Lenalidomide plus dexamethasone versus thalidomide plus dexamethasone in newly diagnosed multiple myeloma: a comparative analysis of 411 patients

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The objective of this case-control study was to compare the efficacy and toxicity of lenalidomide plus dexamethasone (len/dex) versus thalidomide plus dexamethasone (thal/dex) as initial therapy for newly diagnosed myeloma. We retrospectively studied 411 newly diagnosed patients treated with len/dex (228) or thal/dex (183) at the Mayo Clinic. The differences were similar in a matched-pair analysis that adjusted for age, sex, transplantation status, and dexamethasone dose. The proportions of patients achieving at least a partial response to len/dex and thal/dex were 80.3% versus 61.2%, respectively ($P < .001$); very good partial response rates were 34.2% and 12.0%, respectively ($P < .001$). Patients receiving len/dex had longer time to progression (median, 27.4 vs 17.2 months; $P = .019$), progression-free survival (median, 26.7 vs 17.1 months; $P = .036$), and overall survival (median not reached vs 57.2 months; $P = .018$). A similar proportion of patients in the 2 groups experienced at least one grade 3 or 4 adverse event (57.5% vs 54.6%, $P = .568$). Main grade 3 or 4 toxicities of len/dex were hematologic, mainly neutropenia (14.6% vs 0.6%, $P < .001$); the most common toxicities in thal/dex were venous thromboembolism (15.3% vs 9.2%, $P = .058$) and peripheral neuropathy (10.4% vs 0.9%, $P < .001$). Len/dex appears well-tolerated and more effective than thal/dex. Randomized trials are needed to confirm these results. (Blood. 2010;115:1343-1350)

Introduction

Multiple myeloma (MM) is a malignant plasma cell proliferative disorder that accounts for more than 11 000 deaths each year in the United States.[1,2] For more than 40 years, melphalan and prednisone (MP) remained the standard of care for elderly patients. For more than a decade, a combination of vincristine, doxorubicin, and dexamethasone (VAD) was used as pretransplantation induction therapy for patients eligible for stem cell transplantation (SCT).[2-4] The combination of thalidomide plus dexamethasone (thal/dex) has shown significant activity in newly diagnosed MM. Indeed, 2 randomized phase 3 trials compared thal/dex with high-dose dexamethasone alone and reported higher response rates and prolonged time to progression (TTP) in patients receiving thal/dex, even though this did not translate into overall survival (OS) improvement, albeit with relatively short follow-up.[5,6] The main toxicities related to thalidomide therapy were deep vein thrombosis (DVT; 13%-19%) and peripheral neuropathy (3%-7%).[5-7] A randomized study that compared MP with the thal/dex combination in patients not eligible for SCT found that thal/dex resulted in a higher proportion of very good partial response (VGPR) rate and partial response (PR), but TTP, progression-free survival (PFS), and OS were better for MP because of the toxicity of high-dose dexamethasone, especially in patients older than 75 years.[7] A prospective randomized trial comparing thal/dex with standard VAD as pretransplantation induction regimen showed a higher response rate after induction in patients treated with thal/dex, although the benefit was not sustained 6 months after SCT because VGPR rates were almost identical after the high-dose melphalan.[8]

Lenalidomide (CC-5013), an analog of thalidomide, is more potent in preclinical assays than thalidomide[9,10] and has fewer nonhematologic side effects compared with the parent drug.[11,12] In newly diagnosed patients, lenalidomide plus high-dose dexamethasone was compared with high-dose dexamethasone alone in a double-blinded, placebo-controlled trial and was demonstrably superior to high-dose dexamethasone in terms of both response rates and 1-year PFS, but no differences in OS have been reported to date.[13] Another recent phase 3 study compared the combination of lenalidomide plus low-dose dexamethasone with the lenalidomide plus high-dose dexamethasone regimen: major grade 3 or higher toxic effects, including thrombosis (25% vs 9%) and infections (16% vs 6%), were significantly higher in the lenalidomide plus high-dose dexamethasone group, and 1-year OS was significantly better with the association of lenalidomide plus low-dose dexamethasone. The differences were confirmed in both younger and elderly patients.[14]

No randomized trial of thal/dex versus lenalidomide plus dexamethasone (len/dex) has been reported so far, and unfortunately none is ongoing or planned. Thalidomide has significant nonhematologic toxicity, including a high risk of peripheral neuropathy. On the other hand, lenalidomide has more hematologic toxicity than thalidomide, and is not widely available in many

