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ABSTRACT BOOK

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and in CLL patients with poor prognostic features including high risk cytogenetics and/or bulky disease. A phase II trial initiated in the relapsed/refractory setting to compare the safety and efficacy of lenalidomide at 25 mg/d with 10 mg/d resulted in 5 cases of tumor lysis syndrome (TLS). Therefore, in an effort to determine a safe dose and schedule the protocol was amended to a stepwise dose-escalation. Herein we present an interim safety data from the amended protocol. *Methods*. Eligible patients had good creatinine clearance (≥60 mL/min), received prior therapy with an alkylating agent and failed or progressed within a year of completing a fludarabine-based regimen. Lenalidomide was started at 2.5 mg daily dose. Intra-patient dose escalation to 5 mg/d occurred after 28 days with further dose escalations in 5 mg increments performed every 28 days, in 6-patient cohorts, until maximum tolerated dose escalation level (MTDEL) was defined, or the 25 mg/d dose level was attained. Patients continued on therapy until disease progression. TLS prophylaxis with 300 mg/d allopurinol and oral hydration were started 3 days before lenalidomide and continued for 3 cycles, with close monitoring for early signs of TLS (Cairo-Bishop Grading), particularly at drug initiation and dose escalations. *Results*. For 30 patients enrolled, median age was 66 years (range 50-76); 23 patients (76.7%) had bulky disease (LAN ≥5cm), and had failed a median 4 prior therapies (range 2-14): 13 patients (43.3%) were refractory to fludarabine and 6 (20.0%) had failed alemtuzumab. Grade 3-4 adverse events (AEs) were consistent with previous studies of lenalidomide in similar patient populations, and included thrombocytopenia (16.7%) and neutropenia (63.3%), of which 3% were febrile neutropenia. Ten patients (33%) developed tumor flare (3 cases were grade 3) at a median dose of 2.5 mg/d and most commonly during the first cycle. Laboratory TLS occurred in 1 patient at the 2.5 mg/d dose level and resolved without drug interruption. There are 14 patients currently on study and 16 patients discontinued therapy. Reasons for discontinuation included lack of efficacy in 7 patients, of whom 5 did not reach the 10 mg/d dose, and 5 patients developed AEs (at 10 mg/d: 1 AIHA, not attributed to lenalidomide and 1 PE in patient with DVT history and on antithrombotic prophylaxis; at 2.5 mg/every other day: 2 Grade 4 thrombocytopenia and 1 Grade 3 neutropenia). At last follow up lenalidomide was deemed tolerable up to the 15 mg/d dose level and the MTDEL had not been reached. Further escalation to the 20 mg/d dose is under investigation and anticipated for presentation. *Conclusions*. A preliminary safety analysis of lenalidomide stepwise dose escalation was found to be tolerable with MTDEL not yet reached at the 15 mg/d dose level. Close monitoring and prophylaxis were effective in the prevention, early detection and treatment of TLS in this heavily pretreated patient population with bulky disease.

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RELATIONSHIP BETWEEN CYTOGENETIC ANOMALIES AND BIOMARKERS IN BINET STAGE A PATIENTS WITH CHRONIC LYMPHOCYTIC LEUKEMIA AT DIAGNOSIS: PRELIMINARY RESULTS OF A PROSPECTIVE, MULTICENTER 0-CLL1 GISL STUDY

