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Absence of lymphocytosis after starting treatment with cBTKi is a rare phenomenon except for CD49d positive CLL mainly expressed in trisomy 12

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INTRODUCTION

COVALENT BRUTON TYROSINE KINASE INHIBITORS (CBTKI) HAVE REVOLUTIONIZED THE TREATMENT OF CHRONIC LYMPHOCYTIC LEUKEMIA (CLL). THEY TARGET BRUTON TYROSINE KINASE (BTK), WHICH MEDIATES BCR SIGNALING, AND TRIGGERS PATHWAYS INVOLVED IN CELL SURVIVAL, PROLIFERATION AND MIGRATION. BTK INHIBITION IN NEOPLASTIC LYMPHOCYTES RESULTS IN THEIR DEMARGINALIZATION FROM LYMPH NODES INTO PERIPHERAL BLOOD, LEADING TO REDISTRIBUTION LYMPHOCYTOSIS. CHARACTERIZED BY A TRANSIENT INCREASE IN ABSOLUTE LYMPHOCYTE COUNT (ALC) AFTER THERAPY INITIATION, HOWEVER, CASES OF ABSENT OR ATTENUATED LYMPHOCYTOSIS AFTER TREATMENT INITIATION HAVE BEEN REPORTED IN LITERATURE, PARTICULARLY IN PATIENTS WITH TRISOMY 12 (+12). THE CLINICAL IMPACT OF WHICH REMAINS UNKNOWN. TRISOMY 12 CELLS SHOW INCREASED EXPRESSION OF ADHESION INTEGRINS LFA-1, MAC-1 AND VLA4-4, PROMOTING RETENTION OF +12 CLL CELLS WITHIN TISSUES. THE AIM OF THIS STUDY WAS TO DESCRIBE CLL PATIENTS TREATED WITH CBTKI WHO DID NOT SHOW ANY LYMPHOCYTOSIS AFTER TREATMENT INITIATION AND ITS IMPACT ON PROGRESSION-FREE SURVIVAL (PFS), TIME TO NEXT TREATMENT (TTNT) AND OVERALL SURVIVAL (OS).

MATERIAL AND METHODS

WE RETROSPECTIVELY ANALYZED A COHORT OF 346 TREATMENT-NAÏVE CLL PATIENTS FROM 16 ITALIAN CENTERS, ALL TREATED WITH TARGET-DOSE IBRUTINIB, ACALABRUTINIB, OR ZANUBRUTINIB. WE ASSESSED THE MEDIAN ALC AT BASELINE AND ON DAYS +15, +30, +60, +90, +120, +180, +270 AND +360. THEN WE CONDUCTED A DESCRIPTIVE STATISTICAL ANALYSIS BASED ON CLINICAL AND BIOLOGICAL CHARACTERISTICS. ADDITIONALLY, CLINICAL OUTCOMES AS PFS, TTNT AND OS WERE ASSESSED IN 284 PATIENTS WITH SUFFICIENT FOLLOW-UP. THE STUDY WAS CARRIED OUT ACCORDING TO THE HELSINKI DECLARATION, GOOD CLINICAL PRACTICE, AND THE APPLICABLE NATIONAL REGULATIONS AND WAS APPROVED BY THE LOCAL ETHIC COMMITTEE.