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Table 1. Patient characteristics

Characteristic	All patients			High-dose dexamethasone patients		
	thal/dex (n = 183), n (%)	len/dex (n = 228), n (%)	*P*	thal/dex (n = 72)	len/dex (n = 72)	*P*
Median age, y (range)	60.2 (22.2-79.5)	62.9 (29.0-92.9)	.061	63.3 (36.6-78.7)	63.5 (29.0-78.4)	.952
Less than 65 y	125 (68.3)	127 (55.7)	.009	40 (55.6)	40 (55.6)	> .999
Male sex	109 (59.6)	142 (62.3)	.574	44 (61.1)	43 (59.7)	.865
International Staging System						
I/II*	95 (75.4)	151 (77.4)	.673	41 (71.9)	53 (81.5)	.208
III*	31 (24.6)	44 (22.6)	.673	16 (28.1)	12 (18.5)	.208
Missing	57 (31.2)	33 (14.5)	—	15 (20.8)	7 (9.7)	—
Type of M protein						
IgG	105 (57.4)	136 (59.6)	.642	45 (62.5)	40 (55.6)	.397
IgA	34 (18.6)	43 (18.9)	.942	18 (25.0)	17 (23.6)	.846
No serum M protein	2 (1.1)	4 (1.8)	.696	0 (0)	1 (1.4)	> .999
Biclonal	3 (1.6)	5 (2.2)	.737	0 (0)	2 (2.8)	.497
Light-chain only	19 (10.4)	35 (15.4)	.138	5 (6.9)	9 (12.5)	.400
Missing	20 (10.9)	5 (2.2)	—	4 (5.6)	3 (4.2)	—
Cytogenetic						
High-risk*	17 (37.8)	25 (32.9)	.586	4 (40.0)	9 (33.3)	.715
Data missing	138 (75.4)	152 (66.7)	—	62 (86.1)	45 (62.5)	—
Treatment						
High-dose dexamethasone	135 (73.7)	72 (31.6)	< .001	72 (100)	72 (100)	> .999
Transplantation	110 (60.1)	111 (48.7)	.021	37 (51.4)	37 (51.4)	> .999

Percentages may not total 100 because of rounding.
— indicates not applicable.
*Percentage calculated on number of patients for whom data were available.

countries. The goal of this case-control study was to compare the efficacy and the toxicity of thal/dex versus len/dex as primary therapy for newly diagnosed MM patients.

Methods

Patients and treatment schedule

After approval from the Mayo Clinic Institutional Review Board, data from 411 consecutive patients with newly diagnosed symptomatic MM seen at the Mayo Clinic and treated with thal/dex (183 patients) or len/dex (228 patients) were obtained by review of medical records and our existing database. We included all patients started on these agents, regardless of whether or not the treatment was administered as part of a trial to avoid bias in patient selection. Patients in the thal/dex group were treated from January 2000 through March 2008, whereas patients in the len/dex group were treated from March 2004 through December 2008. Thalidomide was given at a dose ranging from 100 mg/day to 400 mg/day continuously; lenalidomide dose was 25 mg/day, days 1 to 21 on a 28-day cycle. All patients received dexamethasone, either at high dose (40 mg orally on days 1-4, 9-12, and 17-20) or at low dose (40 mg orally on days 1, 8, 15, and 22); each cycle was repeated every 4 weeks. Patients were risk-stratified into 2 groups according to genetic abnormalities. The high-risk group was defined by the presence of at least one of the following abnormalities: deletion of p53 (locus 17p13), translocation t(4;14) or t(14;16) by fluorescent in situ hybridization, or loss of chromosome 13 or its long arm or hypodiploidy by metaphase cytogenetics.[15] The standard-risk group included patients without any of these abnormalities. In addition to studying all patients, we also identified for accurate outcome comparison an equal number of pair mates among patients who received high-dose dexamethasone in the thal/dex and len/dex groups. Case matching was performed with respect to age, sex, and SCT status (patients treated with len/dex who received SCT were matched with patients treated with thal/dex who received SCT; patients treated with len/dex who did not receive SCT were matched with patients treated with thal/dex who did not received SCT).

