Bortezomib consolidation after autologous stem cell transplantation in multiple myeloma: a Nordic Myeloma Study Group randomized phase III trial


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Keypoints

1. Bortezomib consolidation after autologous stem cell transplantation improves progression free survival in myeloma
2. Improvement of response is seen with bortezomib consolidation after autologous stem cell in myeloma

Abstract

The Nordic Myeloma Study Group (NMSG) conducted an open randomized trial to compare bortezomib as consolidation therapy given after high-dose therapy (HDT) and autologous stem cell transplantation (ASCT) to no consolidation in bortezomib naïve patients with newly diagnosed multiple myeloma. Overall, 370 patients were centrally randomly assigned three months after ASCT to receive 20 doses of bortezomib given during 21 weeks or no consolidation. The hypothesis was that consolidation therapy would prolong progression-free survival (PFS). The PFS after randomisation was 27 months for the bortezomib group compared to 20 months for the control group (p=0.05). Fifty-one out of 90 patients in the treatment group compared to 32 out of 90 controls improved their response after randomisation (p=0.007). No difference in overall survival was seen. Fatigue was reported more commonly by the bortezomib treated patients in self-reported quality of life (QoL) questionnaires, whereas no other major differences QoL were recorded between the groups. Consolidation therapy seemed to be beneficial for patients not achieving at least a very good partial response (VGPR) but not for patients in ≥ VGPR at randomisation. Consolidation with bortezomib after ASCT in bortezomib naïve patients improves PFS without interfering with QoL.

(This study was registered at www.clinicaltrials.gov as #NCT00417911.)
Introduction

Treatment with high dose melphalan followed by autologous stem cell infusion (ASCT) has improved survival in patients with multiple myeloma and remains gold standard for younger patients even in the era of new drugs. In a previous study, we showed that a reduced initial therapy induced less toxicity but with no reduction in treatment efficacy. Building on these results, we now aimed to explore if consolidation therapy after ASCT could improve treatment results. The proteasome inhibitor bortezomib has proven to be very efficient as relapse treatment also for patients who have previously undergone ASCT. In this open, multicenter phase III randomized trial we compared the effect of bortezomib consolidation initiated three months after ASCT with no consolidation, which was standard procedure within the Nordic countries at the time of the study start. Importantly, patients included in this trial did not receive bortezomib as part of induction therapy. The primary objective of the study was to determine whether the addition of bortezomib consolidation would improve progression-free survival (PFS).

Knowing that many patients have a high quality of life (QoL) during the first period of disease control and that consolidation might interfere with this we also focused on toxicity and QoL during the study period.
Methods

Study design and patients

The study was undertaken at 23 centres in Denmark, Estonia, Finland, Iceland, Norway and Sweden. Patients were enrolled between Oct 2005 and Apr 2009. Clinical data cut off was Apr 2010 when the last randomized patient had been followed for 12 months. An extra update for overall survival was performed Apr 2011. The primary endpoint was PFS and secondary endpoints were response rate, overall survival, quality of life and tolerability.

Myeloma patients with newly diagnosed symptomatic and measurable disease were eligible for inclusion in this trial. All patients had received initial therapy followed by stem cell collection and ASCT. The regimen used for initial therapy was not mandated. However, the patients had to be bortezomib naïve at time of inclusion. The most common initial treatment was Cy-Dex (cyclophosphamide and high dose steroids), used for 169 out of 183 in the control group and 161 out of 187 in the consolidation group. Eight patients in both groups received a combination of thalidomide and steroids and the remaining patients received VAD or similar combinations. Patients were included at the time of ASCT but randomized three months later.

Exclusion criteria were neuropathy > grade 2 according to National Cancer Institute Common Toxicity Criteria (NCI CTC), severe heart disease including myocardial infarction within 6 months before enrolment, heart failure, New York Heart Association (NYHA) ≥ Class III or cardiac amyloidosis, history of hypotension or previous exposure to bortezomib.

