with Thal-Dex or VAD were different (Table 3). The major toxicity of VAD was hematologic, particularly granulocytopenia; it was severe (grade 3-4) in 12% of

### Table 1. Baseline patient characteristics

<table>
<thead>
<tr>
<th></th>
<th>Thal-Dex, N = 100</th>
<th>VAD, N = 100</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ± SD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
<td>54.01 ± 5.75</td>
<td>53.94 ± 5.47</td>
</tr>
<tr>
<td>Stage I</td>
<td>12</td>
<td>12</td>
</tr>
<tr>
<td>Stage II + III</td>
<td>88</td>
<td>88</td>
</tr>
<tr>
<td>IgG, g/dL</td>
<td>4.45 ± 2.06</td>
<td>60</td>
</tr>
<tr>
<td>IgA, g/dL</td>
<td>4.35 ± 1.66</td>
<td>31</td>
</tr>
<tr>
<td>Hb, g/dL</td>
<td>11.01 ± 2.25</td>
<td>11.19 ± 2.00</td>
</tr>
<tr>
<td>PLTs, × 10³</td>
<td>231.51 ± 79.14</td>
<td>233.30 ± 76.53</td>
</tr>
<tr>
<td>BMPCs, %</td>
<td>52.39 ± 26.85</td>
<td>49.20 ± 26.25</td>
</tr>
<tr>
<td>β2-m, mg/L</td>
<td>3.66 ± 5.41</td>
<td>3.49 ± 5.34</td>
</tr>
</tbody>
</table>

— indicates not applicable; NS, not significant; Hb, hemoglobin; PLTs, platelets; BMPCs, bone marrow plasma cells; and β2-m, β2-microglobulin.

### Table 2. Rates of response

<table>
<thead>
<tr>
<th></th>
<th>Thal-Dex, N = 100</th>
<th>VAD, N = 100</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>At least PR</td>
<td>76</td>
<td>52</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>CR</td>
<td>10</td>
<td>8</td>
<td>—</td>
</tr>
<tr>
<td>nCR</td>
<td>3</td>
<td>5</td>
<td>—</td>
</tr>
<tr>
<td>VGPR</td>
<td>6</td>
<td>1</td>
<td>—</td>
</tr>
<tr>
<td>PR</td>
<td>57</td>
<td>38</td>
<td></td>
</tr>
<tr>
<td>NR/PROGR</td>
<td>24</td>
<td>48</td>
<td>&lt; .001</td>
</tr>
</tbody>
</table>

At least partial remission (PR) includes complete remission (CR), near complete remission (nCR), very good partial remission (VGPR), and partial remission (PR). — indicates not applicable; NR/PROGR, no response/progression.

Statistical analysis

Objectives of the study were to compare (i) the rate of response (at least PR) to Thal-Dex with that to VAD, (ii) PBSC yields following Thal-Dex or VAD, and (iii) the toxicity profiles of both of these regimens. Differences between Thal-Dex and VAD were analyzed using the chi-square test or Student t test, as appropriate. Response rates were calculated on an intent-to-treat basis, and 95% exact confidence intervals (CIs) were estimated by means of the probabilities of the binomial distribution. Paired comparisons of baseline versus posttreatment M protein concentrations were performed using the Wilcoxon rank sum test.
patients. Neurotoxicity and severe cardiovascular events, usually congestive heart failure, were found less frequently, in 7% and 3% of patients, respectively. Side effects with Thal-Dex did not require dose reduction or interruption in most of the cases. The most common toxicity was DVT (15% of all cases, including 26% among the first 19 patients who did not receive any prophylaxis and 12% among 81 patients who were subsequently treated with low-dose warfarin); other grade 3 to 4 toxicities included constipation (9%), fatigue (6%), infections (4%), neuropathy (4%), and skin rash (1%). DVT was documented by Doppler ultrasonography and more frequently developed in the lower extremities at a median time of 2 months from start of thalidomide therapy. In a single patient thrombosis was complicated by nonfatal pulmonary embolism. There was no apparent relationship between DVT and the presence of laboratory risk factors for thrombosis, which were normal in 14 patients; a single patient was found to be heterozygous for factor V Leiden gene mutation. Anticoagulation therapy consisting of low-molecular-weight heparin, with or without warfarin, was promptly started after the diagnosis of DVT was established. In 13 patients, thalidomide was safely continued without evidence of progression of DVT, whereas in the last 2 patients the drug was discontinued.