Assessment of efficacy and safety

higher decrease in the serum monoclonal protein (M-protein) levels from baseline and a greater than 90% reduction in 24-hour urine M-protein excretion or less than 200 mg/24 hours (if M-protein was immeasurable, a 50% or higher decrease in the difference between involved and uninvolved free light chain or a 50% or higher reduction in bone marrow plasma cells); for patients with soft-tissue plasmacytomas, a 50% size reduction was required. A VGPR required a 90% or greater reduction in serum M-protein and urinary M-protein less than 100 mg/24 hours or M-protein detectable by immunofixation but not on electrophoresis. A complete response (CR) was defined as negative serum and urine immunofixation, disappearance of any soft tissue plasmacytoma, and less than 5% plasma cells on bone marrow examination. Disease that did not satisfy the criteria for PR, VGPR, CR, or progressive disease was classified as stable disease. Disease progression required any of the following: 25% or greater increase in serum M-protein (absolute $\geq$ 0.5 g/dL) or urine M-protein (absolute $\geq$ 200 mg/dL) or, in case of immeasurable M-protein, in the difference between involved and uninvolved free light chain (absolute $>$ 10 mg/dL) or 25% increase in bone marrow plasma cell percentage; development of new bone lesions, or plasmacytomas; and disease-related hypercalcemia. All responses needed to be confirmed in at least 2 consecutive assessments. TTP was calculated from the start of therapy until progression, relapse, or last known remission (death from causes other than progression were censored); PFS was calculated from the start of therapy until the date of progression, relapse, death from any cause, or known remission; OS was calculated from the start of therapy until the date of death or the date the patient was last known to be alive. All adverse events (AEs) were graded according to the National Cancer Institute Common Terminology Criteria (Version 3.0).[17]

Statistical analysis

The endpoint of this study was to compare the efficacy (response rate, PFS, TTP, and OS) and the toxicity profile (rate of grade 3 or 4 AEs) of these 2 regimens. Outcomes were analyzed on an intention-to-treat basis. The χ^2 test or 2-sided Fisher exact test was used to compare differences in nominal variables, and the rank-sum test was used for continuous variables. Time-to-event analysis was performed using the Kaplan-Meier method.[18] All comparisons were determined by the log-rank test and by the Cox proportional hazards model to estimate crude hazard ratios (HRs) and 95%

Table 2. Second-line salvage regimens

Regimen	thal/dex (n = 139), n (%)	len/dex (n = 97), n (%)	*P*
Transplantation	14 (10.1)	18 (18.6)	.061
Bortezomib-based regimen	21 (15.1)	28 (28.9)	.014
Lenalidomide-based regimen	34 (24.5)	22 (22.7)	.752
Lenalidomide-bortezomib based regimen	0 (0)	4 (4.1)	.028
Thalidomide-based regimen	23 (16.6)	10 (10.3)	.174
Others	47 (33.8)	15 (15.5)	.002

Results

Patient characteristics

Patient characteristics are listed in Table 1. Median age was similar in the 2 groups, although in the thal/dex group 68.3% of patients were younger than 65 years compared with 55.7% in the len/dex group ($P = .009$). A similar proportion of len/dex and thal/dex patients presented with International Staging System (ISS) stage I/II at diagnosis (77.4% vs 75.4%, $P = .673$). Cytogenetic data were available in only 33.3% of patients who received len/dex and 24.6% of patients treated with thal/dex. The proportions of evaluable patients presenting with high-risk cytogenetic in both groups were similar (32.9% vs 37.8%, respectively, in len/dex and thal/dex groups, $P = .586$). The majority of patients received thalidomide and lenalidomide not as part of a clinical trial. Only 64 of 183 (35.0%) patients and 96 of 228 (42.1%) were treated as part of a clinical trial in the thal/dex and len/dex groups, respectively. A high proportion of patients in the thal/dex group received high-dose dexamethasone compared with patients in the len/dex group (73.7% vs 31.6%, $P < .001$), reflecting changing in clinical practice. Patients were allowed to proceed to SCT if they wished and were deemed eligible for such therapy: 39.9% versus 47.5% of patients, respectively ($P = .121$), in the len/dex and thal/dex groups received SCT as front-line therapy within 9 months after initial diagnosis. Overall, 48.7% versus 60.1% of patients, respectively ($P = .021$), received transplantation at some point during their clinical course. A significantly higher proportion of patients treated with len/dex received salvage therapy (as second-line only) with bortezomib-based regimens (bortezomib-based regimens: 28.9% vs 15.1%, respectively, with len/dex and thal/dex, $P = .014$; lenalidomide plus bortezomib-based regimens: 4.1% vs 0%, respectively, with len/dex and thal/dex, $P = .028$; Table 2). Patient characteristics in the subgroup of matched patients receiving high-dose dexamethasone were similar to those of the whole population.

