High-Dose Melphalan Plus Thiotepa as Conditioning Regimen before Second Autologous Stem Cell Transplantation for “De Novo” Multiple Myeloma Patients: A Phase II Study

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Abstract
High-dose melphalan (MEL) is the standard therapy for autologous stem cell transplantation (ASCT) in multiple myeloma (MM), although the optimal conditioning regimen remains yet to be identified. Thiotepa (THIO) appears to be a potentially effective option, with broad-spectrum antitumor efficacy that can be added to myeloablative multiagent regimens for ASCT in hematopoietic tumors. We conducted a phase II trial, adding THIO (275 mg/m²) to high-dose MEL (140 mg/m²) before a second ASCT, in a tandem ASCT strategy, in 64 patients with “de novo” MM. Overall, there was no transplant-related mortality. The incidence of neutropenic fever and mucositis (grades 3 to 4) was 39% and 9%, respectively. Median number of days to neutrophil and platelet engraftment were 11 and 12, respectively. After the second transplantation, the complete response improved to 43.8%. Overall response rate was 86%. After a median follow-up of 18.1 months, 13 patients had progressed and 3 died from MM. Median progression-free survival was not reached, and actuarial 2-year rates of progression-free and overall survival were 71% and 88.9%, respectively. Our results suggest that THIO/MEL is a feasible and safe conditioning regimen for ASCT in MM and should be explored for efficacy in a phase III study.

Introduction
Multiple myeloma (MM) is the hematological malignancy in which clinical research has made the most significant progress in the past 20 years. Until 1980, only melphalan (MEL) plus prednisone could improve the overall survival (OS) of patients [1]. Subsequently, a French study showed that the use of high-dose chemotherapy (HDC) with autologous stem cell transplantation (ASCT) could make a difference in treatment [2]. In the 2000s, a dramatic increase in improvement rates was observed with the advent of immunomodulatory drugs and proteasome inhibitors, and if this trend continues the 5-year survival rate or a patient diagnosed in 2014 would be approximately 66% [3]. The 2010s are characterized by studying the optimal combination, sequence, and duration of therapies, and in the modern era for MM treatment, transplant trials strongly support the use of upfront ASCT in the context of novel agents [4-6]. Until proven otherwise, ASCT remains the standard of care for eligible patients [7,8].

Despite these great advances, MM is widely considered incurable, although some investigators have recently challenged this dogma [9]. The attainment of the deepest response after both induction therapy and ASCT is one of the strongest predictors of long-term outcomes [10-13] and represents a major endpoint of current treatment strategies.

Novel agents are routinely used before ASCT as part of induction therapy to increase response rates [4-6,12]. These novel agents have also been added after ASCT as consolidation [14-16] and maintenance [15-17] therapies to further increase the quality of response.

The current standard conditioning regimen is high-dose MEL [18-20], and ASCT may be single or tandem [2,21,22].

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Few trials have been performed to improve the conditioning regimen side of the HDC procedure [23-32]. The aim of the present study is to evaluate whether a second ASCT with MEL and thiopeta (THIO) is safe and can increase the rate of response in patients with newly diagnosed MM whose first conditioning regimen only included MEL.

METHODS

Eligibility Criteria

Patients with symptomatic, measurable, and newly diagnosed MM age 70 years or younger were eligible for this trial. Other inclusion criteria were a Eastern Cooperative Oncology Group performance status score of at least 2 (on a scale from 0 to 5, with higher scores indicating greater disability) and a life expectancy longer than 6 months, an absolute neutrophil count (ANC) > 1500/mm³, and a platelet count > 75,000/mm³, with normal cardiac and pulmonary function findings and adequate renal function (creatinine clearance > 30 mL/min). The main exclusion criteria included a history of other cancers within the past 3 years and peripheral neuropathy of grade 2 or higher.

