Combination therapy with thalidomide and dexamethasone in patients with newly diagnosed multiple myeloma not undergoing upfront autologous stem cell transplantation: a phase II trial

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Background and Objectives. Thalidomide plus dexamethasone (Thal/Dex) has emerged as an effective alternative to vincristine, doxorubicin and dexamethasone as a pre-transplant induction therapy for newly diagnosed multiple myeloma. However, many patients treated initially with Thal/Dex do not proceed to autologous stem cell transplantation (ASCT) and the time to progression and other outcome measures with Thal/Dex as primary therapy for multiple myeloma are not known. We present the first data on the outcome of patients with newly diagnosed multiple myeloma treated with Thal/Dex who did not undergo upfront ASCT.

Design and Methods. We identified 21 patients with newly diagnosed multiple myeloma treated with Thal/Dex on a phase II clinical trial who did not undergo ASCT due to age, comorbidity or the patient's refusal. Patients received thalidomide at a dose of 200 mg/day orally and dexamethasone 40 mg daily on days 1-4, 9-12, 17-20 (odd months) and days 1-4 (even months). Cycles were repeated every 28 days.

Results. The median age was 66 years (range 36-78). The median duration of follow-up was 21 months (range 1-52). One (5%) patient achieved a complete response, and 9 (43%) had a partial response, so the overall response rate was 48%. Of the remaining patients, 7 (33.3%) had stable disease, one patient did not respond, and three died while on therapy prior to response assessment. The median overall survival and time to progression were 21 months and 18 months, respectively.

Interpretation and Conclusions. The median time to disease progression in patients with multiple myeloma who receive initial therapy with Thal/Dex and who do not undergo ASCT is 18 months.

Key words: multiple myeloma, thalidomide, dexamethasone, therapy.

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Multiple myeloma is a malignancy of terminally differentiated plasma cells.[1] In the last few years there has been significant progress in understanding the biology of myeloma and the role of the microenvironment in disease pathogenesis and progression.[2,3] Myeloma cells stimulate angiogenesis in the bone marrow; this, in part, led to the use of thalidomide as a therapeutic agent, given this drug's known anti-angiogenic properties.[4-7] Although the effects of thalidomide on myeloma are not completely understood, the agent can induce significant responses in up to a third of heavily pretreated patients.[6-8] The current management of patients with myeloma who have a good performance status is induction therapy, to control the disease, followed by autologous stem cell transplantation (ASCT) with high-dose melphalan conditioning.[9,10] Vincristine, doxorubicin and dexamethasone (VAD) has been used as induction therapy for disease control and to minimize stem cell toxicity.[11,12] However, VAD is myelosuppressive and requires the placement of indwelling venous catheters for continuous infusion resulting in a significant risk of catheter-related thrombosis and sepsis and early exposure to the potential neurotoxicity of vincristine, and cardiotoxicity of doxorubicin.

Several studies have documented the significant activity of either dexamethasone or thalidomide alone for the control of multiple myeloma.[6, 7,13,14] We have previously reported on the activity of thalidomide and dexamethasone (Thal/Dex) as induction therapy in patients with newly diagnosed multiple myeloma.[15] In that study, Thal/Dex had significant activity, producing a response rate of 64%.[15] Similar results have also been reported by Weber *et al.* and Cavo *et al.*[16,17] More importantly, a recent case-control study found better response rates to Thal/Dex than to VAD.[18] As a result, Thal/Dex is now commonly used as an oral alternative to VAD as pre-transplant induction therapy in patients with newly diag-

nosed myeloma. The regimen has been shown to have no detrimental effect on the subsequent collection of autologous, mobilized stem cells prior to transplantation.[19] Although ASCT is a relatively safe procedure with a mortality of 1–2% in experienced centers, many patients are not eligible for the procedure because of advanced age or the presence of co-morbidities.[20] In addition, some patients refuse to undergo the procedure and choose to be treated with less aggressive therapy. The time to progression and other survival measures with Thal/Dex as primary therapy for newly diagnosed myeloma are not known. The purpose of this study was to determine the time to progression, progression-free survival and overall survival in patients with newly diagnosed multiple myeloma treated with Thal/Dex who did not undergo upfront ASCT.

