IBRUTINIB TREATMENT AND ITS IMPACT ON CIRCULATING IMMUNE CELLS IN CHRONIC LYMPHOCYTIC LEUKEMIA PATIENTS

F. MORELLI [1], C.M.RAPOLLA [1], A.M.VANNUCCHI [2], A.SANNA [3]

1. Hematology Unit, University of Florence; 2. Center for Innovation and Research in Myeloproliferative Neoplasms, Hematology Unit, Azienda Ospedaliera Universitaria Careggi, University of Florence; 3. Hematology, Department of Oncology, AOU Careggi

Background

Chronic lymphocytic leukemia (CLL) is a B-cell malignancy characterized by immune dysregulation. Infections represent a cause of mortality and morbidity in CLL patients. Ibrutinib (IBR) is a Bruton's tyrosine kinase inhibitor very effective on CLL, but this treatment is burdened by infective complications especially within the first months of therapy. The decline of infections could suggest that immune competence may be restored by IBR directly or by reductions in CLL burden.

Aims

This monocentric prospective study evaluates immunophenotypic changes in circulating immune cells in CLL patients treated with IBR. We collected peripheral blood samples at baseline,3,6 and 12 months of therapy. New samples at 24 months will be collected.

Materials & Methods

We collected clinical and biological data of 26 patients treated with IBR in our Centre since January 2021. Multiparametric flow cytometry was used to characterize immune cells.
Median age at IBR start was 72 (50-84) years.
Fifteen patients were treatment-naive, 7 patients were on second-line therapy. The other 4 have already received at least 2 previous lines. In particular, 11 patients have already received a previous chemo-immunotherapy (CIT).
Patients' characteristics in Table 1.

Results

The only correlation between clinical-biological data and an impact on baseline immune cells was found between a previous exposure to CIT and CD3+HLA-DR+cells (median 1x10^9/L vs 6x10^9/L in chemo-naïve pts (p=0.025).
No differences observed in who have received a chemo-free therapy prior to IBR or based on the previous number of therapy lines.
In Table 2, we report the median values at different timepoints. We observed a statistical difference between baseline and after 12 months as expected for CD19+(p= 0.019).
Another statistically significant difference was observed in the decrease of NK cells(CD3-CD16+CD56+) during treatment (p=0.026).
An infectious complication was observed in 10 pts (38%). In particular, 6 pts experienced COVID-19 (3 mild infections; 3 hospitalization), 4 pneumonia and one single patient experienced both and a complicated urinary tract infection

Table 2:Results

MEDIAN VALUES (x10^9/L)	TIMEPOINTS			
	Baseline	3 months	6 months	12 months
WBC (n.v: 4-10)	34,9 (13-134)	26,5 (13,2-98,1)	11 (5-12)	8,4 (5,3-9,7)
Lympho (n.v: 0,5-5)	25,8 (8,5-126,5)	21,6 (8,4-96,4)	4,9 (0,8-9,7)	2,8 (0,1-4,6)
CD3+HLA-DR+ (n.v: 0-0,59)	0,4 (0,2-0,6)	0,3 (0-1)	0,3 (0,1-0,7)	0,2 (0-0,9)
CD4/CD8 ratio (n.v: 1-3,5)	2,3 (0,7-6)	1,5 (0,6-6,2)	1,4 (0,5-3,3)	1,1 (0,6-2,8)
CD19+ (n.v: 0,1-0,5)	23,7 (6,3-122,7)	57 (8,8-94)	3 (0,3-5,4)	0,5 (0,3-1,9)
CD3+CD4+ (n.v: 0,6-2)	1,1 (0,6-1,5)	0,9 (0,6-6,5)	0,7 (0,3-1,1)	0,7 (0-1)
CD3+ (n.v: 0,57-2,8)	1,5 (0,4-2,5)	2,3 (0,7-10,2)	1,6 (0,4-1,9)	0,9 (0,1-2,7)
LAK cells	0,2 (0,02-0,4)	0,1 (0-0,5)	0,04 (0-0,3)	0,02 (0-0,5)
NK cells (n.v: 0,2.0,4)	0,6 (0,4-1,3)	0,5 (0,1-0,7)	0,01 (0-0,3)	0,008 (0-0,2)

Conclusions

These preliminary data shows that NKT cells, that mediate tumour immunosurveillance, at baseline were higher than expected. With IBR, in our 7 patients in therapy for at least one year, they are reduced by 98% in 12 months. Further data are needed, but these could suggest an impact of IBR on immune system that could help on infective complications.

Table 1:Patients characteristics

		Overall
Number of patients	26 (100%)	
Age (median [range])	72 [52-81]	
Sex (%)	M	21 (81%)
	F	5 (19%)
N. of previous therapy	0	15 (58%)
	1	7 (27%)
	>2	4 (15%)
Previous therapy	CIT	11 (42%)
	Chemo-free	3 (12%)
Months of IBR treatment (n. of patients[%])	>12 months	7 (27%)

Biblio

-Sun C.,**Partial reconstitution of humoral immunity and fewer infections in patients with chronic lymphocytic leukemia treated with ibrutinib.** ***Blood 2015***
-Pleyer C.,**Reconstitution of humoral immunity and decreased risk of infections in patients with chronic lymphocytic leukemia treated with Bruton tyrosine kinase inhibitors.** ***Leuk Lymphoma 2020***
-ZhuS.**Multifaceted Immunomodulatory Effects of the BTK Inhibitors Ibrutinib and Acalabrutinib on Different Immune Cell Subsets - Beyond B Lymphocytes.** ***Front Cell Dev Biol 2021***

Contact information: f.morelli@unifi.it