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Research Article

# Superiority of Bortezomib, Thalidomide and Dexamethasone in Frontline Therapy of Younger Patients with High-Risk Multiple Myeloma: A Single-Center Experience

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**Abstract**

**Introduction:** In July 2012, TD (thalidomide and dexamethasone) was substituted for vtD (low-dose bortezomib, thalidomide and dexamethasone) as our standard induction treatment of younger patients with high-risk multiple myeloma (MM). We aimed to evaluate in our clinical practice, outside clinical trials, whether vtD resulted in an improvement in high-quality responses.

**Methods:** We compared response post-induction, response post-transplant, progression-free survival (PFS) and overall survival (OS) at 3-year between vtD and TD.

**Results:** From a total of 235 consecutive patients newly diagnosed with symptomatic MM, 45 were considered high-risk and eligible to autologous stem cell transplant (ASCT). Twenty-nine and 16 patients received vtD and TD, respectively. After induction, the complete response (CR) rate (44.8% vs. 6.3%, $p$=0.008) and CR plus very-good partial response (VGPR) rate (65.5% vs. 12.5%, $p$=0.002) were significantly higher in the vtD vs. TD group. After ASCT, the CR plus VGPR rate was significantly higher in the vtD group (76.7% vs. 43.8%, $p$=0.023). The overall survival at 3-year was 74.4% vs. 68.8% in the vtD and TD groups, respectively.

**Conclusion:** Outside clinical trials, vtD remains a superior induction regimen compared with TD in transplant-eligible, newly diagnosed patients with high-risk MM.

**Keywords:** Multiple myeloma; Treatment outcome; Induction chemotherapy; Autologous transplantation

## Abbreviations

ASCT: Autologous Stem Cell Transplant; CR: Complete Response; HDT: High-Dose Therapy; ISS: International Stage System; MM: Multiple Myeloma; ORR: Overall Response Rate; OS: Overall Survival; PFS: Progression-Free Survival; PR: Partial Response; TD: Thalidomide, Dexamethasone; VGPR: Very Good Partial Response; vtD: (Low-Dose) Bortezomib, Thalidomide, Dexamethasone

## Introduction

Several new therapeutic interventions have been introduced for multiple myeloma (MM) during the past 50 years leading to a major increase in long-term survival of younger patients [1]. A combination of melphalan and prednisone remained the standard treatment during three decades but the median survival did not exceed three years [2]. The introduction of high-dose therapy with autologous stem-cell transplant (HDT/ASCT) was the first major cause of overall survival (OS) improvement observed in younger patients and extended median OS to 3-4 years [3,4]. However, approximately 40% of the patients achieved partial response (PR) only, long-term remissions remained rare and the vast majority of patients ultimately relapsed [3]. The inclusion of novel agents during induction (thalidomide, bortezomib, lenalidomide) dramatically increased post-induction and post-transplant response rates and substantially changed treatment strategies in the transplant setting [5,6].

Despite marked therapeutic advances for most patients with MM, outcomes of a subgroup of patients with high-risk disease still remained poor at the end of the last decade. Three phase 3 large clinical trials randomized more than 1000 patients to compare double regimens with a triple regimen consisting of bortezomib, thalidomide and dexamethasone (VTD) [6-8]. All trials demonstrated a superiority of the triple regimen across patients with high-risk MM including poor-risk cytogenetics, ISS (International Staging System) 3 and extramedullary disease. Additionally, in the GIMEMA study, VTD managed to overcome the poor prognosis impact of poor-risk cytogenetics [6]. Besides the demonstrated efficacy, VTD avoided impairment of stem-cell collection and significant toxicity and has since then been considered the best induction treatment prior to HDT/ASCT.

The standard of care at our department includes triple regimen as the standard induction treatment for patients with high-risk myeloma




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since July 2012. The main purpose of this study was to evaluate in our clinical practice, outside clinical trials, whether vtD improved high-quality responses compared with TD.