In the Thal-Dex group there were 6 deaths that occurred during treatment due to infection (2 patients), disease progression (1 patient), or other causes (3 patients). Six patients died while on VAD therapy because of disease progression (3 patients), myocardial infarction (1 patient), or other causes (2 patients).

**PBSC collection**

Nine patients treated with Thal-Dex did not proceed to PBSC collection because of toxicity (6 patients), progression (2 patients), or refusal (1 patient). In the VAD group, 9 patients did not undergo PBSC mobilization, 5 due to toxicity and 4 because of progression. In each of the 2 groups, 91% of patients received HD-CTX and G-CSF in an attempt to mobilize and collect PBSCs. PBSC collections were performed as previously reported. The median interval between start of therapy with Thal-Dex or VAD and HD-CTX was 138 days and 142 days, respectively. There was no significant difference between the 2 groups with respect to their characteristics at mobilization therapy with HD-CTX, except for the status of the disease and the size of residual tumor cell mass (see “Response to therapy”). Patients in each of the 2 groups received similar doses of HD-CTX. The median number of collected CD34+ cells was $7.85 \times 10^6$kg for patients with prior exposure to Thal-Dex and $10.5 \times 10^6$kg for patients who received VAD ($P = .4$). Considering $4 \times 10^6$ CD34+kg as the minimum threshold dose to safely perform double autologous transplantation, adequate cell yields were obtained in 83% of patients treated with Thal-Dex and in 88% of patients in the control group ($P = .3$). In both treatment groups the median number of aphereses to collect adequate cell yields was 2.

**Discussion**

Thalidomide, once withdrawn from the market because of teratogenicity, was reintroduced into the clinical practice for the treatment of various disorders such as erythema nodosum leprosum, aphtous ulcers of human immunodeficiency virus, and chronic graft-versus-host disease. Based on the antiangiogenic and immunomodulatory effects, thalidomide was also investigated in several solid tumors and hematologic malignancies, the most striking antitumor activity being observed in MM. Efficacy reported with thalidomide alone and subsequently added dexamethasone in advanced and refractory MM led to the investigational use of these agents as first-line induction of remission. Results of recently conducted phase-2 and -3 clinical trials with Thal-Dex in previously untreated patients with symptomatic disease showed a rate of response similar, or even superior, to that expected with conventional chemotherapy. Hence, after almost 3 decades of unsuccessful clinical studies addressing the search for novel agents with documented antiyeloma activity, the armamentarium for the treatment of MM was greatly expanded by the introduction of thalidomide.

High-dose therapy with autologous stem-cell transplantation is considered the standard of care for patients with newly diagnosed MM who are younger than 65 years of age since it significantly prolonged the survival in comparison with standard-dose therapy. In previously untreated patients, front-line autologous transplantation is generally preceded by 3 to 4 courses of conventional chemotherapy aimed to reduce tumor cell mass before mobilization of stem cells. For this use, VAD has been the standard treatment since it is not toxic to normal bone marrow stem cells and induces early responses, thus allowing patients to proceed to prompt stem-cell mobilization. However, with use the popularity of VAD has been tempered by the inconvenience of a 4-day continuous infusion via an indwelling central line, the risk of catheter-related complications (eg, infections and thrombosis), and toxicity, particularly cardiac, which may preclude patients’ eligibility to subsequently receive stem-cell–supported high-dose therapy, and neuropathy, which may limit the subsequent use of thalidomide or bortezomib in advanced phases of the disease. Obviously, availability of an effective oral alternative to VAD in preparation for autologous transplantation that obviates the disadvantages reported above is likely to be of relevance in clinical practice.

