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Bortezomib before and after autologous stem cell transplantation overcomes the negative prognostic impact of renal impairment in newly diagnosed multiple myeloma: a subgroup analysis from the HOVON-65/GMMG-HD4 trial

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ABSTRACT

Renal impairment is frequent in patients with multiple myeloma and is correlated with an inferior prognosis. This analysis evaluates the prognostic role of renal impairment in patients with myeloma treated with bortezomib before and after autologous stem cell transplantation within a prospective randomized phase III trial. Eight hundred and twenty-seven newly diagnosed myeloma patients in the HOVON-65/GMMG-HD4 trial were randomized to receive three cycles of vincristine, adriamycin, dexamethasone (VAD) or bortezomib, adriamycin, dexamethasone (PAD) followed by autologous stem cell transplantation and maintenance with thalidomide 50 mg daily (VAD-arm) or bortezomib 1.3 mg/m² every 2 weeks (PAD-arm). Baseline serum creatinine was less than 2 mg/dL (Durie-Salmon-stage A) in 746 patients and 2 mg/dL or higher (stage B) in 81. In myeloma patients with a baseline creatinine ≥ 2 mg/dL the renal response rate was 63% in the VAD-arm and 81% in the PAD-arm ($P=0.31$). The overall myeloma response rate was 64% in the VAD-arm versus 89% in the PAD-arm with 13% complete responses in the VAD-arm versus 36% in the PAD-arm ($P=0.01$). Overall survival at 3 years for patients with a baseline creatinine ≥ 2 mg/dL was 34% in the VAD-arm versus 74% in the PAD-arm ($P<0.001$) with a progression-free survival rate at 3 years of 16% in the VAD-arm versus 48% in the PAD-arm ($P=0.004$). Overall and progression-free survival rates in the PAD-arm were similar in patients with a baseline creatinine ≥ 2 mg/dL or <2 mg/dL. We conclude that a bortezomib-containing treatment before and after autologous stem cell transplantation overcomes the negative prognostic impact of renal impairment in patients with newly diagnosed multiple myeloma. *The trial was registered at www.trialregister.nl as NTR213 and at www.controlled-trials.com as ISRCTN 64455289*

Introduction

Renal impairment (RI) affects up to 50% of patients with multiple myeloma (MM).^{1,2} A serum creatinine ≥ 2 mg/dL (177 μ mol/L) at diagnosis is a well-known risk factor for inferior survival in the Durie and Salmon staging system.³ This is also reflected in the International Staging System (ISS)⁴ since serum beta-2-microglobulin is correlated not only with tumor burden but also with renal function.

Bortezomib is administered without dose reductions to myeloma patients with RI.⁵ In relapsed/refractory myeloma patients with a creatinine clearance <50 mL/min it has been shown to improve responses, progression-free survival (PFS) and overall survival (OS).⁶ Combined with chemotherapy it reverted light-chain-induced RI in 62% of patients.⁷ A subgroup analysis of the VISTA trial⁸ in transplant-ineligible myeloma patients found comparable efficacy in patients with or without moderate RI in the bortezomib-melphalan-prednisone arm but patients with creatinine >2 mg/dL were excluded. A recent single-center study⁹ suggested that RI is no longer a negative prognostic factor when thalidomide, lenalidomide

or bortezomib are used as part of first-line therapy. However, the study was retrospective, had no control group and less than 10% of patients had undergone autologous stem cell transplantation (ASCT). So far there are no prospective data from controlled phase III trials regarding the impact of novel agents such as bortezomib on the outcome of first-line treatment in newly diagnosed, transplant-eligible myeloma patients with RI.

The prospective, randomized phase III HOVON-65/GMMG-HD4 trial included patients with RI and investigated a bortezomib-containing regimen as part of a high-dose therapy strategy. While the general results of the study have recently been published,¹⁰ we report here on a planned subgroup analysis focusing on the outcome of patients with a baseline serum creatinine ≥ 2 mg/dL (Durie-Salmon stage B).

Methods

Patients

Eight hundred and thirty-three patients with newly diagnosed symptomatic MM Durie and Salmon stage II or III aged between 18 and 65 years and with adequate performance status were included in

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a prospective clinical study of the HOVON in the Netherlands and Belgium and the GMMG in Germany. Key exclusion criteria included the presence of systemic AL amyloidosis, non-secretory MM, neuropathy grade 2 or higher, a history of active malignancy during the past 5 years, positivity for human immunodeficiency virus, or hepatic dysfunction. Patients could be included regardless of their renal function including dialysis dependence. A total of 827 eligible patients were available for analysis.

