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ORIGINAL ARTICLE

Thalidomide and Dexamethasone Induction Therapy Until Best Response in Recently Diagnosed Patients with Multiple Myeloma: Results From a Pilot Study

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ABSTRACT

Background: Novel therapies for multiple myeloma are not affordable for all healthcare systems. **Objectives:** The objectives of this study were to evaluate the response rates, overall survival, event-free survival, and toxicity of thalidomide and dexamethasone administered until best response in recently diagnosed patients with multiple myeloma. **Methods:** All recently diagnosed multiple myeloma patients meeting the inclusion criteria received the same treatment with thalidomide and dexamethasone. **Results:** We studied 28 patients. Overall response rate was 75%. Complete response, partial response, and very good partial response were 25.0, 32.1, and 17.9%, respectively. The most frequent adverse event related to therapy was neuropathy. Median overall survival was 66 months, and median event-free survival was 39 months (range, 27.6-50.4). Variables that negatively affected overall survival on multivariate analysis included the presence of extramedullary disease, t(14;16), and chromosome 13 deletion. **Conclusions:** Induction therapy with thalidomide and dexamethasone until obtaining the best response in patients with recently diagnosed multiple myeloma was a useful and safe strategy. It represents an alternative for patients with limited access to costly drugs. (REV INVES CLIN. 2015;67:304-12)

Key words: Multiple myeloma. Treatment. Thalidomide. Dexamethasone.

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INTRODUCTION

Multiple myeloma (MM) is the prototype of a spectrum of diseases known as plasma cell dyscrasias. It is a neoplastic disease of unknown etiology, characterized by the abnormal proliferation of plasma cells that produce excessive quantities of a specific immunoglobulin isotype.

In the United States, 14,000 new cases of MM are diagnosed every year[1], representing 1% of all cancers and 10-15% of hematological neoplasias[2].

Early studies implicated angiogenesis inhibition as a therapeutic target in MM[3-7]. Recent studies have revealed that cereblon (CRBN) is the molecular target of the immunomodulatory drugs. Cereblon is a substrate receptor of the cullin ring E3 ubiquitin ligase complex (CRL4^{CRBN}). Thalidomide binds to CRBN to inhibit the function of this complex, which is the regulation of DNA repair, replication, and transcription. Cereblon is the primary target of thalidomide teratogenicity. T-cell co-stimulation by immunomodulatory drugs is cereblon-dependent since they promote the interaction of the transcription factors Aiolos and Ikaros binding to CRL4^{CRBN} with enhanced ubiquitination, which results in proteosomal degradation of T lymphocytes.

The first study reporting treatment efficacy of thalidomide in relapsing MM patients was by Singhal, et al. Most patients had relapsed after autologous stem cell transplantation. Their response (defined as a > 50% decrease in M protein) was documented in 32% of patients. Thalidomide dosage varied between 200 and 800 mg/day[8].

Subsequently, other reports emerged on the use of thalidomide as a single agent in refractory MM with response rates between 24 and 65%[9-14].

There are many studies that proved the combination therapy with thalidomide and dexamethasone as an effective treatment in refractory MM. The overall response rate with this treatment is 41-55%[15-17], and 63-72% in untreated MM[18,19].

In the past decade, MM therapy has radically changed due to the development of treatment regimes that include immunomodulating agents (thalidomide, lenalidomide) and proteasome inhibitors (bortezomib). These treatment regimens have increased response rates and overall survival (OS). Unfortunately, lenalidomide and bortezomib are expensive and not affordable drugs for every healthcare system, particularly those of developing countries.

The primary objective of this study was to evaluate the response rates, and the secondary objectives were to evaluate OS and event-free survival (EFS), in patients treated with thalidomide and dexamethasone as induction therapy, and to evaluate the toxicity of this regimen according to the NCI Common Terminology Criteria for Adverse Events, Version 3.0.

