THE IMPACT OF THALIDOMIDE MAINTENANCE THERAPY VARIES DEPENDENT UPON BIOLOGICAL RISK GROUPING

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Recent studies have shown a clinical benefit for maintenance therapy in myeloma, however, the impact may vary dependent upon the underlying biology of the disease. An important question is whether maintenance can facilitate progression of high risk disease. Genetic alterations, such as t(4;14), del(17p) and +1q, can be used to define different biological behaviours, and we have shown that the presence of more than one adverse iFISH lesion can define a group of patients with very aggressive disease. We have studied the impact of thalidomide maintenance dependent upon risk status in the MRC IX study.

The trial comprised an intensive and a non-intensive pathway based on patient eligibility for autologous transplant. Patients were subsequently randomized to receive maintenance thalidomide versus no maintenance. iFISH results with a complete data set for adverse IgH translocations, +(1)(q21) and del(17)(p13) were available in 368 cases. Patients were characterized as having standard (SR), high (HR) or ultra-high risk (UHR) disease based on the number of co segregating iFISH lesions (0, 1 or >1). We also looked at defined biological subtype of disease: t(4;14), t(11;14) and hyperdiploidy were considered in isolation or plus an additional adverse lesion. In isolation del(13q) was not of prognostic significance and was not considered in the analysis. Progression free survival (PFS) and overall survival (OS) were calculated from maintenance randomization.

Results are summarized in Table 1. On overall population the median PFS and OS for maintenance and for control arm were 19.7 vs 14.7 months (p=0.066) and 37.4 vs 42.9 months (p=0.168), respectively. In the control arm the median PFS of SR, HR and UHR was of 20.2; 13.4; 6.7 (p=0.008) and the median OS was of 48.2; 44.7; 26.8 months (p=0.014), respectively. In the maintenance arm the median PFS was 29.6; 11.7; 6.5 (p=0.008) and for OS was 48.6; 29.6; 23.5 months (p=0.000). Compared to the control arm, SR patients receiving maintenance had a longer PFS with a similar OS, while the HR patients had similar PFS yet impaired OS. The outcome of the UHR was poor irrespective of whether maintenance was given or not.

The outcome of t(4;14) was unfavorable in the control arm. Thalidomide maintenance improved the outcome of patients t(4;14) negative (n=325) or with t(4;14) in isolation (n=13), with a trend towards a better PFS; in particular, for t(4;14) positive patients, median PFS for maintenance and controls were 24.6 vs 7.2 months, respectively. OS was similar between treatment arms. t(4;14) plus an additional lesion (n=30) identified a group with a particularly poor outcome irrespective of whether

maintenance was given or not. t(11;14) positive patients (n=54) had a favorable outcome; thalidomide maintenance did not discernibly affect PFS and OS. The impact of maintenance was similar whether the translocation was present in isolation (n=39) or in association with another lesion (n=15). The outcome of hyperdiploid patients (n=134) was favorable with a median PFS and OS of 21.2 and 44.4 months, respectively; cases receiving maintenance had an improved PFS (p=0.003), with similar OS. Low risk FISH with hyperdiploidy receiving maintenance had the best PFS and OS (median 36.7 and 50.1 months respectively). Hyperdiploidy associated with another lesion (n=85) behaved as the HR group.

Maintenance thalidomide is effective in prolonging PFS in biological LR patients and in patients with t(4;14) in isolation. Conversely, in patients with biologically defined HR disease maintenance thalidomide may not impair PFS but can impair OS. The outcome of cases with very aggressive disease (UHR or as t(4;14) plus an additional lesion) is governed by factor others than thalidomide maintenance.

Table 1. PFS and OS (in months) according to biological risk groups

	PFS			**OS**		
	Thalidomide	No maintenance	***p***	Thalidomide	No maintenance	***p***
SR	29.6	20.2	**0.004**	48.6	48.2	**0.718**
HR	11.7	13.4	**0.904**	29.6	44.7	**0.022**
UHR	6.5	6.7	**0.475**	23.5	26.8	**0.612**
p	**0.008**	**0.008**		**0.000**	**0.014**	
No t(4;14)	23.0	16.1	**0.060**	37.5	44.4	**0.195**
t(4;14)	24.6	7.2	**0.280**	31.1	36.1	**0.588**
t(4;14)+1	5.3	6.0	**0.813**	24.1	16.7	**0.185**
p	**0.000**	**0.000**		**0.052**	**0.045**	
No t(11;14)	22.1	14.7	**0.362**	37.9	43.2	**0.138**
t(11;14)	18.8	18.8	**0.455**	41.3	42.8	**0.883**
t(11;14)+1	11.7	12.2	**0.145**	29.6	37.1	**0.138**
p	**0.621**	**0.136**		**0.735**	**0.843**	
No hyperdiploidy	14.0	13.3	**0.417**	36.0	39.6	**0.348**
Hyperdiploidy	36.7	22.7	**0.003**	50.1	48.6	**0.527**
Hyperidiploidy+1	8.7	11.1	**0.197**	26.4	42.4	**0.025**
p	**0.000**	**0.081**		**0.000**	**0.246**	