The study was approved by the Ethics Committees of the Erasmus Medical Center and University, Rotterdam and of the University of Heidelberg, and by the local Ethics Committees of the participating German institutions. All patients gave written informed consent and the trial was conducted according to the European Clinical Trial Directive 2005 and the Declaration of Helsinki concerning human rights.

Renal function

Renal function was assessed by serum creatinine level at study baseline (BLC) and classified using a cut-off BLC of 2 mg/dL, according to stage "A" or "B" of the Durie and Salmon classification.⁵ Creatinine clearance was calculated with the formula of Cockcroft-Gault. Renal response was defined as complete, partial or minor (CR_{renal}, PR_{renal} or MR_{renal}, respectively) according to the criteria formulated by the International Myeloma Working Group (IMWG).¹¹ Briefly CR_{renal} is defined as an increase in creatinine clearance from <50 to 60 mL/min or better, a PR_{renal} is an increase from <15 to 30-59 mL/min and a MR_{renal} is an increase from <15 to 15-29 mL/min or from 15-29 to 30-59 mL/min.

Study design and treatment

The study design and treatment protocol have been described elsewhere.¹⁰ Briefly, patients were randomized 1:1 to vincristine, doxorubicin and dexamethasone (VAD) induction therapy, intensification with high-dose melphalan and ASCT, followed by maintenance therapy with thalidomide 50 mg daily (VAD-arm); or induction with bortezomib, doxorubicin and dexamethasone (PAD),¹² high-dose melphalan/ASCT, followed by maintenance with bortezomib 1.3 mg/m² i.v. two-weekly for 2 years (PAD-arm). High-dose melphalan was given at a dose of 200 mg/m² or 100 mg/m² in patients with a creatinine clearance <40 mL/min.

Statistical analysis

All analyses were performed according to the intention-to-treat

principle. Response rates between subgroups were compared using a chi-squared test.

PFS and OS were estimated by the Kaplan-Meier method. Survival endpoints were analyzed using Cox regression analysis to evaluate the impact of treatment arm and creatinine level. Hazard ratios (HR) and corresponding 95% confidence intervals (95% CI) were determined. Kaplan-Meier curves for PFS and OS for each of four groups based on treatment arm and baseline creatinine were generated to illustrate survival, and were compared using the log-rank test.

The data cut-off date for this report was April 12, 2011. The median follow up of the 588 patients still alive was 41 months (maximum, 66 months). All reported *P* values are two-sided and have not been adjusted for multiple testing.

Results

Of 827 eligible patients 746 (90%) had a BLC <2 mg/dL and 81 (10%) had a BLC ≥2 mg/dL. The median creatinine serum level in the latter group was 3.33 mg/dL (range, 2.00–18.3) with a calculated median creatinine clearance of 26 mL/min (range, 7 - 49). The median BLC was 1.00 mg/dL (range, 0.35-18.3) in the VAD-arm and 0.96 mg/dL (range, 0.01-8.99) in the PAD-arm. Forty-five patients in the VAD-arm (11%) and 36 patients (9%) in the PAD-arm had a BLC ≥2 mg/dL. The distribution of the baseline characteristics according to BLC and study arm is presented in Table 1. The proportions of both ISS stage III and high-risk genetic features such as del17p or t(4;14) were significantly higher in the subgroup of patients with BLC ≥2 mg/dL.

Treatment and toxicity

Of 81 patients with BLC ≥2 mg/dL, 80 received at least one cycle of induction treatment and 63 completed all three cycles. In the VAD-arm 12 patients did not complete induction treatment (reasons given: early death in 4 patients, pneumonia in 2, disease progression in 2, renal failure in 2, aspergillosis in 1 and sepsis in 1) compared to six patients in the PAD-arm (reasons given: early death in 2, pulmonary insufficiency in 1, cardiac failure in 2 and poor performance status in 1). When comparing the rate of adverse events between patients with or without BLC ≥2 mg/dL the safety

Table 1. Baseline characteristics according to baseline serum creatinine and study arm.

