

## [Abstract 06]

### GENOMIC ABNORMALITIES IN WALDENSTRÖM MACROGLOBULINEMIA (WM)

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The classification of WM in the REAL classification is that of lymphoplasmacytic lymphoma (LPL). Scattered reports in the literature have described patients with 14q32 translocations, including single instances of the t(8;14)(q24;q32). The diagnostic criteria of these reports have not been uniform and at least in some cases the metaphases were obtained when the tumors had evolved to more aggressive variants. Thus the prevalence of IgH translocations in WM had remained, until recently, unknown. We were unable to find IgH translocations or other recurrent marker chromosomal abnormalities. Because of the presence of IgH switch-mediated translocations in multiple myeloma, we studied the integrity of the IgH locus switch  $\mu$ -region in WM. We have found that there is germline configuration for the IgH switch  $\mu$ -region. This is consistent with the lack of isotype switch mediated translocations, and the lack of physiologic isotype switching indicated by the production of the monoclonal IgM protein. Deletions of 13q14 and 17p13.1 are rare at the time of diagnosis (<5%) and predominantly present at low frequency (15%) of the previously treated patients.

We made the observation of a high rate of 6q deletions in patients with WM. This had been observed the recurrence of 6q in the karyotypes of patients with WM. We first evaluated 24 patients with cytogenetic pellets for evidence of 6q21 deletions and estimated that between 40 to 60% of patients harbor deletions at this site. In a subsequent study we found that 17 of 34 patients (50%) had abnormalities of chromosome 6; one had monosomy and 16 had interstitial deletions that spanned from 6q21 to the sub-telomeric region. The most commonly deleted region was 6q23, and detected in 16 of 34 (47%) patients using a BAC clone that contains the *c-myb* oncogene. Deletions of 6q21 and using a BLIMP containing BAC were observed in 12 of 34 patients (35%). In the majority of cases the pattern of involvement were of greater than 75% of the cells implicating clonal selection. All of the IgM MGUS patients studied were normal and harbored no deletions of 6q using the aforementioned probes. Recent gene expression data has shown significant and clear difference in gene expression profiling between samples with 6q deletions and those without them. Further data will be presented at the meeting.

There are as of yet no clinical implications ascribed to 6q deletions in WM. However our data suggests the hypothesis that patients with detectable 6q deletion have more advanced clonal states. This would be further in support of 6q deletions being progression events in WM. There was a trend towards a higher BM clonal involvement (average 46% and range between 10%-90%) than the group without 6q deletion (average 18.2% and range between 10%-35%)( $p=0.02$ ). This is not secondary to a technical ability to detect the clonal cells since we have shown repeatedly our ability to detect chromosome abnormalities in states of minimal clonal involvement when using the immunofluorescent detection of cytoplasmic immunoglobulin chains. Likewise the concentration of the serum monoclonal protein level is slightly increased in patients with 6q deletion. Other criteria such as the hemoglobin level, serum viscosity and  $\beta_2$ -microglobulin did not show much difference between two groups, but retained the same trends. These observations are only that and are limited by the limited number of samples studied. Answering this question appears to be of high clinical relevance and one that should be attainable with ease in our laboratory and clinical investigations.