

multiple myeloma/WM

536 EFFICACY AND SAFETY OF CLADRIBINE (2CDA) AND RITUXIMAB® COMBINATION TREATMENT FOR PATIENTS WITH WALDENSTRÖM'S MACROGLOBULINEMIA (WM): REPORTS OF A MULTICENTER STUDY

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Introduction: Combination of nucleoside analogues and R represents an effective treatment of WM. Aim of the study was to test the efficacy of R-2CdA for the treatment of newly diagnosed/pre-treated WM pts requiring systemic treatment.

Methods: The combination therapy was R at standard schedule (375 mg/mq) on day 1 followed by 2CdA 0.1 mg/kg (sc injection) for 5 consecutive days. Each cycle was administered monthly for a total of 4 cycles. Clinical responses were evaluated two months after the end of treatment, according to Response Criteria from the 3rd International Workshop on WM. From December 2003 to November 2006, 29 pre-treated/newly diagnosed pts affected by WM were enrolled in the study. Pts characteristics included: sex (M/F) 10/19, median age 64 (range 36-75 yrs), a median IgM level before treatment of 2567mg/dL; 17 pts were newly diagnosed. Anemia (10 pts), neurologic symptoms (6 pts) and symptomatic cryoglobulinemia (4 pts) represented the main reasons to start the treatment.

Results: Twenty-five out of 29 pts received all four cycles of R-2CdA: one patient stopped the treatment after one cycle because of PD and 2 pts received only two cycles of R-2CdA because of cardiac toxicity. One patient discontinued R after two cycles due to intolerance and completed the treatment with 2CdA as single agent. The therapy was well tolerated even if flu-like syndrome was more frequent (30%) and severe (25%) than reported in other NHL pts. Treatment delays occurred only in 5 pts due to haematologic toxicity (G3 neutropenia in 2 pts) or extra-haematologic complications. No major infectious were observed despite the lack of antimicrobial prophylaxis. Overall 86% of responses were observed with 1 CR, 19 PR and 5 MR. At a median follow-up of 26 months, 4 pts in PR converted to CR while 3 pts had a PD.

Conclusions: The combination of R-2CdA we used seems to be safe and active in WM pts requiring a treatment and confirms the observation of delayed responses reported by other authors with similar combination therapy.

537 FLUDARABINE BASED COMBINATIONS ARE HIGHLY EFFECTIVE AND SAFE AS FIRST-LINE OR SALVAGE TREATMENT FOR PATIENTS WITH WALDENSTRÖM'S MACROGLOBULINEMIA

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Introduction/Background: Alkylating-agents or single-agent purine analogues are safe and moderately effective as first-line treatment for patients (pts) with Waldenström's Macroglobulinemia (WM). However, efficacy is limited in relapsed/refractory WM. Combinations of Fludarabine (F) with alkylators and/or Rituximab (R) are promising but data are limited.

Material and Methods: 26 episodes of I.V. F-combination therapy were administered to 24 pts from 12/94-09/07: FC (F 25mg/m² d1-3, cyclophosphamide (C) 250mg/m² d1-3; n=9); FCR (FC+R 375mg/m² d1; n=11); FM (F+mitoxantrone (M) 10mg/m² d1; n=3); FR, n=1).

Patient characteristics: Median age 58 yrs [range: 37-89], 88% male, 6 previously untreated (25%), median number of prior therapies 2 [0-7], prior single-agent F in 5 (21%), 11 pts (46%) were alkylator-refractory, median time from diagnosis 25 Mo [0-153], baseline paraprotein (PP) 31 g/L [7-64].

Results: A total of 95 cycles were administered, median 4 [1-6] per pt. Grade 3/4 neutropenia and infections complicated 19% and 18% of cycles, respectively. One pt died from sepsis. Of 23 evaluable pts 18 (78%) responded, all partial (>50% fall in PP; median 87%). The median time-to-progression for all pts was 43 Mo. With a median follow-up of surviving pts of 57 Mo, the 5- and 10-year-actuarial survival rates are 72±12%, and 63±13%. Within the limitations of sample-size, there were no significant differences in response rates between patient sub-groups, regimens, R-utilisation (75% with R, 90% without) or known prognostic parameters. Two heavily pre-treated pts subsequently developed secondary AML/MDS (1 fatal) at 61 and 99 Mo. post-treatment. With a median follow-up of 43 Mo. [6-91] all 6 previously untreated pts remain alive and progression-free.