Creatinine at baseline (mg/dL)	< 2	≥2		≥2	≥2
Study arm				VAD	PAD
N.	746	81		45	36
Age [year] (median, range)	57 (25-65)	57 (38-65)	<i>P</i> =0.64	57 (39-65)	57 (38-64)
Creatinine [mg/dL] (median, range)	0.94 (0.01-1.99)	3.33 (2.00-18.3)	<i>P</i> <0.001	3.36 (2.00-18.3)	3.32 (2.10-8.99)
Beta 2 MG [mg/L] (median, range)	3.2 (0.0-42.5)	13.3 (4.2-63.0)	<i>P</i> <0.001	13.3 (4.9-63.0)	13.3 (4.2-44.8)
ISS (n., %)			<i>P</i> <0.001		
I	288 (39)	-		-	-
II	268 (36)	6 (7)		3 (7)	3 (8)
III	122 (16)	66 (81)		38 (84)	28 (78)
Unknown	68 (9)	9 (11)		4 (9)	5 (14)
del13q (n., %)*	269 (41)	43 (61)	<i>P</i> =0.001	27 (66)	16 (55)
del17p (n., %)*	48 (9)	17 (28)	<i>P</i> <0.001	11 (29)	6 (26)
t (4;14) (n., %)*	55 (12)	15 (30)	<i>P</i> <0.001	9 (29)	6 (32)

Beta 2 MG: Beta 2 microglobulin. *P* values are given for the comparison of parameters in patients with BLC<2 mg/dL versus BLC≥2 mg/dL. There were no significant differences between the VAD-arm and the PAD-arm in patients with BLC≥2 mg/dL. *Only for patients with FISH data available, which was the case for del13q in 733 patients, for del17p in 602 patients, and for t(4;14) in 512 patients.

profile appeared to be comparable except for greater hematologic toxicity during induction for patients with elevated BLC. The distribution of adverse events during the first cycle of induction according to baseline renal function is shown in Figure 1A. Within the patients with BLC ≥ 2 mg/dL there were no significant differences in the frequency and type of adverse events between the VAD-arm and the PAD-arm (all CTC grade 2: 30 % *versus* 39%, grade 3: 32% *versus* 31%, grade 4: 14% *versus* 19%).

Of 81 patients with BLC ≥ 2 mg/dL, 57 (70%) received high-dose melphalan, which was given at the full dose of 200 mg/m² to 39 patients, at 140 mg/m² to 1 patient and at 100 mg/m² in 17 patients while 24 patients did not proceed to high-dose therapy. Of the 57 patients receiving high-dose melphalan, 29 were treated in the VAD-arm and 28 in the PAD-arm. The distribution of adverse events during the first course of high-dose therapy seemed to be comparable in patients with BLC ≥ 2 mg/dL and in those with BLC < 2 mg/dL, as illustrated in Figure 1B. Twenty-eight patients in the GMMG received a second ASCT with either 200 mg/m² (n=18) or 100 mg/m² (n=10) of melphalan with dose reduction in 6/14 (43%) in the VAD-arm and 4/14 (29%) in the PAD-arm. This difference was not statistically significant (P=0.70). After high-dose therapy 42 of 57 patients (74%) started maintenance treatment, 20 with thalidomide in the

VAD-arm and 22 with bortezomib in the PAD-arm.

During the course of the study serious adverse events were reported in 62% of patients with BLC < 2 mg/dL *versus* 81% with BLC ≥ 2 mg/dL. The most frequent reason for classifying an adverse event as serious was hospitalization in 74% in both subgroups. Serious adverse events were judged by the investigators as definitely or probably related to the study treatment in 34% of patients with BLC < 2 mg/dL *versus* 37% with BLC ≥ 2 mg/dL. The types of serious adverse events were comparable in the two subgroups and are listed in Table 2.

Renal response

Of 81 patients with BLC ≥ 2 mg/dL, 60 were evaluable for renal response before high-dose therapy. All had a calculated creatinine clearance < 50 mL/min at baseline. Using the criteria proposed by the IMWG,¹¹ 28 (47%) patients achieved a CR_{renal}, 1 a PR_{renal}, 10 (12%) a MR_{renal} and 21 (26%) had no response. Forty-three patients (71%) regained a creatinine level < 2 mg/dL on study treatment. In the 57 patients proceeding to high-dose therapy the median creatinine level was 1.14 mg/dL (range, 0.60 – 6.9) before the high-dose therapy with 38 patients (67%) reaching a level < 2 mg/dL. Before high-dose therapy there was no significant difference in renal function between the two treatment