Design and Methods

Eligibility

Patients with previously untreated and symptomatic myeloma who received Thal/Dex as initial therapy for myeloma on a Mayo Clinic Phase II clinical trial and who did not undergo upfront ASCT were studied. The eligibility and response criteria, response rate and toxicity profile for the parent phase II clinical trial have been reported previously.[15] Briefly, patients were required to have measurable disease, defined as a serum monoclonal (M) protein ≥20g/L and/or urine M protein ≥400mg/24 hours and at least 10% bone marrow plasma cells. Patients with a hemoglobin concentration less than 70 g/L, an absolute neutrophil count less than 1×10^9/L, a platelet count less than 25×10^9/L or an Eastern Cooperative Oncology Group (ECOG) performance score of 4 were excluded. Women of childbearing potential who refused to use two methods of contraception, and women who were either pregnant or nursing were not eligible for the study. Similarly, men who were unwilling to use a condom were not allowed on the study. In addition, all women of childbearing age were required to have a pregnancy test before study entry and every two weeks while on the study. All patients gave written informed consent before study entry. The study and consent forms were approved by the Mayo Institutional Review Board in accordance with federal regulations and the Declaration of Helsinki. All the physicians prescribing thalidomide and all study participants adhered to the requirements of the System of Thalidomide Education and Prescribing Safety (STEPS) program.

Treatment schedule

Thalidomide was given orally at a dose of 200 mg daily. If grade 2 or higher toxicity was encountered, the dose of thalidomide was reduced to 50 or 100 mg daily. Dexamethasone was given at a dose of 40 mg daily on days 1 to 4, 9 to 12, 17 to 20 on odd cycles and days 1 to 4 on even cycles with cycles given every 28 days.[15]

Response and toxicity criteria

The primary end-point of this trial was a confirmed response at two consecutive evaluations at least 4 weeks apart. The response and progression criteria used in this study are standard Mayo Clinic and ECOG criteria. A response was defined as a reduction of serum and urine M protein by at least 50% accompanied by a similar reduction of soft tissue plasmacytomas if present. In patients with only a urine M spike, a 90% or greater reduction in the protein level was required for a response. A complete response required complete disappearance of M protein in the serum and urine by immunofixation and absence of M plasma cells in the bone marrow while a partial response was defined by at least a 50% decrease in the serum M protein. Disease progression was defined as a 50% increase in the M protein over the lowest response level. An increase in the size of existing lytic bone lesions or soft tissue plasmacytomas or the appearance of new lytic lesions also constituted progression.[15] A repeat M protein evaluation was required to confirm progression based on serum or urine monoclonal protein increase. However, if progression in the M protein was accompanied by any other unequivocal evidence of progression, a repeat measurement was not necessary. Disease that did not satisfy the criteria for response, complete response, partial response or progression was categorized as stable disease. In addition to the above criteria, responses are also reported using the criteria established by Blade *et al.*[21] The study was initiated before the introduction of the European Bone Marrow Transplant (Blade) criteria for response.[21] Thus, time to progression and progression-free survival for this study could not be defined according to the EBMT criteria. The National Cancer Institute Common Toxicity Criteria (2.0) were used to grade adverse effects.

Statistical analysis

Fisher's exact test was used to compare differences in nominal variables. Overall survival was defined as the time from study entry to death. Time to progression was defined as the time from study entry to disease progression. Progression-free survival was defined as time from study entry to disease progression or death from any cause. The survival analyses were performed using the Kaplan-Meier method.

Results

In the parent clinical trial, 50 patients were enrolled and 29 proceeded to an ASCT after four to six cycles of

therapy with Thal/Dex. The remaining 21 patients are the subjects of this report. Of the 21 patients, 11 were male and 10 were females. The median age was 66 years (range, 36–78). All patients had symptomatic myeloma that required therapy. The demographic and laboratory characteristics of these patients are listed in Table 1. Based on the International Staging System (ISS), ten had stage 1 disease (47%), five (24%) had stage II disease and six (29%) had stage III disease. The patient distribution is similar to that of the initial description of the ISS in which 30% of the patients had Durie Salmon stage 1 disease.

