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Background: Chemo-immunotherapy (CIT) is associated to an increased risk of HBV reactivation in patients (pts) affected by lymphoproliferative disorders. Occult hepatitis B infection (OBI) is defined by the presence of anti-HBc antibodies, HBsAg negativity with or without anti-HBs antibodies and HBV-DNA serum negativity. Guidelines suggest lamivudine prophylaxis in OBI/CLL pts treated with CIT. No data are available about the need for prophylaxis in OBI/CLL pts treated with BTK inhibitors.

Aims: The objective of this study is to evaluate if OBI/CLL pts need lamivudine or HBV-DNA monitoring.

Table 1.

Table 1: OBI/CLL patients characteristics and results.

GIMEMA Study LLC1010	22 Italian GIMEMA centres			Prophylactic antiviral therapy with lamivudine and HBV-DNA monitoring		
Characteristics	Overall 111 pts			No =38	Yes =73	p- value
	Sex: M/F, n		76/35	26/12	50/23	>0.99
	Median age (range)		64 (39-86)	63 (48-81)	65 (39-83)	0.43
	Binet stage, n (%) 106/111	A B C	10 (9) 51 (48) 45 (42)	2 (5) 21 (55) 15 (39)	8 (12) 30 (44) 30 (44)	0.44
	IGHV, n (%) 84/111	unMut Mut	60 (71) 24 (29)	25 (83) 5 (17)	35 (65) 1 (35)	0.083
	FISH, n (%) 106/111	NK Del 13q Tris 12 Del 11q Del 17p	33 (31) 20 (19) 12 (11) 13 (12) 28 (26)	13 (34) 8 (21) 3 (8) 4 (11) 10 (26)	20 (29) 12 (18) 9 (13) 18 (26) 20 (29)	0.92
Response of CLL after IBR at 12 months, n (%) 98/111	CR/CRi, n (%)		10 (10)	3 (9)	7 (11)	0.56
	PR/PR-L, n (%)		74 (75)	23 (72)	53 (77)	
Time to IBR, n (%) 107/111	IBR 1 line		26 (24)	9 (24)	17 (25)	0.66
	After less than 12 months from last treatment		31 (29)	13 (34)	18 (26)	
	After more than 12 months from last treatment		50 (47)	16 (42)	34 (49)	
	Unknown		4	0	4	
Reactivation overall by therapy, n (%)	Reactivation overall, n (%)		5 (4.5)	4 (11)	1 (1.4)	**0.046**
	Reactivation (serological) overall, n (%)		2 (1.8)	2 (5.3)	0	0.12
	Reactivation (clinical) overall, n (%)		3 (2.7)	2 (5.3)	1 (1.4)	0.27
Details for Pts with reactivation, n	IBR 1 line		1	1 occult	0	
	IBR > 2 lines		4	1 occult	0	
	After more than 12 months from last treatment			2 clinical	1 clinical	

Methods: We analyzed 111 OBI/CLL pts (14%), among 781 CLL pts treated with IBR in 22 Italian GIMEMA centres until January 2019. Median age was 64 years. At IBR start, 9%, 48%, 42% pts were on Binet stage A, B, C respectively; 71% pts had unmutated IGHV, 26% pts had 17p deletion. Twenty-six (23%) OBI/CLL pts were treatment naïve at IBR start; 44 (40%) pts, 18 (16%) and 23 (20%) had been previously treated with 1, 2 or >2 lines of CIT respectively. Seventy-three OBI/CLL pts on IBR underwent prophylaxis with lamivudine, while 38 pts were only subjected to HBV-DNA monitoring every 3 months. Table1.

Results: Viral reactivation was observed in 5 pts. Four of them (2 with clinical reactivation and 2 with serological one) belonged to the HBV-DNA monitoring group; one patient experienced clinical reactivation on the lamivudine prophylaxis group (p=0.046). Both kinds of reactivation occurred in the first 3-6 months of IBR. In the HBV-DNA monitoring group, one patient was treatment naïve and experienced only serological reactivation; 3 pts were previously treated with CIT, at least 12 months before the IBR, and experienced both serological (1) and clinical (2) activation Table1. Serological reactivation was only recorded on the HBV-DNA monitoring group as those were the only pts who underwent a systematic screening schedule in the following months, thus were diagnosed with HBV reactivation (and treated with lamivudine) in the absence of any clinical suspicion.