RESULTS

WE IDENTIFIED 51/346 PATIENTS (15%) WHO DID NOT DEVELOP LYMPHOCYTOSIS FOLLOWING CBTKI INITIATION. THESE PATIENTS DEMONSTRATED A PERSISTENT REDUCTION IN ALC FROM DAY 15 ONWARD. NO SIGNIFICANT DIFFERENCES IN LYMPHOCYTE KINETICS OR FREQUENCY OF NON-LYMPHOCYTOSIS WERE FOUND BETWEEN THE THREE CBTKI AGENTS. ACCORDING TO THE CYTOGENETIC PROFILE, 45% HAD CLL WITH +12, 18% DEL(17P), 25% DEL(11Q), 35% DEL(13Q) AND 12% NORMAL KARYOTYPE. ONLY FOR 22/51 PATIENTS WE HAD DATA ABOUT CD49D (VLA-4 INTEGRIN ALFA SUBUNIT) EXPRESSION BEFORE STARTING TREATMENT: 16/22 (73%) PATIENTS CD49D+ AND 6/22 (27%) CD49D-. REGARDING IMMUNOGLOBULIN HEAVY CHAIN VARIABLE REGION (IGHV) GENE MUTATIONAL STATUS: 71% HAD UNMUTATED IGHV AND 29% HAD MUTATED IGHV. NO STATISTICAL DIFFERENCES IN LYMPHOCYTE KINETICS WERE OBSERVED BETWEEN MUTATED AND UNMUTATED IGHV.
WE NOTICED THAT THE +12 PATIENTS (20/51 PATIENTS) HAD A SMALLER INCREASE IN BLOOD LYMPHOCYTOSIS FROM THE FIRST TO THE SIXTH MONTH. IN +12 CLL PATIENTS, WE DID NOT STUDY THE SPECIFIC ROLE OF CD49D+ DUE TO ITS WIDESPREAD EXPRESSION (89%) IN THIS GROUP OF PATIENTS. WE FURTHER ANALYZED THE ROLE OF CD49D IN PATIENTS WITHOUT +12 (13/22 PATIENTS) TO DETECT THE INDEPENDENT ROLE OF CD49D. ALL CD49D+ CLL PATIENTS (8/13 PATIENTS) SHOWED A MORE PRONOUNCED REDUCTION IN LYMPHOCYTE COUNTS DURING THE FIRST 3 MONTHS OF THERAPY. CLINICAL OUTCOMES WERE ASSESSED IN 284 PATIENTS, COMPARING THOSE WITH (N=244) AND WITHOUT (N=40) CBTKI-INDUCED LYMPHOCYTOSIS. NO SIGNIFICANT DIFFERENCES WERE OBSERVED IN PFS, TTNT AND OS, REGARDLESS OF PRESENCE OR ABSENCE OF LYMPHOCYTOSIS (PFS P=0.9651; TTNT P=0.5346; OS P=0.6848).

CONCLUSION

THE ABSENCE OF LYMPHOCYTOSIS DURING CBTKI THERAPY IN CLL IS ASSOCIATED WITH SPECIFIC BIOLOGICAL FEATURES, NOTABLY CD49D EXPRESSION AND TRISOMY 12. CD49D APPEARS TO BE THE KEY DRIVER OF THE NO-LYMPHOCYTOSIS PHENOTYPE, WHILE +12 MAY HAVE AN INDIRECT ROLE DUE TO ITS STRONG ASSOCIATION WITH CD49D. IMPORTANTLY, LACK OF LYMPHOCYTOSIS AFTER CBTKI TREATMENT DOES NOT CORRELATE WITH INFERIOR OUTCOMES (PFS, TTNT, OS) COMPARING PATIENTS WITH OR WITHOUT LYMPHOCYTOSIS. INDEPENDENTLY OF CD49D EXPRESSION, FUTURE STUDIES WITH LARGER COHORTS AND EXTENDED FOLLOW-UP ARE WARRANTED TO CLARIFY THE PROGNOSTIC IMPACT OF CD49D ON LONG-TERM OUTCOMES IN THIS SETTING.

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INTRODUCTION

COVALENT BRUTON TYROSINE KINASE INHIBITORS (CBTKI) ARE A CLASS OF DRUGS THAT HAVE REVOLUTIONIZED THE TREATMENT OF CHRONIC LYMPHOCYTIC LEUKEMIA (CLL) [1]. THEY TARGET BRUTON TYROSINE KINASE (BTK), AN ENZYME ACTIVATED BY B CELL RECEPTOR (BCR) STIMULATION IN B LYMPHOCYTES, WHICH TRIGGERS PATHWAYS INVOLVED IN CELL SURVIVAL, PROLIFERATION AND MIGRATION [2]. BTK INHIBITION IN NEOPLASTIC LYMPHOCYTES RESULTS IN THEIR DEMARGINALIZATION FROM LYMPH NODES INTO PERIPHERAL BLOOD. THIS PHENOMENON OF CELL REDISTRIBUTION WAS WIDELY STUDIED, LEADING TO A STANDARD DESCRIPTION OF LYMPHOCYTOSIS KINETICS DURING CBTKI THERAPY: AN INITIAL FURTHER INCREASE OF THE PRE-EXISTING LYMPHOCYTOSIS DURING THE FIRST MONTH OF THERAPY, FOLLOWED BY A GRADUAL DECLINE OVER TIME, SOMETIMES LEADING TO NORMALIZATION OF THE ABSOLUTE LYMPHOCYTE COUNT (ALC) [3]. A FEW PUBLISHED SERIES HAVE REPORTED ABBREVIATED, THOUGH NOT ABSENT, LYMPHOCYTOSIS AFTER TREATMENT INITIATION WITH CBTKI, ESPECIALLY IBRUTINIB IN PATIENTS WITH TRISOMY 12. THOMPSON ET AL. PUBLISHED IN 2014 DATA ABOUT ABBREVIATED LYMPHOCYTOSIS IN TRISOMY 12 (+12) CLL CELLS DURING IBRUTINIB TREATMENT, NOTING THAT THE MECHANISMS REMAIN UNKNOWN [4]. TRISOMY 12 CELLS SHOW INCREASED EXPRESSION OF INTEGRINS LFA-1, MAC-1 AND VLA4-4; THE UP-REGULATION OF THESE INTEGRINS AND THEIR SIGNALING ENHANCES ITGA4/ITGB1-MEDIATED MOTILITY AND ADHESION PROMOTING RETENTION OF +12 CLL CELLS WITHIN TISSUES. [5,6]

