Ten patients affected by WM were enrolled in this study, until December 2016. The patients required treatment for the onset of symptoms as anemia (6 patients), B symptoms such as weight loss (3 patients), peripheral neuropathy and hyperviscosity syndrome as loss of eyesight (one patient), respectively. The median number of CHL and RTX cycles administered was 8 (range 1-8) and 6 (range 3-6), respectively. The median total dose of CHL administered during treatment was 512 mg per patient and the median dose of RTX was 3600 mg per patient. In one patient, therapy was discontinued after 3 courses of CHL and 1 course of RTX because of the onset of severe pancytopenia and esophagus necrosis which led to the death of the patient. Two patients with low burden of paraprotein were able to avoid the two purging cycles of CHL, undergoing the 6 planned cycles of CHL-RTX. During the period under examination, none of the patients experienced a dose reduction of either CHL or RTX because of hematological/extra-hematological toxicities. ORR was 80%, one patient showed CR, one achieved a VGPR and six PR. Median PFS was reached after 31 months (range: 1-93 months) from the beginning of the treatment. All patients except for one, who died because of progressive disease during treatment, are alive at a median follow-up of 54 months. CHL-RTX was a very well tolerated regimen: only one patient developed grade 2 neutropenia without infective complications; no patient but one died of progressive disease and was admitted into hospital. The presented data showed that the association of CHL-RTX is safe and effective, CHL-RTX appeared as a good option as first line treatment in elderly patients with comorbidities for its measured balance between toxicity and response.

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CONTINUOUS LOW DOSE ALKYLANT THERAPY IS EFFECTIVE IN T-CELL PROLYMPHOCYTIC LEUKEMIA

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T-cell prolymphocytic leukemia (T-PLL) is a rare and aggressive mature T cell lymphoproliferative disorder, typically affecting elderly people, characterized by clonal expansion of CD4+ or CD4+/CD8+ lymphocyte cells with prolymphocyte morphology. Among cytogenetic abnormalities, recurrent alterations include inv(14) and t(X;14). Alemtuzumab represents the frontline therapy with median PFS and OS of 7 and 24 months, respectively. Alternative regimen like bendamustine showed PFS of few months. The aim of this study was to provide data on the efficacy and safety of a less intensive but continuous therapy in T-PLL patients not eligible to alemtuzumab therapy. We analyse a small cohort of 6 patients affected by T-PLL. Confirmation of diagnosis was achieved through combined morphologic, immunophenotypic and cytogenetic analysis. Clinical characteristics and therapy related parameters, including response, outcome and adverse effects were studied. Median age at the diagnosis was 72 years (range 63-85). All patients were characterized by CD4+/CD8 phenotype. Although a dominant V was reported in each patient, any clusterization to a specific V chain was detected. Cytogenetic analysis was available for 5 patients, with 2 patients presenting t(X;14), 2 patients with inv(14) and one patient with complex karyotype. HTLV antigens were not detected in any patient. At diagnosis, all patients presented lymphocytosis (18,000-75,000/mm3) with hepato-splenomegaly (3/6), diffuse lymphoadenopaty (4/6) and one patient with pulmonary interstitial disease. Five patients received continuous low dose cyclophosphamide (50-100 mg/die), one monthly chlorambucil chemotherapy. The ORR was 100% with 1 complete hematological response and 5 partial responses. Median PFS and OS were 15,5 and 20 months, respectively. Two patients died, one for progressive disease and one for severe sepsis. Hematological toxicities were mild with G2 neutropenia and G3 anemia observed in 2 patients. Non hematological toxicities were exclusively infectious events observed in 3/6 patients, with one lethal sepsis in old age patient. Our data provide evidence that low dose continuous alkylating therapy is effective and relatively safety in patients not eligible to intensive therapy. Although low quality of response, patients displayed similar PFS and OS rates to those treated with alemtuzumab and higher towards patients treated with other regimens.

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THE APOBEC MUTATIONAL ACTIVITY IN MULTIPLE MYELOMA: FROM DIAGNOSIS TO CELL LINES

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Next generation sequencing (NGS) studies have highlighted the role of aberrant activity of APOBEC DNA deaminases in generating the mutational repertoire of multiple myeloma (MM). However, the contribution of this mutational process across the landscape of plasma cell dyscrasias, or its prognostic role, has never been investigated in detail. To answer these unexplored aspects of MM biology, we used published NGS data from our own work as well as others, including the large CoMMpass trial for a total of 1153 whole-exomes of MM. Furthermore, we investigated 5 MGUS, 6 primary plasma cell leukemias (pPCL) and 18 MM cell lines (MMCL). Overall, we identified signatures of two mutational processes, one related to spontaneous deamination of methylated cytosines (30% of variants, range 0-100%) and one attributed to aberrant APOBEC activity (70% of variants, range 0-100%). APOBEC contribution was extremely heterogeneous among MM patients, but was correlated with a higher mutational burden (r=0.71, p=<0.0001) and with MAF gene translocations t(14;16) and t(14;20). The activity of APOBEC increased from MGUS to MM to pPCL, both in terms of absolute number of mutations and as percentage contribution. In MMCL we instead observed a bi-modal distribution whereby 8 cell lines showed the highest numbers of mutations caused by APOBEC (5/8 carried MAF translocations), while 10 where virtually devoid of APOBEC mutations (0/10 carried MAF translocations). The contribution of APOBEC to the total mutational repertoire in MM had a clear prognostic impact. MM patients with APOBEC mutations in the lowest quartile had a survival advantage over patients with APOBEC mutations in the highest quartile both in terms of progression-free survival (3-y PFS 46% *vs* 67% months, p=<0.0001) and overall survival (3-y OS 52% *vs* 83%, p=0.0084). This association was retained in a multivariate model that included age, gender, cytogenetic class, ISS, and quartiles of mutational load both in PFS [p=0.02, HR 2.06 (95IC 1.11-3.81] and OS [p=0.02, HR 2.88 (95IC 1.17-7.09)]. Interestingly we found that APOBEC mutations in the 4th quartile retained its independent prognostic respect to high mutational load and presence of MAF translocations. Overall, our data suggest that APOBEC-mediated mutagenesis is strongly involved in MM pathogenesis and its activity persists during different phases of evolution, playing a critical role in MM genomic complexity, and impacting prognosis of the patients.

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MULTIPLE MYELOMA BONE LYTIC LESIONS CHARACTERIZATION BY WB-LDCT SCAN AND 18F-FDG PET/MRI

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