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First-line therapy with thalidomide and dexamethasone in preparation for autologous stem cell transplantation for multiple myeloma

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A B S T R A C T

Background and Objectives. The marked synergy of thalidomide and dexamethasone in advanced and refractory multiple myeloma (MM) provided the basis for a phase 2 clinical study aimed at investigating the efficacy and toxicity of this combination as first-line therapy for patients less than 65 years old with newly diagnosed disease.

Design and Methods. Both thalidomide and dexamethasone were administered for 4 months in an attempt to reduce tumor cell mass before collection of peripheral blood stem cells (PBSC) and subsequent double autologous transplantation. Thalidomide was given at the fixed dose of 200 mg/day; dexamethasone was administered at the dose of 40 mg/day on days 1-4, 9-12 and 17-20 in odd cycles and 40 mg/day on days 1-4 in even cycles, repeated monthly.

Results. Seventy-one patients with symptomatic MM were evaluated for response and toxicity. On an intent-to-treat basis, the overall response (≥ partial remission) rate was 66%, including 17% of patients who attained a complete remission or a very good partial remission. In addition to common toxicity of thalidomide, deep-vein thrombosis was a troublesome adverse event (16%). Nine patients (13%) required thalidomide discontinuation because of toxicity, including 3 patients who died during the study treatment. Fifty-nine patients proceeded to PBSC mobilization and yielded a median number of 7.1×10^6 CD 34^+ cells/kg.

Interpretation and Conclusions. The combination of thalidomide and dexamethasone is an effective and relatively well tolerated induction regimen for previously untreated patients with MM. This combination may provide an oral alternative to vincristine-doxorubicin-dexamethasone in preparation for autologous stem cell transplantation.

Key words: multiple myeloma, thalidomide, autologous transplantation.

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Over the last decade, there have been reports of major advances in the management of patients with multiple myeloma (MM) as a result of the use of autologous stem cell transplantation[1,2] and, more recently, of novel, *biological* agents targeting both the tumor clone and the bone marrow microenvironment.[3,4] In this setting, thalidomide represents a new treatment paradigm, because of its alternative mechanisms of action which include disruption of myeloma-bone marrow stromal cell interactions, inhibition of cytokine secretion, antiangiogenic activity and immunomodulatory effects.[5-7] Remarkable antimyeloma efficacy, reported to be about 30% with thalidomide alone[8-12] and 50% with added dexamethasone[13-15] in advanced and refractory MM, provided the basis for recent clinical trials aimed at investigating the role of these drugs as first-line therapy for patients with symptomatic MM.[16,17] In 2002, we started a multicenter, phase 2 clinical study with combined thalidomide and dexamethasone for primary induction of remission in patients with *de novo* MM who were candidates to receive double autologous peripheral blood stem cell (PBSC) transplantation. An analysis of efficacy and toxicity was planned to be performed on the first 70 patients who could be evaluated and the results of this analysis are reported here.

Design and Methods

Eligibility

Patients were eligible to enter the study if they were less than 65 years of age, were previously untreated and had a confirmed diagnosis of symptomatic MM. Eligible

patients were required to have measurable disease, as defined by the presence of M protein in the serum in excess of 1 g/dL and, in case of Bence Jones MM, of urinary light chain excretion exceeding 200 mg/day. Pregnant or nursing women were not eligible to enter the study. Patients with a prior history of thrombosis or venous thromboembolism were also excluded. All patients gave written informed consent prior to enrollment into the study. The Ethics Committee of each participating center gave approval for the study.

Study design and treatment

By study design, thalidomide and dexamethasone were administered for 4 months in an attempt to reduce tumor cell mass before collection of PBSC. Thalidomide was given at the starting dose of 100 mg/day for 14 days and then increased to the dose of 200 mg/day. Dexamethasone was administered at the dose of 40 mg/day on days 1-4, 9-12 and 17- 20 in odd cycles and 40 mg/d on days 1-4 in even cycles, repeated monthly. Thalidomide was witheld from patients with grade 4 toxicity; if grade 3 toxicity was recorded, the dose of thalidomide could be reduced by 50%. Patients who proceeded to PBSC collection received high-dose cyclophosphamide (HD-CTX) (7 g/m^2) and granulocyte colony-stimulating factor (G-CSF) (5 μg/kg/day starting on day +2 from HD-CTX and continuing until completion of the PBSC collection). Thalidomide was discontinued the day before administration of HD-CTX.