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Background. The clinical heterogeneity of chronic lymphocytic leukemia (CLL) requires parameters to stratify patients into prognostic subgroups to adapt treatment ranging from 'watch and wait' to allogeneic stem cell transplantation. Different parameters such as lymphocyte doubling time, β-2 microglobulin, CD38 and ZAP-70 expression, immunoglobulin variable heavy chain (IgVH) mutation status and genetic abnormalities have been integrated in clinical practice. By using fluorescence *in situ* hybridization (FISH), cytogenetic abnormalities can be found in approximately 80% of patients. *Aims*. In the present study, we performed FISH analysis to detect the major cytogenetic alterations in a series of patients in Binet stage A included in the prospective multicenter O-CLL1 GISL study started in April 2007. *Methods*. Molecular markers characterization and FISH analyses were previously reported (Cutrona *et al*. Haematologica, 2008; Fabris *et al*. GCC, 2008). *Results*. Up to date, 275 patients have been enrolled in the trial and FISH data concerning trisomy 12 and 13q14, 17p13, 11q23 deletions were available in 192 patients. At least one abnormality was found in 131/192 (68.2%) patients. The most frequent abnormality was del(13)(q14) (100/192, 52%), followed by trisomy 12 (25/192, 13%) (in one case accompanied by 17p13 deletion), del(17)(p13) (6/192, 3%) and del(11)(q22.3) (10/192, 5%). 13q14 deletion was found as a sole abnormalities in 90 patients; in the remaining cases, it was combined with del(17)(p13) (3 pts), trisomy 12 (1 pts) and del(11q)(22.3) (6 pts). Among patients with 13q14 deletions, 71 were monoallelic, 7/100 biallelic, whereas 22 showed combined biallelic and monoallelic deletion patterns. We also analyzed the relationship between each single abnormality and CD38 and ZAP-70 expression, and IgVH mutational status. In particular, the CD38 percentages were 8.4±1.8 (mean value±SD), 19.5±2.8, 45.1±7.1, 30.3±8.4, 52.9±9.9 for del(13)(q14), normal, trisomy 12, del(11)(q22) and del(17)(p13) FISH alterations (p<0.0001), respectively. The percentages of IgVH mutations significantly (p<0.0001) correlated with cytogenetic alterations; namely, 5.3±0.4 for cases with del(13q14), 4.6±0.6 in normal, 1.8±0.6 in trisomy 12, 0.2±0.1 in del(11)(q22) and 1.6±1.7 in the 4 cases with del(17p13). Similarly, a significantly (p=0.0005) lower mean value of ZAP-70 expression was accounted in del(13q14) (29.7±2.3) as compared with normal cases (34.6±3.2), trisomy 12 (43.8±5.4), del(11)(q22) (55.9±9.7) and del(17)(p13) (54.8±11.8). Based on a scoring system in which 1 point was assigned to each unfavorable biomarker (i.e. CD38, ZAP-70 or IgVH mutational status) we stratified our series in three different groups from 0 to 3 according to the absence or presence of one, two or all three biomarkers. Similarly, cytogenetic abnormalities were clustered in 3 risk groups [i.e. low del(13)(q14) and normal; intermediate (trisomy 12); and high risk del(11)(q22) and del(17)(p13)] as suggested by others. Interestingly, 72/77 cases scoring 0 for the biomarkers, gathered in the low FISH group. Conversely, out of the 13 cases with high FISH risk, 10 cluster in scoring 2-3. *Conclusions*. Our preliminary results indicate that in Binet stage A CLL patients at diagnosis cytogenetic abnormalities with an expected negative clinical impact are relatively few (16/192, 8%) but significantly associated with prognostic biomarkers which negatively predict the clinical outcome in CLL.

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BETA2-MICROGLOBULIN IS A BETTER PREDICTOR OF TREATMENT-FREE SURVIVAL IN PATIENTS WITH CHRONIC LYMPHOCYTIC LEUKAEMIA IF ADJUSTED ACCORDING TO GLOMERULAR FILTRATION RATE

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Background. Even in the era of newer and sophisticated prognostic markers, β2-microblobulin (B2M) remains a simple but very powerful predictor of treatment-free survival (TFS) and overall survival (OS) in patients with chronic lymphocytic leukaemia (CLL). However, B2M levels are heavily influenced by the patient's glomerular filtration rate (GFR). *Aims*. To evaluate whether GFR-adjusted B2M (GFR-B2M) had improved prognostic value compared to unadjusted B2M in a cohort of over 450 consecutive CLL patients from two separate institutions. *Methods*. Inclusion in this study was base purely on the confirmed diagnosis of CLL as defined by the WHO. Institutional databases from Hospital Sant Pau (HSP), Barcelona, and Birmingham Heartlands Hospital (BHH)