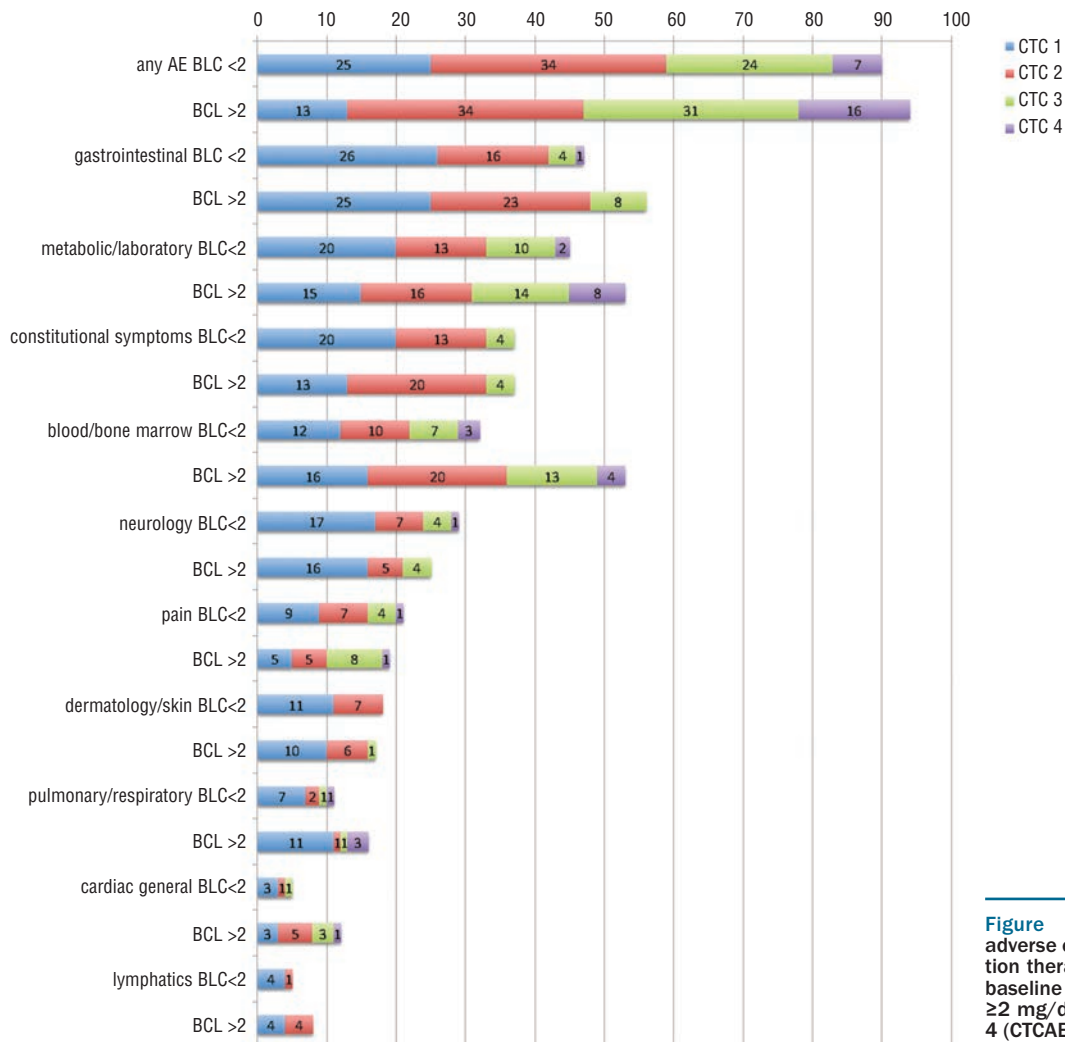


Figure 1A. Percentages of adverse events (AE) during induction therapy cycle 1 according to baseline creatinine (< 2 mg/dL or ≥ 2 mg/dL) and CTCAE grades 1-4 (CTCAE version 3.0).

arms, with a median creatinine level of 1.41 mg/dL (range, 0.65–6.9) in the VAD-arm and 1.10 mg/dL (range, 0.60–5.9) in the PAD-arm ($P=0.43$) and a median creatinine clearance of 51 mL/min (range, 12–147) in the VAD-arm versus 65 mL/min (range, 11–180) in the PAD-arm ($P=0.42$). As far as concerns renal responses, after three cycles of induction treatment, in the VAD-arm 13 (43%) patients were in CR_{renal}, 1 (3%) patient was in PR_{renal} and 5 (17%) patients had a MR_{renal} (overall renal response rate, 63%) whereas in the PAD-arm, 18 (58%) patients had a CR_{renal} and 7 (23%) had a MR_{renal} (overall renal response rate, 81%) with no significant difference between the two arms ($P=0.31$).