PATIENTS AND METHODS

Study design

The study was approved by the local Ethics Committee (local Ethics Committee protocol number: 1604). It was conducted in accordance with the guidelines stipulated in the Declaration of Helsinki. All enrolled patients signed an informed consent form. All recently diagnosed MM patients meeting the inclusion criteria received the same treatment: thalidomide: initial dose 50 mg orally at night; the dose was increased weekly by 50 mg until 200 mg was reached depending on drug tolerance. Dexamethasone: 40 mg orally on days 1-4, 9-12, and 17-20. Aspirin 100 mg orally every 24 hours since treatment initiation, omeprazole 20 mg orally every 24 hours, sennosides 17.2-34.4 mg in case of constipation. Each cycle was repeated every four weeks until the best response was obtained, or if there was unacceptable toxicity, disease progression, or the patient's wish to withdraw the consent for treatment. We defined best response as: a decrease in monoclonal paraprotein to < 25% (compared with the immediately previous monoclonal spike) after two treatment cycles. In the case of disappearance of the monoclonal component on protein electrophoresis, the status of the monoclonal band by protein immunofixation was assessed after two treatment cycles. The response criteria used were the International Myeloma Working Group Uniform Response Criteria (IMWG): complete response (CR), partial response (PR), very good partial response (VGPR), stable disease, and progressive disease[20].

Table 1. Dose modification according to National Cancer Institute Common Terminology Criteria for Adverse Events toxicity

Drug	Dose modification
Thalidomide	a) Peripheral neuropathy Grade 1 toxicity: thalidomide reduction by 50% Grade 2 toxicity: thalidomide discontinued until symptom resolution or decreased to grade 1 and then thalidomide resumed, reduced by 50% Grade 3 or 4 toxicity: thalidomide suspended indefinitely b) Any other grade 2 toxicity: thalidomide reduction by 50% (if administered dose was 50 mg, it was administered every other day) c) Any other grade 3 toxicity: thalidomide was discontinued; if it improved to grade ≤ 2, then thalidomide reinitiated at 50% of the initial dose
Dexamethasone	Grade ≥ 3 toxicities: dexamethasone discontinued until symptom resolution and then resumed with a dose reduction by one level 1st level reduction: 20 mg orally on days 1-4, 9-12, and 17-20 2nd level reduction: 20 mg orally on days 1-4 and 17-20

The use of zoledronic acid or pamidronate as part of supportive therapy was allowed. Dose modification according to toxicity is shown in table 1. The relative dose intensity (RDI) for thalidomide and dexamethasone was calculated as a function of total dose intended per cycle, divided by the actual dose received at a given cycle. The index of RDI was calculated per cycle.

Eligibility criteria

Inclusion criteria for this study were: recently diagnosed symptomatic patients with MM according to the IMWG[20] and previously untreated; measurable disease defined as serum monoclonal protein ≥ 1.0 g/dl and/or urinary monoclonal protein ≥ 200 mg/24 hours, or free light chain ≥ 10 mg/dl and abnormal ratio; and a signed Informed Consent. Exclusion criteria were: patients with non-secreting MM (absence of quantifiable monoclonal protein), history of previous malignant disease (except *in situ* cervical or breast cancer, basal cell or skin squamous cell carcinoma) unless the patient had been disease-free for ≥ 5 years; pregnant or lactating women; grade ≥ 2 peripheral neuropathy; females in reproductive age who could not use, or who refused, birth control with two methods; and males refusing to use barrier birth control methods.

Statistical analysis

Continuous variables were described as medians and ranges, categorical variables were described as frequencies and proportions. To estimate proportion differences between groups, Fisher's exact test was used. Survival analysis was determined by Kaplan-Meier curves. Survival-related prognostic factors were analyzed with the Cox proportional hazards regression model. Overall survival was calculated from the time of treatment initiation until death or the last date in which we could ascertain that the patient was alive. Event-free survival was calculated from the time of treatment initiation to the date of progression, relapse, or death due to any cause. Analyses were performed using SPSS, v.20.0.

RESULTS

Patients

We included 28 patients between February 2006 and October 2011. Median follow-up was 31 months (range, 2-75). Patient demographic characteristics at diagnosis are shown in table 2. Six patients (21.4%) were considered of high-risk by karyotype (chromosome 13 or 17 deletion) or FISH (deletion of 17p13.1, t(4;14),t(14;16)), and only one had t(11;14).