Response criteria

Criteria for defining complete remission (CR), partial remission (PR), or progressive disease were those previously reported by Bladè *et al.*[18] In addition, a near-complete remission (nCR) was defined by the absence of M protein on routine electophoresis (but positive immunofixation), whereas a decrease in serum M protein concentration ≥ 90% was categorized as a very good partial remission (VGPR). Patients who met previously reported criteria of no change or minimal response[18] were classified as having no response. Evaluation of response to thalidomide and dexamethasone was performed on days +30, +60, +90 and +120 after the start of therapy.

Toxicity criteria

Adverse events were assessed monthly and graded according to the National Cancer Institute Common Toxicity Criteria (version 2.0).

Statistical analysis

The trial was designed to accrue 130 patients in order to assess the efficacy and toxicity of first-line thalidomide-dexamethasone combination therapy. The primary efficacy variable was the proportion of patients who attained a response, either complete or partial. Secondary end points of the study were toxicity and PBSC collection.

Table 1. Patients' baseline characteristics.

	N. pts. (%)	*Median (range)*
Age (years)		56 (42-65)
M component isotype		
IgG (g/dL)	39 (55)	3.8 (1.1-13.2)
IgA (g/dL)	21 (30)	4.2 (0.6-7.8)
Bence Jones (g/24h)	10 (14)	3.4 (1.0-13.5)
IgD	1 (1)	
Stage II+III	63 (89)	
β2-microglobulin (mg/L)		2.8 (0.1-12.7)
≥ 3.5	27 (40)	
C-reactive protein (mg/L)		3.6 (0.1-77)
Lactate dehydrogenase (IU/L)		305 (106-981)
Chromosome 13 deletion	33 (47)	

Results

Patients' characteristics

Between January 2002 and March 2003, 71 patients with previously untreated MM entered the study. Their baseline characteristics are listed in Table 1. Eighty-nine percent of patients had advanced clinical stage. Additional parameters predictive of poor prognosis, including high β2 microglobulin levels and chromosome 13 abnormalities (monosomy and/or deletion) (D 13) as detected by fluorescence *in situ* hybridization (FISH), were found in 40% and 47% of patients, respectively. Eight of the 33 patients with D 13 by FISH had chromosome 13 abnormalities which were also detectable by conventional cytogenetics.

Treatment received

The median duration of treatment with thalidomide and dexamethasone was 4 months. Sixty-two patients (87%) completed the four months of therapy and 91% of them received 80% of the planned dose of thalidomide. Patients who proceeded to PBSC collection received HD-CTX at a median of 138 days (range, 101 to 204 days) after the start of thalidomide therapy. PBSC collections were performed as previously reported.[19]

Response

On an intent-to-treat basis, response (≥ PR) was documented in 47 patients (66%), including 12 patients (17%) who attained CR/nCR (8%) or a VGPR (9%). Five patients (7%) had a minor response, while

Table 2. Response to thalidomide-dexamethasone therapy calculated on an intent-to-treat basis.

	N. pts.	*%*
CR+nCR	6	8
VGPR	6	9
PR	35	49
MR	5	7
NR or Progression	19	27

CR: complete remission; nCR: near-complete remission; VGPR: very good partial remission; PR: partial remission; MR: minor remission; NR: no response.

Table 3. Deep-vein thrombosis following thalidomide-dexamethasone therapy.

	All pts.	*Pts. not receiving Warfarin*	*Pts. receiving Warfarin*
N. pts	71	19	52
N. pts with DVT (%)	12 (16)	5 (26)	7 (13)
Median time to DVT (months) (range)	2 (1-4)	1 (1-4)	2 (1-3)
Sites of DVT			
Distant lower limb	6	3	3
Proximal lower limb	6	2	4
Response status at DVT			
≥ PR	8	2	6
NR	4	3	1

PR: partial remission; NR: no response.

the remaining 19 patients (27%) either failed to respond (n=11) or showed disease progression (n=8) (Table 2). Among responders, a decrease in serum M protein concentration ≥ 50% was registered in 80% of patients within the first month of therapy and in the remaining patients after 2 months (3%) or after 3 months (17%) of therapy. There was no statistically significant difference in the response rate between patients with and without D 13 (60% vs 73%, respectively).