Conclusions: From the collected evidence, it seems reasonable to suggest that prophylactic treatment should be considered appropriate and started in pts who were previously treated with CIT. For the treatment naïve group, a clinical choice could be performed, knowing that reactivation could seldomly occur and be detected in time to promptly treat the pts, but prophylaxis is not mandatory for a favourable clinical course.

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SUCCESSFUL TREATMENT WITH IMATINIB FOR SYSTEMIC MASTOCYTOSIS ASSOCIATED WITH MDS/MPN

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Systemic mastocytosis (SM) is a rare hematological neoplasm characterized by the abnormal proliferation and accumulation of mast cells. Clinical manifestations are heterogeneous depending on the tissue infiltration and mast cell mediators released by their degranulation. The gain-of-function point mutations at codon 816 of KIT gene, high serum tryptase level, and expression of CD25 represent minor diagnostic criteria, however, the unique major one is depicted by bone marrow (BM) biopsy. A subset of SM occurs with other hematological neoplasms, most frequently myeloid malignancies such as myeloproliferative neoplasms (MPN), chronic myelomonocytic leukemia and myelodysplasia (MDS). Here we report the case of a 56-year-old female patient affected by SM associated with a hematological neoplasm: she presented with thorax skin rash and a blood test revealed white blood cell count of 12.3 x 10^9/L, increased basophils (3.08 x 10^9/L) and platelets 567 x 10^9/L. Screening of JAK2, CALR, MPL and BCR/ABL1 mutations was negative. Therefore, the patient underwent a BM biopsy, which showed the typical clusters of mast cells associated with an MDS/MPN and a grade 2 reticulin fibrosis. Second-level analyses showed an increased serum tryptase level (148 ng/mL) and peripheral CD34+ cells (172/µL). The abdominal ultrasonography showed a spleen diameter of 19 cm. NGS myeloid panel (Illumina MiSeqTM) detected no mutations in any of the 30 genes analyzed, among them, KIT mutations were negative. Therefore, imatinib 400 mg daily was started, and after 3 months of therapy the patient achieved a significant symptoms improvement. In addition, the BM biopsy showed an outstanding response of SM and an improvement in both MDS/MPN and the grade of fibrosis (MF-1) (Figure 1). Serum tryptase level decreased up to 3 ng/ml and spleen diameter up to 16 cm. The therapy with imatinib was well tolerated, except for grade 3 thrombocytopenia. Platelet count was restored after 2 weeks of imatinib interruption; treatment was resumed at lower dosage with no thrombocytopenia recurrence. To our knowledge, there are no data in the

literature concerning effective therapeutic option in this specific setting. Being aware of the limits of the present report, mainly the short follow-up, we can speculate that imatinib may represent a safe and effective option, not only in the context of non-KIT D816V mutated SM, but also leading to a clinical and histological improvement as far as MDS/MPN is concerned.

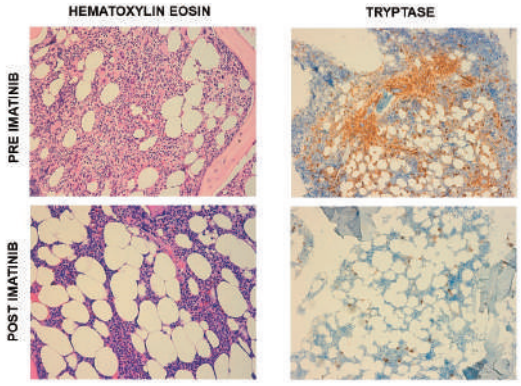

Figure 1.

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IBRUTINIB IN CHRONIC LYMPHOCYTIC LEUKEMIA: A SINGLE-CENTER LONG-TERM ANALYSIS

