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Title: ACALABRUTINIB IN THE TREATMENT OF RICHTER SYNDROME

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Session Title: Chronic lymphocytic leukemia and related disorders - Clinical

Background:

Richter's syndrome is an aggressive histologic transformation of chronic lymphocytic leukemia , most commonly to diffuse large B-cell lymphoma, occurring in about 2-15% of patients with CLL. Outcomes for patients with RS are generally poor with median overall survival of 5.9–11.4 months and ongoing unmet clinical need for effective therapies. B-cell receptor signaling through Bruton tyrosine kinase is one of the essential growth pathways for CLL. Acalabrutinib is a highly selective, potent BTK inhibitor has shown significant efficacy in relapsed/refractory and untreated CLL.

Aims:

improving the outcomes of patients with RS

Methods:

We reported 5 cases of Richter syndrome treated with acalabrutinib in combination with immunochemotherapy in the period from June 2020 to February 2023. Table 1 shows the characteristics of 5 CLL pts who developed biopsy-proven DLBCL. The median time to transformation from CLL was 33,8 months (range 4-66 months). Determination of clonal association with CLL by blot hybridization was not available, but in 4 pts the p53 expression was studied by immunohistochemical method to determine the pathogenetic pathway of RS development and the PD-1 expression confirm the clonal association with CLL

Results:

At the time of transformation, 2 pts were initially treated with rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) with a suboptimal response, then acalabrutinib was added, 2 pts received 6 cycles of R-CHOP+ acalabrutinib and 1patient - 5 cycles R-CVP + acalabrutinib. The overall response was 80% (1 pts had a CR and 2 PR), stabilization of the tumor process was achieved in 1 patient. The 3 pts with CR and PR are currently receiving acalabrutinib, 1 prs had progression of DLBCL after 15 months of acalabrutinib therapy and 1 pts died from Covid19- infection on the background of stabilization of the disease Acalabrutinib was well-tolerated; no patient required discontinuation as a result of adverse events.

At the time of CLL diagnosis (table1)

Patient	1	2	3	4	5
Age, y	75	28	64	34	65
Sex	M	F	M	F	M
Rai stage	II	II	II	II	II
CLL therapy	Rituximab monothera py Efficacy - CR	none	FCG , 6 cycle Efficacy - CR	FCR 6 cycles Efficacy - CR_i	none
Time from last CLL therapy to RS diagnosis months	66	45	48	4	6
Localizat ion of the tumor	Periphera l, retroperi toneal LN, stomach	Periphera l LN, nasal sinuses, upper palate	Retroperi toneal LN, colon	Tumor of the tongue root	Oropharyn x, right tonsil, periphera l and retroperi toneal LN
Subtype	GCB- type	Non-GCB	Non-GCB	Non-GCB	Non-GCB

At the time of DLBCL diagnosis (table 1- continuation)

Patient	1	2	3	4	5
Age, y	82	32	69	35	66
WBC $\times 10^9$/L	5,53	6,23	10,25	0,84	30,27
Hemoglobin, g/dL	12,4	11,6	10,7	6,6	14,0
Platelet $\times 10^9$/L	178,0	294,0	120,0	41,0	331,0
Bone marrow lymphocytes, %	21	44	17.2	8.2	55
IGHV mutation status	not possible to establish	Unmutated	Unmutated (CLL1 subgroup)	not possible to establish	Unmutated
FISH	Normal	Normal	Normal	Normal	Deletion of 17p13/TP5 3
Mutation TP53	No mutations	No	No	No	Mutation p.R248W in exon 7
Mutation NOTCH1	-	Mutation c7544	No	No	Mutation c 7389
p53/PDL-1 expression	+/+	-	+++/+ ++	++/++	+++/+ ++
Related with CLL	De novo	unknown	clonally related	clonally related	clonally related
Duration of acalabrutinib therapy, months	27	20	15	9	10
Best response	PR	CR	Clinical benefit	Stable disease	PR
Status at most recent follow-up	Acalabrutinib therapy continues	Acalabrutinib therapy continues	Death from the progression of DLBCL	Death by COVID19	Acalabrutinib therapy continues

Summary/Conclusion:

Our experience suggests that acalabrutinib in combination with immunochemotherapy has potential as a novel therapeutic approach for patients with Richter syndrome.

Keywords: Chronic lymphocytic leukemia