Toxicity

Side effects of thalidomide treatment were mild in most of the patients and generally did not require dose reduction. There were 6 patients in whom thalidomide was discontinued because of toxicity (deep-vein thrombosis in 2 patients, infection in 2 patients, neuropathy in 1 patient, constipation in 1 patient). Three additional patients died during thalidomide therapy due to different causes: infection (1 patient), heart failure (1 patient) and unknown cause (1 patient). Overall, more common grade 3-4 toxicities consisted of DVT (16%), constipation (14%), fatigue (10%), infections (7%), neuropathy (6%) and skin rash (2%). Among the first 19 patients who entered the study and did not receive any prophylaxis against DVT, the incidence of thromboembolic complications was 26%.[20] Based on these observations, the protocol was amended and fixed low-dose prophylactic warfarin (1.25 mg daily) was introduced. A consecutive series of 52 patients entered the amended protocol and 7 of them (13%) had DVT (Table 3). Notably, in 2 of these 7 patients DVT occurred 10 and 30 days after warfarin had been discontinued. In all patients DVT was documented by Doppler ultrasonography and developed in the lower extremities at a median time of 2 months after the start of thalidomide therapy (Table 3). In a single patient DVT was complicated by non-fatal pulmonary embolism. The status of MM at the time of DVT was as follows: responsive disease, 66% of cases; refractory disease, 34% of cases (Table 3). Previously reported baseline laboratory evaluation for risk factors for thrombosis[20] excluded primary hypercoagulable states in 11 of the 12 patients who had thrombotic complications; a single patient was found to be a heterozygote for the factor V Leiden gene mutation. For most of the patients who received fixed low-dose warfarin, the International Normalized Ratio of the prothrombin time (INR) remained within the normal range. Anticoagulation therapy consisting of low-molecular-weight heparin, with or without warfarin, was promptly started after the diagnosis of DVT had been established. In 10 patients thalidomide was safely continued without evidence of progression of DVT, whereas in the last 2 patients the drug was discontinued.

Collection of PBSC

Twelve patients did not undergo PBSC mobilization because of toxicity (7 patients) or progressive MM (5 patients). Among the remaining 59 patients who proceeded to PBSC mobilization and received HD-CTX, the median number of $CD34^+$ cells collected was 7.1×10^6/kg. The median number of aphereses was 2 (range, 1 to 4). Considering 2×10^6 $CD34^+$/kg as the minimum number of stem cells required to safely support a single course of high-dose therapy, 80% of patients had adequate cell yields to receive double autologous transplantation.

Discussion

Thalidomide was firstly explored for the treatment of advanced and refractory MM by Singhal *et al.* in 1999.[3] The rationale for using this drug in patients with progressive MM relied upon the notion that increased bone marrow angiogenesis correlates with advanced phases of MM[21] and on data from previous

studies showing the antiangiogenic activity of thalidomide *in vitro*.[22] Response rates of about 30% of patients initially reported by Singhal *et al*.[3] were subsequently extended and confirmed by other groups in independent series of patients.[8-12] Hence, after almost three decades of unsuccessful clinical trials addressing the search for novel drugs with documented antimyeloma activity, the therapeutic armamentarium for the management of MM has been expanded by the introduction of thalidomide. Adddition of dexamethasone to thalidomide in patients who failed to benefit from prior therapy, including both thalidomide and dexamethasone given as single agents, further increased responses by approximately 20%, up to an overall response rate of 50% to 55%.[13-15] These data suggested a synergistic activity of thalidomide and dexamethasone[23] and prompted several groups to explore this combination also in patients with previously untreated MM.[16,17]

The aim of the present study was to evaluate the efficacy and toxicity of thalidomide and dexamethasone administered as primary therapy in an attempt to reduce tumor cell mass before autologous transplantation. For this use, combined vincristine, doxorubicin and pulse dexamethasone (VAD) has been considered for many years the standard treatment[1,2,24] because of the rapidity of response and, more importantly, the lack of stem cell injury. However, with use the popularity of VAD has been tempered by the inconvenience and economic costs of a 4-day continuous infusion, the risk of cathether-related complications (e.g. infections and thrombosis) and toxicity.[25] Obviously, availability of an effective, oral alternative to VAD, which obviates its disadvantages without interfering with stem cell collection, is likely to be of clinical relevance.