Response to therapy

Based on standard International Myeloma Working Group criteria, the response rate was significantly higher in len/dex patients compared with thal/dex patients (Table 3). On intention-to-treat analysis, considering all 411 patients, a significantly higher proportion of patients achieved at least a PR with len/dex compared with thal/dex (80.3% vs 61.2%, respectively, $P < .001$). A significant difference between the 2 groups was also found in terms of both VGPR or better (34.2% vs 12.0%, $P < .001$) and CR rate (13.6% vs 3.3%, $P < .001$), respectively. These differences remained significant when the analysis was restricted to 144 patients who received high-dose dexamethasone; len/dex (n = 72) patients obtained a significantly higher proportion of PR or better (90.3% vs 61.1%, $P < .001$), VGPR or better (50.0% vs 9.7%, $P < .001$), and CR (22.2% vs 2.8%, $P < .001$).

Survival

The median duration of follow-up for survivors from diagnosis was 20.9 months in the len/dex group and 46.5 months in the thal/dex group. Duration of therapy was significantly longer in the len/dex patients compared with the thal/dex patients: 36.7% vs 12.6% of patients who did not stop treatment to receive SCT were still receiving immunomodulatory drugs at 1 year ($P < .001$). A significantly higher proportion of patients in the len/dex group was still receiving therapy at the time of analysis compared with patients in the thal/dex group (18.4% vs 7.1%, respectively, $P = .001$). In the following analyses, patients who received SCT and patients who switched to another chemotherapy regimen before progression were censored at the date of transplantation/chemotherapy.

Among all patients, TTP was significantly better in the len/dex group (median, 27.4 months) than in patients receiving thal/dex (median, 17.2 months, HR = 0.64; 95% CI, 0.44-0.93; $P = .019$; Figure 1A). This was also confirmed in the subgroup of pair mates receiving high-dose dexamethasone (median TTP, 33.0 months vs 15.3 months, HR = 0.52; 95% CI, 0.28-0.94; $P = .030$; Figure 1B). Similarly, PFS was significantly higher in len/dex patients,

Table 3. Best responses to treatment

	All patients			High-dose dexamethasone patients		
Response	thal/dex (n = 183), n (%)	len/dex (n = 228), n (%)	*P*	thal/dex (n = 72), n (%)	len/dex (n = 72), n (%)	*P*
CR or VGPR	22 (12.0)	78 (34.2)	< .001	7 (9.7)	36 (50.0)	< .001
PR or better	112 (61.2)	183 (80.3)	< .001	44 (61.1)	65 (90.3)	< .001
CR	6 (3.3)	31 (13.6)	< .001	2 (2.8)	16 (22.2)	< .001
VGPR	16 (8.7)	47 (20.6)	< .001	5 (6.9)	20 (27.8)	.001
PR	90 (49.2)	105 (46.1)	.528	37 (51.4)	29 (40.3)	.181
SD	42 (22.9)	26 (11.4)	.002	21 (29.2)	3 (4.2)	< .001
PD	1 (0.6)	5 (2.2)	.232	1 (1.4)	1 (1.4)	> .999
NA	28 (15.3)	14 (6.1)	—	6 (8.3)	3 (4.2)	—