Response to therapy

The median number of chemotherapy cycles required to reach the best response was 6.5 (range, 2-12). Responses to treatment are shown in table 3. Overall responses (CR + PR + VGPR) were 75%: seven patients experienced CR (25%), nine PR (32.1%), and five VGPR (17.9%).

Table 2. Patient's demographic and clinical characteristics

Characteristic	No. Patients (%)
Total patients	28 (100)
Gender	
Female	17 (60.7)
Male	11 (39.3)
Age (years)	55 (42-76)
Median (range)	
Durie-Salmon stage	
IA	5 (17.9)
IB	2 (7.1)
IIA	15 (53.6)
IIB	0 (0)
IIIA	0 (0)
IIIB	6 (21.4)
ISS disease stage	
I	10 (35.7)
II	9 (32.1)
III	9 (32.1)
ECOG	
1	19 (67.9)
2	6 (21.4)
3	2 (7.1)
4	1 (3.6)
Myeloma subtype	
IgG kappa	7 (25)
IgG lambda	1 (3.6)
IgA kappa	1 (3.6)
IgA lambda	11 (39.3)
Light chain	7 (25.0)
Biclonal	1 (3.6)
Bone lesions	23 (82.1)
Plasmacytoma	3 (10.7)

ISS: International Staging System; ECOG: Eastern Cooperative Oncology Group.

Toxicity

The most frequently observed adverse event was neuropathy, detected in 64.2% of patients; however, only two patients progressed to grade 3 (7.14%). Other adverse events developed in over 10% of cases, and included constipation, Cushing and edema, deep venous thrombosis, and pneumonia. There were three deaths in the induction phase, one due to pneumonia and two in which the cause of death was unknown. Table 4 summarizes the most frequent adverse events.

Dexamethasone was reduced to level 1 in 15 patients (54%), and in 10 of them (36%) it was further reduced to level 2. The median of time to dose reduction level 1 was four months (range, 2-4), and to dose reduction level 2 was six months (range, 4-9). Twelve patients (43%) did not require any reduction.

Table 3. Response to treatment

Response	No. Patients (%)
Complete response	7 (25.0)
Very good partial response	5 (17.9)
Partial response	9 (32.1)
Stable disease	1 (3.6)
Progressive disease	4 (14.3)
Not evaluated	2 (7.1)

Table 4. Adverse events according to National Cancer Institute Common Terminology Criteria for Adverse Events

Adverse event	No. (%)	Grade 3 or 4 No. (%)
Neuropathy	18 (64.2)	2 (7.14)
Cushing	5 (17.9)	0 (0)
Pneumonia	4 (14.2)	4 (14.2)
Constipation	3 (10.7)	1 (3.6)
DVT	3 (10.7)	1 (3.6)
Cellulitis	2 (7.1)	0 (0)
Cytopenias	1 (3.6)	0 (0)
Bradycardia	1 (3.6)	1 (3.6)
Somnolence	1 (3.6)	0 (0)

DVT: deep venous thrombosis.

Thalidomide was reduced in 12 patients (43%), and in six patients (21%) it was suspended indefinitely during the study. The median of time to the first reduction was six months (range, 3-10), and to discontinuation was eight months (range, 4-11). Fourteen patients (50%) did not require any reduction.

The RDI is shown in figure 1. Analysis of RDI per cycle shows that dexamethasone mean RDI was maintained above 74% until cycle 5, and thalidomide mean RDI was maintained above 74% until cycle 9.
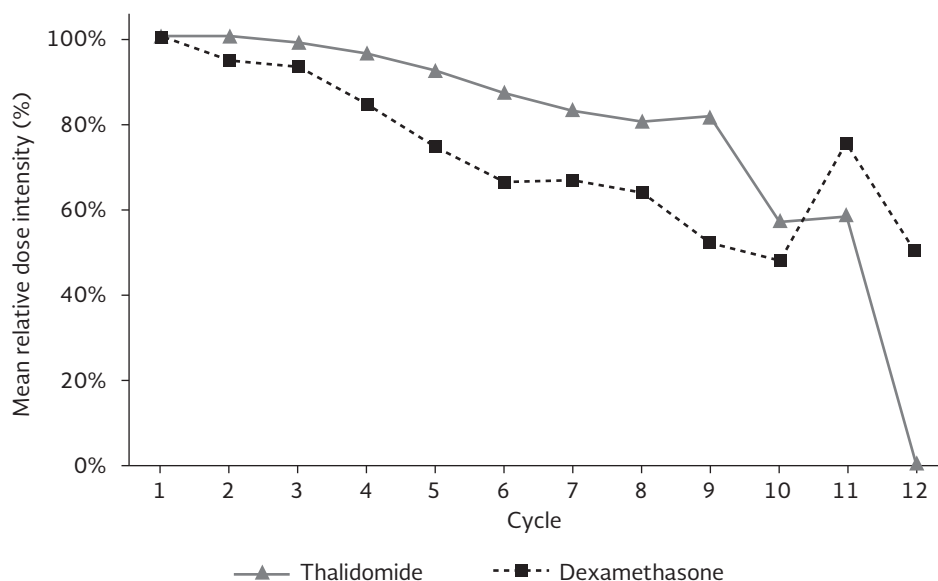
Autologous transplant