Study Design

This multi-institutional, single-arm, prospective phase II study was performed at the Hematology and Stem Cell Unit, La Maddalena Hospital, Palermo, Italy; at the Hematology and Stem Cell Transplant Unit, Reggio Calabria, Italy; and at the Hematology Unit, National Tumor Institute, Naples, Italy. The study was approved by the institutional review boards of the participating centers and was conducted according to the Declaration of Helsinki and the International Conference on Harmonisation Guidelines for Good Clinical Practice. All patients provided written informed consent.

All patients received a bortezomib-based induction therapy [34]. Patients who had a refractory disease (progression or no response) to induction chemotherapy were excluded. High-dose cyclophosphamide (3-4 g/m²) and granulocyte colony-stimulating factor were used to mobilize stem cells. The minimum target dose of CD34+ cells, to safely support 2 sequential courses of high-dose therapy, was 8 × 10^6/kg.

Four to 6 weeks after the administration of HDC, patients received MEL (200 mg/m²), given as a single i.v. dose (day -2), followed by a peripheral blood stem cell infusion (≥ 2 × 10^6 CD34+ cells/kg) 48 hours later (day 0). Three to 6 months after the first autotransplantation, patients with at least stable disease received a second ASCT with THO/ MEL as the conditioning regimen. THO/MEL was administered as follows: THO 275 mg/m² on day -5 and MEL 140 mg/m² i.v. on day -2. Autologous peripheral blood stem cells (≥ 2 × 10^6 CD34+ cells/kg) were infused on day 0. No consolidation or maintenance therapies were permitted.

Supportive Care

During the aplastic phase in both ASCT procedures, all patients received oral prophylaxis with ciprofloxacin at 500 mg twice daily or levofloxacin at 500 mg b.i.d. by mouth until neutrophil recovery and with acyclovir at 800 mg twice daily from day +3 post-transplantation until approximately day +90. *Pneumocystis jiroveci* prophylaxis with trimethoprim/sulfamethoxazole, 1 double-strength tablet 2 or 3 times weekly, was started after hematological recovery and continued for 3 months. Granulocyte colony-stimulating factor (filgrastim or lenograstim) 5 mg/kg/day was started at day +5 until neutrophil recovery. RBC and platelet transfusions were given to maintain hemoglobin levels ≥ 8 g/dL and platelet counts ≥ 10 × 10^9/L or in case of symptomatic anemia and/or minimal mucocutaneous hemorrhagic syndrome. Patients received i.v. hydration and electrolyte support as per institutional policy.

Evaluation of Response and Toxicity

The primary objective of this study was to evaluate treatment-related toxicity and treatment-related mortality (TRM), time to neutrophil and platelet engraftment after THO/MEL, and cumulative incidence of neutrophil and platelets recovery. Secondary objectives were to evaluate the complete response (CR) rate, the overall response rate (defined as CR + very good partial response [VGPR]), progression-free survival (PFS), and OS. The evaluation of response occurred at enrollment and at days +30 and +100 after both ASCTs. Moreover, we compared toxicities and engraftment rate between the first and second transplant.

Adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (version 3.0; http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/ctcaev3.pdf). Time to neutrophil engraftment was defined as the duration between day 0 and the first of 3 consecutive days of ANC > 5 × 10^9/L. Time to platelet engraftment was defined as the duration between day 0 and the first day of platelet count sustained at > 20 × 10^9/L without transfusion in the previous 7 days. TRM was defined as mortality from any cause other than disease progression within 100 days from transplantation.

Response and progression were reported by investigators according to criteria of the European Group for Blood and Marrow Transplantation (EBMT) [35] with the addition of a category for VGPR (≥ 90% reduction in serum M protein and < 100 mg urine M protein per day) [36]. Bone marrow biopsy and aspirate samples were obtained at baseline and as needed to confirm CR. Patients with CR who lacked confirmation from bone marrow biopsy samples were downgraded to VGPR.