Response to therapy

The median duration of therapy was 5 months (5 cycles) with the range being from 1 to 42 months. Based on the criteria originally used in the parent trial, one patient achieved a complete response (5%) and nine (43%) had a partial response, giving an overall response rate of 48%. Seven patients (33%) had stable disease, one patient had no response to the combination of thalidomide and dexamethasone, and three patients died while on study prior to response assessment. Based on the Blade criteria for a response, one patient achieved a complete response, and nine patients achieved a partial response (response rate, 48%). In addition, four patients had a minor response; the response rate including minor responses was 67%. Of the remaining patients, two had stable disease, two had no response, and the remaining three could not be evaluated for response.

Survival and time to progression

All patients have discontinued therapy. Six patients experienced progression while on therapy. Nine patients could not continue therapy for a variety of reasons other than progressive disease. In three patients, therapy had to be stopped due to adverse effects; three patients died while on study, and two more patients refused further therapy. In one patient therapy had to be stopped because of an underlying medical condition. The three deaths were due to pancreatitis, infection, and suspected pulmonary embolism. The median overall survival for this cohort of patients was 21 months and the median time to progression was 18 months (Figure 1), while progression-free survival was 11 months.

Toxicity

The most common adverse effects were fatigue (42%), constipation (42%), paresthesiae (38%), edema (29%), tremor (17%) and dizziness (17%). Grade 3 or 4 toxicity was observed in nine patients (42.8%). The major grade 3-4 toxicities attributable to the therapeutic regimen are listed in Table 2. Of the 21 patients in this study, one had a documented episode of deep venous thrombosis. Another patient died suddenly at his local hospital after developing acute dyspnea. The presumed diagnosis was pulmonary embolism, although clinically the patient did not have evidence of deep venous thrombosis.

Table 1. Clinical and laboratory characteristics of the cohort.

Characteristic	*Number (Range)*	*%*
Gender		
Male	11	52
Female	10	48
Age (years)	66 (36 - 78)	
Immunoglobulin isotype		
IgG	15	71.4
IgA	4	19
Non-secretory	2	9.6
Light chain		
κ	15	71.4
λ	6	28.6
Bone marrow plasma cells (%)	50 (20–85)	
Plasma cell labeling index	0.8 (0–8)	
Serum albumin (g/dL)	3.6 (2.6–5.4)	
β-2 microglobulin (mg/dL)	3.34 (1.0–33)	
C-reactive protein	0.5 (0.4–3.9)	
International Staging System		
I	10	47
II	5	24
III	6	29

Table 2. Grade 3 and 4 toxicity in the cohort of patients (n=24).

Toxicity	*Incidence (%)*
Thrombosis	2 (9.5)
Constipation	1 (4.8)
Sedation	1 (4.8)
Neuropathy	1 (4.8)
Edema	1 (4.8)
Fatigue	1 (4.8)
Fever	1 (4.8)
Syncope	1 (4.8)
Anxiety	1 (4.8)
Cardiovascular	1 (4.8)
Inner ear	1 (4.8)

**One patient had grade 5 toxicity with fatal pancreatitis.*

Discussion

In the last decade, there have been major developments in therapy for multiple myeloma.[22] Many agents have been introduced that have significant activity against the disease, including thalidomide, lenalidomide, and bortezomib.[6,7,23] Combinations of chemotherapeutic agents are increasingly available and the role of ASCT is becoming better defined.[12, 24-26] There is a large cohort of patients with myeloma who do not undergo