All patients signed a written informed consent before inclusion. The study was approved by the ethical committees and health authorities in all participating countries and conducted in accordance with the Helsinki declaration of 1975 and the Guidelines for Good Clinical Practice. This study was registered at www.clinicaltrials.gov as #NCT00417911.
Randomization

Patients were randomly assigned in a 1:1 ratio three months after ASCT to receive 20 doses of bortezomib during 21 weeks starting no later than within two weeks after randomization or to no further treatment. Stratification factors were age (< 60 years vs. ≥ 60) and single vs. double ASCT. The clinical investigators at each site called the research unit at Lunds University Hospital where randomization was performed using a computerized system.

Consolidation therapy

Bortezomib was given as single drug intravenously in six cycles. In the first two cycles, bortezomib was given twice weekly, day 1, 4, 8 and 11 in a 3 weeks schedule followed by four cycles in which bortezomib was given once weekly day 1, 8 and 15 in a four weeks schedule. Starting dose was 1.3 mg/m² but subsequent doses could be reduced due to neuropathy and/or haematological toxicity according to the standard pre-specified dose-modification algorithm. No doses were postponed. If a dose due to any cause could not be administered, it was reported as reduced to zero. In total, a maximum of 20 doses were given during 21 weeks. No corticosteroids, apart from a dose equivalent to less than prednisone 50 mg daily for no more than one week due to other medical conditions, or any other antineoplastic drugs were allowed. A total of six patients, one control and five bortezomib treated patients did receive steroids. Three due to chronic obstructive lung disease and one each for vasculitis, haemolytic anemia and high fever. In one case the dose was higher than permitted and that patient was censored at the time of start of steroid treatment. Bisphosphonates were administered according to national guidelines.
Diagnostic, response and relapse criteria

Symptomatic myeloma was defined using the criteria of the International Myeloma Working Group (IMWG). Disease response and relapse were defined according to the European Group for Blood and Marrow Transplantation (EBMT) incorporating near CR (nCR) and very good partial response (VGPR). Since immunofixation data were lacking in a proportion of patients, nCR and CR are reported together. Patients with no measurable M-protein but for whom no bone marrow examination confirming CR was performed were included in the VGPR group.

Follow-up evaluation

All patients were evaluated with serum and urine electrophoresis monthly for the first year and then every second month until disease progression. A bone marrow examination needed to be done to confirm CR. All data were reviewed according to Good Clinical Practice (GCP) criteria by an independent academic contract research organisation. After disease progression patients were followed for survival. Survival time was measured from randomization i.e. 3 months after ASCT until disease progression or death from any cause (PFS) or death from any cause (OS).

Health-related quality of life

Health-related quality of life (HRQOL) was assessed prospectively by use of the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30, version 3.0). Scoring of the EORTC QLQ-C30 was performed according to published methods. The questionnaire has previously been shown to be reliable and valid for myeloma patients.
The questionnaires were filled in at baseline (time of randomization), at 8 weeks after randomization, and then every three months until two years and every six months until 3.5 years. The baseline questionnaires were administered by a physician or nurse and were filled in by the patients before randomization. The subsequent sets of questionnaires were mailed to the patient’s homes with a stamped returned envelope.

**Statistical analysis**

The hypothesis of this study was that consolidation treatment with bortezomib would prolong median PFS with 12 months. To prove this with a power of 80 % and a significance level of 5 % (two-sided test), 396 patients needed to be included of whom at least 80 % would be randomized, that is at least 159 patients per arm.

The proportions of patients with a given characteristic were compared using Fisher’s exact test for variables with frequency scale and Mann-Whitney U test for the remaining variables. A Mann-Whitney U test was also used to calculate the significance of differences in the EORTC QLQ-C30 score between the control group and bortezomib group. Based on a previous work in myeloma patients, the minimal important difference in a HRQOL scale score was classified as a difference of at least 6 points (0-100 scale).15

PFS and OS rates were calculated according to the Kaplan-Meier method, and survival comparisons between groups were made by the Log-Rank Test. PFS and survival was calculated from randomization, i.e. three months after high-dose therapy and approximately six months after start of induction therapy. The statistical analyses were performed in SPSS Statistics 18 for Windows (IBM Corporation, Somers, NY, USA).
Results

Patients and baseline characteristics

Figure 1 shows the study profile. 403 patients were included at time of ASCT. A total of four patients were excluded due to non-secreting disease (2) or not fulfilling diagnostic criteria (2). Of the remaining 399 patients, 29 were not randomized due to withdrawn consent (17), neuropathy (4), progressive disease before randomization(4), logistical reasons (2), early death (1) or severe infection (1). Of the remaining 370 patients, 187 were randomized to bortezomib consolidation therapy and 183 to the control group.