METHODS

THE AIM OF THIS STUDY WAS TO DESCRIBE CLL PATIENTS TREATED WITH CBTKI WHO DID NOT SHOW ANY LYMPHOCYTOSIS AFTER TREATMENT INITIATION AND ITS IMPACT ON PROGRESSION-FREE SURVIVAL (PFS), TIME TO NEXT TREATMENT (TTNT) AND OVERALL SURVIVAL (OS).

WE STUDIED LYMPHOCYTOSIS KINETICS IN CLL PATIENTS TREATED IN FIRST LINE WITH CBTKI AS IBRUTINIB, ACALABRUTINIB AND ZANUBRUTINIB, AT TARGET DOSE. WE ENROLLED 346 PATIENTS FROM 16 ITALIAN CENTERS AND ASSESSED FOR EACH ONE THE MEDIAN ALC AT BASELINE AND ON DAYS +15, +30, +60, +90, +120, +180, +270 AND +360. THEN WE CONDUCTED A DESCRIPTIVE STATISTICAL ANALYSIS BASED ON CLINICAL AND BIOLOGICAL CHARACTERISTICS. ADDITIONALLY, CLINICAL OUTCOMES WERE ASSESSED IN 284 OUT OF 326 PATIENTS WITH SUFFICIENT FOLLOW-UP. PFS, TTNT AND OS WERE CALCULATED USING THE KAPLAN-MEIER METHOD, WITH GROUP COMPARISONS BY LOG-RANK TEST. THE STUDY WAS CARRIED OUT ACCORDING TO THE HELSINKI DECLARATION, GOOD CLINICAL PRACTICE, AND THE APPLICABLE NATIONAL REGULATIONS AND WAS APPROVED BY THE LOCAL ETHIC COMMITTEE. ALL PATIENTS PROVIDED WRITTEN INFORMED CONSENT.