Myeloma response

The overall response rate (at least PR) after induction was 68% in patients with BLC <2 mg/dL compared to 49% for those with BLC ≥2 mg/dL ($P=0.001$, Figure 2). Over the duration of the trial treatment the rate of patients achieving at least a PR was 88% for those with a BLC <2 mg/dL and 74% for those with a BLC ≥2 mg/dL ($P<0.001$, Figure 2). In

Table 2. Numbers of serious adverse events according to baseline creatinine (with possibly multiple serious adverse events per patient).

Baseline creatinine (mg/dL)	<2	≥2
N.	935	146
Deep venous thrombosis	59 (6%)	6 (4%)
Pulmonary embolism	27 (3%)	3 (2%)
Polyneuropathy	97 (10%)	9 (6%)
Gastrointestinal	90 (10%)	14 (10%)
Cardiac	48 (5%)	9 (6%)
Infection	386 (41%)	58 (40%)
Myeloma-related	75 (8%)	21 (14%)
Bleeding/thrombocytopenia	19 (2%)	5 (3%)
Wasting	17 (2%)	2 (1%)
Osteonecrosis of the jaw	3 (0%)	-
Other	111 (12%)	17 (12%)
Unknown	3 (0%)	2 (1%)

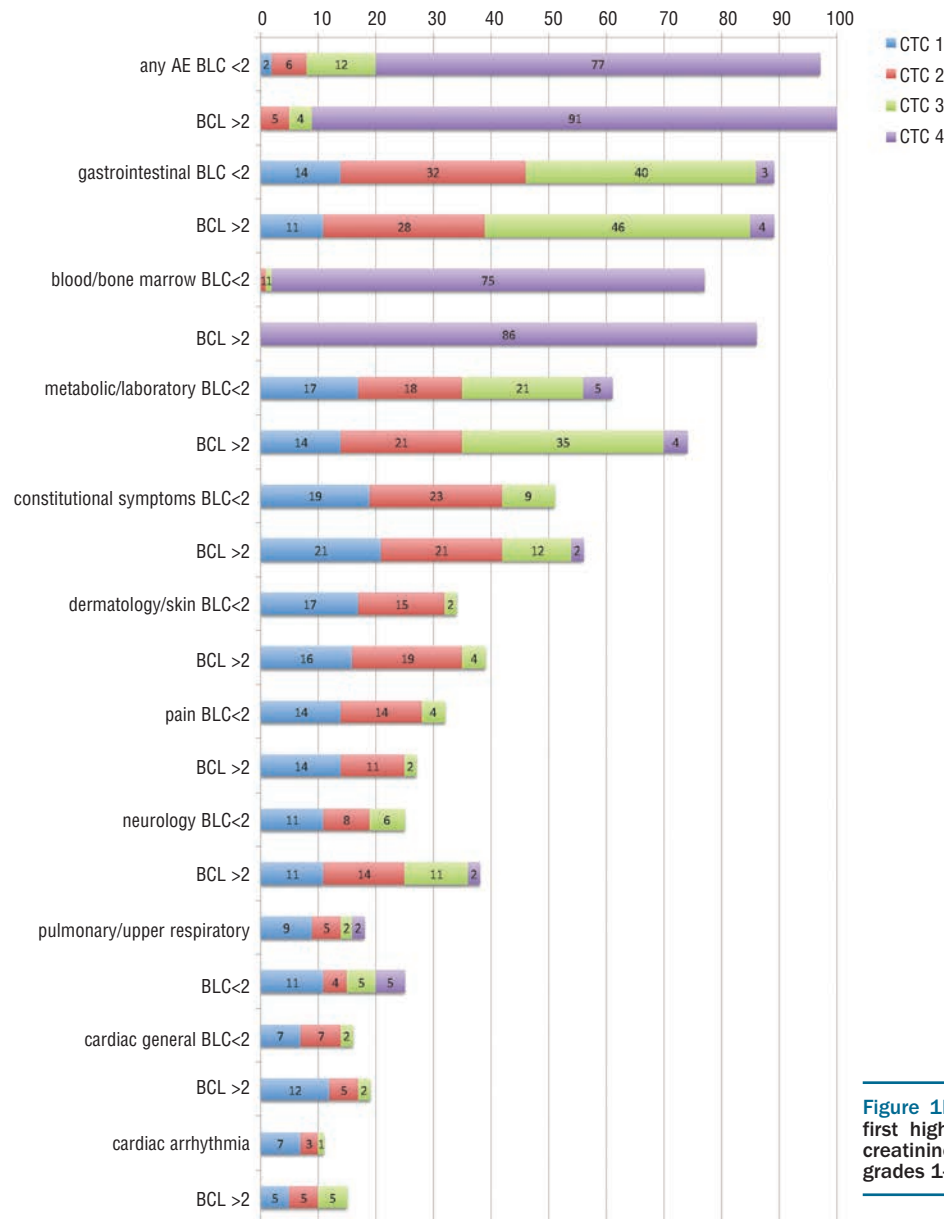


Figure 1B. Percentages of events (AE) during first high-dose therapy according to baseline creatinine (<2 mg/dL or ≥2 mg/dL) and CTCAE grades 1-4 (CTCAE version 3.0).

the subgroup of 81 patients with BLC ≥ 2 mg/dL, there were significant differences in response depending on the treatment arm (Figure 3): after one to three cycles of induction treatment the overall response rate in the bortezomib-containing PAD-arm was 75%, with 33% of patients achieving at least a very good PR, compared to 36% and 9% in the VAD-arm ($P=0.003$), respectively. This difference remained detectable when considering the best response achieved any time during trial treatment (89% versus 64%, $P=0.01$), mainly due to a higher CR rate of 36% in the PAD-arm compared to 13% in the VAD-arm.

Progression-free and overall survival

