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THE EVOLUTION OF TREATMENTS AND OUTCOME OF PATIENTS WITH CHRONIC LYMPHOCYTIC LEUKEMIA TREATED AT FONDAZIONE POLICLINICO UNIVERSITARIO AGOSTINO GEMELLI IRCCS: A MONOCENTRIC EXPERIENCE OF THE LAST 30 YEARS.

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INTRODUCTION

The covalent Bruton's Tyrosine Kinase inhibitors (cBTKi) and B-Cell Lymphoma-2 inhibitor (BCL2i) have changed the treatment approach into the chronic lymphocytic leukemia (CLL) over the last 10 years. This Italian monocentric retrospective observational study describes the treatment patterns and outcomes of patients (pts) with CLL, to better understand the impact of treatment sequencing in the novel targeted-agents era.

METHODS

CLL patients treated between 1992 and 2022 and prospectively registered in the institution's electronic database were included. Time-to-event outcomes were evaluated using Kaplan Meier method. Time to next treatment (TTNT) was defined as time from treatment start to the start of subsequent therapy or death. Time to next treatment failure or death (TTNTF) was defined as time from treatment discontinuation to the discontinuation of subsequent therapy or death.

Table 1. Patients characteristics

		Entire cohort (n=637)	Treated cohort (n=318)
Age, years (median, IQR)		64 (56-72)	65 (58-72)
Gender, n (%)	Male	369 (57.9)	201 (63.2)
	Female	268 (42.1)	117 (36.8)
FISH analysis, n	Deletion 17p	30/475	28/279
	Deletion 13q	202/470	123/276
	Deletion 11q	42/470	36/276
	Trisomy 12	72/470	43/276
TP53, n (%)	Mutated	46 (7.2)	42 (13.2)
	Unmutated	280 (44.0)	190 (59.7)
	missing	311 (48.8)	86 (27.0)
Del (17p) and/or TP53 mut, n		59/315	53/227
IGHV, n (%)	Mutated	246 (38.6)	118 (37.1)
	Unmutated	170 (26.7)	137 (43.1)
	missing	221 (34.7)	63 (19.8)
First line treatment, n(%)	No	319 (50.1)	
	Yes	318 (49.9)	318 (100%)
Time to Treatment, months (median, IQR)			24 (7-51)

Table 2. Treatment regimens and sequencing

318/637 CLL patients treated between 1992 and 2022		
First line Treatment, n (%)	cBTKi +/- antiCD20	75 (23.6)
	BCL2i +/- antiCD20	14 (4.4)
	cBTKi+BCL2i	2 (0.6)
	CT+antiCD20	162 (50.9)
	CT	53 (16.7)
	Other	12 (3.8)
cBTKi-exposed, n (%)		157 (49.4%)
BCL2i-exposed, n (%)		60 (18.9%)
BCL2i-exposed cBTKi-naïve, n (%)		34 (10.7%)
cBTKi- and BCL2i- exposed, n (%)		26 (8.2%)
CIT, cBTKi- and BCL2i-exposed, n (%)		17 (5.3%)
cBTKi- and BCL2i-naïve, n (%)		127 (39.9%)

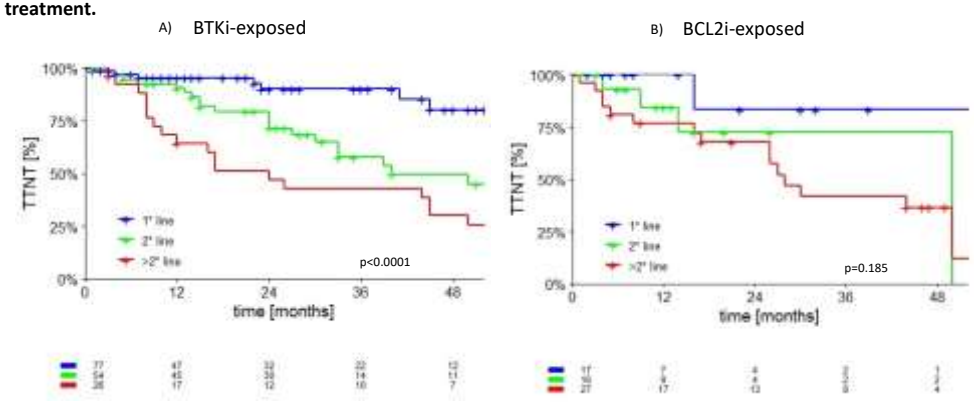
cBTKi: covalent Bruton's Tyrosine Kinase inhibitors; BCL2i: B-Cell Lymphoma-2 inhibitor; CIT o CT: chemoimmunotherapy

RESULTS (1)

