Thalidomide, dexamethasone and pegylated liposomal doxorubicin (ThaDD) for newly diagnosed multiple myeloma patients over 65 years

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Running title: ThaDD for elderly de novo MM patients

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**Author contribution:**
All the authors were involved in the accrual of patients, chart review, draft review and manuscript approval. MM and MO were responsible for data collection. MO, PL, MM and LC were involved in conception, design, data analysis of the study. MO and LC were responsible for manuscript writing.
Abstract
We present the results of a phase II study using thalidomide, dexamethasone and pegylated liposomal doxorubicin (ThaDD) in the treatment of 50 newly diagnosed multiple myeloma patients over 65 years. Thalidomide was administered orally 100 mg at bedtime continuously, dexamethasone orally 40 mg days 1-4 and 9-12 and pegylated liposomal doxorubicin intravenously 40 mg/m² on day 1 over the 28-days cycle. Response was assessed according to the EBMT criteria. Seventeen (34%) patients achieved CR, 7 (14%) nCR, 5 (10%) VGPR, 15 (30%) PR and 5 (10%) MR resulting in an ORR of 98%. Only one patient (2%) presented progressive disease. Time to progression (TTP), event-free survival (EFS) and overall survival (OS) projected at 3 years were 60%, 57% and 74% respectively, and these parameters were significantly higher in those patients achieving a response ≥ VGPR versus those who did not. Grade 3-4 nonhematologic adverse events were constipation (10%), fatigue (6%), tremors (4%), mucositis (4%) and palmar-plantar erythro-dysesthesia (2%). Grade 3-4 neutropenia occurred in 12% of patients. Grade 3-4 infections and thrombo-embolic accidents were observed in 22% and 14% of patients, respectively. In the treatment of elderly patients with newly diagnosed multiple myeloma, ThaDD is a very effective regimen with manageable toxicity.
Introduction

Despite the fact that almost two third of multiple myeloma (MM) patients are over 65, no standard effective therapies have been yet identified for this population. The melphalan-prednisone combination (MP) is relatively well tolerated but does not provide satisfactory results. High-dose therapy followed by stem cell autotransplantation is not recommended in every single case or it may present an unacceptable toxicity in patients older than 70 years: intermediate melphalan doses (140 or 100 mg/m²), even if suitable for elderly patients, offer less satisfactory results than in younger patients, with a not negligible morbidity and mortality. Targeted therapy has opened up new horizons for the treatment of MM. These new drugs target not only particular intracellular pathways but also interfere with the exchanges occurring between plasmacells and bone marrow microenvironment, exchanges that are responsible for drug resistance and capable of preventing apoptosis. Thalidomide is actually the drug that has been better investigated when compared with new therapeutical agents. Administered as single agent, in combination with dexametasoné or with conventional chemotherapy, it has been found to offer very promising results in untreated MM patients. In particular, the best results were observed when thalidomide was combined with melphalan or with antracyclines, although the toxicity of these combinations was severe and withdrawals from study protocols were frequent also in younger patients. However, it is yet unclear what is/are the better agent/s or regimen/s to combine with thalidomide-dexamethasone in order to improve their efficacy minimising the toxicity, especially in older patients.

Assuming that elderly patients often present comorbidities, poor performance status and little bone marrow backup, we designed a specific regimen for patients older than 65 years. It included low-dose thalidomide to reduce dose-dependent side effects; pegylated-lyposomal doxorubicin, showing promising antimyeloma activity with both lower cardiotoxicity and myelotoxicity compared with those reported with conventional form; high-dose pulsed dexamethasone, having a pivotal role in the...
treatment of MM. Here we present the results of a phase II, multi center study utilizing the above regimen (ThaDD) in MM patients over 65 years of age.
Patients and Methods

Study design and patients

This is a prospective, multicenter, phase II study on a combined treatment with pegylated liposomal doxorubicin, dexamethasone and thalidomide (ThaDD) in newly diagnosed patients with MM. From March 2003 to March 2005, 50 consecutive patients from 9 institutions were enrolled. Age, performance status (PS), cardiopulmonary, liver and renal functions did not prevent the inclusion of patients but we excluded patients affected by other neoplasms, drug-resistant infections, pre-existing grade \( \geq 2 \) peripheral neuropathy and presenting psychiatric disorders. The study was approved by local Ethics Committees and all patients signed a written informed consent before entering the study.