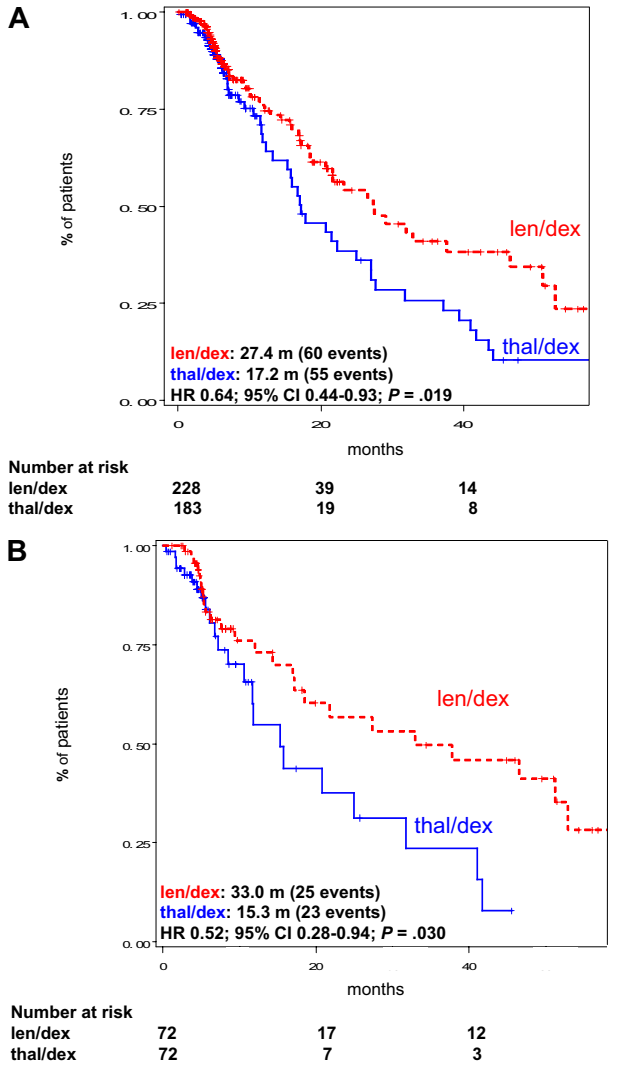

Figure 1. TTP in the intention-to-treat population of patients treated with len/dex and thal/dex. (A) TTP in all patients, regardless of dexamethasone dose. (B) TTP in pair mates who received high-dose dexamethasone. Median TTP is provided in the figure. m indicates months.

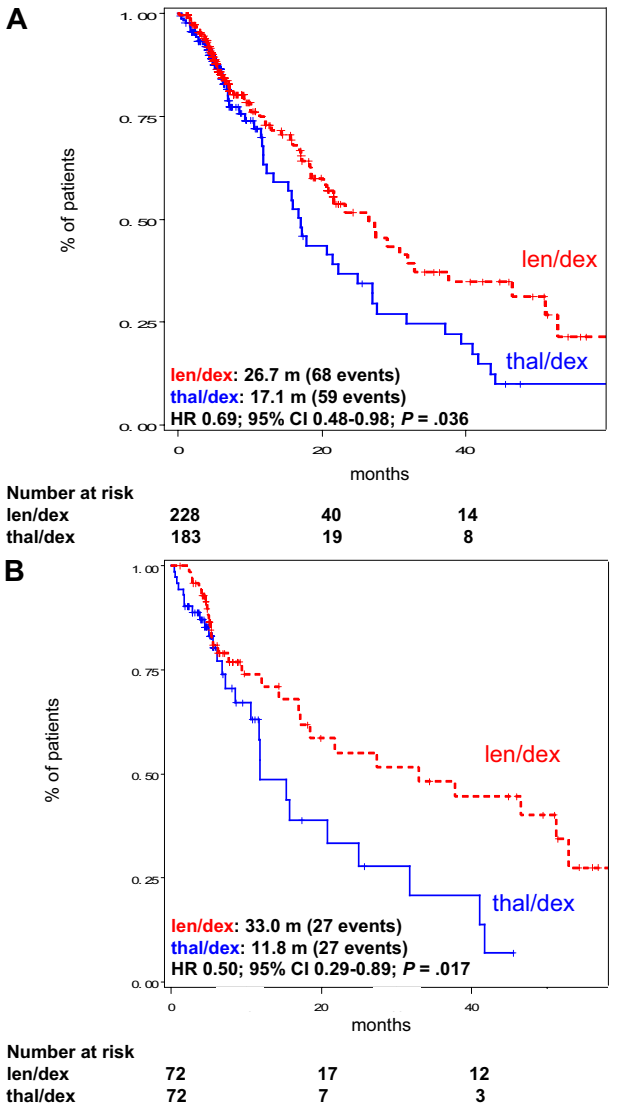

Figure 2. PFS in the intention-to-treat population of patients treated with len/dex and thal/dex. (A) PFS in all patients, regardless of dexamethasone dose. (B) PFS in pair mates who received high-dose dexamethasone. Median PFS is provided in the figure. m indicates months.

both considering all patients (median, 26.7 months vs 17.1 months, HR = 0.69; 95% CI, 0.48-0.98; $P = .036$; Figure 2A) and pair mates receiving high-dose dexamethasone only (33.0 months vs 11.8 months, HR = 0.50; 95% CI, 0.29-0.89; $P = .017$; Figure 2B). These analyses were then repeated without censoring at the date of therapy patients who received SCT or switched to another chemotherapy regimen. Both TTP and PFS, for all patients and for high-dose dexamethasone pair mates only, remained significantly better with len/dex (survival curves are provided in the supplemental data, available on the *Blood* website; see the Supplemental Materials link at the top of the online article).