Conclusion: F-combination therapy is highly active in WM, both, untreated and alkylator-refractory, leading to high response rates and prolonged remissions.

538 MONITORING OF RESIDUAL DISEASE IN MULTIPLE MYELOMA (MM) PATIENTS USING A NOVEL NEPHELOMETRIC ASSAY

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Scanning bands on serum electrophoresis gels (SPE) is the traditional measurement method for monoclonal immunoglobulins in MM. However, many IgA monoclonal immunoglobulins migrate into the β region making identification and quantification difficult. In addition, IgG assessment may be inaccurate due to saturation of the recycling FcRN (neonatal receptor) with high serum concentrations.

Here we report preliminary results using immunoassays to determine the serum IgAk/IgAl or IgGk/IgGl ratios in MM patients and the use of these ratios for tumour monitoring. Normal ratio ranges were produced using 100 normal (blood donor) serum samples. Patient samples were archived sera collected in the VIIth UK Medical Research Council myeloma trial.

Presentation sera were assayed for 20 IgA (10 IgAk /10 IgA λ) and 20 IgG (10 IgGk /10 IgG λ) patients. All 40 presentation sera had elevated concentrations of the relevant total immunoglobulins and highly abnormal Igk/Ig λ ratios. In 5 IgA patients (4 IgAk /1 IgA λ) serial samples were taken through the course of chemotherapy. In 2/5 patients the ratios indicated residual disease when IFE results were negative. In 1 patient the monoclonal immunoglobulin was obscured by other proteins on SPE so was unmeasurable. The disease course could however, be monitored by changes in the IgAk/IgA λ ratio. In a second patient IgAk/IgA λ ratio indicated progression earlier than IFE. In 9 IgG patients (4 IgGk /5 IgG λ) serial samples were taken through the course of chemotherapy. In 4/4 patients who did not achieve CR, the ratio remained abnormal throughout. In 3/5 patient achieving CR IgGk/IgG λ ratios indicated earlier relapse. In conclusion the use of sensitive nephelometric assays that do not rely upon SPE interpretation may provide a useful tool in the diagnosis and monitoring of MM. Furthermore, analysis of the IgGk/IgG λ ratio corrects for variable metabolism of IgG, provides quantitative results, and is more sensitive than IFE for the measurement of residual disease in some patients.

539 APPLICATION OF FREELITE FOR EVALUATION OF TREATMENT RESULTS FOR MULTIPLE MYELOMA

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Freelite method (The Binding Site, Ltd.) is recognised as an effective method for diagnostics and monitoring patients with various monoclonal gammopathies, including IIMM, non-secreting MM, AL-amyloidosis, MGUS. This current study accessed the utility of free light chain (FLC) monitoring for patients with IIMM.

Sera from 20 patients with stage III MM were investigated. FLC concentration was determined by Freelite method for patients undergoing treatment for MM and compared with residual disease (RD) burden. Patients were divided into two groups based on the value of RD burden (presented as percentages), which was calculated as a ratio of given paraprotein (PIg) concentration to initial PIg concentration. First group – 15 patients with PIg > 50%, second group – 5 patients with PIg < 50%.

Patients from the 1st group with κ -MM (n=11) had median κ -FLC concentration equal to 290 mg/L (18.2–1453), which was above the κ normal range (3.3–19.4). Patients from the same group with λ -MM (n=4) showed median λ -FLC concentration equal to 333 mg/L (75.8–924), which also was above the range for λ normal values (5.7–26.3). In the 2nd group the median κ -FLC concentration was 17.3 mg/L (4.9–30.7) for patients with κ -MM (n=3), which was within the κ normal range (3.3–19.4); and the median λ -FLC concentration was 23.2 mg/L (16.7–29.6) for patients with λ -MM (n=2), which also was in the range for λ normal values (5.7–26.3).

Analysis of FLC κ/λ ratio showed patients with κ -MM from the 1st group (except one patient) having κ/λ ratio values >1.65, which are higher than the normal range (0.26–1.65); whereas patients from the same group with λ -MM had a κ/λ ratio <0.26, which is below the normal range. Four patients from the 2nd group (BJ- κ and BJ- λ MM) demonstrated a κ/λ ratio within the normal range and 1 patient with BJ- κ MM had a κ/λ ratio >1.65. Serum FLC concentration, obtained by the Freelite method, was well correlated with PIg concentration as well as with RD burden and clinical observations. The lack of correlation in a few cases may serve as a reason for reconsidering the results of the treatment for those patients.