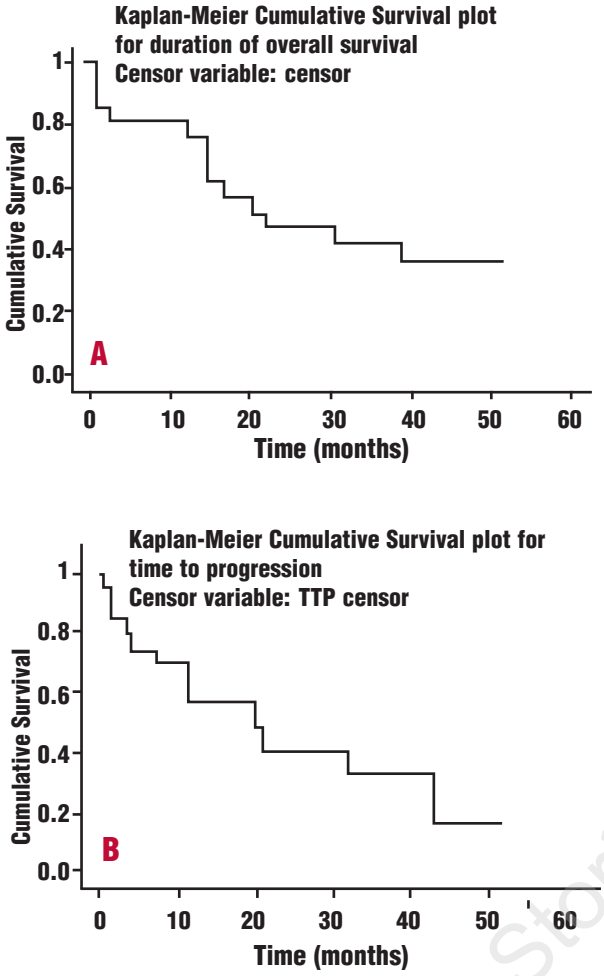

Figure 1. Kaplan-Meier estimate of overall survival (A) and time to progression (B) in this cohort of patients.

upfront ASCT because of advanced age, comorbid conditions, or because they refuse this procedure. Such patients are typically offered therapy with melphalan and prednisone.[27-29] The combination of melphalan and prednisone is associated with a response rate of up to 50% and a median overall survival of 35 months.[27-30] Although Thal/Dex was developed as a replacement for VAD as induction therapy prior to ASCT, it is increasingly being used as initial therapy for patients who are not candidates for ASCT in an attempt to avoid alkylators early in the course of the disease.

In this study, we report on the outcome of a cohort of patients with newly diagnosed multiple myeloma who were treated with Thal/Dex as initial therapy and who did not proceed to ASCT. Thal/Dex therapy was associated with a response rate of 48% and a time to disease progression of 18 months. The median overall survival of this cohort of patients was 21 months. Since non-transplant candidates were allowed entry into this trial, and the cohort excluded those eligible for ASCT, the results are similar to those seen with the melphalan-prednisone regimen. The response rates appear inferior to those of previously published studies on Thal/Dex. This is probably related to patient selection issues that generally limit retrospective analyses, as evidenced by the possibility that patients not responding well to therapy had a greater likelihood of being denied transplantation. This possibility is supported by the fact that based on the current study and the published results of the parent trial, one can calculate that the response rate in the patients who underwent transplantation in the parent trial would be 76%, higher than the response rate reported for the overall cohort of 50 patients (64%). In addition, the older age of the patients in the currently reported subgroup may have contributed to a lower response rate; older patients with relapsed disease treated with thalidomide have been reported to have inferior responses.[31] Because an intent-to-treat analysis was used, all three patients on the parent trial who died prior to response assessment were included in the present study, which lowers the response rate of this cohort compared to that of the cohort that proceeded to transplant. Finally the lower response rate may also be related to random error because of the small sample size studied.

As a result of patient selection issues and the fact that all early deaths within the first 4 months of therapy, including those that occurred in potential transplant candidates, were included in this study population, the survival and progression-free survival estimates we report likely underestimate true intent-to-treat results. The time-to-progression estimates on the other hand are not influenced by these factors and likely represent true estimates. However, many patients stopped therapy early, and median duration of treatment was only 5 months. Our finding of similar time to progression rates in patients who discontinued therapy before progression and those who continued treatment until their disease did progress is in contrast to the result of a recent randomized study by Attal and colleagues in which a benefit was found from continuing with maintenance thalidomide therapy until disease progression.[32] This discrepancy in results may be due to sample size issues and thus the time to progression in patients treated until progression could, potentially, be longer than 18 months. The discrepancy could also be related to the difference in the patient cohorts studied in the two trials: Thal/Dex in newly diagnosed patients who did not undergo transplantation (our study) versus post-transplantation maintenance therapy with thalidomide in *thalidomide naïve* patients (Attal and colleagues).