Three patients (10.7%) received high-dose melphalan (200 mg/m^2) and autologous transplant as consolidation therapy. Their OS were 50, 66, and 29 months.

Overall survival and event-free survival

Median OS was 66 months (range, 34-not calculable) and median EFS was 39 months (range, 27.6-50.4). Figures 2 A and B show the OS and EFS Kaplan-Meier

Figure 1. Relative dose intensity (dose intended/dose delivered/time) of thalidomide and dexamethasone. Thalidomide mean relative dose intensity was maintained above 74% until cycle 5, and thalidomide mean relative dose intensity was maintained above 74% until cycle 9.

DISCUSSION

This study arose from the need to search for a strategy that would increase the rate of responses and the outcomes of patients with MM in a scenario in which access to drugs such as bortezomib and lenalidomide as well as autologous bone marrow transplantation is limited due to high costs. The purpose of this study was to determine the impact of

curves. On univariate analysis, variables affecting OS were extramedullary disease, chromosome 13 deletion, t(14;16), and patients with high-risk cytogenetics, as a group. The first three variables were still significant on multivariate analysis, HR: 41 (95% CI: 4.1-381.7), p = 0.001; HR: 9.2 (95% CI: 1.1-77.1), p = 0.039; HR: 32.97 (95% CI 1.2-868.8), p = 0.036, respectively. On univariate analysis of EFS, female gender and having been treated with bisphosphonates were variables that improved this outcome, but they did not remain significant on multivariate analysis. After five years, the OS of patients achieving CR was 86%, compared to 58% in the group that did not achieve CR. This difference was not statistically significant, probably due to the small number of patients. Figure 2 (c) shows the OS Kaplan-Meier curve in terms of CR.

thalidomide/dexamethasone administration until the best response was achieved in each patient, the quality of these responses, OS, EFS, and toxicity.

In this report, the number of female patients was higher than that of male patients and the most common isotype was IgA. According to the GLOBOCAN 2012 report, in Mexico, the percentage of MM female patients was 46%. However, in our database from 2007 to 2012, we diagnosed 73 patients with MM, of which 55% were female, and IgG isotype was the most common (48%) followed by IgA (30%). Therefore, we think that the higher frequency of IgA isotype found in our report was just a population bias.

A previously published series of patients treated with 4-6 cycles of thalidomide/dexamethasone that were not candidates for autologous transplant, yielded the following results: CR 5%, OS 21 months, and EFS 11 months[21]. Parameters defining CR and OS were more stringent in our study. We must underscore that the median age in that study[21] was 66 years (range, 36-78), higher than in our study.

