progression. In CLL cells HIF-1 is constitutively expressed even in normoxia and modulates the interactions with SC. The aims of this study were to understand the HIF-1 regulatory pathways in TP53 disrupted (TP53dis) CLL cells and to evaluate the ability of HIF-1 inhibition to exert a direct cytotoxic effect and to potentiate fludarabine cytotoxicity toward TP53dis CLL cells. CLL cells were considered TP53dis when TP53 mutation or 17p deletion were present. Otherwise CLL cells were considered wild type (TP53wt). CLL cells were cultured alone or with the M2-10B4 SC under normoxic or hypoxic conditions and exposed to fludarabine and/or the HIF-1 inhibitor BAY 87-2243. We evaluated the activity of ERK1-2, Ras, RhoA, RhoA kinase, Akt by Western Blot or specific immunoassay kit. HIF-1 expression was assessed by RT-PCR and Western Blot. Cell viability was analyzed by AnnexinV/propidium Iodide immunostaining. TP53dis CLL cells showed a significantly higher HIF-1A gene expression compared to TP53wt CLL cells, and also had higher amount of HIF-1 protein. Accordingly, TP53dis CLL cells overexpressed the HIF-1 target genes p21, Bcl-2 and ENO1, and had a more active glycolysis than TP53wt CLL cells. Hypoxia further increased HIF-1 expression in both TP53dis and TP53wt CLL cells. Similarly, the co-culture of CLL cells with SC further upregulated HIF-1 in both subsets via the activation of Akt, Ras- and RhoA-dependent signaling cascades. BAY87-2243 efficiently inhibited HIF-1 and induced a significant reduction in viability of CLL cells in both subsets. *In vitro* fludarabine-resistant CLL cells showed higher levels of HIF-1A gene compared to fludarabine-sensitive, and the inhibition of HIF-1 with BAY87-2243 restored fludarabine-induced cytotoxicity. Lastly, HIF-1 inhibition was also able to reverse the SC-mediated resistance to fludarabine cytotoxicity in both TP53dis and TP53wt CLL cells. Based on our results, HIF-1 represents an interesting therapeutic target in CLL, in particular for the high-risk disease subset.

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IBRUTINIB IN THE MANAGEMENT OF RELAPSED/REFRACTORY CHRONIC LYMPHOCYTIC LEUKEMIA PATIENTS: A REAL-LIFE MONOCENTRIC EXPERIENCE

E. Albi, B. Del Papa, E. Dorillo, P. Aureli, M.G. Cantelmi, T. Zei, R. Iacucci Ostini, R. Ciurnelli, F. Falzetti, P. Sportoletti

Institute of Hematology-Centro di Ricerche Emato-Oncologiche (CREO), University of Perugia

Background: Ibrutinib is an irreversible inhibitor of Bruton tyrosine kinase showing significant efficacy in chronic lymphocytic leukemia (CLL) treatment. Routine healthcare may provide data complementary to that from clinical trials, in order to implement recommendations for disease management in real world settings. *Aim:* The aim of this retrospective study was to evaluate the outcome and toxicity of 25 CLL patients (pts) treated with Ibrutinib in real-life clinical practice in our Institution. *Methods:* Pts received ibrutinib 420 mg once-daily until progression or unacceptable toxicity. Overall response rate (ORR) including partial response (PR) with lymphocytosis (PR-L) was assessed using updated iwCLL criteria. *Results:* The median age was 70 years (range 54-93) with a male to female ratio of 2.1:1, 68% pts had Rai stage III/IV and 24% had lymphadenopathy ≥10cm. Pts received a median of 2 prior lines of therapy (range 1-6). The IGVH mutational status was unmutated in 13/25 pts and del(17p)/TP53 mutation was detected in 4/25 pts. After drug initiation, peripheral lymphocytosis was observed in 16 pts with peak levels at 1-month (median change from baseline in ALC was 191.2%±116.8-672.6%). In CLL with pre-existing cytopenias, a gradual improvement of anemia and thrombocytopenia was observed during treatment. ORR was 60% (32% PR, 20% PR-L, 8% CR). Out of 25 pts there were six with stable disease and four with disease progression or histological transformation. At a median follow up of 8 months, the median progression free survival (PFS) and overall survival (OS) have not yet been reached. The estimated PFS and OS rate at 8 months were 84% and 83% respectively. PFS and OS were significantly shorter in pts with del(17p)/TP53mut than in non-del(17p) patients (p=0.018 and p=0.026, log rank test). Ibrutinib was well tolerated. Common extra-hematologic AEs included infections (20%), diarrhea (16%) and skin lesions (8%). Hematologic AEs observed were neutropenia (12%), anemia (4%), thrombocytopenia (4%). Hematomas occurred in 16% of pts without any major bleeding. Grade of side effects was >3 in 6.6% of cases. The most frequent grade ≥3 AE was diarrhea (8%). Treatment was discontinued due to AEs in 2 pts and disease progression in 4 pts. Of all treated pts, 72% are still in treatment with Ibrutinib. *Conclusions:* Ibrutinib is highly effective and tolerable drug in CLL in general community. Yet, del(17p)/TP53 mutation remains a therapeutic challenge.