Baseline evaluation included medical history and physical examination, blood count, serum protein electrophoresis, 24-h urine Bence Jones protein determination and electrophoresis, liver and renal function assessment, \( \beta_2 \)-microglobulin, C-reactive protein, x-rays, bone marrow aspiration or biopsy and FISH investigation. Unfavourable cytogenetics was defined as chromosome 13 abnormalities, t(4;14), t(14;16) and complex karyotypes.

All patients receiving at least one cycle of chemotherapy were considered evaluable for the assessment of both toxicity and response.

Toxicity, as per the National Cancer Institute (NCI) criteria, was assessed on a weekly basis during the first 28-days cycle and monthly in the course of treatment afterwards with medical interview, physical examination and lab tests.

Response to treatment was rated according to the EBMT criteria.\(^{14}\) Furthermore, we included two other categories: near-complete remission (nCR), defined as no detectable monoclonal protein by electrophoresis with positive immunofixation, and very good partial remission (VGPR) defined as a \( \geq 90\% \) reduction in serum paraprotein. In order to evaluate response, serum and/or urine electrophoresis were performed once a month and bone marrow aspirate after three cycles of therapy. A
complete restaging was performed at the completion of chemotherapy. Subsequently, patients were followed with history, physical examination and laboratory tests every 3 months, bone marrow aspirate every 6 months and skeletal X-rays every year.

**Treatment**

Patients received intravenous pegylated liposomal doxorubicin (Caelyx®) 40 mg/m² diluted in 250 ml of 5% dextrose solution over 1 h on day 1 every 28 days in day-hospital, dexamethasone 40 mg orally on days 1-4 and 9-12 and thalidomide 100 mg each evening continuously. Thalidomide was prepared in the Umberto I Hospital Pharmacy. Pegylated liposomal doxorubicin and dexamethasone were administered for three cycles, while in those patients responding in a percentage ≥ VGPR were administered two additional cycles, whereas those achieving a response ≤ PR were given three additional cycles. Patients showing progression were dropped. Supportive therapy included 1.25 mg/day warfarin, vitamin B6, zoledronic acid, erythropoietin and hypoglycaemic drugs or insulin if the blood glucose was higher than 180 mg/dl. No antibacterial prophylaxis was initially given to patients. Due to the high incidence of respiratory infections, occurring after the first 28 cycles of chemotherapy, we administered 250 mg of ciprofloxacin twice a day for all the next cycles. If patients developed ≥ grade 3 neutropenia following pegylated liposomal doxorubicin infusion, granulocyte colony stimulating factor (G-CSF) was then administered for all subsequent cycles without reducing dosage. A 25% dose reduction and 2 weeks delay in the administration of pegylated liposomal doxorubicin were required when grade 4 mucositis and palmar-plantar erythrodysesthesia occurred. Drug discontinuation was mandatory in the event of grade 3-4 cardiotoxicity. Dexamethasone has to be reduced to 20 mg or discontinued in case of ≥ grade 2 muscular toxicity. The onset of ≥ grade 3 neurotoxicity was the only situation leading to thalidomide discontinuation, whereas the occurrence of other side effects, thromboembolic disease and infectious complications did not.
**Statistical methods**

The study primary end-points were response rate and toxicity. Secondary end-point included time to progression (TTP), event-free survival (EFS) and overall survival (OS). Outcome was analysed on a modified intent-to-treat basis.

It was assumed that the combination would induce a response rate (defined as a reduction by \( \geq 50\% \) of myeloma proteins) 20\% higher than that reported with conventional MP regimen. Considering an \( \alpha \)-value < 0.05 and a \( \beta \)-value of 0.80, 43 patients have to be enrolled according to Simon’s two stage design.