Statistical Analysis

Data were summarized as median and range (continuous variables) or as absolute frequencies and percentages (binary variables), as appropriate. Within-patient comparisons were made by the Wilcoxon rank test (for continuous variables) and the McNemar test (binary date), as appropriate. Response rates, survival, and toxicity were summarized by descriptive statistics. PFS and OS were investigated by the Kaplan-Meier method. The response rate after THO/MEL was calculated and compared with MEL (200 mg/m²) response rates. The degree of uncertainty (precision) around PFS and OS was expressed as point estimate and the corresponding 95% confidence interval. Data analysis was performed by SPSS for Windows (version 20.0.0; IBM, Armonk, NY).

RESULTS

Study Population

Sixty-four consecutive transplant-eligible patients who had received prior bortezomib-based induction therapy for MM and with sensitive disease were enrolled and constituted the treatment population. All patients were followed for toxicity, stem cell engraftment, and treatment response. Patient baseline demographics and disease characteristics are summarized in Table 1. Briefly, patients had a median age of 56 (range, 24 to 70) and 58% were men. Intermediate (stage II) or high-risk (stage III) disease was present in 75% of patients defined by Durie-Salmon criteria and in 55% of patients as defined by the International Staging System. Data on cytogenetic abnormalities, del(13q), t(4;14), and del(17p), detected by fluorescence in situ hybridization on highly purified bone marrow plasma cells were available in 78% of patients. The isotype distribution of M-proteins reflected the typical MM population (IgG, 64%; IgA, 26%; free light chain only, 10%).

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age, yr (range)</td>
<td>56 (24-70)</td>
</tr>
<tr>
<td>Male gender</td>
<td>37 (58%)</td>
</tr>
<tr>
<td>Durie-Salmon stage of myeloma on diagnosis</td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>19 (30%)</td>
</tr>
<tr>
<td>III</td>
<td>45 (70%)</td>
</tr>
<tr>
<td>ISS stage of myeloma on diagnosis</td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>20 (30%)</td>
</tr>
<tr>
<td>II</td>
<td>32 (50%)</td>
</tr>
<tr>
<td>III</td>
<td>6 (10%)</td>
</tr>
<tr>
<td>Unknown</td>
<td>6 (10%)</td>
</tr>
<tr>
<td>FISH analysis for cytogenetic abnormalities</td>
<td></td>
</tr>
<tr>
<td>Presence of del(13q)</td>
<td>33 (66%)</td>
</tr>
<tr>
<td>Presence of t(4;14) and del(17p)</td>
<td>12 (24%)</td>
</tr>
<tr>
<td>Presence of t(4;14) with or without del(17p)</td>
<td>5 (10%)</td>
</tr>
<tr>
<td>Monoclonal protein type</td>
<td></td>
</tr>
<tr>
<td>IgG</td>
<td>64%</td>
</tr>
<tr>
<td>IgA</td>
<td>26%</td>
</tr>
<tr>
<td>Light chain only</td>
<td>10%</td>
</tr>
</tbody>
</table>

ISS indicates International Staging System; FISH, fluorescence in situ hybridization.

- Fifty patients were available for assessment.

Stem Cell Engraftment

The median number of CD34+ cells reinfused was 5.1 × 10^6/kg (range, 3.3 to 7.1). All patients were successfully engrafted at day +30.
engrafted. The median number of days to neutrophil and platelet engraftment were 11 (range, 9 to 17) and 12 (range, 10 to 22), respectively. Median number of days with ANC < 500/mL was 6 (range, 4 to 13). The transfusion requirements stood at 1 (range, 0 to 5) and 1 (range, 0 to 3) for RBC and platelet units, respectively. The engraftment kinetics seen for THIO/MEL conditioning at second transplant were similar to those reported previously with the first MEL (200 mg/m²) conditioning regimen (Table 2).