In 2002 we designed a phase-2 clinical study aimed to explore the activity and toxicity of Thal-Dex as first-line induction of remission for patients who were candidates to receive autologous stem-cell transplantation. Similar studies were also conducted at the Mayo Clinic and MD Anderson Cancer Center. Response rates seen in these studies, ranging from 64% to 72%, provided demonstration of marked activity for primary Thal-Dex therapy but did not establish whether this combination is or is not superior to standard-dose chemotherapy. In an attempt to address this issue, in the present study we analyzed a series of 100 patients with symptomatic MM who were primarily treated with Thal-Dex. Their clinical outcome was compared with that of an equal sample of historic patients who received VAD therapy. Appreciating the difficulty of drawing firm conclusions from historic controls, an effort was undertaken to account for differences in relevant prognostic features by matching patients closely for age, clinical stage, and serum β₂-microglobulin level. Of concern, the 2 groups of patients were also comparable for the planned duration of therapy and the total dose of dexamethasone that was planned to be administered over the entire treatment period.
Using an intent-to-treat approach and stringently defined response criteria, we found that the response (at least PR) rate to Thal-Dex (76%) was significantly higher than that observed with VAD (52%). The frequency of response to VAD was comparable to that previously reported by Alexanian et al,20 and subsequently found by other groups using this regimen in preparation for autologous transplantation.24,25 Higher rates of response, up to 80%, were reported in other studies.21,22,26 Differences among studies with respect to baseline patient characteristics, treatment modalities (eg, duration, continuous or bolus infusion of vincristine and doxorubicin, total dose of dexamethasone), and criteria used to define response hamper a meaningful comparison of data and may easily explain the wide range of results reported so far.

In addition to the rate of response to Thal-Dex, we also evaluated the magnitude of tumor reduction, as reflected by the size of residual monoclonal immunoglobulins. Posttreatment serum levels of IgG and IgA M proteins were significantly lower in the Thal-Dex group compared with the control group. The observation that primary therapy with Thal-Dex effected more profound reduction in tumor burden than VAD in preparation for subsequent autologous transplantation is important since a low pretransplantation size of M protein was found to be a predictor of postransplantation attainment of CR.27

Since autologous transplantation remains the most effective treatment strategy for the management of de novo MM, it is important that the primary induction regimen administered before transplantation is of low toxicity and does not impair the collection of PBSCs. In this light, several groups recently proposed the use of dexamethasone alone as a possible alternative to more toxic chemotherapies in preparation for subsequent high-dose therapy.28 With the low dosage and limited duration of thalidomide therapy used in the present study, no irreversible toxicities were seen. DVT was the most frequent non-dose-related complication, occurring in 15% of patients. In all of them, episodes of DVT were nonfatal and in only 2 patients DVT was the cause of treatment discontinuation; in the remaining patients thalidomide was safely continued once full anticoagulation with low–molecular weight heparin, and eventually added warfarin, was introduced. Similar rates of DVT to that seen in the present study were reported in 2 other studies with primary Thal-Dex therapy, ranging from 12% to 15%.13,14 These values are higher than the 2% frequency of thromboembolic complications previously observed with thalidomide alone29 or the 8% seen with Thal-Dex among patients with refractory MM.30 Mechanisms that lead to an increased risk of DVT for MM patients who receive primary therapy with Thal-Dex or thalidomide plus doxorubicin-containing chemotherapy31 are still poorly defined and probably multifactorial. In the present study, no identifiable baseline prothrombotic laboratory abnormalities were found to be predictive of DVT. In particular, we were not able to confirm previously reported data showing a higher frequency of acquired activated protein C resistance in the absence of factor V Leiden mutation.31 A substantial increase in factor VIII coagulant activity and von Willebrand factor antigen was reported by others with the use of thalidomide in advanced and refractory MM.32 However, elevated coagulation factors observed in these patients are more likely to be related to the status of MM rather than to thalidomide therapy.33 Controversies exist concerning the need to use routine prophylactic anticoagulation therapy in all patients receiving primary thalidomide therapy, as well as on the efficacy of different therapies used so far. Aspirin, warfarin at different doses, and low–molecular weight heparin have variously been employed, reflecting the limited knowledge about the pathophysiology of thalidomide-related DVT. In the present study we observed a decrease in the rate of DVT from 26% in the first cohort of patients to 12% in the second cohort who received warfarin at subtherapeutic doses. Although warfarin prophylaxis for these latter patients was instituted soon after the last accrual to the first cohort, the study was not randomized and data need to be cautiously interpreted. A lack of clinical benefit with prophylactic low-dose warfarin was reported by other groups in the context of first-line therapy with Thal-Dex with or without combined chemotherapy.14,34 At the opposite, prophylactic low–molecular weight heparin virtually reduced the risk of DVT to baseline in patients primarily treated with intensive chemotherapy regimens including thalidomide.35 Attempts to reduce the risk of DVT below the 10% range are warranted in order to make thalidomide a safe drug for the treatment of patients with de novo MM.