Univariate analysis of factors affecting response was performed by Chi-squared test for contingency table while Cox proportional hazard model was applied to recognize factors affecting time-dependent variables. TTP, EFS and OS were calculated from enrolment to disease progression or death due to progression, any event (except therapy interruption due to toxicity) and death, respectively. For the comparison of the TTP, EFS and OS according to response (< VGPR vs \( \geq \) VGPR), we performed a landmark analysis using as starting point the date scheduled for response confirmation (4-5 months after the start of first cycle). The curves were plotted according to the Kaplan-Meier method and they were compared by log-rank test. A \( p<0.05 \) was considered significant. All analyses were performed with SPSS software.
Results

Patients characteristics
Fifty untreated MM patients were enrolled in this study and their characteristics at study entry are shown in Table 1. It must be noted that 64% of patients were older than 70 years, PS was ≥ 2 in 20%, ISS ≥ 2 in 74% and β2-microglobulin level ≥ 3.5 mg/l in 60% of patients. Moreover, 14% of patients presented impaired renal function and 7 out of 29 patients (24%) with valuable FISH analysis showed unfavourable abnormalities.

Response to therapy
After 4 cycles of therapy, 17 out of 50 patients (34%) achieved CR, 7 nCR (14%), 4 VGPR (8%), 14 PR (28%) and 7 MR (14%) resulting in a 98% ORR (Table 2). Only one patient (2%) showed signs of progressive disease. At the end of therapy, 1 patient achieved VGPR and 1 PR both from MR. The maximal response to treatment was reached after a median of 2 cycles (range 1-4). During treatment 3 patients died, two of heart failure and one of multiple organ failure after the response was assessed.

All 7 patients with impaired renal function achieved an objective response (4 ≥ VGPR, 2 RP, 1 MR) and normal renal function was restored.

No single characteristics was significantly associated with quality of response (< VGPR vs ≥ VGPR).

Survival
After a median 18 months follow-up (range 6-36), 12 patients relapsed and 10 died (3 during treatment; 7 in follow-up). Seven patients (14%) underwent autotransplant and were censored at the time of transplant. Median CD34+ cells yielded was 8.3 x 10^6/kg (range 4.8-12.6). All patients engrafted rapidly after intermediate or high-dose melphalan.
Median TTP, EFS and OS were not reached whereas TTP, EFS and OS projected at 3 years were 60%, 57% and 74% (Figure 1A, B, C).

No single characteristic was significantly predictive of PFS, EFS and OS except response to treatment. Landmark analysis demonstrated that patients achieving a response ≥ VGPR had a significantly higher 3-years TTP (78% vs 40%; p=0.0315), EFS (78% vs 37%; p=0.0213) and OS (84% vs 61%; p=0.0532) (Figure 2 A, B, C).

**Compliance to therapy**

Overall, we administered 206 cycles of ThaDD (median 4; range 1-6).

Two patients (4%) refused to continue therapy, one because of the occurrence of pulmonary embolism and another for septic shock. In one patient pegylated liposomal doxorubicin dosage was reduced for the occurrence of severe mucositis whereas 11 patients (22%) underwent the scheduled treatment with a few days delay because of infection in 9 cases, severe neutropenia in one patient and mucositis in another one.

One patient discontinued dexamethasone because of muscle aches and severe asthenia and 2 patients (4%) interrupted thalidomide treatment for the occurrence of grade 3 tremors while 2 patients refused to continue thalidomide because of severe constipation.

**Hematological toxicity and infection**

Neutropenia of any grade and grade 3/4 occurred in 42% and 12% of patients, respectively. Twenty-one patients (42%) experienced a febrile episode (10% of all courses), being of ≥ grade 3 in 22% of them (5% of courses). In the majority of cases (90%) fever occurred in non-neutropenic patients and following the first 3 cycles (90%). However, during the first 28 cycles (5 patients) administered without antibiotic prophylaxis we documented 7 infectious complications (25%) whereas in subsequent 178 courses, in which we administered ciprofloxacin 250 mg twice daily, only 14 new episodes of infections (7%) occurred. Lung infiltrates were identified in 7 episodes (14%). Eleven episodes were classified as FUO, one patient developed
neutropenic septic shock and in the last two patients urinary infection and ocular abscess were documented. No patient experienced herpetic or other opportunistic infections and none died from infections. Only one patient was dropped from the protocol because of infectious complications (septic shock).