OS was significantly higher among len/dex patients, both considering all patients (median not reached vs 57.2 months, HR = 0.60; 95% CI, 0.40-0.92; $P = .018$; Figure 3A) and matched patients receiving high-dose dexamethasone only (median not reached vs 50.0 months, HR = 0.35; 95% CI, 0.18-0.68; $P = .002$; Figure 3B). Early deaths (during the first 4 months of therapy) were reported in 6 of 228 (2.6%) patients receiving lenalidomide and

Given the longer duration of therapy in patients treated with len/dex, probably in part related to a higher treatment discontinuation rate because of AEs in thal/dex group ("Toxicity and deaths"), survival analyses were repeated excluding patients who stopped treatment for toxicity in both groups: again, TTP, PFS, and OS were significantly longer for patients who received lenalidomide.

Subgroup analyses

We studied the effect of therapy by ISS stage. In patients who presented with ISS stage I or II at diagnosis, OS was better in patients treated with len/dex compared with thal/dex, both considering all patients (HR = 0.57; 95% CI, 0.32-1.00; $P = .052$) and high-dose pair mates only (HR = 0.20; 95% CI, 0.08-0.50; $P < .001$). In contrast, in patients with stage III ISS, no survival differences were found between patients receiving lenalidomide and patients treated with thalidomide, but this may be a function of small sample size.

There were no significant differences in OS of patients present-

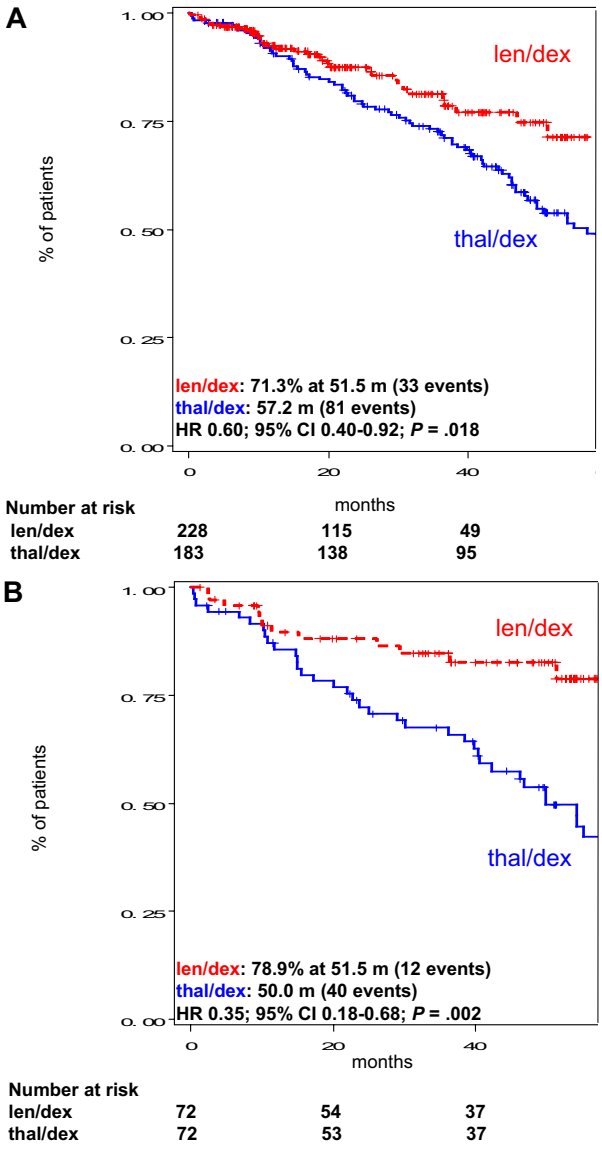

Figure 3. OS in the intention-to-treat population of patients treated with len/dex and thal/dex. (A) OS in all patients, regardless of dexamethasone dose. (B) OS in pair mates who received high-dose dexamethasone. Median OS is provided in the figure. m indicates months.