As previously emphasized, a main reason for the widespread use of VAD in patients who are candidates for autologous stem-cell transplantation is the lack of toxicity to normal bone marrow stem cells. Because of early concerns that thalidomide may interfere with stem-cell collection, possibly through modulation of adhesion molecules on bone marrow stromal cells, an important end point of our study was PBSC procurement. Analysis revealed that 83% of patients easily reached the minimum target number of at least 4 × 10^9/kg CD34+ cells considered to be adequate to safely perform double autologous transplantations.36 Of concern, thalidomide did not need to be discontinued until the day before administration of HD-CTX and allowed a median yield of 7.85 × 10^9/kg CD34+ cells. Similar quantities of collected CD34+ cells were reported in patients comparably treated by Weber et al,14 using G-CSF as mobilization therapy, and by Ghobrial et al,36 after mobilization with HD-CTX, 3 g/m², and granulocyte-macrophage colony-stimulating factor. In this latter study, as in our study, there was no significant difference in number of CD34+ cells collected or number of days of collection between the Thal-Dex group and a control group of patients who received primary therapy with dexamethasone alone or VAD. On the basis of these results, it appears that short exposure to thalidomide is not a risk factor for impaired stem-cell procurement and allows collection of sufficient numbers of PBSCs to support 2 to 3 courses of high-dose therapy.

In summary, results of this retrospective case–matched comparison of Thal-Dex with the standard VAD regimen as initial therapy in preparation for autologous stem-cell transplantation for MM provided demonstration of the superiority of Thal-Dex in terms of response and extent of tumor reduction. Obviously, these data should be cautiously interpreted since the study, albeit well controlled, was not randomized. However, it is worthy of note that conclusions herein reported were consistent with the results of a recently completed phase-3 study aimed at comparing Thal-Dex with dexamethasone alone for patients with previously untreated MM.16 Given that high-dose dexamethasone is the most active component of VAD, it is tempting to replace this complex-and-cumbersome-to-administer combination with an oral regimen like Thal-Dex, which avoids the morbidity and risks associated with central venous access as well as the discomfort of continuous infusion of cytotoxic drugs and patients’ possible hospitalization. While irreversible toxicities were not seen with limited exposure to Thal-Dex, the increased risk of DVT associated with the use of this regimen in previously untreated patients should be considered. Recently, newer and safer immunomodulatory derivatives of thalidomide, like CC-5013, that exert similar or higher antitumor activity without teratogenic effects of thalidomide have shown promising results in limited phase-2 studies performed in both
refractory and newly diagnosed MM patients. Based on these findings, the combination of CC-5013 and dexamethasone as primary therapy for MM is currently under evaluation in 2 large phase-3 studies conducted by the Eastern Cooperative Oncology Group and the Southwest Oncology Group. Thalidomide immunodrivatives could hopefully replace thalidomide in clinical practice in the near future. Until then, thalidomide will continue to play a major role in the treatment of MM.

Acknowledgments

This article is dedicated to Dr Cavo’s Father and Mother.

References

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