Baseline characteristics are shown in Table 1. All variables were equally distributed between the two groups.

Completion of consolidation treatment

The median number of bortezomib injections received were 19 and the median given dose was 90 % (calculated as total given dose divided by total planned dose for each patient).

Survival

The overall median follow-up time was 38 months. The median progression-free survival (PFS) was prolonged for patients randomized to bortezomib consolidation (27 months vs 20 months, \( P = 0.05 \)), figure 2A.

Patients achieving at least VGPR at any time experienced significant longer PFS compared to those who did not (28 months vs 16 months, \( P < 0.001 \)) irrespective if the patient was randomized to bortezomib treatment or not, figure 2B. Beneficial effect of bortezomib
consolidation was only seen in patients not achieving at least VGPR after ASCT, figure 2C and 2D. Further, no difference in PFS was seen in patients being in ≥ VGPR at randomization compared to those improving their response to ≥ VGPR during the study, data not shown. Since only 15 patients underwent a double ASCT no meaningful statistics could be calculated comparing single and double ASCT. No difference in PFS was seen for patients under the age of 60 years compared to those aged 60 or over, data not shown. After three years of follow up the overall survival was similar in both treatment groups, about 80%, figure 2E.

**Response rate**

The response rates at randomization 3 months after ASCT and best response during the study, calculated on an intention-to-treat-basis are presented in table 2. At randomization there was no difference in response rate between the groups, about 20% of all randomized patients had achieved CR/nCR and about 40% had achieved at least VGPR. Measured as best response achieved during the study, there was a difference with more bortezomib treated patients achieving at least VGPR (71% vs 57% \( P < 0.01 \)) and a trend towards more patients achieving CR/nCR (45% vs 35% \( P = 0.055 \)). Improvement of response from PR to at least VGPR was also more common in patients receiving bortezomib consolidation (51 of 90 patients, 57% vs 32 out of 90, 36%, \( P = 0.007 \)).

**Toxicity**

Sensory peripheral neuropathy was reported by 57% of patients in the treatment group versus 24% in the control group. Neuropathic pain was reported by 34% and 12% respectively. Sensory neuropathy > grade 2 on the CTC toxicity scale were experienced by 5% of bortezomib treated patients versus 1% for controls (\( P < 0.04 \)), whereas neuropathic pain > grade 2 was experienced by 6% versus 1% (\( P < 0.006 \)), figure 3.
Haematological toxicity was mild and manageable. It seemed as if the reduction of neutrophil and platelet counts was less pronounced during the last four treatment cycles when bortezomib was given once weekly, figure 4.

Two cases of secondary primary malignancy were reported. One of the bortezomib treated patients developed a breast cancer and one patient in the control group developed a rectal cancer.

**Health-related quality of life**

Baseline questionnaires were available for 311 patients (84%). There were no significant differences in HRQOL score between the bortezomib group and the control group at baseline. After 8 weeks, there were statistically significant more fatigue and nausea/vomiting in the bortezomib group ($P < 0.01$). However, only the fatigue scale reached what we previously had set as a cut off for clinically relevant changes (6 points on a 0-100 scale) figure 5. There were no significant differences in HRQOL scores between the bortezomib group and the control group during the rest of the study period.
Discussion

This randomized, multicenter phase 3 trial in newly diagnosed myeloma patients showed that consolidation with bortezomib after ASCT did improve response and resulted in a statistical significant 7 month prolongation of PFS in bortezomib naïve patients. However, the study hypothesis of a 12 month prolongation of PFS was not confirmed. Our data indicates that the prolongation of PFS was mediated by an increased proportion of patients achieving an improvement in the quality of the response after bortezomib consolidation. Supporting this theory are the findings that the proportion of patients improving their grade of response was significantly higher for the treatment group and that the beneficial effect of bortezomib consolidation on PFS only was seen in patients not achieving at least VGPR after ASCT. Finally, there was no difference in PFS for patients in ≥ VGPR after ASCT compared to those who achieved it later during the study.