Nonhematological Toxicity

All subjects were followed from day 0 through day + 180 post—second transplant for nonhematological toxicity. After THIO/MEL, nearly all patients experienced mild nausea or vomiting (84.4%); however, there were only 6.3% grade 3 toxicities. The incidence of mucositis was 86%; only 6 of 64 patients (9%) experienced grades 3 to 4 mucositis. There were 3 cases of hepatic toxicity (grades 3 to 4), and the incidence of diarrhea (grades 3 to 4) was 6%. Twenty-five patients (39%) had a fever. Infections documented by imaging studies, such as chest radiographs, and physical examination in the absence of positive cultures were reported in 3% of febrile episodes. A causative organism was identified in 5 (8%), including 2 with Streptococcus mitis bacteremia, 1 with Escherichia coli bacteremia, 1 with microsporidia enterocolitis, and 1 with rotavirus enterocolitis, all of which resolved with antibiotic therapy. We did not observe any cardiac or renal toxicity. There was no TRM (Table 3).

Response Assessment

Responses to induction therapy before and after ASCT are shown in Figure 1. At the end of induction therapy, 26.6% and 37.5% of the patients had achieved a CR and a VGPR, respectively. After the first and second transplantation, the CR improved to 35.9% and 43.8%, respectively. Overall response rates were 75% after the first transplant and 86% after the second transplant (P < .001) (Figure 1). After a median of 18.1 months (range, 6.3 to 33.6) of follow-up after the second ASCT, 13 patients had progressed and 3 died from MM. Median PFS was not reached, and actuarial 2-year PFS rate was 71% (95% confidence interval, 53% to 88%) (Figure 2). Median OS was not reached. Actuarial 2-year OS rate was 88.9% (95% confidence interval, 76% to 100%) (Figure 3).

Table 2

<table>
<thead>
<tr>
<th></th>
<th>Second Transplant (THIO/MEL Conditioning Regimen)</th>
<th>First Transplant (MEL Conditioning Regimen)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of transplants</td>
<td>64 (3.3-7.1)</td>
<td>64 (2.1-6.1)</td>
<td>n.s.</td>
</tr>
<tr>
<td>CD34+ cells infused, median × 10⁶/kg (range)</td>
<td>11 (9-17)</td>
<td>11 (9-20)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Time to neutrophil engraftment, median days (range)</td>
<td>12 (10-22)</td>
<td>12 (10-20)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Time to platelet engraftment, median days (range)</td>
<td>16 (14-30)</td>
<td>15 (14-35)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Duration of hospitalization, median days (range)</td>
<td>8 (5-13)</td>
<td>8 (5-13)</td>
<td>n.s.</td>
</tr>
</tbody>
</table>

n.s. indicates not significant.

DISCUSSION

Even with major changes in the treatment of MM patients with the introduction of novel agents, ASCT continues to play a primary role in the armamentarium of anti-MM therapy [4,5,7,8]. High-dose MEL is the most widely used drug as a preparative regimen for ASCT in MM [18] and MEL200 is considered the gold standard schedule [19,20]. This regimen was initially reported in the early 1990s by the Arkansas [37] and the Royal Marsden group [38] when, in newly diagnosed patients, the researchers reported a high CR rate with low extramedulillary toxicity. In a randomized study, Moreau et al. [39] demonstrated that MEL at 200 mg/m² improved PFS and OS when compared with the combination of MEL (140 mg/m²) with 8 Gy of total body irradiation. Other trials using the intensification of the MEL dose have not demonstrated significant improvement in terms of outcome and were associated with a higher incidence of side effects [40]. Targeting exposure to MEL by using area under the curve in the latter setting has become particularly appealing, as recently reported [41].

A more effective conditioning regimen may induce deeper responses and longer remission duration, and various clinical trials were performed to improve the conditioning regimens before ASCT [18,20,23-32]. One strategy added more agents to MEL. The Spanish group prospectively investigated whether the use of oral busulfan (BU) 12 mg/kg plus MEL (140 mg/m²) (BU/MEL) resulted in a longer PFS compared with MEL at 200 mg/m² or MEL at 140 mg/m² plus total body irradiation. The final analysis showed that conditioning with BU/MEL was associated with longer PFS but equivalent OS, compared with that achieved with MEL (200 mg/m²). However, this result should be counter-balanced against the higher frequency of veno-occlusive disease—related deaths in the BU/MEL group [21].

