haematologica

the hematology journal

13th Congress of
the European Hematology Association
Copenhagen, Denmark, June 12 - 15, 2008

ABSTRACT BOOK

2008 | s1
ISSN 0390-6078
Journal of the European Hematology Association
Published by the Ferrata-Storti Foundation, Pavia, Italy
Volume 93, supplement no. 1, June 2008
www.haematologica.org

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0440

MELPHALAN + PREDNISONE *vs* MELPHALAN + PREDNISONE + THALIDOMIDE IN INDUCTION THERAPY FOR MULTIPLE MYELOMA IN ELDERLY PATIENTS: FIRST INTERIM RESULTS OF THE DUTCH COOPERATIVE GROUP HOVON

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Background. The Dutch cooperative group HOVON started a randomised phase III study in elderly myeloma patients in September 2002 comparing the standaard Melphalan and Prednisone treatment with the combination Melphalan, Prednison and Thalidomide (HOVON 49 study). Patients with a multiple myeloma > 65 years of age with a stage IB or higher were candidates for this study. *Methods*. Melphalan was given in a dose of 0.25 mg/kg and prednisone 1 mg/kg for 5 days every 4 weeks. Thalidomide was given daily with ina dose of 200 mg. A maximum of 8 cycles was planned. If there was still a response further therapy was allowed till a plateau phase was reached. When a good response and a plateauphase was reached the patients who were randomised for Thalidomide received maintenance therapy with Thalidomide 50 mg/day till progression of their disease. It was planned to enter 420 patients in the study. However accrual decreased significantly due to positive outcome of other studies with Thalidomide. Therefor the study was stopped after the inclusion of 344 patients. This is the first analysis based upon the data of the first 320 patients. *Results*. 344 patients were entered. The first 320 patients were analysed for this report. 7 patients were non-eligible due to either being stage IA or not having a measurable tumor parameter. From one patient there was not a signed informed consent available. Eleven patients were excluded from this analysis because of insufficient data available at the time of evaluation. Thus data are presented of 301 patients; 149 in the M+P arm and 152 in the M+P+T arm. The median age was 72 years in both groups. The arms were well matched for age, sex, stage of the disease, performance status and type of M-protein. The best response on protocol was as folows M+P response rate 47% (with a CR 1%, VGPR 8% and PR 38% respectively) and for M+P+T arm a response rate of 63% (with a CR 1%, VGPR 28% and PR 34%) which was significantly better (p<0.001). There was a significant difference in the Event Free Survival in favour of the M+P+T arm (p< 0.001) but no difference was observed for the Progression Free Survival (p=0.08) and Overall Survival (p=0.28). *Toxicity*. Only one third of all the patients received cycle 3 of Melphalan and Prednison according the planned protocol. In all the other patients the doses had to be reduced and or delayed. Grade 2,3 and 4 toxicity of any type was seen in 59% of the patients in the M+P arm and in 87% of the M+P+T patients. This difference was mainly due to grade 2 and grade 3 neurotoxicity. After three cycles only 36% of the patients used the full Thalidomide dose and after 6 cycles this was only 28%. No differences between the two arms were seen for other toxicities. *Conclusions*. In this randomised phase III study we did observe a significant improvement in the Resonse Rate, the quality of the responses and time to response in favour of the M+P+T arm. This did translate in an improvement of the Event Free Survival but not in the Overall Survival. The toxicity of the five days schedule with 0.25 mg/kg/day Melphalan led to a substantial number of patients who did not received the planned therapy. Thalidomide added significantly to the toxicity (mainly neurotoxicity) of the treatment. We were unable to confirm the positive effect with Thalidomide as part of front-line therapy on Overall Survival as it was seen in other studies

0441

OVERALL SURVIVAL WITH DEXAMETHASONE IN PHASE III MULTIPLE MYELOMA TRIALS AFTER ADJUSTMENT FOR CROSS-OVER TO LENALIDOMIDE

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Background. In pivotal trials (MM-009/010) evaluating lenalidomide plus high dose dexamethasone (Len+Dex) *vs* Dex alone, 47% of the latter switched to Len±Dex at disease progression or following ethical study unblinding. Given the significantly better efficacy of Len+Dex, survival with Dex alone is overestimated. *Aims.* Use external data on survival to adjust Dex survival for the cross-over to Len±Dex. *Methods.* Pooled data from the UK Medical Research Council (MRC) MM IV, V, VI, and VIII trials enrolled between 1980 and 1997 were used to derive an equation predicting survival with second-line conventional therapies (including VAD, ABCM, Melphalan and cyclophosphamide), according to patient and disease characteristics. Applying this equation to MM-009/010 Dex patients yielded their expected survival without cross-over to Len±Dex. This was used to estimate survival for this subgroup in a lifetime simulation by adjusting the scale parameter of the post-progression survival equation estimated from MM-009/010. Since survival patterns change with additional lines of treatment, further calibration was necessary for multiple prior therapies. As patient-level data for this subgroup were not available from MRC, published Mayo clinic data on median survival with conventional therapies for patients with two prior therapies (12.6 months) was used to adjust the predicted median from the trial-based, MRC-calibrated equation. The simulation model was then used to compare long-term survival with Len+Dex *vs* Dex alone without cross-over. *Results.* Of 873 MRC patients who initiated second-line conventional treatment, 826 had died, with 17.6 months median survival from starting second-line treatment. Survival did not differ significantly between Dex- and non-Dex-containing regimens (p-value=0.79). Exponential survival with age, performance status, M-protein, B2M and time to progression as predictors provided best fit to the data. Application using this equation to predict survival for MM-009/010 Dex patients with one prior therapy yielded a median survival of 16.2 months (95%CI: 13.1-20.1) compared to 33.6 months (95%CI: 27.1-NE) observed with cross-over to Len±Dex. The median survival for patients with multiple prior therapies was 12.6 months (95%CI: 10.2 - 15.6), compared to 27.3 months (95%CI: 23.3-33.3) with cross-over to Len±Dex. The calibrated lifetime simulation yielded estimated mean survival of 2.2 life-years with Dex alone compared with 5.6 life-years with Len+Dex for patients with one prior therapy, and 1.5 life-years for Dex alone compared with 4.2 life-years for Len+Dex for patients with multiple prior therapies. *Conclusions*. Lenalidomide delivers significantly larger survival gains in this life-limiting orphan disease when appropriate adjustment has been made for the cross-over that occurred in the trials.

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