No difference in OS was seen and this could be due to the fact that treatment at progression today is very effective and there are many treatment options. More patients in the control group did receive bortezomib containing combinations after first relapse, 48 versus 19. Apart from this there were small differences in second line therapy; a second ASCT was given to 17 of controls and 18 of patients receiving bortezomib consolidation, thalidomide 25 vs 27, lenalidomide 2 vs 9, chemotherapy combinations 10 vs 13 and radiation alone 10 vs 4. A landmark analysis starting at the time of relapse did not show any difference in estimated OS (4.0 years for controls versus 3.9 years for patients randomized to consolidation.

The role of consolidation and maintenance therapy is still unclear in myeloma therapy. The earliest experiences with chemotherapy were disappointing\textsuperscript{16-17} and the beneficial effect of corticosteroids as single drug maintenance\textsuperscript{18} has been questioned.\textsuperscript{19} Meta-analyses of
interferon alfa have shown positive effect but at the cost of substantial tolerability problems.\textsuperscript{20} Several studies have shown prolonged PFS and some even prolonged OS when thalidomide has been given as consolidation or maintenance after ASCT but with substantial toxicity, mainly neurological.\textsuperscript{21} An interesting finding in the French study, IFM 99-02, is that the beneficial effect of thalidomide was only seen in patients achieving less than VGPR after ASCT.\textsuperscript{22} Hence, the effect of thalidomide in the IFM study and of bortezomib in our study both seem to have been mediated by improving the degree of treatment response. In contrast, data from the British study, MRC IX, indicates that the effect of thalidomide given after ASCT has an effect of maintenance more than consolidation since the beneficial effect of thalidomide treatment did not differ due to response after ASCT.\textsuperscript{23} Similar results were seen in 2 studies using lenalidomide as maintenance therapy after ASCT.\textsuperscript{24-25} Regardless of response after ASCT, this treatment approach seemed to be beneficial.

In recent years, several studies and meta-analyses indicate that achievement of complete response or at least very good partial response after ASCT is associated with a better outcome.\textsuperscript{26-27} These data supports the consolidation concept that is to apply a short course of treatment in order to reduce the number of residual tumour cells, which is shown by improved response status in patients with insufficient response after ASCT.

Consolidation with bortezomib after ASCT in combination with other drugs has been reported. In a recently published update, it was shown that the combination of bortezomib, thalidomide and dexamethasone is superior to thalidomide and dexamethasone alone, given as consolidation therapy after double ASCT. In this study, the same combinations are also used as initial therapy before ASCT. Using landmark analysis, the authors show that the superior results of the triplet combination over the double, are further improved by consolidation therapy and the beneficial effect is most evident in patients not achieving at least nCR after ASCT.\textsuperscript{28} Even if it is dubious to compare results between studies, PFS in this Italian study is
clearly longer than in our study, indicating that using different drugs in combination can be very effective as consolidation therapy. When our study was planned there were already data suggesting that corticosteroids did improve the effect of bortezomib in the relapse setting. However, since studies have implied that steroids do have an effect of their own given as consolidation therapy, we chose to give bortezomib as single drug, avoiding confusion about the results.

A weakness in the present study is that a repeat bone marrow examination not always was performed in order to confirm or reject CR. Patients with no measurable M-protein but for whom no bone marrow examination confirming CR was performed were downgraded to VGPR. This means that patients in the VGPR response category are a heterogeneous group containing both patients in true CR as well as patients with only a 90 % reduction of the original M protein. Unfortunately, cytogenetics was not available for more than a proportion of the patients. The reason for this was that FISH analysis was not standard at the time of the study in the Scandinavian countries and the study was performed also at smaller local hospitals with limited access to cytogenetic techniques.

An interesting and important finding that limits the difference between the two patient groups in this study is that about 17 % of the controls also improved their response. However, in the clinic it is not a rare finding that patients do improve their response up to one year after ASCT.