Two phase III trials designed in parallel were conducted to answer two separate questions concerning the efficacy of thalidomide/dexamethasone at short term (four months) developed by Eastern Cooperative

Figure 2. Kaplan-Meier plots for overall survival (A), event-free survival (B), and overall survival by complete response (C). Five-year overall survival for patients that reached complete response was 86% (continuous line) compared to 58% of patients that did not (dotted line).
CR: complete response.
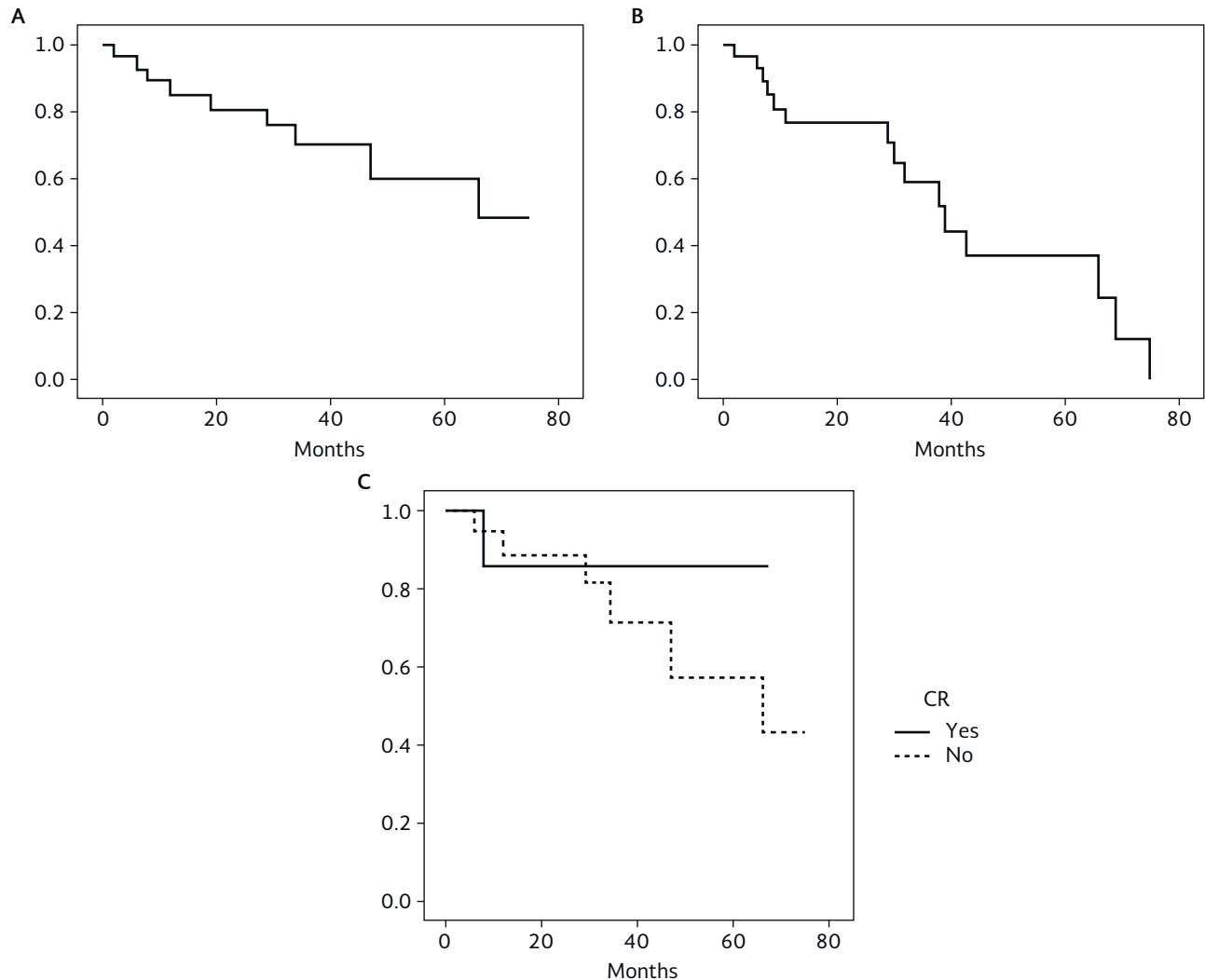
Oncology Group, and at long term (until progression) developed in the USA, Australia, Poland, and Spain. In the first study[18], since therapy was limited to four cycles, complete responses were achieved only in 4% of the patients. In the second study[22], therapy was administered until progression or undue toxicity. Median age was 64 years (range, 39-86). The treatment schedule differed from the one given in the present study in the dexamethasone dose. They administered dexamethasone 40 mg orally on days 1-4, 9-12, and 17-20 during cycles 1 through 4, and 40 mg orally on days 1-4 beginning with cycle 5. Patients treated with thalidomide/dexamethasone reached CR in 7.7% and VGPR plus CR in 44%. The OS at 30 months was 59%, and median PFS was 15 months. As expected due to the lower dexamethasone dose, pneumonia and peripheral neuropathy grades 3 or 4 were less frequent (Table 4); on the other hand, since thromboprophylaxis was not mandatory, deep vein thrombosis was more frequent and they reported pulmonary embolism as well (6.8% grade 3 or 4). In our study, the dexamethasone dose was not reduced beyond a specific cycle, and it was reduced as required by toxicity. The higher rates of CR and VGPR in our study emphasize the role of high-dose dexamethasone.