The PFS rate was 30% at 3 years and 20% at 5 years for patients with BLC ≥ 2 mg/dL and 46% and 26%, respectively with BLC < 2 mg/dL, ($P<0.001$). Treatment in the PAD-arm led to a marked improvement in PFS rate from 16% to 48% at 3 years in patients with a BLC ≥ 2 mg/dL ($P=0.004$) and in patients with BLC < 2 mg/dL, respectively (3-year PFS was 43% in the VAD-arm versus 48% in the PAD-arm; $P=0.023$). The Kaplan-Meier survival curves for PFS for all four groups are shown in Figure 4A.

The OS rate was significantly inferior in patients presenting with a BLC ≥ 2 mg/dL, being 51% at 3 years and 33% at 5 years versus 78% (at 3 years) and 61% (at 5 years) in patients with a BLC < 2 mg/dL ($P<0.001$). The OS rate at 3 years for patients with a BLC ≥ 2 mg/dL was significantly higher in patients treated in the PAD-arm (74%) than in those in the VAD-arm (34%, HR = 0.33, 95% CI = 0.16-0.65, $P<0.001$), while the OS was similar in both arms in patients with BLC < 2 mg/dL.

Within the PAD-arm OS at 3 years was very similar in patients with BLC < 2 mg/dL (79%) and those with BLC ≥ 2 mg/dL (74%, HR = 0.94, 95% CI = 0.71-1.25; $P=0.68$). The Kaplan-Meier survival curves for OS for all four groups are shown in Figure 4B.

Discussion

Although RI is frequent in newly diagnosed MM, many study protocols^{8,13-15} use thresholds for renal function in their inclusion criteria, leading to an underrepresentation of such high-risk patients in the study cohorts. Since the HOVON-

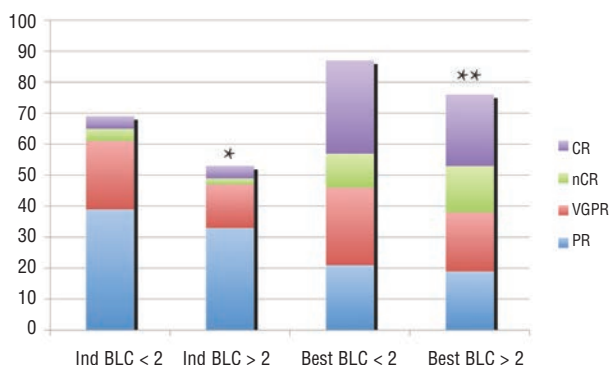


Figure 2. Myeloma response according to baseline creatinine (intent-to-treat). BLC: baseline creatinine, Ind: response after induction treatment, Best: best response achieved any time on study treatment. BLC < 2 mg/dL: n=746, BLC ≥ 2 mg/dL: n=81. * $P=0.001$ compared to BLC < 2 mg/dL; ** $P<0.001$ compared to BLC < 2 mg/dL.