RESULTS

FROM OUR ANALYSIS, WE FOUND THE ABSENCE OF LYMPHOCYTOSIS IN 51/346 PATIENTS (15%). AMONG THESE, WE OBSERVED A HIGH INCIDENCE OF +12 (45% OF PATIENTS), WHICH IS HIGHER THAN EXPECTED ACCORDING TO DÖHNER CLASSIFICATION [7], HIGH EXPRESSION OF CD49D (73%), ESPECIALLY IN +12 GROUP. (TAB 1) THESE PATIENTS SHOWED AN IMMEDIATE AND PERSISTENT REDUCTION IN CIRCULATING LYMPHOCYTES FROM DAY 15 THROUGH THE 1-YEAR FOLLOW-UP. THE ABSENCE OF LYMPHOCYTOSIS OCCURRED ACROSS ALL THREE CBTKI DRUGS, WITHOUT STATISTICALLY SIGNIFICANT DIFFERENCES IN LYMPHOCYTE COUNTS AMONG THE THREE GROUPS. (FIG. 1A) ALSO THE PERCENTAGE OF CLL PATIENTS WITHOUT LYMPHOCYTOSIS WAS SIMILAR FOR THE THREE CLASSES OF CBTKI: 23/137 IN IBRUTINIB (17%), 21/151 IN ACALABRUTINIB (14%) AND 7/58 IN ZANUBRUTINIB (12%). ANALYZING THE COHORT ACCORDING TO THE CYTOGENETIC PROFILE, WE FOUND THAT 45% HAD CLL WITH +12, 18% DEL(17P), 25% DEL(11Q), 35% DEL(13Q) AND 12% NORMAL KARYOTYPE. ONLY FOR 22/51 PATIENTS WE HAD DATA ABOUT CD49D (VLA-4 INTEGRIN ALFA SUBUNIT) EXPRESSION BEFORE STARTING TREATMENT. AMONG THESE, 16 PATIENTS HAD A CLL CD49D-POSITIVE CELLS (CD49D+) AND 6 A CLL CD49D-NEGATIVE CELLS (CD49D-). THUS, THE 73% (16/22) OF THE PATIENTS HAD AT LEAST ONE NEOPLASTIC LYMPHOCYTE SUBPOPULATION EXPRESSING CD49D. REGARDING IMMUNOGLOBULIN HEAVY CHAIN VARIABLE REGION (IGHV) GENE MUTATIONAL STATUS, THE 71% OF THIS GROUP HAD UNMUTATED IGHV, WHILE ONLY THE 29% HAD MUTATED IGHV. NO STATISTICAL DIFFERENCES IN LYMPHOCYTE KINETICS WERE OBSERVED BETWEEN MUTATED AND UNMUTATED IGHV DURING THE STUDY PERIOD. DUE TO THE LIMITED SAMPLE SIZE, WE GROUPED ALL PATIENTS TREATED WITH IBRUTINIB, ACALABRUTINIB, AND ZANUBRUTINIB FOR ANALYSIS. (FIG. 1B) WHEN WE CONSIDERED LYMPHOCYTE COUNTS IN PATIENTS WITH TRISOMY 12 VERSUS PATIENTS WITHOUT TRISOMY 12, WE NOTICED THAT THE FIRST GROUP HAD A SMALLER INCREASE IN BLOOD LYMPHOCYTOSIS FROM THE FIRST TO THE SIXTH MONTH. IN +12 CLL PATIENTS, WE DID NOT STUDY THE SPECIFIC ROLE OF CD49D+ DUE TO ITS WIDESPREAD EXPRESSION (89%) IN THIS GROUP OF PATIENTS. (FIG. 1C)) WE FURTHER ANALYZED THE ROLE OF CD49D IN PATIENTS WITHOUT +12 (13/22 PATIENTS) TO DETECT THE INDEPENDENT ROLE OF CD49D VERSUS +12. FROM THIS ANALYSIS CONDUCTED IN 13 PATIENTS WITH AVAILABILITY OF CD49 EXPRESSION, 8 WERE CD49D+ AND 5 CD49D-. ALL CD49D+ CLL PATIENTS (8/13 PATIENTS) SHOWED A MORE PRONOUNCED REDUCTION IN LYMPHOCYTE COUNTS DURING THE FIRST 3 MONTHS OF THERAPY. (FIG. 1D) IN THE 284 PATIENTS ANALYZED FOR SURVIVAL OUTCOMES (244 WITH CBTKI-INDUCED LYMPHOCYTOSIS, 40 WITHOUT), NO SIGNIFICANT DIFFERENCES WERE FOUND IN PFS (P=0.9651), TTNT (P=0.5346) AND OS (P=0.6848), BETWEEN PATIENTS WITH OR WITHOUT CBTKI-INDUCED LYMPHOCYTOSIS.

TABLE 1 (TAB 1)

BASELINE CLINICAL AND BIOLOGICAL CHARACTERISTICS, IN PATIENTS WHO DID NOT SHOW LYMPHOCYTOSIS AFTER TREATMENT WITH CBTKI.

	Ibrutinib (n=23)	Acalabrutinib (n=21)	Zanubrutinib (n=7)	Total (n=51)
Median Age	72 (63–77)	72 (65–78)	80 (74–82)	72 (63–82)
Male Sex (%)	44	71	86	61
Female Sex (%)	56	29	14	39
Rai Stage III-IV (%)	35	48	71	45
Binet Stage C (%)	22	43	57	35
Lymph Nodes <5 cm (%)	70	67	75	69
Splenomegaly >12 cm (%)	74	76	71	75
Unmutated IGHV (%)	70	76	57	71
Trisomy 12 (%)	39	47	57	45
Del(13q) (%)	35	47	0	35
Del(11q) (%)	17	37	14	25
Del(17p) (%)	17	26	0	18
Normal Karyotype (%)	13	5	29	12