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The covalent inhibition of Bruton tyrosine kinase with ibrutinib has demonstrated a significant clinical impact in patients with de novo and relapsed/refractory chronic lymphocytic leukemia (CLL) in need of treatment, with benefits in progression-free survival (PFS) and overall survival (OS) even in cases with unfavorable cytogenetics and molecular markers. All patients records with symptomatic CLL treated with ibrutinib have been retrospectively reviewed. Forty-six patients received ibrutinib either as frontline (N=10) or second or more advanced treatment (N=36). Median age at disease diagnosis was 62 years, with 41 male and 15 female patients. Median number of previous treatments for pretreated patients was 1 (range 1-4), mainly including chemoimmunotherapy. Eighteen patients presented with TP53 mutations; 17 had the deletion of chromosome 17p; 19 displayed an unmutated immunoglobulin variable heavy chain status. Median overall number of cycles was 26 (12-80). Among patients treated frontline, 4 patients were in Binet stage A, 5 in stage B and 1 in stage C, with a median cumulative illness rating scale (CIRS) of 5 (range 1-8). Best responses included 1 complete response (CR) and 6 partial responses (PR), for an overall response rate (ORR) of 70%. Patients receiving ibrutinib as a second or later line presented with Binet stage A in 9 cases, B in 14 and C in 10 (3 cases unavailable) and had a median CIRS of 5 (range 0-16). Best responses were 1 CR and 27 PR (ORR 72.2%). Median PFS was 28.8 and 21.1 months for patients treated frontline and as second/later line, respectively. Median OS was not reached for those treated frontline and 4.9 years for patients treated as second/later line. Richter transformation occurred in 5 patients (11%) at a median time of 16 months since the initial dose. At a median time of 3.8 years, 12 patients required further therapy (10 patients shifted to venetoclax). Hematological adverse events (AEs) consisted of grade 4 neutropenia, thrombocytopenia and anemia in 6, 4 and 1 case; grade 3 neutropenia in 6 cases and grade 1-2 thrombocytopenia in 2 cases. Grade 3-4 extrahematological AEs were: diarrhea, cutaneous rash, utero-vesical prolapse, vasculitis and urosepsis. No atrial fibrillation or bleeding were registered. Ibrutinib is effective and well tolerated in CLL patients treated frontline and with relapsed disease. Responses obtained in a real life setting are comparable with results from registration trials.

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FRONTLINE THERAPY WITH OBINOTUZUMAB CHLORAMBUCIL IN CLL PATIENTS: A REAL-LIFE EXPERIENCE

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Introduction: Obinutuzumab-Chlorambucil (G-Chl) actually is the standard of care in untreated chronic lymphocytic leukemia (CLL) patients (pts) with comorbidities. The treatment has been approved since 2017 and proved to be safe and effective with a good toxicity profile. Although chemo-immune treatment in target-therapy era plays a marginal role, the time-limited schedule of G-Chl represents a valid option for elderly unfit pts.

Aims: We conducted this retrospective study to evaluate efficacy and safety of G-Chl in a real-life setting.

Methods and patients: We enrolled 36 consecutives untreated CLL pts in six Tuscan centers, median age was 73 years (59-85). Twenty patients were male, 16 females. FISH status was available in 27/30 pts (14 negative, 7 deletion 13q, 4 trisomy 12 and 2 deletion 11q), IGHV status was analyzed in 22 pts only (13 mutated, 9 unmutated), TP53 mutation was investigated in 8 pts without any evidence of mutation. RAI stage at time of treatment was I in 5, II in 13, III in 12 and IV in 6 pts, respectively. CIRS>= 6 was in 14 pts. G-Chl was administered as normal clinical practice. Median follow-up was 23.4 months

Results: The overall response rate (ORR) was 75%: 12 pts (33%) achieved complete response, 15 pts (42%) partial response, 2 pts (6%) progression disease, in 7 pts (19%) the response was not available due to the ongoing treatment. Minimal residual disease (MRD) in peripheral blood was evaluated in 14 pts (9 negative, 5 positive). Median PFS was 28 months (16-40 months). We did not observe any significant impact on PFS by FISH status, IGHV status, RAI stage, CIRS>=6 and age>=70 years, respectively (p=0.882; p=0.181; p=0.848; p=0.501; p=0.305). In our cohort, MRD status was the only statistically significant prognostic factor on PFS (median PFS: 41 months for MRD- and 26 months for MRD+; p=0.049). Median time to next treatment was 36 months: as second-line therapy 7 pts received BTKi, 1 venetoclax, 1 idelalisib and 1 chlorambucil. We observed 1 clinical TLS, 7 infusion reactions, 7 thrombocytopenia (29% G>=3), 10 neutropenia (33% G>=3), 2 febrile neutropenia and 1 pneumonia (G2).

Conclusions: Our experience is consistent with PFS and ORR data, as reported in literature. G-Chl seems to maintain a good safety and tolerability profile. The time-limited schedule makes this treatment a valid option for elderly patients, especially for those who did not have a caregiver or did not display a good treatment compliance.