This phase 2 study enrolled previously untreated patients with symptomatic MM under the age of 65 who were candidates to receive double autologous transplantation. Most of the patients had advanced clinical stage and approximately 40% to 50% had high-risk disease, as defined by the presence of elevated serum β2 microglobulin levels and/or chromosome 13 abnormalities. Using stringent criteria for evaluation of response,[18] we observed on an intent-to-treat basis an overall response rate of 66%, including 17% of CR/nCR or VGPR. These results were consistent with those recently reported by two other groups using the same treatment combination in comparable groups of patients[16,17] and did not differ from the rate of response expected by administering a more complex combination of VAD.[26] Of concern, response to thalidomide-dexamethasone was not influenced by chromosome 13 abnormalities. The rapidity of response seen with combined thalidomide-dexamethasone was also similar to that previously reported with VAD[26] and permitted early stem cell harvesting.

Because of early concerns that prior exposure to thalidomide may interfere with stem cell mobilization,[27,28] possibly through modulation of cell surface molecules involved in the adhesion cascade,[29,30] an important end point examined in our study was the success of PBSC collection. Considering 2×10^6/kg $CD34^+$ cells as the minimum dose necessary to perform a single autologous transplantation safely, 80% of the patients who received HD-CTX yielded sufficient cells to receive two sequential courses of high-dose therapy. The median number of $CD34^+$ cells collected was 7.1×10^6/kg, a value similar to that reported under similar conditions by Weber *et al*. using only G-CSF[17] and by Ghobrial *et al*. with combined HD-CTX (3 g/m^2) and G-CSF.[31] Differently from the study by Ghobrial *et al*., in our study patients had their thalidomide discontinued the day before administration of HD-CTX. On the basis of these results, it appears that short exposure to thalidomide therapy does not adversely affect the collection of an adequate number of PBSC to support two sequential courses of high-dose therapy.

Although most of our patients did not need to interrupt therapy or to reduce the doses, thalidomide was not without toxicity. In addition to the most common side effects, which were generally mild and well manageable, DVT emerged as the most troublesome adverse event associated with primary thalidomide-dexamethasone therapy. The frequency of DVT among patients with advanced and refractory MM was reported to be less than 5% with the use of thalidomide alone and increased substantially, up to 16%, when thalidomide was combined with chemotherapy regimens containing doxorubicin.[6,7] A high risk of DVT, ranging from 10% to 28%, was also observed among patients with *de novo* MM who received thalidomide combined with dexamethasone or with chemotherapy regimens that included doxorubicin and dexamethasone.[16,17,20,32,33] The rate of DVT observed in our study (16%) was in the range reported in previous studies. In accordance with prior observations, episodes of DVT occurred early in the course of therapy. However, no relationship between thrombosis and response to induction therapy could be demonstrated. In addition, we were unable to identify any laboratory prothrombotic abnormality that was predictive of an increased risk of DVT, including acquired activated protein C (APC) resistance. In contrary, other groups found a higher frequency of APC resistance, in the absence of factor V Leiden mutation, among patients who had episodes of DVT.[34] Recently, a substantial increase in factor VIII coagulant activity and von Willebrand factor antigen was reported in patients receiving thalidomide therapy for refractory MM or other tumors, although it is unclear whether elevated coagulation factors were related to the thalidomide therapy or to the status of malignancy.[35,36] Further studies are need-

ed in order to elucidate the pathogenetic mechanisms underlying the prothrombotic state associated with primary thalidomide therapy for MM. In the meantime, there is a consensus on the need to reduce the risk of thromboembolic complications for these patients. Due to the lack of prospective, randomized studies addressing this issue, data on the best prophylaxis against DVT are conflicting. After fixed low-dose warfarin had been introduced into our study, we observed a 50% decrease in the frequency of DVT, from 26% down to 13%. In contrast, no clinical benefit from low-dose warfarin was reported by others who eliminated excessive thromboembolic complications by therapeutic anticoagulation with warfarin or low molecular weight heparin.[17,37]

In summary, the results of the present analysis show that the thalidomide-dexamethasone combination is an effective and relatively well tolerated induction regimen for previously untreated patients with MM. Based on the high rate of response and lack of stem cell injury, this combination might provide an oral alternative to VAD in preparation for autologous stem cell transplantation. Obviously, results of ongoing phase III clinical trials comparing first-line thalidomide-dexamethasone versus conventional therapies must be awaited before definite conclusions concerning the role of thalidomide as initial therapy for MM can be drawn. Furthermore, additional important issues that need to be addressed in future clinical trials include the role of thalidomide in combination with chemotherapy or with proteasome inhibitors for induction of remission before autologous stem cell transplantation and/or as consolidation of remission or maintenance therapy after autologous transplantation.