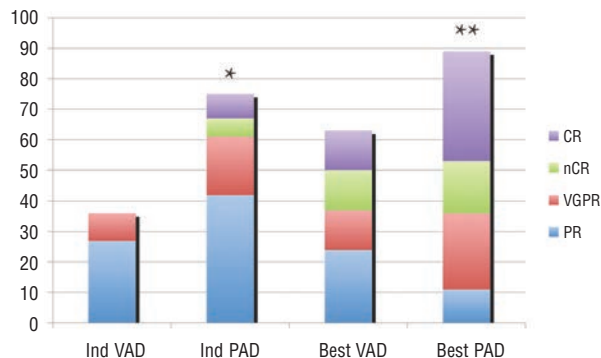


Figure 3. Response in the subgroup of 81 patients with BLC ≥ 2 mg/dL according to treatment arm (intent-to-treat). BLC: baseline creatinine, Ind=response after induction treatment, Best: best response achieved any time on study treatment. VAD-arm: n=45, PAD-arm: n=36. * $P=0.003$ compared to VAD-arm; ** $P=0.01$ compared to VAD-arm.

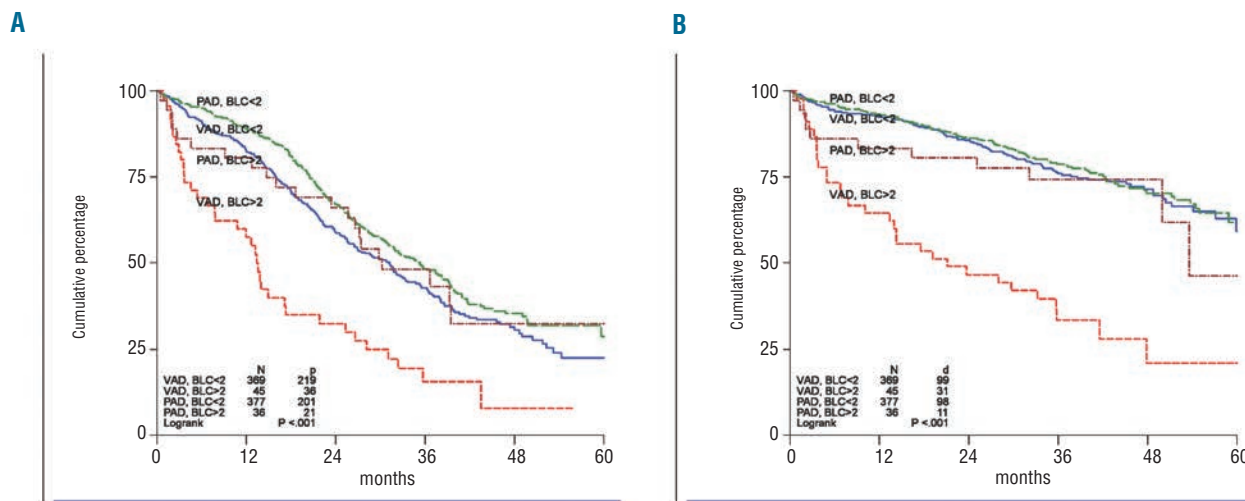


Figure 4. Progression-free survival (A) and overall survival (B) according to baseline creatinine (BLC) and treatment arm. PAD: bortezomib for induction and maintenance, VAD=VAD for induction and thalidomide for maintenance.

65/GMMG-HD4 included patients regardless of renal function we were able to analyze the feasibility and efficacy of a bortezomib-based treatment before and after ASCT in patients with RI based on data from a prospective randomized study.

During induction patients with BLC ≥ 2 mg/dL showed a comparable profile of adverse events as those with BLC < 2 mg/dL except for increased hematologic toxicity. The frequency and distribution of serious adverse events were not significantly different between the two subgroups indicating that the treatment protocol was feasible in a large multicenter trial including patients with RI up to the age of 65 years.

Both induction regimens with VAD or PAD led to a reduction of the serum creatinine level to less than 2 mg/dL in the majority of patients and 70% of patients with a BLC ≥ 2 mg/dL actually proceeded to high-dose therapy with full-dose melphalan, in most cases with no differences between both arms. The treatment-related mortality after ASCT could be limited to 2%, which compares favorably to previously published results in patients with RI.^{16,21} There was no difference in frequency or duration of maintenance treatment with either thalidomide (VAD-arm) or bortezomib (PAD-arm).