The combination of Thal/Dex has been associated with venous thromboembolic events and the incidence of this complication may be as high as 16% in treated patients.[17,33,34] This has prompted most clinicians to treat patients on thalidomide with prophylactic antithrombotic therapy such as warfarin or low molecular weight heparin. In one study, therapy with low molecular

weight heparin essentially eliminated the risk of thromboembolic events associated with thalidomide.[35] Our patients did not receive any thromboprophylaxis and there was possibly one fatal event. Since our study population was small, this aspect requires further evaluation.

In conclusion, more data are needed on the combination of Thal/Dex as initial therapy for patients with multiple myeloma who are not candidates for high-dose therapy and ASCT. The combination yields a time to disease progression of 18 months when used as initial therapy. Our study is limited by its sample size and the heterogeneity of patients not undergoing transplantation, who may either refuse to undergo the procedure or be ineligible because of their age, comorbid conditions or performance status. Nevertheless this study provides the first data on the estimated time to progression that physicians can expect with such an approach, and also demonstrates the limitations of Thal/Dex as primary therapy. A double-blind randomized trial comparing Thal/Dex to dexamethasone alone as primary therapy for myeloma is currently ongoing and will shed greater light on the overall survival and time to progression with this combination. Other investigators are evaluating combinations of melphalan, prednisone and thalidomide,[36] as well as melphalan, prednisone, and bortezomib in this setting.

DD, SVR, TEW, MAG, RAK, AD, and PRG were involved in conception and design of the study, provision of study patients, data analysis and interpretation, and manuscript review and approval. JAL, RF, MQL and SH were involved in the conception and design of the study, provision of study patients, and manuscript review and approval. GSN was involved in data analysis, manuscript writing, review and approval. SVR has received grant support from Celgene for the conduct of clinical trials at Mayo Clinic. RAK has served as a consultant for Celgene.