MC designed the study, interpreted the results and drafted the article; EZ, PT, CC, DC, AdV, PT and GP collected and analyzed data; NT and MT performed cytogenetic and FISH analyses; PT reviewed the article; MC, ST and MB gave final approval for the version to be published.

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Appendix

The following is a list of additional investigators who participated in the study:

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References

1. Attal M, Harousseau JL, Stoppa AM, Sotto JJ, Fuzibet JG, Rossi JF, et al. A prospective, randomized trial of autologous bone marrow transplantation and chemotherapy in multiple myeloma. N Engl J Med 1996;335:91-7.
2. Child JA, Gareth JM, Davies FE, Owen RG, Bell SE, Hawkins K, et al. High-dose chemotherapy with hematopoietic stem-cell rescue for multiple myeloma. N Engl J Med 2003;348:1875-83.
3. Singhal S, Mehta J, Desikan R, Ayers D, Roberson P, Eddlemon P, et al. Antitumor activity of thalidomide in refractory multiple myeloma. N Engl J Med 1999; 341:1565-71.
4. Richardson PG, Barlogie B, Berenson J, Singhal S, Jagannath S, Irwin D, et al. A phase 2 study of bortezomib in relapsed, refractory myeloma. N Engl J Med 2003; 348:2609-17.
5. Hayashi T, Hideshima T, Anderson KA. Novel therapies for multiple myeloma. Br J Haematol 2003;120:10-7.
6. Cavenagh JD, Oakervee H. Thalidomide in multiple myeloma: current status and future prospects. Br J Haematol 2003; 120:18-26.
7. Dimopoulos MA, Anagnostopoulos A, Weber D. Treatment of plasma cell dyscrasias with thalidomide and its derivatives. J Clin Oncol 2003;23:4444-54.
8. Juliusson G, Celsing F, Turesson I, Lenhoff S, Adrianson M, Malm C. Frequent good partial remissions from thalidomide including best response ever in patients with advanced refractory and relapsed myeloma. Br J Haematol 2000;109:89-96.
9. Barlogie B, Desikan R, Eddlemon P, Spencer T, Zeldis J, Munshi N, et al. Extended survival in advanced and refractory multiple myeloma after single-agent thalidomide: identification of prognostic factors in a phase 2 study of 169 patients. Blood 2001;98:492-4.
10. Yacoub-Agha I, Attal M, Dumontet C, Delannoy V, Moreau P, Berthou C, et al. Thalidomide in patients with advanced multiple myeloma: a study of 83 patients-report of the intergroupe francophone du myélome. Hematol J 2002; 3:185-92.
11. Tosi P, Zamagni E, Cellini C, Ronconi S, Patriarca F, Ballerini F, et al. Salvage therapy with thalidomide in patients with advanced relapsed/refractory multiple myeloma. Haematologica 2002; 87: 934-42.
12. Mileshkin L, Biagi JJ, Mitchell P, Underhill C, Grigg A, Bell R, et al. Multicenter phase 2 trial of thalidomide in relapsed/refractory multiple myeloma: adverse prognostic impact of advanced age. Blood 2003;102:69-77.
13. Dimopoulos MA, Zervas K, Kouvatseas G., Galani E, Grigoraki V, Kiamouris C, et al. Thalidomide and dexamethasone combination for refractory multiple myeloma. Ann Oncol 2001;12:991-5.
14. Palumbo A, Giaccone L, Bertola A, Pregno B, Bringhen S, Rus C, et al. Low-dose