Thrombocytopenia occurred in 12% of patients, but none of grade ≥ 3. Nearly all patients (95%) were administered erythropoietin in order to prevent severe anemia.

**Nonhematological toxicity**

Nonhematological toxicity is shown in Table 3. Most side effects were rated mild to moderate but 18 patients (36%) experienced grade 3-4 adverse events. Severe side effects related to thalidomide were fatigue (6%), constipation (4%) and tremors (4%).

Regarding toxicity by pegylated lyposomal doxorubicin, 2 patient (4%) experienced grade 3-4 mucositis and one grade 3 palmar-plantar erythrodysesthesia.

Dexamethasone mainly caused slight muscle weakness but one patient developed severe miopathy.

Venous thromboembolic events occurred in 7 patients (14%) but only one patient showed clinical evidence of pulmonary embolism. All events involved the femoral or popliteal veins.
Discussion

High-dose therapy (HDT) followed by autologous stem cell transplantation (ASCT) has improved the outcome of both young\textsuperscript{15} and elderly patients with multiple myeloma.\textsuperscript{2,3} However, nearly half of MM patients results ineligible for this procedure because of old age, inadequate end-organ function or because they refuse transplantation. These patients have a poor short-term prognosis, whichever conventional therapy they receive. Therefore the melphalan prednisone combination remains the standard treatment for older MM patients although the results are entirely unsatisfactory.\textsuperscript{16} It is obvious that more effective alternative treatments are needed for elderly MM patients. Thalidomide-dexamethasone is becoming the upfront regimen prior to HDT and ASCT.\textsuperscript{17} However, this combination administered to patients not candidated to autotransplant led to results similar to those achieved with conventional chemotherapy.\textsuperscript{8} Better results can be obtained when chemotherapeutic agents are added to or administered before \textsuperscript{18} the combination thalidomide-dexamethasone.\textsuperscript{10-13} At present, it remains unclear which single- or other chemotherapy regimen is the best one to be combined with thalidomide-dexamethasone in order to achieve a higher CR rate associated with an acceptable toxicity. Moreover, it is unknown whether the best quality of response obtained with these combinations does impact survival parameters of MM patients.

We decided to explore a VAD-like regimen in which vincristine was replaced by thalidomide, since the administration of both drugs has been considered conflicting in terms of neurotoxicity. Standard doxorubicin was replaced by a pegylated liposomal form, being less toxic and potentially more effective than the conventional agent because of its pharmacokinetics properties. Dexamethasone was given in adequate doses since it plays a key role in the treatment of MM.