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ANALYSIS OF PROGNOSTIC FACTORS AND TIME TO FIRST TREATMENT IN YOUNG PATIENTS (<55 YEARS) WITH CHRONIC LYMPHOCYTIC LEUKEMIA: A SINGLE CENTER EXPERIENCE

A. Giordano, P. Curci, R. Rizzi, M. Delia, A. Ricco, A. Mestice, M.S. De Candia, M.A. Urbano, B. Daraia, S. D'Agostino, S. Mallano, R. De Robertis, L. Anelli, G. Specchia

Azienda Ospedaliero Universitaria Consorziale Policlinico Bari

Chronic Lymphocytic Leukemia (CLL) is the most common leukemia among elderly people in the western world. Younger CLL patients (≤55 years) account for only 10% to 15% of the CLL population. Clinical characteristics and outcomes of Younger CLL patients are a matter of debate; a better knowledge is a crucial objective to identify patients with different prognostic features. In our study we investigated clinical characteristics and time to first treatment of younger patients with CLL treated at our Institution. We retrospectively evaluated patients (pts) with *de novo* CLL treated at the University Hospital of Bari (Italy) between April 2006 and February 2017.At diagnosis pts were studied for clinical characteristics and biological prognostic factors: age, -2 microglobulin, absolute lymphocyte count, sex, Rai stage, number of involved lymph node groups, pattern of bone marrow involvement, splenomegaly, mutational status of the immunoglobulin heavy chain gene variable region (IGVH). Patients were divided into two groups according to age: younger CLL pts (≤55 years) and older CLL pts (>55 years). Cytogenetic abnormalities at diagnosis were detected by FISH in 20 pts in the younger group and 35 pts in the older group. Time to first treatment (TFT) was measured as the time elapsed between diagnosis and first treatment.Patients were divided in two groups according to age. The first group included younger CLL pts (≤55 years); the second group included older CLL pts (>55 years). Univariate analyses were performed in each group to evaluate the correlation between age and clinical variables at diagnosis. TTF was also calculated and compared in the two groups. In total 75 pts were included; 24 pts under 55 years at diagnosis and 51 older pts at diagnosis. Statistically significant differences were seen between the 2 groups regarding absolute lymphocyte count (<50,000 *versus* >50,000 P<.001), -2 microglobulin (normal *versus* elevated; P=.009); splenomegaly (present *versus* absent; P=.035), cytogenetic abnormalities by FISH (P>.001), all significantly more common among older patients. By contrast, no statistically significant difference between the 2 groups was seen for TTF (P:0.139). In conclusion, although adverse prognostic markers were less common in our study among younger patients at diagnosis, the time to progression of younger pts in terms of TFT was similar to that in the older population. Multicentric studies and larger cohorts of patients are warranted to confirm these data.

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CHLORAMBUCIL PLUS RITUXIMAB AS FRONT-LINE THERAPY FOR ELDERLY PATIENTS WITH COMORBIDITIES AFFECTED BY WALDENSTROM MACROGLOBULINEMIA. A SINGLE CENTER EXPERIENCE

I. Innocenti[1], A. Corbingi[1], F. Autore[1], F. Sorà[1], M. Luigetti[2], D. Soldati[1], R. Pasquale[1], S. Sica[1], L. Laurenti[1]

[1]Istituto di Ematologia, Fondazione Policlinico A. Gemelli, [2]Istituto di Neurologia, Fondazione Policlinico A. Gemelli

Waldenstrom Macroglobulinemia (WM) is a rare B lymphoproliferative disorder characterized by an infiltration in bone marrow of lymphoplasmacytic lymphocytes producing an IgM monoclonal gammopathy. The standard first line treatment is Rituximab, Cyclophosphamide and Dexamethasone (DRC). We conducted a retrospective analysis of Chlorambucil-Rituximab (CHL-RTX) used as front-line treatment in elderly patients (≥65years) with comorbidities. CHL was administered at 1 mg/kg for each cycle every 28 days p.o. at a fixed daily dose of 10 mg starting from Day 1 and repeated for 8 cycles. RTX was added to CHL from the 3rd cycle onwards and was administered on Day 1 of each cycle at a dose of 375 mg/m^2 for 6 cycles.