## Materials and Methods

We searched retrospectively our myeloma report data base from January 2009 to December 2014 for patients newly diagnosed with symptomatic MM who had induction treatment at our department. Patients aged less or equal to 65 years with a suitable ECOG (Eastern Cooperative Oncology Group) performance status and normal organ function were considered eligible for HDT/ASCT after induction once they had achieved at least partial response (PR). Multiple myeloma patients are referred for transplant to the Bone Marrow Transplant Unit of our hospital. For this observational study, only patients with high-risk MM were included. High-risk MM was defined by the presence of at least one of the following criteria, as stated in the literature [9]: 1) ISS stage 3, 2) renal insufficiency (eGFR < 40 ml/min), 3) extramedullary disease, 4) translocation t(4;14) and/or deletion del(17p), 5) advanced bone disease. From January 2009 to June 2012, our patients received a double regimen: TD and from July 2012 to December 2014, our patients received triple regimen: vtD. TD consisted of thalidomide 200mg daily (escalating doses in the first two cycles: 50 mg on days 1-14 and 100 mg on days 15-28 of the first cycle; 150 mg on days 1-14 of the second cycle and 200 mg afterwards) and dexamethasone 40 mg orally on days 1-4 (all cycles) and 9-12 (first four cycles) at 4-week intervals for four to eight cycles. vtD consisted of four to eight 3-week cycles of bortezomib 1mg/m$^2$on days 1, 4, 8 and 11, thalidomide 100 mg daily (escalating doses in the first cycle: 50 mg on days 1-15 and 100 mg afterwards) and dexamethasone 40 mg orally on days 1-2, 4-5, 8-9 and 11-12. All patients with high-risk MM were assigned to tandem transplant. Response and progression were assessed according to the International Myeloma Working Group criteria at the end of induction therapy and around day 100 after transplant. Progression-free survival was calculated from the date of diagnosis to the date of progression/relapse or death. Overall survival was calculated from the date of diagnosis to the date of death from any cause or the last visit. Patient follow-up ended at March, 31, 2016. Primary endpoint was response post-induction. Other endpoints analyzed included response post-transplant, progression-free survival (PFS) and overall survival (OS) at 3-year. Descriptive statistics and statistical analyses were performed in Statistical Package for the Social Sciences (SPSS) v.18.

## Results

### Population

From 2009 to 2014, a total of 235 consecutive patients were newly diagnosed with symptomatic myeloma, of which 102 were considered eligible for transplant. Fifty-two of these patients presented with high-risk MM. Seven patients were treated with different regimens and were excluded from this analysis. Of the 45 patients treated according to our standard of care, 16 and 29 patients received TD and vtD, respectively. The median duration of induction treatment for both groups was eight cycles. Data on cytogenetic abnormalities were available in a subset of 39 patients. Table 1 summarizes patients' clinical characteristics. No significant differences were found between the two groups although the proportion of male patients was higher in the vtD group. A total of 32 patients underwent HDT/ASCT: 11 patients in TD (three underwent one ASCT and eight had a tandem transplant) and 21 in vtD (13 underwent one ASCT and eight had a tandem transplant). Sixteen patients who entered the transplant phase underwent a second transplant and two additional patients were awaiting a second transplant at the end of the study. Reasons for not undergoing the second transplant (n=14 patients) were: insufficient peripheral blood stem cells (n=6 patients), comorbidities (n=3 patients), early progression after transplant (n=2 patients), patient refusal (n=1 patient), enrollment in a clinical trial (n=1 patient) and missing follow-up (n=1 patient).