Some of the strengths of the study are that bortezomib was given as single drug, meaning that observed effects can only be attributed to this substance. Further, the QoL data shows that the additional therapy did not interfere with quality of life, which is very important when focusing on PFS. The risk of neurotoxicity might be reduced with a more restrictive dose-modification algorithm and our study showed that the haematological toxicity was more pronounced when bortezomib was given twice weekly compared to once weekly. The only significant
differences in QoL, fatigue and nausea/vomiting after 7 weeks, did also disappear when the less frequent dose schedule was used. For elderly patients, it has already been suggested that administration of bortezomib once weekly makes the treatment more tolerable.\textsuperscript{30} Also, modification of administration might be beneficial since there now are data showing that by administrating bortezomib subcutaneously instead of intravenously the incidence and severity of neuropathy can be significantly reduced\textsuperscript{31}

In conclusion, our study shows that consolidation with bortezomib after ASCT improves PFS and indicates that this is due to improvement of response. The treatment was well tolerated indicated by no important interference with QoL, low frequency of severe toxicity and that most patients received their treatment without any dose reduction. The relatively short treatment period might have been a reason for the good tolerability. Results from other studies imply that efficacy might be enhanced if bortezomib is given in combination with other agents and that tolerability could be even further improved enhancing the possibility of long term treatment.
Acknowledgements

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Authorship

Contribution: U.-H.M., P.G., O.H., S.L., and J.W. designed and directed the study and edited the manuscript. All other authors contributed patients to the study and edited the manuscript.

Conflict of interest disclosure: U.-H.M, P.G., K.R. and A.W. have received honoraria from Janssen and Celgene. J.W serves on an advisory board for Celgene. The remaining authors declare no competing financial interests.

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References


Table 1. Baseline characteristics.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Bortezomib</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years(^a)</td>
<td>59.1 (9.90)</td>
<td>58.7 (8.80)</td>
</tr>
<tr>
<td>Male(^b)</td>
<td>59 (111)</td>
<td>60 (109)</td>
</tr>
<tr>
<td>Double ASCT(^b)</td>
<td>5 (9)</td>
<td>3 (6)</td>
</tr>
<tr>
<td>Myeloma subtype(^b)</td>
<td>n=187</td>
<td>n=183</td>
</tr>
<tr>
<td>IgG</td>
<td>55 (103)</td>
<td>63 (116)</td>
</tr>
<tr>
<td>IgA</td>
<td>26 (50)</td>
<td>21 (39)</td>
</tr>
<tr>
<td>Light chain</td>
<td>18 (33)</td>
<td>14 (25)</td>
</tr>
<tr>
<td>Other</td>
<td>1 (1)</td>
<td>2 (3)</td>
</tr>
<tr>
<td>ISS disease stage(^b)</td>
<td>n=125</td>
<td>n=141</td>
</tr>
<tr>
<td>I</td>
<td>38 (48)</td>
<td>41 (58)</td>
</tr>
<tr>
<td>II</td>
<td>38 (48)</td>
<td>31 (44)</td>
</tr>
<tr>
<td>III</td>
<td>23 (29)</td>
<td>28 (39)</td>
</tr>
<tr>
<td>(\beta_2)-microglobulin (mg/L)(^c)</td>
<td>3.0/4.9</td>
<td>3.4/5.1</td>
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<td>Albumin (g/L)(^c)</td>
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<td>37.0/36.2</td>
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<td>Creatinine ((\mu)mol/L)(^c)</td>
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<td>Haemoglobin (g/L)(^c)</td>
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<td>110.0/111.7</td>
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<td>Platelets ((\times10^9)/L)(^c)</td>
<td>249.0/252.9</td>
<td>243.0/253.9</td>
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<tr>
<td>FISH analysis for cytogenetic abnormalities(^b)</td>
<td>n=73</td>
<td>n=66</td>
</tr>
<tr>
<td>Absence of del(13q), t(4;14), or del(17p)</td>
<td>75.3 (55)</td>
<td>63.7 (42)</td>
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<tr>
<td>Presence of del(13q)(^d)</td>
<td>21.9 (16)</td>
<td>16.7 (11)</td>
</tr>
<tr>
<td>Presence of t(4;14) and/or del(17p)</td>
<td>19.2 (14)</td>
<td>19.7 (13)</td>
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</table>

