Bortezomib-based induction followed by stem cell transplantation in light chain amyloidosis: results of the multicenter HOVON 104 trial

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HOVON 104, supplementary data

Methods

The study was approved by the ethics committees of the UMC Utrecht, the University of Heidelberg, and all participating sites. All patients gave written informed consent. The study was conducted in accordance with the European Clinical Trial Directive and the Declaration of Helsinki (registered at *www.trialregister.nl*; NTR3220).

The full protocol can be seen at the HOVON site: http://www.hovon.nl/studies/studies-per-ziektebeeld/mm.html?action=showstudie&studie_id=82&categorie_id=3

Additional exclusion criteria;

- Any serious medical condition, laboratory abnormality, or psychiatric illness that would prevent the subject from signing the informed consent form,
- Any psychological, familial, sociological and geographical condition potentially hampering compliance with the study protocol and follow-up schedule,
- Pregnant or breast feeding females,
- Presence of other active malignancy or a history of active malignancy during the past 5 years, with the exception of nonmelanoma skin cancer, stage 0 cervical carcinoma, or treated early-stage prostate cancer provided that prostate-specific antigen is within normal limits,
- Hypersensitivity to boron or mannitol,
- Uncontrolled infection,
- Positive for HIV or infectious hepatitis, B or C (screening obligatory),
- bilirubin > 2x ULN
- Absolute neutrophil count < 1.0×10^9/L,

- Concurrent diagnosis of B-cell NHL or B-CLL,
- Previous organ transplantation,
- Unwilling or unable to use adequate contraception

Exclusion criteria before stem cell mobilization were symptomatic pleural effusions, uncontrolled infection, symptomatic orthostatic hypotension, ANC < $1.0x10^9$/L, bilirubin > 2x ULN, and the start of SCM > 12 weeks after start of the last course of bortezomib treatment.

Treatment design

Patients with pre-existing PNP grade 2 without neuropathic pain or PNP grade 1 with neuropathic pain at study entry started with a 25% dose reduction of bortezomib, i.e. 1.0 mg/m^2 and once per week schedule in a 5 week cycle. Also patients with a moderate or severe hepatic dysfunction at study entry or during treatment received a lower dose of bortezomib of 0.7 mg/m^2. Guidelines for dose reductions of both bortezomib and dexamethasone were installed for hematologic and non-hematologic toxicities.

Hematologic and organ response criteria

CHR definition consisted of a negative serum and urine M protein immunofixation (IF) test and a normal FLC ratio with a normal absolute value of the iFLC. Very good partial response (VGPR) was defined as the difference between involved and uninvolved FLC (dFLC) of < 40 mg/l. All values were calculated from baseline, or from lowest value reached (nadir) and all progression categories require two consecutive assessments.

Flow cytometry protocol

For the analysis of PC in BM, 1 x 10^6 cells were incubated with titrated monoclonal antibodies (CD19, CD27, CD38, CD45, CD56, cytKappa, cytLambda and CD138) . In short, sample incubation was performed in a total volume of 180 µl. Cells were incubated for 15 minutes at room temperature in the dark. After washing, the cells were fixed, (reagents A, IntraStain, Dako Cytomation) washed and incubated with intra-cytoplasmic VS38c, lambda and kappa and permeabilisation reagents (reagents B, IntraStain, Dako Cytomation) for 15 minutes at room temperature. After the final washing step cells were directly analyzed. IntraStain was used according to manufacturer's procedure for simultaneous detection of surface and intracellular antigens. PC were identified as described by Rawstron et al. Using CD38, CD138 and light scatter characteristics PC's were identified and sequentially analyzed for CD56, CD19 and cytoplasmic kappa or lambda light chain expression. Total amount of plasmacells from the whole nucleated bone marrow cellularity as well as total amount of abnormal plasmacells were calculated. .Cell analysis was performed on a 3-laser Canto II flowcytometer (Becton Dickinson).

Statistical design and endpoints

For the sample size calculation the following assumptions were made. The null hypothesis was a CR rate at 6 months after SCT (CHR6mo) of 30% and we expected an increase of the CHR6mo to 50%. With an 80% power and 2-sided significance level of $\alpha = 0.05$, 44 eligible patients were required based on sample size calculation of one-sample proportion. In order to overcome possible dropouts due to ineligibility, 50 patients were registered.

Secondary endpoints were overall survival (OS), which was measured from the time of registration until death, patients still alive or lost to follow up were censored at the day they were last known to be alive, progression free survival (PFS), which was measured from time of registration until hematologic progression, relapse or death, whichever occurs first, hematologic response rate after induction therapy, maximal response rate, both hematologic and organ, time to response, both hematologic (defined as ≥PR) and organ, duration of response, both hematologic and organ, safety (type, frequency, and severity of adverse events (CTCAE grade ≥ 2 except for neurotoxicity for which also grade 1 was recorded), relationship of AE to study drug, and evaluation of prognostic factors for survival. OS and PFS analysis were performed using a Kaplan-Meier method from date of registration till cutoff date on 28 August 2018.

Potential baseline characteristics that may affect patients not proceeding to SCT after induction therapy were tested via a univariate logistic regression model. These baseline characteristics were type of hospital (high vs low number of included patients), eGFR >30 and < 50 vs eGFR ≥50 ml/min, NYHA I vs II, NT- proBNP as continuous variable, plasma cells < 10% vs ≥ 10% , dFLC < vs ≥ 180 mg/L, number of organs involved ≤2 vs >2, MAYO stage, nervous system involvement and cardiac involvement. The impact of aforementioned baseline characteristics were also tested on OS and PFS via univariate Cox regression. For flow cytometry data, we computed aPCs/BMPC ≥ 95% as a binary variable and tested the association of this binary variable with not proceeding to auto-SCT, PFS, and OS. For these analyses we also used a logistic regression model and a univariate Cox regression.

A 2-sided p-value of <0.05 was considered statistically significant and all analysis were performed using Stata 15.1.