Of 637 registered CLL patients, 318 (49.9%) received treatment (characteristics in Table 1-2). Of 318 treated patients, cBTKi-exposed were 157 (49.4%). Patients BCL2-exposed, but cBTKi-naïve, were 34 (10.7%). Patients who received both a cBTKi and BCL2i +/- antiCD20 (double-exposed) were 26 (8.2%). Seventeen patients (5.3%) received chemoimmunotherapy, cBTKi, and BCL2i. Patients cBTKi- and BCL2i-naïve were 127 (39.9%). Of 157 patients, 77 (49%) received cBKTi frontline, 55 (35%) in second line, 28 (17.8%) after >2 lines of treatment. Need for a subsequent treatment or death after cBTKi therapy was 10.4% (n=8) after frontline cBTKi, 41.8% (n=23) after second line, 67.9% (n=19) after >2 lines of treatment; collectively, it was 30.6% (48/157). Deaths during BTKi were 16 (10.2%). Four patients were retreated with cBTKi. For the 34 BCL2i-exposed cBTKi-naïve patients, BCL2i was administered frontline in 13 (38.2%), in second line in 12 (35.3%), after >2 lines of treatment in 11 (32.3%). Need for a subsequent treatment or death after BCL2i therapy in this group was 7.7% (n=1) after frontline BCL2i, 25% (n=3) after second line, 27.3% (n=3) after >2 lines of treatment; collectively, it was 17.6% (6/34). Deaths during BTKi were 7 (11.7%). Four patients were retreated with BCL2i. For the 26 double-exposed patients, 96.1% (n=25) received BCL2i after cBTKi. Collectively, the need for subsequent treatment or death was 38.5% (10/26). Deaths in double-exposed were 4 (15.4%).

Five-year TTNT in cBTKi-exposed patients were 80% (median not reached), 40% (median 40 months), 21% (median 24 months) months in first, second and subsequent lines respectively ($p < 0.0001$). Five-year TTNT in BCL2i-exposed patients were 83% (median not reached), 72% (median not reached), 12% (median 28 months) in first, second and subsequent lines respectively ($p=0.185$). Stratifying BCL2i-exposed patients in first line and relapsed/refractory, 5-year TTNT were 83% (median not reached) and 42.5% (median 30 months) ($p=0.089$). Kaplan Meier curves are shown in Figure 1.

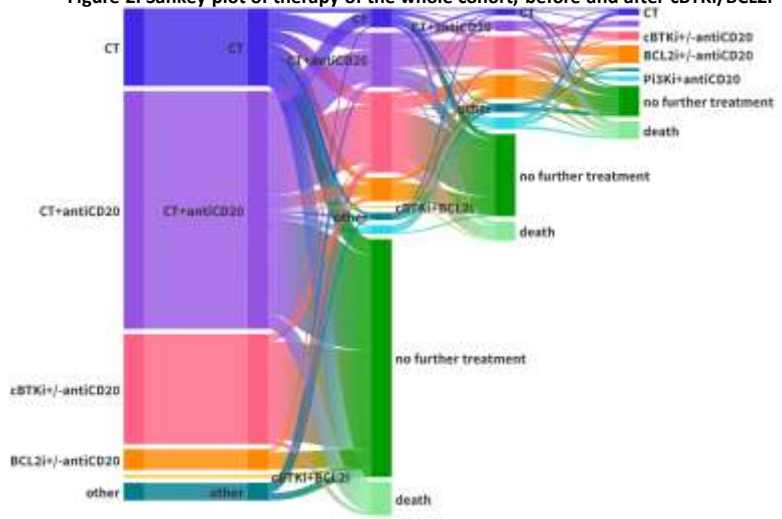
Figure 1. Time to next treatment in BTKi-exposed (A) and BCL2i-exposed (B) patients according to the line of treatment.



RESULTS (2)

The treatment sequence of the entire cohort is shown in the Sankey plot in Figure 2. Median TTNTF was 9 months (range 1-87) for all patients who discontinued the cBTKi independently of the line of treatment, and 17 months (range 8-49) for those who discontinued both a cBTKi and BCL2i. Our results were superimposable with previous experiences for patients relapsing after cBTKi, while they were slightly higher in double-exposed patients. Mato et al. reported TTNTF after frontline BTKi 11.3 months and after second line 7.8 months, and our cohort was mostly composed of patients taking cBTKi in first or second line (Mato AR, et al. Clin Lymphoma Myeloma Leuk. 2023). Eyre et al. reported a median time to progression or death of 9.2 months (Eyre TA, et al. Leuk Lymphoma 2023). TTNTF in double-exposed patients reported by Mato et al. was inferior (5.5 months) compared to our cohort (median TTNTF 17 months) probably for two main reasons: firstly 4 out of 6 patients in this group underwent HSCT for high-risk CLL features or Richter's transformation; secondly patients treated with BCL2i have a shorter observation time because of the later approval in Italy. Nevertheless, these data reinforce the idea that, considering the worsening outcome after multiple targeted agents, patients in the condition to receive treatment urgently need new viable alternatives after current treatments have been exhausted.

Figure 2. Sankey plot of therapy of the whole cohort, before and after cBTKi/BCL2i



CONCLUSIONS

Despite its limitations, this study shows how anticipating target therapy improved the outcome of CLL patients. Nonetheless, the poor outcomes in advanced lines of therapy also highlight the need for even more effective treatments, especially for younger and high-risk patients.

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