\(^a\) median (IQR)  
\(^b\) % (n)  
\(^c\) median/mean  
\(^d\) Regardless of absence or presence of t(4;14) and/or del(17p).
Table 2. Response rates.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Bortezomib</th>
<th>Control</th>
<th>Test&lt;sup&gt;a&lt;/sup&gt;</th>
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<tbody>
<tr>
<td></td>
<td>n</td>
<td>% (n)</td>
<td>n</td>
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<tr>
<td>At randomisation</td>
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<td></td>
</tr>
<tr>
<td>≥ nCR</td>
<td>20.1 (36)</td>
<td>20.6 (37)</td>
<td></td>
</tr>
<tr>
<td>VGPR</td>
<td>19.6 (35)</td>
<td>18.3 (33)</td>
<td></td>
</tr>
<tr>
<td>PR</td>
<td>51.4 (92)</td>
<td>50.0 (90)</td>
<td></td>
</tr>
<tr>
<td>MR</td>
<td>7.3 (13)</td>
<td>8.9 (16)</td>
<td></td>
</tr>
<tr>
<td>SD</td>
<td>1.7 (3)</td>
<td>2.2 (4)</td>
<td></td>
</tr>
<tr>
<td>Best response</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>≥ nCR</td>
<td>45.1 (82)</td>
<td>35.0 (64)</td>
<td></td>
</tr>
<tr>
<td>VGPR</td>
<td>25.8 (47)</td>
<td>22.4 (41)</td>
<td></td>
</tr>
<tr>
<td>PR</td>
<td>25.3 (46)</td>
<td>38.3 (70)</td>
<td></td>
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<tr>
<td>MR</td>
<td>2.7 (5)</td>
<td>3.3 (6)</td>
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<tr>
<td>SD</td>
<td>0.5 (1)</td>
<td>0.5 (1)</td>
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<tr>
<td>PD</td>
<td>0.5 (1)</td>
<td>0.5 (1)</td>
<td></td>
</tr>
<tr>
<td>≥ nCR</td>
<td>45.1 (82)</td>
<td>35.0 (64)</td>
<td></td>
</tr>
<tr>
<td>≥ VGPR</td>
<td>70.9 (129)</td>
<td>57.4 (105)</td>
<td></td>
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</table>

<sup>a</sup>Fisher’s Exact Test, Exact Sig. (2-sided)
<sup>b</sup>Eleven patients had unconfirmed responses at the time of randomization
<sup>c</sup>Five patients had incomplete follow up
Figure legends

Figure 1. Flow diagram of 403 patients included in the NMSG bortezomib consolidation study.

Figure 2. Analysis of outcome from start of consolidation therapy. Kaplan-Meier estimates of PFS for bortezomib treated patients vs controls (A), PFS for patients achieving ≥VGPR vs patients achieving < VGPR (B), PFS for patients in < VGPR at randomization (C), PFS for patients in ≥VGPR at randomization (D) and OS for bortezomib treated patients vs controls (E)

Figure 3. Neurological toxicity. Number of patients experiencing neuropathic pain and peripheral sensory neuropathy by treatment arm.

Figure 4. Hematological toxicity. Mean neutrophil and platelet count for patients randomized to bortezomib during the consolidation period.

Figure 5. Quality of life. Score for fatigue by treatment arm.
403 patients included

4 excluded
  2 non-secreting disease
  2 not fulfilling diagnostic criteria

29 not randomised
  17 withdrawn informed consent
  4 neuropathy
  4 progressive disease
  2 logistical reasons
  1 severe infection
  1 death

187 bortezomib consolidation

183 control
Figure 2.
Figure 3. Neurological toxicity

- **Max grade of neuropathic pain**
  - **Velcade**
  - **Control**

- **Max grade of peripheral sensory neuropathy**
  - **Velcade**
  - **Control**
Figure 4. Hematological toxicity
Figure 5. Quality of Life

Fatigue

![Bar chart showing fatigue scores for different questionnaire numbers. The chart compares control and bortezomib groups.](image)
Bortezomib consolidation after autologous stem cell transplantation in multiple myeloma: a Nordic Myeloma Study Group randomized phase III trial