292 IDENTIFICATION OF NOVEL CHROMOSOMAL ABNORMALITIES IN HUMAN MYELOMA CELL LINES BY MULTICOLOR FLUORESCENCE IN SITU HYBRIDIZATION

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Introduction: Conventional cytogenetic analysis of lymphoma cell lines often reveals complex changes with unresolved abnormalities, such as marker chromosomes, and is limited in detecting small and cryptic aberrations. Here we show, that multicolor fluorescence in situ hybridization (M-FISH) is a powerful method to elucidate such complex and cryptic aberrations and is able to identify novel, recurrent genetic abnormalities.

Material and methods: Eight human myeloma cell lines were investigated by M-FISH. The modal chromosome number was hypertriploid in 4 cell lines, hypotriploid in 3 cases and one cell line showed a hypodiploid karyotype. The G-banded published karyotypes (no conventional karyotype available for AMO-1) showed 45 unclear additions of genetic material of unknown origin, 8 marker chromosomes and 3 unbalanced translocations with unknown partner chromosomes.

Results: All these abnormalities could be resolved by applying M-FISH. All cell lines analyzed with M-FISH showed complex karyotypes with 11 to 25 structural and at least 4 numerical aberrations. The most frequent genetic changes were unbalanced translocations. We could further identify 4 balanced translocations and one isochromosome 10q, which could not be detected by conventional karyotyping (published karyotypes). The chromosomal regions 1p and 1q, 4q, 8q, 11q, 13q, 14q and 17q were most frequently involved in the rearrangements. Recurrent breakpoints were detected in 1q11 (5x), 8q24 (5x), 11q13 (4x), 13q14 (4x), 4q21 (3x), 8q21 (3x), 14q32 (3x), 21p11 (3x). Besides the well known breakpoints in 8q24, 13q14 and 14q32 we detected several novel recurrent breakpoints in our study. These are currently explored on the molecular level. Deletions were seen very frequently (22x), concerning almost in all cases the long arm of the chromosome. Deletion of the q arm of chromosome 6 was detected in three times, deletions of 11q and 1q each in two times with different breakpoints.

Conclusions: These regions now should be further investigated to detect minimal deleted regions and identify relevant genes. This work was supported by the Roggenbuck-Stiftung.

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294 INCIDENCE OF LIGHT CHAIN ESCAPE IN UK MRC MYELOMA VII TRIAL

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Introduction: For some intact immunoglobulin Multiple Myeloma (MM) patients in remission, relapse is accompanied by a marked rise in monoclonal free light chains (FLCs) with no associated increase in intact immunoglobulin concentrations - a phenomenon termed ''light chain escape (LCE)''. Recent case reports have suggested LCE might be more prevalent with modern chemotherapy and detected earlier by serum FLC analyses. In this study, the frequency of LCE in MM patients with IgG vs IgA paraproteins and treated on intensive vs non-intensive chemotherapy regimens was compared.

Methods: Stored sera from the first 60 IgA and 58 IgG patients recruited to the Myeloma VII trial (randomised between intensive and non-intensive chemotherapy) were utilised. There were sufficient frozen sera and complete data for 36/60 IgA and 30/58 IgG MM patients. Representative sera from presentation, maximum response and relapse were utilised for sFLC measurement and results compared with recorded urine FLC (urine FLC/creatinine ratio) and serum intact immunoglobulin measurements. Results were classified as ''true'' LCE (rising sFLC concentrations with stable or falling intact immunoglobulin concentrations) or ''partial'' LCE (the increase in the involved serum FLC concentration was at least 40% greater than the increase in monoclonal intact immunoglobulin concentration).

Results: IgA patients showed 8% (3/36) with true LCE and 11% (4/36) with partial LCE. For IgG patients the figures were 3% (1/30) and 10% (3/30) respectively. Of patients showing true LCE, 4/4 had received non-intensive treatment and of patients with partial LCE, 3/7 had been treated non-intensively. For all 11 patients showing some form of LCE, this was corroborated by the urine results in 5/11. For 6/11 the amounts of FLC in the urine were insufficient for consistent analysis.

Conclusion: The results from this study support the use of the serum FLC assay for monitoring intact immunoglobulin MM patients to detect LCE. True LCE was seen in 3/36 IgA MM patients and 1/30 IgG MM patients. These preliminary findings do not indicate any greater frequency of LCE with intensive chemotherapy but suggest that it might be more apparent with serum FLC analysis compared with UBJP analysis.

295 BENDAMUSTINE AND PREDNISONE IN COMBINATION WITH BORTEZOMIB IN THE TREATMENT OF PATIENTS WITH ADVANCED MULTIPLE MYELOMA

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Introduction: Bortezomib is a novel proteasome inhibitor that has shown important clinical efficacy either as a single agent or in combination with other cytostatic agents in relapsed/refractory multiple myeloma (MM). The combinated treatment of bortezomib with bendamustine and prednisone (BPV) was assessed to determine the efficacy and toxicity of this regiment in patients with advanced MM.

Methods: Between January 2005 and July 2007, 46 patients (median age 63; range 31-77 years) with relapsed or refractory MM (29 patients stage III a, 17 patients III b) were treated with bendamustine 60 (-80) mg/qm on day 1 and 2, bortezomib 1,3 mg/qm on day 1, 4, 8 and 11, and prednisone 100 mg on day 1, 2, 4, 8 and 11. Cycles were repeated every 21 days until maximum response or progressive disease. The time from first diagnosis ranged from 1 to 183 (median 36) months. The duration of the last remission before beginning the BPV-therapy was 6 (range 0-36) months. Previous therapy lines (median 2, range 1-6) included 18 x thalidomide, 10 x autologous PBSCT, and 9 x autologous/allogeneic PBSCT. 16 patients were refractory to the last treatment. 22 patients had preexistent severe thrombocytopenia, leukocytopenia or anemia (WHO grade 3 or 4). Response was assessed using EBMT criteria modified to include near complete remission (nCR) and very good partial remission (VGPR).

Results: 36 patients (78 %) responded after at least one cycle of chemotherapy with 2 CR, 5 nCR, 6 VGPR, 15 PR and 8 MR. 4 patients had stable disease and 6 patients had a progress. With a median follow up of 13 months, EFS, and OS at twelve months for patients without severe haematological toxicities due to previous treatments (n=24) were 46 % and 79 %, respectively. Outcome for these patients was significantly better compared to patients with severe haematological toxicities (grade 3 or 4, n=22) where EFS, and OS were 10 % and 22 %, respectively ($p<0,01$). The median number of the BPV-treatment was 2 (1-7) cycles. 20 of 36 responding patients showed a rapid decrease of the myeloma protein and reached the best response after the first cycle and 12 after the second cycle. The regimen was well-tolerated with few significant side effects reported. New cytopenias occured infrequently (four patients had a thrombocytopenia grade 3, and two patients had a grade 4 thrombocytopenia). 1 patient had a moderate new polyneuropathy (grade 2).

Summary: These results indicate that the combination of bortezomib, bendamustine and prednisone is effective and well tolerated in a heavily pretreated population of patients with relapsed or refractory MM.