Table 5. Summary of response and survival rates in other studies

Study	Regimen	CR (%)	≥ PR (%)	PFS (median, months)	OS (median, months)
Rajkumar	Thal/Dex	5	48	11	21
IFM 99-06	MPT	13	76	28	52
GIMEMA	MPT	16	76	22	45
IFM01-01	MPT	7	62	24	44
NMSG study	MPT	13	57	15	29
HOVON study	MPT	ND	66	13 (EFS)	40
Current study	Thal/Dex	25	75	39 (EFS)	66

CR: complete response; PR: partial response; PFS: progression-free survival OS: overall survival; EFS: event-free survival; IFM: Intergroupe Francophone du Myélome; GIMEMA: Gruppo Italiano Malattie Ematologiche dell'Adulto; NMSG: Nordic Myeloma Study Group; HOVON: Hemato-Oncologie voor Volwassenen Nederland; Thal/Dex: thalidomide/dexamethasone; MPT: melphalan, prednisone, thalidomide; ND: not determined.

If we compare the results of thalidomide/dexamethasone administration until achieving the best response, with phase III results of the melphalan/prednisone/thalidomide (MPT) arm of a trial comparing MPT vs. melphalan/prednisone, the median age of patients in these studies was also higher than that of our group[23-27]. Although MPT is a triple drug combination, the steroid used is prednisone, which is a less potent drug than dexamethasone in the treatment of MM. Complete remission rates varied between 7 and 16%, median OS was 29-52%, and PFS was 13-28%.

Although it is inappropriate to compare those reported OS with ours due to the great difference in patients' median ages, our CR rate practically doubled that obtained with MPT, and relapses occurred at least 11 months earlier than the ones of the patients treated with our strategy. Table 5 depicts response rates and outcomes of several studies.

The frequency of grade 3 and 4 infections referred in our study is similar to that in the MPT study, but more frequent than in the study by Rajkumar, et al.[21].

Only one patient developed grade 3 deep venous thrombosis in our study. Unlike Rajkumar's study[21] in which no patient received prophylactic anti-thrombotic therapy, it was mandatory that all patients in our cohort be treated with aspirin 100 mg/day, except in cases that were anti-coagulated for medical reasons. The frequency of thrombosis was also lower than that reported by the GIMEMA group (11%)[24], but in that study no anti-thrombotic prophylaxis was initially administered; once half of the patients had been recruited, a frequency of grade 3 or 4 thrombosis of 17% was observed; afterwards, prophylactic enoxaparin was administered during the first four chemotherapy cycles, resulting in a decrease of the number of these episodes to 3%. The GIMEMA[24] and IFM 99-06[26] studies reported grade 3 or 4 thrombosis in 12% of cases and neither used anti-thrombotic prophylaxis.

The frequency of grade 3 or 4 peripheral neuropathy was 7%, similar to that reported in two MPT series. The HOVON[27] study reported a rate of peripheral neuropathy of 23%, but that study administered thalidomide as maintenance therapy. Table 6 summarizes the adverse events in different studies.

As expected, extramedullary disease, chromosome 13 deletion, and t(14;16) were deleterious factors in OS. One patient's karyotype showed a 19p13 deletion; this chromosomal abnormality has been previously described in MM[28,29], but its prognostic significance has not been determined. It has also been described in pre-B acute lymphoblastic leukemia. This gene encodes the immunoglobulin enhancer-binding factor E12/E47. This patient's disease was characterized by extramedullary plasmacytomas of the larynx and colon, and the 19p13 deletion was the only chromosomal abnormality detected.