thalidomide plus dexamethasone is an effective salvage therapy for advanced myeloma. Haematologica 2001;86:399-403.
15. Anagnostopoulos A, Weber D, Rankin K, Delasalle K, Alexanian R. Thalidomide and dexamethasone for resistant multiple myeloma. Br J Haematol 2003; 121: 768-71.
16. Rajkumar SV, Hayman S, Gertz MA, Dispenzieri A, Lacy MQ, Greipp PR, et al. Combination therapy with thalidomide plus dexamethasone for newly diagnosed myeloma. J Clin Oncol 2002; 20: 4319-23.
17. Weber D, Rankin K, Gavino M, Delasalle K, Alexanian R. Thalidomide alone or with dexamethasone for previously untreated multiple myeloma. J Clin Oncol 2003; 21:16-9.
18. Bladè J, Samson D, Reece D, Apperley J, Bjorkstrand B, Gahrton G, et al. Criteria for evaluating disease response and progression in patients with multiple myeloma treated with high-dose therapy and haematopoietic stem cell transplantation. Br J Haematol 1998; 102:1115-23.
19. Lemoli RM, Martinelli G, Zamagni E, Motta MR, Rizzi S, Terragna C, et al. Engraftment, clinical, and molecular follow-up of patients with multiple myeloma who were reinfused with highly purified CD 34^+ cells to support single or tandem high-dose chemotherapy. Blood 2000; 95:2234-9.
20. Cavo M, Zamagni E, Cellini C, Tosi P, Cangini D, Cini M, et al. Deep-vein thrombosis in patients with multiple myeloma receiving first-line thalidomide-dexamethasone therapy. Blood 2002;100:2273.
21. Vacca A, Ribatti D, Roncali L, Ranieri G, Serio G, Silvestris F, et al. Bone marrow angiogenesis and progression in multiple myeloma. Br J Haematol 1994; 87: 503-8.
22. D'Amato RJ, Lougran MS, Flynn E, Folkman J. Thalidomide is an inhibitor of angiogenesis. Proc Natl Acad Sci USA 1994;91:4082-5.
23. Hideshima T, Chauhan D, Shima Y, Raje N, Davies FE, Tai YT, et al. Thalidomide and its analogues overcome drug resistance of human multiple myeloma cells to conventional therapy. Blood 2000; 96:2943-50.
24. The UK Myeloma Forum Guidelines Working Group. Diagnosis and management of multiple myeloma. Br J Haematol 2001;115:522-40.
25. Cavo M, Benni M, Ronconi S, Fiacchini M, Gozzetti A, Zamagni E, et al. Melphalan-prednisone versus alternating combination VAD/MP or VND/MP as primary therapy for multiple myeloma: final analysis of a randomized clinical study. Haematologica 2002;87:934-42.
26. Alexanian R, Barlogie B, Tucker S. VAD-based regimens as primary therapy for multiple myeloma. Am J Hematol 1990; 33:86-9.
27. Munshi N, Desikan R, Anaissie E, Zangari M, Badros A, Lim S, et al. Peripheral blood stem cell collection (PBSC) after CAD + G-CSF as part of total therapy II in newly diagnosed multiple myeloma (MM): influence of thalidomide (Thal) administration. Blood 1999; 94:578a[abstract].
28. Desikan RK, Jagannath S. Therapeutic dilemmas with thalidomide in multiple myeloma: case discussions. Semin Oncol 2001;28:593-6.
29. Nogueira AC, Neubert R, Helge H. Thalidomide and the immune system. 3. Simultaneous up- and down-regulation of different integrin receptors on human white blood cells. Life Sci 1994;55:77-92.
30. Geitz H, Handt S, Zwingenberger K. Thalidomide selectively modulates the density of cell surface molecules involved in the adhesion cascade. Immunopharmacology 1996; 31:213-21.
31. Ghobrial IM, Dispenzieri A, Bundy KL, Gastineau DA, Rajkumar SV, et al. Effect of thalidomide on stem cell collection and engraftment in patients with multiple myeloma. Bone Marrow Transplant 2003;32:587-92.
32. Osman K, Comenzo R; Rajkumar SV. Deep venous thrombosis and thalidomide therapy for multiple myeloma. N Engl J Med 2001;344:1951-2.
33. Zangari M, Anaissie E, Barlogie B. Increased risk of deep-vein thrombosis in patients with multiple myeloma receiving thalidomide and chemotherapy. Blood 2001;98:1614-5.
34. Zangari M, Saghafifar F, Anaissie F, Badros A, Desikan R, Fassaa A, et al. Activated protein C resistance in the absence of factor V Leiden mutation is a common finding in multiple myeloma and is associated with an increased risk of thrombotic complications. Blood Coagul Fibrinolysis 2002;13:187-92.
35. Ward CM, Yen T, Harvie R. Elevated levels of factor VIII and von Willebrand factor after thalidomide treatment for malignancy: relationship to thromboembolic events. Hematol J 2003;4 Suppl 1:S251.
36. Minnema MC, Fijnheer R, De Groot PG, Lokhorst HM. Extremely high levels of von Willebrand factor antigen and of procoagulant factor VIII found in multiple myeloma patients are associated with activity status but not with thalidomide treatment. J Thromb Haemost 2003;1:445-9.
37. Barlogie B, Shaughnessy J, Tricot G, Jacobson J, Zangari M, Anaissie E, et al. Treatment of multiple myeloma. Blood 2004;1:20-32.