An alternative to oral BU is i.v. BU. Blanes et al. [31] compared i.v. BU 9.6 mg/kg and MEL (140 mg/m²) versus MEL (200 mg/m²). The results showed a similar overall response rate and CR/near Complete Remission rate in both

<table>
<thead>
<tr>
<th>Number of transplants</th>
<th>64</th>
<th>64</th>
<th>n.s.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever ≥ 38.2°C</td>
<td>25</td>
<td>21</td>
<td>33%</td>
</tr>
<tr>
<td>Fever origin Vaccines</td>
<td>0</td>
<td>0</td>
<td>n.s.</td>
</tr>
<tr>
<td>CVC related</td>
<td>5</td>
<td>3</td>
<td>8%</td>
</tr>
<tr>
<td>No. of days of fever &gt; 38.2°C, median (range)</td>
<td>3 (1-22)</td>
<td>3 (2-18)</td>
<td>n.s.</td>
</tr>
<tr>
<td>No. of days antibiotic therapy, median (range)</td>
<td>6 (0-25)</td>
<td>6 (0-18)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Gastrointestinal toxicity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepatitis, grade 3</td>
<td>3</td>
<td>5</td>
<td>6%</td>
</tr>
<tr>
<td>Gastrointestinal toxicity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of RBC transfusions, median (range)</td>
<td>1 (0-5)</td>
<td>0 (0-11)</td>
<td>P &lt; .05</td>
</tr>
<tr>
<td>No. of PLT transfusions, median (range)</td>
<td>1 (0-3)</td>
<td>1 (0-6)</td>
<td>n.s.</td>
</tr>
</tbody>
</table>

FUO indicates fever of unknown origin; CVC, central venous catheter; PLT, platelet.
groups of patients. PFS and time to progression was, however, longer among patients receiving BU/MEL when compared with those receiving a MEL-only conditioning regimen. No case of veno-occlusive disease was observed.

The same authors [32] analyzed the results of ASCT with i.v. BU 9.6 mg/kg and MEL (140 mg/m²) preparative regimens in patients who had received a modern induction treatment containing bortezomib. Overall response rate and CR after transplant were 100% and 49%, respectively.

Mark et al. [26] conducted a phase I trial adding escalating doses of bendamustine to MEL (200 mg/m²). A maximum tolerated dose was not encountered, and the highest dose level cohort of bendamustine 225 mg/m² + MEL was expanded to further evaluate safety. The regimen did not increase transplantation risk or toxicity, and no TRM was reported. The authors reported an overall response rate of 80% at day +100 and a CR or improved rate of approximately 45% at 1 year post-ASCT.

THIO is a polyfunctional alkylating agent, similar in structure to nitrogen mustard, that damages the DNA of cancer cells and was designated as an orphan drug by the European Medicines Agency on January 29, 2007. High-dose THIO appears to have broad-spectrum antitumor efficacy [42], which can be added in myeloablative multiagent regimens for ASCT in both solid [43,44] and hematopoietic tumors [45-48]; the drug was designated by the US Food and Drug Administration as a conditioning treatment before ASCT on April 2, 2007.

In our study the choice of THIO was based on the documented sensitivity of myeloma cells to the drug in the

![Figure 1](image1.png)

**Figure 1.** Day 100 response rates after transplant. PR indicates partial response.

![Figure 2](image2.png)

**Figure 2.** Progression-free survival.

N = 64 patients, 13 with progression of disease. Median progression-free survival not reached. Actuarial 2-year PFS = 71% (95% CI, 53 to 88)
context of resistance to previous treatments [49] and the decision was made to explore a double alkylator-based regimen. The dose-limiting toxicity of THIO is notably on the gastrointestinal tract (mucositis and diarrhea) and the central nervous system (drowsiness and seizure). In the MM autologous setting, the recommended dose ranges from 150 mg/m² per day to 250 mg/m² per day, administered for 3 consecutive days before depending on the combination with other chemotherapeutic medicinal products, without exceeding the total maximum cumulative dose of 750 mg/m² during the time of the entire conditioning treatment (see www.ema.europa.eu/docs/en_GB/.../WC500090252.pdf.)