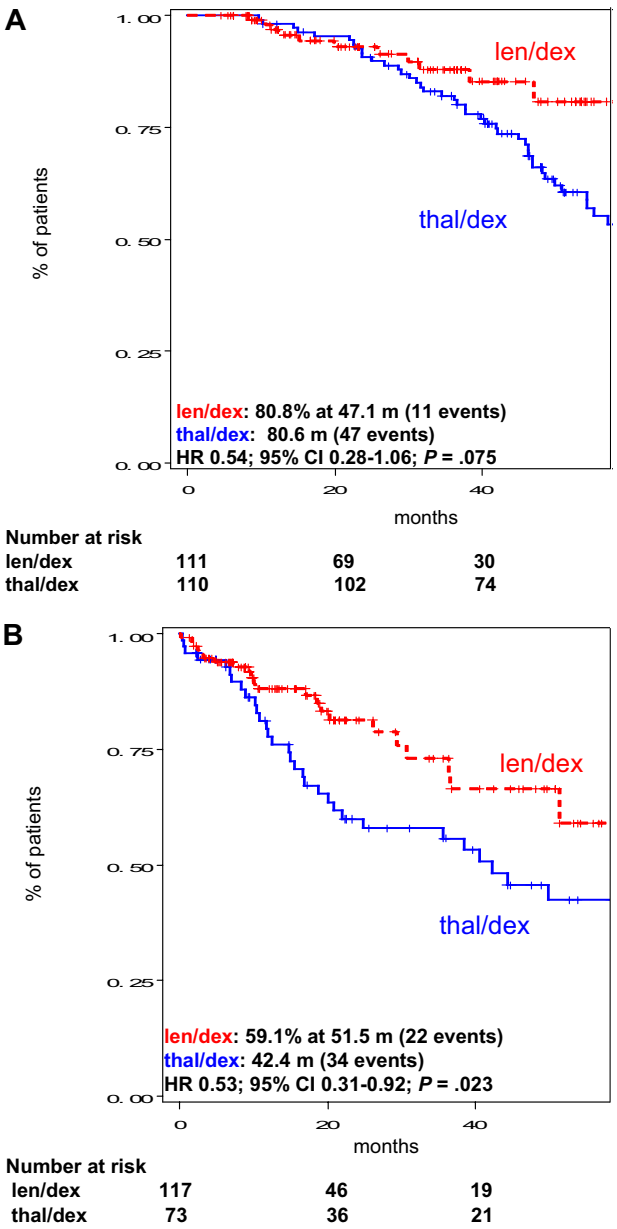

Figure 4. Subgroup analysis of OS in the intention-to-treat population of patients treated with len/dex and thal/dex according to transplantation status. (A) OS in patients who received transplantation. (B) OS in patients in patients who did not receive transplantation. Median OS is provided in the figure. m indicates months.

$P = .652$), nor for patients with standard-risk cytogenetics (HR = 0.87; 95% CI, 0.31-2.43; $P = .795$), which again is probably the result of small sample size.

In the subgroup of patients who underwent SCT, there was a trend toward better OS in the len/dex group compared with thal/dex treated patients (median not reached vs 80.6 months, HR = 0.54; 95% CI, 0.28-1.06; $P = .075$; Figure 4A). In the subgroup of patients who did not receive SCT, OS was significantly longer with len/dex (median not reached vs 42.4 months, HR = 0.53; 95% CI, 0.31-0.92; $P = .023$; Figure 4B). In this subgroup of patients, response rate and TTP were significantly better with len/dex, too. Considering only patients who stopped treatment to pursue SCT (similar treatment duration in the 2 groups), OS was significantly longer in len/dex patients compared with thal/dex (median not reached vs 54.4 months, respectively, in len/dex and thal/dex, HR = 0.38; 95% CI, 0.15-0.96; $P = .040$).

patients and thal/dex patients treated after March 2004: OS was significantly longer in the 228 patients treated with len/dex compared with 108 patients treated with thal/dex (median not reached for len/dex vs 54.4 months for thal/dex, HR = 0.60; 95% CI, 0.37-0.96; $P = .033$). In addition, subgroup analysis of OS of thal/dex patients only, treated before March 2004 and after March 2004, showed no differences between the 2 groups (HR = 1.07; 95% CI, 0.67-1.73; $P = .767$).

Toxicity and deaths

Major grade 3 or 4 toxicities observed with len/dex and thal/dex are listed in Table 4. A total of 131 (57.5%) patients receiving len/dex and 100 (54.6%) patients receiving thal/dex experienced at least

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