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References

1. Kyle RA. Diagnosis of multiple myeloma. Semin Oncol 2002;29:2-4.
2. Cheung WC, Van Ness B. The bone marrow stromal microenvironment influences myeloma therapeutic response in vitro. Leukemia 2001; 15:264-71.
3. Dalton WS. The tumor microenvironment: focus on myeloma. Cancer Treat Rev 2003; 29 Suppl 1:11-9.
4. 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.
5. Rajkumar SV, Kyle RA. Angiogenesis in multiple myeloma. Semin Oncol 2001; 28:560-4.
6. 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.
7. Rajkumar SV, Fonseca R, Dispenzieri A, Lacy MQ, Lust JA, Witzig TE, et al. Thalidomide in the treatment of relapsed multiple myeloma. Mayo Clin Proc 2000; 75:897-901.
8. D'Amato RJ, Lentzsch S, Anderson KC, Rogers MS. Mechanism of action of thalidomide and 3-aminothalidomide in multiple myeloma. Semin Oncol 2001; 28:597-601.
9. Harousseau JL, Attal M, Divine M, Marit G, Leblond V, Stoppa AM, et al. Autologous stem cell transplantation after first remission induction treatment in multiple myeloma. A report of the French Registry on Autologous Transplantation in Multiple Myeloma. Stem Cells 1995;13 Suppl 2:132-9.
10. 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. Intergroupe Francais du Myelome. N Engl J Med 1996;335:91-7.
11. Alexanian R, Barlogie B, Tucker S. VAD-based regimens as primary treatment for multiple myeloma. Am J Hematol 1990; 33: 86-9.
12. Johnson RJ, Owen RG, Smith GM, Child JA, Galvin M, Newton LJ, et al. Peripheral blood stem cell transplantation in myeloma using CD34 selected cells. Bone Marrow Transplant 1996;17:723-7.
13. Friedenberg WR, Kyle RA, Knospe WH, Bennett JM, Tsiatis AA, Oken MM. High-dose dexamethasone for refractory or relapsing multiple myeloma. Am J Hematol 1991; 36:171-5.
14. Alexanian R, Dimopoulos MA, Delasalle K, Barlogie B. Primary dexamethasone treatment of multiple myeloma. Blood 1992;80: 887-90.
15. 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.
16. 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.
17. Cavo M, Zamagni E, Tosi P, Cellini C, Cangini D, Tacchetti P, et al. First-line therapy with thalidomide and dexamethasone in preparation for autologous stem cell transplantation for multiple myeloma. Haematologica 2004;89:826-31.
18. Cavo M, Zamagni E, Tosi P, Tacchetti P, Cellini C, Cangini D, et al. Superiority of thalidomide and dexamethasone over vincristine-doxorubicin-dexamethasone (VAD) as primary therapy in preparation for autologous transplantation for multiple myeloma. Blood 2005;106:35-9.
19. Ghobrial IM, Dispenzieri A, Bundy KL, Gastineau DA, Rajkumar SV, Therneau TM, et al. Effect of thalidomide on stem cell collection and engraftment in patients with multiple myeloma. Bone Marrow Transplant 2003;32:587-92.
20. Harousseau JL. High-dose therapy in multiple myeloma. Ann Oncol 2002;13 Suppl 4: 49-54.
21. Blade 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 by high-dose therapy and haemopoietic stem cell transplantation. Myeloma Subcommittee of the EBMT. European Group for Blood and Marrow Transplant. Br J Haematol 1998; 102: 1115-23.
22. Kyle RA, Rajkumar SV. Multiple myeloma. N Engl J Med 2004; 351:1860-73.
23. 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.
24. Corso A, Barbarano L, Zappasodi P, Cairoli R, Alessandrino EP, Mangiacavalli S, et al. The VAD-DCEP sequence is an effective pre-transplant therapy in untreated multiple myeloma. Haematologica 2004; 89:1124-7.
25. Attal M, Harousseau JL, Facon T, Guilhot F, Doyen C, Fuzibet JG, et al. Single versus double autologous stem-cell transplantation for multiple myeloma. N Engl J Med 2003; 349:2495-502.
26. Harousseau JL, Attal M. High-dose therapy in multiple myeloma. Hematol J 2003;4: 163-70.
27. Bergsagel DE, Bailey AJ, Langley GR, MacDonald RN, White DF, Miller AB. The chemotherapy on plasma-cell myeloma and the incidence of acute leukemia. N Engl J Med 1979;301:743-8.
28. Cooper MR, McIntyre OR, Propert KJ, Kochwa S, Anderson K, Coleman M, et al. Single, sequential, and multiple alkylating agent therapy for multiple myeloma: a CALGB Study. J Clin Oncol 1986;4:1331-9.
29. Boccadoro M, Marmont F, Tribalto M, Avvisati G, Andriani A, Barbui T, et al. Multiple myeloma: VMCP/VBAP alternating combination chemotherapy is not superior to melphalan and prednisone even in high-risk patients. J Clin Oncol 1991;9:444-8.
30. Salmon SE, Haut A, Bonnet JD, Amare M, Weick JK, Durie BG, et al. Alternating combination chemotherapy and levamisole improves survival in multiple myeloma: a Southwest Oncology Group Study. J Clin Oncol 1983;1:453-61.
31. 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.
32. Attal M, Harousseau JL, Leyvraz L, Doyen D, Hulin C, Benboubker L, et al. Maintenance treatment with thalidomide after autologous transplantation for myeloma: second analysis of a prospective randomized study of the Intergroupe Francophone du Myelome (IFM 99 02). Haematologica 2005; 90 Suppl 1:17.
33. Zangari M, Anaissie E, Barlogie B, Badros A, Desikan R, Gopal AV, et al. Increased risk of deep-vein thrombosis in patients with multiple myeloma receiving thalidomide and chemotherapy. Blood 2001; 98:1614-5.
34. Zangari M, Barlogie B, Thertulien R, Jacobson J, Eddleman P, Fink L, et al. Thalidomide and deep vein thrombosis in multiple myeloma: risk factors and effect on survival. Clin Lymphoma 2003;4:32-5.
35. Zangari M, Barlogie B, Anaissie E, Saghafifar F, Eddlemon P, Jacobson J, et al. Deep vein thrombosis in patients with multiple myeloma treated with thalidomide and chemotherapy: effects of prophylactic and therapeutic anticoagulation. Br J Haematol 2004; 126:715-21.
36. Palumbo A, Bertola A, Musto P, Caravita T, Callea V, Cangialosi C, et al. Prospective randomized trial of oral melphalan, prednisone, thalidomide (MPT) vs oral melphalan, prednisone (MP): an interim analysis. Blood 2004;104:270a[Abstract].