The rates of renal recovery in the bortezomib-containing PAD-arm (55% CR_{renal} and 21% MR_{renal} with an overall renal response rate of 76%) compare favorably with those previously obtained with PAD and reported by Ludwig *et al.*:⁷ 31% CR_{renal}, 7% PR_{renal} and 24% MR_{renal}. Although we could not demonstrate a significant difference in renal response between the study arms, there was a trend for all analyzed renal parameters to be better in the PAD-arm than in the VAD-arm. In view of the limited number of patients in this subgroup analysis we cannot exclude that the absence of significant differences in renal response may be due to a lack of statistical power.

There was a significant improvement in myeloma response with an overall response rate (\geq PR) of 75% after three cycles of PAD *versus* 36% after three cycles of VAD. In the French IFM 2005-01 study comparing bortezomib + dexamethasone *versus* VAD as induction regimen,¹⁵ there was also a higher overall response rate for the bortezomib regimen (79% *versus* 63%). Although no analysis regarding renal function was reported, the difference within the ISS stage 3 cohort was more pronounced (77% *versus* 57%). However this benefit in response did not translate into an improved PFS or OS. This difference from our results may be due to the addition of doxorubicin in the induction regimen and/or the use of maintenance with bortezomib in the PAD-arm of our protocol. In the French study lenalidomide or no maintenance treatment was given, since the majority of patients were subsequently included in a maintenance trial (IFM 2005-02). With very comparable overall response rates to induction the addition of doxorubicin is unlikely to be the reason for the improvement in survival in our study in comparison to the IFM 2005-01 trial. It does, therefore, appear that patients with high-risk myeloma, as defined by their having RI, may derive particular benefit from bortezomib when it is used not only for induction but also for maintenance after ASCT. Two recent studies^{22,23} have shown improved PFS with lenalidomide maintenance after ASCT. Both study protocols excluded patients with a serum creatinine ≥ 2 mg/dL; however, in view of the high renal response after induction found in our study, maintenance with lenalidomide after ASCT may also be a future option for patients presenting with renal

failure at diagnosis.

Since FISH results were available for most patients, our results indicate for the first time that patients with RI have an increased frequency of adverse genetic features such as del17p or t(4;14). We previously demonstrated in the HOVON65/GMMG HD4 study²⁴ that patients with these adverse factors benefit from the combination of bortezomib and high-dose therapy. Still, only a third of the patients with a BLC ≥ 2 mg/dL had del17p or t(4;14). *Vice versa* only about 25% of patients with del17p or t(4;14) also had a serum creatinine ≥ 2 mg/dL. Thus there was only a partial overlap between both types of high-risk myeloma and the higher rate of adverse genetic features in the cohort of patients with BLC ≥ 2 mg/dL found in our study is certainly not sufficient to explain the worse prognosis in myeloma patients with RI. This is supported by a recent analysis from the MRC Myeloma IX study²⁵ which also included patients undergoing ASCT: ISS stage (reflecting in part renal function as explained earlier) and genetic risk factors such as del17p or changes involving chromosome 14 were found to be independent predictors of both OS and PFS.

We confirmed the negative prognostic impact of RI in the VAD-arm of our study, finding a 3-year OS rate of only 34% in patients with BLC ≥ 2 mg/dL compared to 76% in those with BLC < 2 mg/dL. In contrast there was no effect of RI on OS or PFS in the PAD-arm, implying that the integration of bortezomib into a high-dose treatment protocol appears to abrogate the negative prognostic impact of RI in newly diagnosed myeloma patients. Retrospective cohort studies^{9,26} have suggested that the use of novel agents in the frontline treatment of MM patients with RI have improved results in a way that RI may no longer have a negative prognostic impact,^{27,28} in particular when using modern three-drug regimens.²⁹ The high rates of myeloma and renal response, in particular to bortezomib, in patients with moderate RI in two prospective trials^{8,30} have further supported this view. However both trials excluded patients with markedly elevated creatinine.

This subgroup analysis of a large randomized phase III study in newly diagnosed MM patients demonstrates for the first time in a prospective trial that the negative impact of RI, as classified by Durie-Salmon stage "B", can be overcome by incorporating bortezomib both before and after ASCT. The addition of bortezomib to a high-dose regimen should, therefore, be considered as a standard of care in otherwise transplant-eligible MM patients presenting with RI.

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Authorship and Disclosures

Information on authorship, contributions, and financial & other disclosures was provided by the authors and is available with the online version of this article at www.haematologica.org.

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