With the present combination, 58% of patients showed a \( \geq 90\% \) reduction in serum M protein level and 48% experienced its negativization (CR and nCR) with an excellent compliance to treatment. Better responses were achieved mainly within 3 months
from therapy initiation, EFS and OS were respectively 65% and 70% at 3 years. It must be highlighted that patients who achieved high quality responses had a significantly better TTP, EFS and OS by landmark analysis. This means that a higher quality response obtained with this protocol turn in better survival parameters. Our results are clearly superior to those obtained with conventional chemotherapy in terms of both response rate and survival.19-21 Among studies assessing the efficacy of the thalidomide-based regimens in untreated elderly MM patients, the only one which is comparable to ours in terms of median age, exclusion criteria and administered thalidomide dose is Palumbo et al13, who treated 129 patients with an association of thalidomide, oral melphalan and prednisone. With this regimen he observed combined CR/nCR in 28% of patients, near half the value that we obtained (48%). This difference may be explained either by low dose melphalan and steroids used in order to reduce toxicity or to an actual superior antitymoma activity of the pegylated liposomal doxorubicin-dexamethasone combination versus the melphalan-prednisone one. Grade 3-4 hematologic, neurologic and vascular toxicities were more frequent in MPT combination and, despite a higher incidence of grade 3-4 infections we observed, no patients developed opportunistic infections, even if no antiviral prophylaxis was administered. Actually the introduction of ciprofloxacin antibiotic prophylaxis led to a significant reduction of infections rate (< 10%). Moreover, no patients died for infectious complications. Although no deaths were related to thromboembolic events and our incidence of DVT (14%) is close to the lowest rates reported by other studies,10-13, 18 it needs to be reduced. Even though the best DVT prophylaxis in patients receiving thalidomide-based regimens has not been established so far, retrospectively we believe that fixed-dose warfarin might have been inadequate as DVT prophylaxis in our protocol. We think that in the future trials and in clinical practice more effective DVT prophylaxis than fixed-dose warfarin should be considered in patients treated with thalidomide and antracyclines.
Other authors reported the results of chemotherapy combinations with thalidomide, dexamethasone and pegylated liposomal doxorubicin but, unlike us, they also administered vincristine. Hussein et al, with 400 mg of thalidomide daily, obtained a ≥ nCR response rate which was almost similar to ours but the incidence of neurologic and vascular toxicities was much higher despite the median age of Hussein’s study population (59 years) was lower than in our patients cohort (71.5 years). Moreover, in a recent study the same authors reported that patients, receiving full dose vincristine in the DVd-T regimen, showed a significantly worse PFS than those receiving the reduced dose or stopping vincristine. Administrating a combination similar to DVd-T but with a lower dose of thalidomide (200 mg daily) and dexamethasone, Zervas et al achieved only a 10% CR rate in a study population, including also younger patients. Schutt et al, using epirubicine, high-dose thalidomide and low dose dexamethasone reported a 19% CR rate but the frequency of neurologic toxicity, vascular and infectious complications were nearly prohibitive. Our observations and data from the cited studies suggest the following: the response to thalidomide combined with chemotherapy is not dose-dependent; high-dose dexamethasone proves to be crucial; liposomal pegylated doxorubicin seems more effective than both epirubicin and low dose melphalan and, if administered as a single agent without vincristine, offers excellent results with minor toxicity.

Furthermore elderly MM patients have to be evaluated as to whether or not they will be suitable candidates for HDT. Actually, in patients aged 50-70 treated with intermediate-dose melphalan (100 mg/m²) with ASCT, Palumbo et al obtained a 25%CR+nCR rate and 37% EFS at 3 years. Using a higher dose of melphalan (140-200 mg/m²) Badros et al achieved a 27 %CR rate and a 20% EFS at 3 years after tandem transplants performed in patients ≥ 70 years old. Both the authors reported acceptable toxicity, particularly in patients where melphalan did not exceed 140 mg/m². These results showed that high-dose therapy is feasible and effective also in elderly patients, implying that any regimen designed for patients older than 65 years
should not preclude this procedure and our combination allows this. Actually, in our study 7 patients considered eligible for HDT were successfully treated with mobilization and autotransplant. However, we believe that it may be questionable to perform autotransplant in older MM patients considering the results of the thalidomide, steroids and chemotherapy combinations. Well designed studies warrant to address this issue.

Recently, new drugs such as lenalidomide and bortezomib have been introduced in the treatment of MM patients. In a phase I-II study, Mateos at al used the combination bortezomib-melphalan-prednisone in 53 previously untreated elderly patients. He obtained a 39% CR/nCr rate despite a high frequency and seriousness of hematologic and neurologic toxicities as well as opportunistic infections. Lenalidomide was associated also with melphalan-prednisone in 24 patients over 65 years of age. No CR/nCr have been achieved and hematologic, dermatological and metabolic toxicities were not negligible.

In conclusion, the ThaDD combination has been very effective in the treatment of newly diagnosed elderly MM patients. The toxicity was very manageable also in older fragile patients and complications such as infections and DVT can be prevented with adequate antibiotic and antithrombotic prophylaxes. Moreover, our combination consented to perform HDT as consolidation therapy. We think that ThaDD therapy has to be explored further in comparative studies to confirm our results.
Acknowledgments

