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POSTER ABSTRACTS

654.MULTIPLE MYELOMA: PHARMACOLOGIC THERAPIES

MRD and Molecular Risk Status Help to Define Optimal Maintenance Delivery Strategies after ASCT: Long Term Outcomes of the UK MRA Myeloma XI Trial Comparing Lenalidomide to Observation

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Introduction

In the phase III UKMRA/NCRI Myeloma XI trial 1248 patients were randomised between lenalidomide maintenance and observation after induction therapy and ASCT. At a median of 31 months (m) follow-up there was a significant improvement in progression free survival (PFS) and overall survival (OS). Median PFS was 57m (95%CI 50-not reached) in the lenalidomide group and 30m (25-32) in the observation group (HR 0·48 [95%CI 0·40, 0·58]; p<0·0001 and 3-year OS was 87·5% [95%CI 84·3-90·7] with lenalidomide and 80·2% [95%CI 76·0, 84·4] with observation; HR 0·69 [95% CI 0·52-0·93]; p=0·014. Here we present updated analysis after a median of 101 months follow up and explore outcomes by subgroups including transplant eligibility, MRD status, cytogenetic risk and duration of therapy.

Methods

Myeloma XI was a phase III trial with a pathway for transplant eligible (TE) newly diagnosed myeloma patients who, after immunomodulatory agent-based induction therapy and autologous stem cell transplant, were randomised between lenalidomide maintenance (Len, 10mg 21/28 days planned to continue till disease progression) or observation (Obs). Centrally analysed cytogenetic data was available for a representative subset of patients. High-risk was defined as presence of t(4;14), t(14;16), t(14;20), del(17p) or gain(1q) and ultra-high risk the presence of more than one lesion. MRD assessment was performed using next generation flow cytometry with a median sensitivity of $2x10^{-5}$.

Results

After a median of 101m of follow up lenalidomide maintenance was associated with a significantly prolonged median PFS 33 vs 66m, HR 0.57 [95% CI 0.50, 0.65], p<0.001. This improvement in PFS was consistent across cytogenetic risk groups (SR median PFS 37 vs 83m, HR 0.49 [95%CI 0.37, 0.66], p<0.001, HiR 29 vs 59m, HR 0.45 [95%CI 0.31, 0.66], p<0.001, UHiR 11 vs 23m, HR 0.50 [95%CI 0.28, 0.88]), p=0.017. Median overall survival was not significantly different in the overall population (116 vs 130m, HR 0.91 [95%CI 0.77, 1.09], p=0.316) but there was evidence of heterogeneity by genetic risk status with those patients having only one cytogenetic lesion having a significant OS benefit (SR OS at 7 years 67% vs 72%, HR 0.90 [95% CI 0.61, 1.34], HiR 42 vs 64%, HR 0.58 [95% CI 0.37, 0.90], UHiR 25 vs 25%, HR 0.91 [95% CI 0.46, 1.79]).

MRD negative status at both ASCT+3m and ASCT+9m timepoints was strongly associated with improved PFS (ASCT+3m HR 0.55 [95%CI 0.46, 0.65], ASCT+9m HR 0.41 [95%CI 0.31, 0.54]) and OS (ASCT+3m HR 0.72 [95%CI 0.58, 0.89], ASCT+9m HR 0.52 [0.36, 0.75]). There was evidence of benefit of lenalidomide maintenance over observation in the MRD positive group for both PFS and OS and in the MRD negative group for PFS but not OS. Patients converting to MRD negativity by 9m appeared to have similar long outcomes to those achieving MRD negativity at the earlier time point.

Multiple cut-point analysis confirmed previous findings suggesting a benefit for lenalidomide maintenance beyond 4-5 years in the overall population. There was no evidence of an adverse impact on overall survival with longer duration therapy. For patients MRD negative at the start of maintenance the benefit of ongoing maintenance appeared to lose significance earlier, after 3 years.

With extended follow-up the median duration of maintenance is 36 cycles [range 1-146]. Around half of patients stopping maintenance did so due to disease progression (51.5%). In the remainder, the most common reason cited was toxicity (19.6%). 79% of patients required a lenalidomide dose modification during their maintenance course. No new specific toxicity signals were identified with longer-term follow up. Cumulative incidence of second primary malignancies at 8 years was 7.0% (95%CI 4.79%, 9.12%) in the observation arm and 12.4% (95%CI 10.13%, 14.71%) in the lenalidomide arm.

Conclusions

Taken together these data can help define the optimal maintenance strategy for different patient groups. For patients with standard risk disease who become MRD negative after ASCT, limited duration maintenance approaches could be considered and should be evaluated in randomised studies. Patients with single high-risk lesions appear to have the greatest benefit, with an overall survival benefit from maintenance continued to progression. Patients with UHiR disease and those MRD positive at 9 months after ASCT have poor long-term outcomes and should be considered for combination maintenance approaches.

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