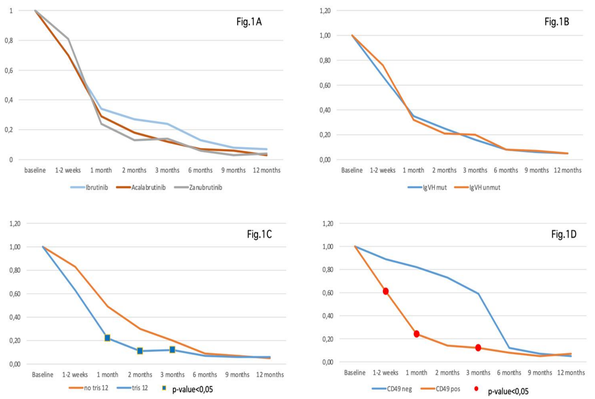
FIGURE. 1.

Relative ALC reduction based on target therapies and biological characteristics.

Fig. 1A. Relative ALC reduction in patients treated with ibrutinib, acalabrutinib, and zanubrutinib.

Fig. 1B. Relative ALC reduction in patients treated with cBTKi with mutated (IGVH mut) and unmutated (IGVH unmut) IGHV.
Fig. 1C. Relative ALC reduction in patients with and without trisomy 12. Patients with trisomy 12 showed a significantly more rapid lymphocyte decline at 1, 2, and 3 months ($p < 0.05$), as indicated by blue markers.

Fig. 1D. Relative ALC reduction in patients without trisomy 12, with positive (CD49 pos) and negative (CD49 neg) CD49d expression. CD49d-positive patients exhibited a significantly faster lymphocyte decline at day 15, 1 month, and 3 months ($p < 0.05$), as indicated by red markers.



DISCUSSION AND CONCLUSION

Among patients who did not show a further rise of lymphocytosis after starting cBTKi therapy, we found no significant difference based on drug used (ibrutinib, acalabrutinib and zanubrutinib) and IGHV mutational status. These data have not yet been investigated in literature for acalabrutinib and zanubrutinib in patients who did not show lymphocytosis after starting cBTKi therapy. In contrast, our group has published data showing differences in lymphocytosis kinetics due to mutated IGHV in patients during treatment with cBTKi of first and second generation (Ibrutinib vs Acalabrutinib) [8]. We observed a more rapid lymphocyte decrease in +12 CLL patients. This difference was statistically significative and confirmed, even in this setting, what is already known from literature (Thompson et al. 2014), even if our study lacks day 7 lymphocyte counts to confirm Thompson data about a speedy and brief lymphocytosis, that disappeared from day 15 [4] Almost all patients with +12 expressed CD49d, the alpha subunit of integrin VLA-4 that represent the main adhesion molecule expressed by CLL cells, allowing neoplastic lymphocytes retention in lymph nodes [5,9]
To discovery the exact roles of +12 and CD49d+ lymphocytes on the lack of redistribution lymphocytosis, we analyzed CD49d expression in patients without +12. We found that CD49d was expressed in the 62% and was negative in the 38% of CLL patients, those CD49d+ patients showed a statistically significant faster decrease in ALC compared to CD49d- patients.
In addition to biological profiling, we observed no significant differences PFS, TTNT and OS between patients who experienced cBTKi-induced lymphocytosis and those who did not. These findings suggest that the absence of lymphocytosis does not adversely affect clinical outcomes, though the interpretation is limited by sample size and follow-up duration. Notably, this partial contrasts with some previously published data (Tissino et al. 2018), who considered the role of CD49d+ CLL-patients, where reduced or absent lymphocytosis after ibrutinib therapy has been associated with shorter PFS. [9] In our study we compared frontline CLL patients treated with first and second generation of cBTKi with or without lymphocytosis, but we did not stratify patients with CD49d expression. However, those findings may be influenced by biological stratification and treatment era. The novelty of our study lies in the inclusion of second-generation BTKi (acalabrutinib and zanubrutinib) and the real-world setting across multiple centers.

In conclusion, our data indicate that the adhesion molecule CD49d seems to be the main "no lymphocytosis" predictive factor in cBTKi-treated CLL patients, whereas +12 plays an indirect role due to high prevalence of CD49d expression in this subgroup, without impacting time-dependent parameters (PFS, TTNT). Future studies with larger cohorts and extended follow-up are warranted to clarify the prognostic impact of CD49d on long-term outcomes in this setting.

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