Results from an Israeli study [50] showed that treatment with etoposide, THIO, and MEL in MM may be more effective than MEL alone before ASCT. In particular, patients who received the 3-drug combination had a longer time to progression (44 versus 17 months) and longer OS (not yet reached after a median of 108 months follow-up versus 59 months) than those who received MEL alone. However, the researchers reported that the 3-drug combination appeared to be more toxic than MEL alone.

We used a strategy of a tandem transplant in “de novo” sensitive-disease patients and explored if the second transplant with a double alkylator-based regimen (THIO + MEL) was feasible, safe, and efficacious. The tandem ASCT approach achieved an improvement in OS [2], even though a survival benefit was mainly seen in those patients who failed to achieve at least a VGPR [21,22].

In this trial the choice to administer THIO at 275 mg/m² was made to reduce the risk of synergistic toxicity between the MEL and THIO on the gastrointestinal tract. We decided on in any case a myeloablative dosage. The engraftment kinetics and toxicities, seen for THIO/MEL conditioning, are similar to those reported previously with MEL (200 mg/m²) conditioning, consisting primarily of mild mucositis and gastrointestinal toxicity [18]. In our study, oral mucositis occurred in 86% of subjects, with most patients experiencing grades 1 to 2 mucositis. Given these data, the association of THIO and MEL (140 mg/m²) does not appear to significantly increase mucositis risk compared with MEL at 200 mg/m². TRM was 0% at +100 days post-transplantation. Furthermore, in the comparison between the first and the second transplant, there was no difference in terms of toxicity and bone marrow engraftment.

It is too early to draw definitive conclusions regarding the efficacy of THIO in a tandem ASCT approach for MM. We reported an overall response rate of 86% at day +100 and a CR rate of approximately 44% after THIO/MEL ASCT. The 2-year PFS and OS are on par with what is expected from MEL200 in the new drug era.

There are some critical issues in the present study because we evaluated the response using the EBMT registry response criteria. Although the CR and the overall response rates were not the main objective of the study, assessing the response to treatment is a key determinant of MM treatment. Recently, the International Myeloma Working Group...
response criteria were developed from EBMT/International Bone Marrow Transplant Registry and Autologous Blood and Bone Marrow Transplant Registry response criteria [35] with revisions and improvements to help uniform reporting [36,51]. It is recommended that the International Myeloma Working Group uniform response criteria should be used in future clinical trials. Free light chain testing can help to demonstrate progressive improvements in the quality of response, and the free light chain ratio is required for documenting stringent CR.

However, considering its good tolerability, THIO/MEL could be an effective treatment option especially in elderly MM patients. Moreover, stratification of patients into various risk groups based on the chromosomal markers is being used by some centers for prognostic counseling, selection, and sequencing of therapy approaches. The utility of this information is to determine prognostic and clinical recommendations as a more effective conditioning regimen.

Our study was not designed to carry out a detailed cost analysis. However, the length of hospitalization accounted for most of the costs of an autograft procedure. In this trial the median duration of hospitalization was similar between the first and second transplant. For this reason it is likely that the addition of THIO in the conditioning regimen does not determine an increase in the cost of the procedure [52].

Following this study, we are going to evaluate the efficacy of the association between THIO and MEL200, which is the current standard conditioning in MM patients [19]. Subsequently, the regimen should be explored for efficacy in a phase III study. The next randomized study should be planned to address safety, therapeutic activity, and cost efficacy of the 2 conditioning regimens.

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