**Table 1:** Clinical characteristics of 45 patients newly diagnosed with high-risk multiple myeloma.

| | TD, n=23 | vtD, n=29 |
|---|---|---|
| **Median age**, years (interquartil range) | 56 (54-61) | 57 (47,5-63,5) |
| **Male/Female** | 11/12 | 18/11 |
| **ISS** | | |
| 1 | 5 | 8 |
| 2 | 7 | 12 |
| 3 | 11 | 9 |
| **M-protein type** | | |
| IgG | 12 | 11 |
| IgA | 3 | 11 |
| Light chain | 8 | 6 |
| Non-secretor | - | 1 |
| **Del(17p) and/or t(4;14)** | 4 | 6 |

**Abbreviations:** Ig: Immunoglobulin; ISS: International Stage System; M-protein: Monoclonal Protein; TD: Thalidomide and Dexamethasone; vtD: Low-Dose Bortezomib and Thalidomide and Dexamethasone

### Clinical response

After induction, an overall response rate (ORR) of 86.2% was achieved in patients treated with vtD vs. 68.8% in patients treated with TD. High-quality response rates were significantly higher in the vtD group (Table 2). The CR (complete response) rate was approximately seven fold higher for patients treated with vtD (44.8% vs. 6.3%, $p$=0.008). The CR plus VGPR (very good partial response) rate was approximately five fold higher for patients treated with vtD (65.5% vs. 12.5%, $p$=0.002). On an intention-to-treat analysis of

**Table 2:** Response rates of 45 patients newly diagnosed with high-risk multiple myeloma.

| | TD, n=16 | vtD, n=29 | *p* |
|---|---|---|---|
| **After induction, %** | | | |
| CR | 6.3 | 44.8 | 0.008 |
| ≥ VGPR | 12.5 | 65.5 | 0.002 |
| ≥ PR | 68.8 | 86.2 | NS |
| **After HDT/ASCT, %** | | | |
| CR | 31.3 | 55.2 | NS |
| ≥ VGPR | 43.8 | 76.7 | 0.023 |
| ≥ PR | 81.3 | 89.7 | NS |

Abbreviations: CR: Complete Response; PR: Partial Response; VGPR: Very Good Partial Response; HDT/ASCT: High-Dose Therapy/Autologous Stem Cell Transplant; TD: Thalidomide and Dexamethasone; vtD: Low-Dose Bortezomib and Thalidomide and Dexamethasone

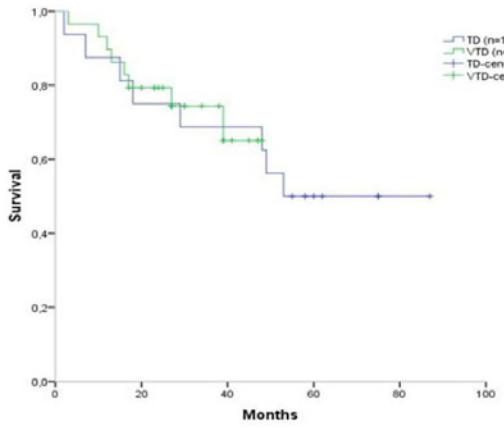


**Figure 1:** Kaplan Meyer curves for overall survival from 45 patients newly diagnosed with high-risk multiple myeloma according to induction regimen FU – follow-up.

clinical responses after HDT/ASCT, there was no difference in the ORR between both groups (89.7% vs. 81.3%) although the CR plus VGPR rate remained significantly higher in the vtD group (76.7% vs. 43.8%, $p$=0.023). The CR rate was similar in both groups. In patients with poor-risk cytogenetics, the CR rate was higher in the vtD group both post-induction (50% vs. 0%) and post-transplant (67% vs. 25%).

### Follow-up

The median follow-up was higher in the TD group (54 months vs. 27 months) as expected by the design of the study. A median PFS of 35 months vs. 32 months was obtained for patients treated with TD vs. vtD, respectively. The estimated overall survival at 3-years was 68.8% vs. 74.4% for patients treated with TD vs. vtD, respectively (Figure 1).