Patients that achieved CR had an OS of 86% at five years. Achieving CR and maintaining it has a direct impact on OS; this has been previously shown in patients treated with total therapy 2 (TT2)[30] that had an OS at three years of almost 90% in the group that went into CR and maintained it, vs. 65% in the group that did not achieve CR. Another study showed that achieving CR is an independent factor in the long-term outcome,

Table 6. Summary of grade 3 or 4 adverse events in other studies according to National Cancer Institute Common Terminology Criteria for Adverse Events

Study	Regimen	Infection (%)	Thrombosis (%)	Peripheral neuropathy (%)
Rajkumar	Thal/Dex	5	10	6
IFM 99-06	MPT	13	12	6
GIMEMA	MPT	10	12	8
IFM01-01	MPT	ND	6	2
NMSG study	MPT	ND	ND	6
HOVON study	MPT	28	3	23
Current study	Thal/Dex	14	4	7

IFM: Intergroupe Francophone du Myélome; GIMEMA: Gruppo Italiano Malattie Ematologiche dell'Adulto; NMSG: Nordic Myeloma Study Group; HOVON: Hemato-Oncologie voor Volwassenen Nederland; Thal/Dex: thalidomide/dexamethasone; MPT: melphalan, prednisone, thalidomide; ND: not defined.

regardless of age and International Staging System score[31].

The use of high dexamethasone doses (480 mg/month) is considered unnecessary when using a treatment regimen that includes bortezomib or lenalidomide, and it may even be deleterious in terms of adverse events and mortality when compared with the use of low dexamethasone doses[32]. Lenalidomide and thalidomide have similar structures and mechanisms of action. Both drugs direct cytotoxic effects on myeloma cells and are capable of inducing apoptosis or programmed cell death[33]. Also, these agents are capable of stimulating T-cell, interleukin-2 (IL-2), and interferon (IFN)-γ production. Lenalidomide has been shown to be anywhere from 50 to 2,000 times more potent than thalidomide in the stimulation of T-cell production, and 50-100 times more potent in the stimulation of IL-2, and IFN-γ production. The augmentation of T-cell response leads to an increased production of IL-2, which in turn leads to alterations in the number and function of natural killer (NK) cells, increasing the activity of NK-dependent cytotoxicity. In addition, thalidomide and lenalidomide have been shown to inhibit the production of tumor necrosis factor (TNF)-α through two mechanisms: increasing the degradation of TNF-α mRNA and increasing the activity of α-1-acid glycoproteins, which have intrinsic anti-TNF-α activity[34,35]. Such inhibition leads to decreased myeloma cell growth and survival. Here, too, lenalidomide has been shown to be more potent than thalidomide. Some suggest that lenalidomide may be up to 50,000 times more potent in inhibiting TNF-α than thalidomide[36]. In addition, these agents

are capable of modulating the expression of cell surface adhesion molecules, interfering with growth signaling between myeloma cells and bone marrow stromal cells[37]. Lastly, these agents are capable of reducing angiogenesis through the inhibition of the secretion of vascular endothelial growth factor (VEGF), a pro-angiogenic cytokine that is secreted by bone marrow stromal cells and myeloma cells[38]. Inhibition of VEGF leads to alterations in the microvasculature of the bone marrow environment and inhibits myeloma cell growth and proliferation.

The role of low-dose dexamethasone in combination with thalidomide remains to be determined. Our regimen-associated mortality was 10.7%, which is not negligible; however, the CR and OR (25 and 75%, respectively) as well as an EFS of 39 months in the absence of newer and more potent drugs makes this regimen an attractive strategy. High-dose dexamethasone also increases the risk of thrombosis, but the frequency of grade 3-4 thrombosis was 4% when using aspirin as prophylactic therapy.

In the current study we reported better EFS and OS than other series treated with thalidomide/dexamethasone, as well as higher CR rates. It is possible that our results reflect the effect of uninterrupted therapy versus limited number of cycles.

Induction therapy with thalidomide and dexamethasone until achieving the best response in patients with recently diagnosed MM is a useful and safe strategy. It represents an affordable alternative for patients with limited access to more expensive drugs.

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