[Abstract 36]

POLYMORPHISMS IN FCγRIIIA (CD16) RECEPTOR EXPRESSION ARE ASSOCIATED WITH CLINICAL RESPONSE TO RITUXIMAB IN WALDENSTROM'S MACROGLOBULINEMIA.

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Background: Rituximab is an important therapeutic for Waldenstrom's macroglobulinemia (WM). Polymorphisms in FcγRIIIA (CD16) receptor expression modulate human IgG_1 binding, and antibody dependent cell mediated cytotoxicity, and may therefore impact responses to rituximab.

Methodology: Sequence analysis of the entire coding region of FcγRIIIA was undertaken in 58 patients with WM whose outcomes to Rituximab were known.

Results: Variations in five codons of FcγRIIIA were identified; two were commonly observed (FcγRIIIA-48, and FcγRIIIA–158) and predicted for amino acid polymorphisms at FcγRIIIA-48: Leucine/Leucine (L/L); Leucine/Arginine (L/R); and Leucine/Histidine (L/H) and FcγRIIIA-158: Phenylalanine/Phenylalanine (F/F); Phenylalanine/Valine (F/V); and Valine/Valine (V/V). A clear linkage between these polymorphisms was detected; all patients with FcγRIIIA-158F/F were always FcγRIIIA-48L/L, and patients with either FcγRIIIA-L/R or –L/H always expressed at least one valine at FcγRIIIA-158 ($p \leq 0.001$). Responses trended higher for patients with FcγRIIIA-48L/H (38.5%) versus -L/R (25.0%) and -48L/L (22.0%), and were significantly higher for patients with FcγRIIIA-158V/V (40.0%) and -V/F (35%) versus -158F/F (9.0%) ($p=0.030$). Responses for patients with FcγRIIIA-48L/L were higher when at least one valine was present at FcγRIIIA-158 ($p=0.057$), thereby supporting a primary role for FcγRIIIA-158 polymorphisms in predicting rituximab responses. With a median follow-up of 13 months, no significant difference in the median time to progression and progression free survival was observed when patients were grouped according to their FcγRIIIA-48 and -158 polymorphisms.

Conclusion: The results of these studies support a predictive role for FcγRIIIA-158 polymorphisms and responses to rituximab in WM.