## Discussion

Even though it remains an incurable disease, several new treatments have brought excitement and hope to the MM community. During the last five decades, the median survival extended from 2-3 years to approximately 10 years or longer [10,11]. On the basis of three phase 3 large clinical trials, three-drug induction regimens including bortezomib and dexamethasone (VD) are currently considered the standard of care for ASCT-eligible, newly diagnosed MM patients. Low-dose bortezomib and thalidomide was associated with a low incidence of peripheral neuropathy (3%) in the French trial [8]. Considering their dismal prognosis, patients with high-risk disease would benefit the most from VD-based regimens so we changed our standard of care earlier for these patients. Later on, we extended the triple regimen to all previously untreated MM who are eligible for HDT/ASCT. Recently, a phase 3 study by Moreau et al showed the superiority of VTD over VCD in preparation for ASCT [12].

Our vtD response rates are in line with the ones achieved in those randomized studies. There was a significant superiority of vtD over TD in CR and ≥ VGPR rates after induction therapy. There was also a superiority of vtD in ≥ VGPR rate post-transplant. Depth of response has been shown as one of the most important prognostic factors in MM and the achievement of deep remissions represents a therapeutic goal for younger MM patients [13-15]. Our 44.8% post-induction CR rate is slightly higher than that achieved by the Spanish group (35%), which was the highest among the three. Approximately 71% of our patients underwent the planned HDT/ASCT which is similar to the 73% in the Spanish group and lower than the 89% and 90% in the Italian and French groups, respectively. These similar results are likely because of the similar dose intensity administered in our study (4 to 8 full-dose cycles of vtD) comparing to the Spanish group (6 full-dose cycles). The difference in response rates observed in our study did not translate into a significant improvement in PFS and OS. Differences in follow-up times and in the number of transplants (single/tandem) between patients treated with TD vs. vtD might have had the effect of decreasing any differences in survival. Additionally, the reduced sample size might have hampered the establishment of a significant association in OS.

Bortezomib-based induction is the preferred treatment regimen for patients with high-risk myeloma. In the Italian study, VTD overcame the unfavorable prognosis of poor-risk cytogenetics [6]. Some groups are suggesting that tandem ASCT may offer an improved benefit for high-risk patients [9,16]. A pooled analysis that included over 600 patients with newly-diagnosed MM from different large European cooperative group studies showed a possible beneficial role of double ASCT in improving outcomes for newly-diagnosed MM patients with poor prognosis [17]. In our study, 16 patients completed the tandem transplant (eight patients in both TD and vtD). Of the TD group, three patients achieved CR and the median PFS was 51 months. Of the vtD group, six patients achieved CR and the median PFS was 34 months. Several factors, however, may limit the feasibility of tandem transplant in MM [18]. Fourteen out of the 32 patients (43,8%) who entered the transplant phase in our study did not complete the tandem transplant program which is in accordance with previously reported data [18]. Maintenance therapy with bortezomib for patients harboring poor-risk cytogenetics has been suggested following the results of HOVON-65/GMMG-HD4 trial [19]. However, the two arms of this trial differed both in the induction and maintenance therapies, hampering its conclusions. Further evidence is needed before the use of bortezomib in the maintenance setting can be recommended [20].

Our study has several limitations which have to be pointed out. The small patient number is the most important limitation. Although we did not present data for patients without high-risk disease, our impression for clinical response is also encouraging. Second, it is a single-center study and these results may not be generalized to other centers. However, the relative numbers of patients that underwent HDT/ASCT and that completed the tandem transplant are consistent with studies from other countries, a fact that lends general relevance to our findings. Due to its retrospective design, results must be interpreted with caution due to problems of selection bias. Variation of supportive care over time is another unavoidable limitation. Similar to other hematologic malignancies, supportive care has played an increasingly important role in the management of patients with MM and its contribution to the superiority of the triple regimen is difficult to evaluate. Finally, patients were selected from the MM report data base and some cases may have been missed.

## Conclusions

Our study confirms, outside clinical trials, the superiority of vtD over TD as induction regimen in the treatment of transplant-eligible, newly diagnosed patients with high-risk MM.

## Acknowledgment

This study was performed at the Department of Onco-Hematology, Portuguese Institute of Oncology - Porto, Portugal.

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