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References


Table 1. Baseline characteristics of 50 patients

<table>
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<tr>
<th>Characteristics</th>
<th>No of patients (%)</th>
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<tr>
<td>Age (median, range)</td>
<td>71.5 (65-78)</td>
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<tr>
<td>&gt; 70 years</td>
<td>32 (64)</td>
</tr>
<tr>
<td>&gt; 75 years</td>
<td>7 (14)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>29 (58)</td>
</tr>
<tr>
<td>Female</td>
<td>21 (42)</td>
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<td>Immunoglobulin heavy chain type</td>
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<tr>
<td>Ig G</td>
<td>30 (60)</td>
</tr>
<tr>
<td>Ig A</td>
<td>11 (22)</td>
</tr>
<tr>
<td>Light chain only</td>
<td>7 (14)</td>
</tr>
<tr>
<td>Non-secretory</td>
<td>2 (4)</td>
</tr>
<tr>
<td>Unfavourable cytogenetic/assessable cytogenetic</td>
<td>7/29 (24)</td>
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<td>Durie-Salmon stage</td>
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<tr>
<td>I</td>
<td>9 (18)</td>
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<tr>
<td>II</td>
<td>2 (4)</td>
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<tr>
<td>III</td>
<td>39 (78)</td>
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<tr>
<td>ISS stage</td>
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<td>I</td>
<td>13 (26)</td>
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<tr>
<td>II</td>
<td>23 (46)</td>
</tr>
<tr>
<td>III</td>
<td>14 (28)</td>
</tr>
<tr>
<td>Performance Status (WHO ≥ 1)</td>
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<tr>
<td>Serum β2-microglobulin ≥ 3.5 mg/l</td>
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<tr>
<td>Serum albumin &lt; 3.5 g/dl</td>
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<td>Serum creatinine &gt; 2 g/dl</td>
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<tr>
<td>Hemoglobin ≤ 11.5 g/dl</td>
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<tr>
<td>Platelets count ≤ 130 x 10⁹/l</td>
<td>8 (16)</td>
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ISS indicates International Staging System
Table 2. Response to therapy

<table>
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<tr>
<th>Response category</th>
<th>After 4 cycles of therapy</th>
<th>At the end of therapy</th>
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<tr>
<td></td>
<td>No. of patients (%)</td>
<td>No. of patients (%)</td>
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<tr>
<td>Complete remission (CR)</td>
<td>17 (34)</td>
<td>17 (34)</td>
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<tr>
<td>Near-complete remission (nCR)</td>
<td>7 (14)</td>
<td>7 (14)</td>
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<tr>
<td>Very good partial remission (VGPR)</td>
<td>4 (8)</td>
<td>5 (10)</td>
</tr>
<tr>
<td>Partial remission (PR)</td>
<td>14 (28)</td>
<td>15 (30)</td>
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<tr>
<td>Minor response (MR)</td>
<td>7 (14)</td>
<td>5 (10)</td>
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<tr>
<td>Progressive disease</td>
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### Table 3. Major nonhematological toxicities

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Grade 1-2, No. of patients</th>
<th>Grade 3, No. of patients</th>
<th>Grade 4, No. of patients</th>
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<td>Alopecia</td>
<td>12</td>
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<td>0</td>
</tr>
<tr>
<td>PPE</td>
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<td>1</td>
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</tr>
<tr>
<td>Rash</td>
<td>4</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Peripheral neuropathy</td>
<td>5</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Constipation</td>
<td>21</td>
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<td>1</td>
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<tr>
<td>Dizziness</td>
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</tr>
<tr>
<td>Somnolence</td>
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<tr>
<td>Fatigue</td>
<td>22</td>
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<td>0</td>
</tr>
<tr>
<td>Tremors</td>
<td>10</td>
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<tr>
<td>Muscular weakness</td>
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<tr>
<td>Venous thromboembolic disease</td>
<td>0</td>
<td>6</td>
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PPE indicates palmar-plantar erythrodysesthesia
Figure 1
Figure 2

Panel A: Time to progression
- ≥VGPR
- < VGPR
- p = 0.0315

Panel B: Event-free survival
- p = 0.0213

Panel C: Overall survival
- p = 0.0532

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Figure 1. Progression-free survival (A), event-free survival (B) and overall survival (C) of 50 patients treated with ThaDD regimen.

Figure 2. Landmark comparison of time to progression (A), event-free survival (B) and overall survival (C) in patients obtaining a response ≥ VGPR (- - -) or < VGPR (– – –)
Thalidomide, dexamethasone and pegylated liposomal doxorubicin (ThaDD) for newly diagnosed multiple myeloma patients over 65 years

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