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Chemotherapy-free regimens for Richter transformation: a bridge, but not yet a destination

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Richter transformation (RT) is an aggressive histologic transformation of chronic lymphocytic leukemia (CLL), most commonly to diffuse large B-cell lymphoma (DLBCL), and is characterized by dismal long-term outcomes.[1] Conventional treatment for RT includes chemoimmunotherapy such as R-CHOP, largely adopted from DLBCL regimens, which yield only modest complete response rates, and overall survival (OS) is less than 12 months.[2] Furthermore, the older age and associated comorbidities that accompany patients with RT often preclude consolidation with allogeneic stem cell transplantation (allo-SCT), further limiting the chances of durable remissions. Thus, effective and tolerable treatment strategies remain a significant unmet need for this high-risk population. Previous data have demonstrated that the incorporation of targeted agents, including Bruton's tyrosine kinase (BTK) inhibitors and B-cell lymphoma (BCL)-2 inhibitors for RT can yield responses of 50-60% with progression-free survival (PFS) of around 10 months in the frontline setting.[3-6]

Here, Tadmor et al present the results of a phase II, open-label, single-arm, multicenter investigator-initiated trial evaluating fixed duration obinutuzumab, ibrutinib, and venetoclax (GIVe-RS) for patients with RT.[7] Patients received 6 cycles of obinutuzumab, ibrutinib at a dose of 560 mg daily initiated on day 1 of cycle 1, with venetoclax ramp-up initiated on cycle 1 day 15 up to 400 mg daily continuously through cycle 12. The study enrolled 12 patients with a median age of 78 years (range, 52 – 85 years) at the time of RT diagnosis. A total of 3 patients had received prior therapy for CLL, all being chemoimmunotherapy, 8 patients were treatment naïve for RT, and 4 patients had relapsed and/or refractory (R/R) RT following treatment with prior R-CHOP based regimens. The median interval from CLL diagnosis to transformation was 66 months. Genomic characteristics were available for a subset of patients; 5/7 patients (71%) had IGHV unmutated CLL, while no *TP53* mutations (0/5 tested) or del(17p) (0/7 tested) were identified. The clonal relationship between CLL and RT was not reported.

The 3-month overall metabolic response (OMR) and complete molecular response (CMR) rates per Lugano 2014 criteria among the 10 evaluable patients were 70% and 40%, respectively, with corresponding 6-month rates among 8 evaluable patients of 37.5% and 25%, respectively. The median PFS was 4.4 months with a median OS of 7.8 months. At last follow-up, 10 patients (80%) have died, with the causes of death attributable to progressive disease, severe diarrhea, infection, neurological deterioration, and acute myeloid leukemia. The treatment-emergent adverse events were consistent with the given regimen, most notably hematologic (40-50% incidence of neutropenia or thrombocytopenia), diarrhea, and rash. Notably, cardiovascular events were uncommon.

While the GIVe-RS regimen demonstrated the ability to induce early metabolic responses in a moderately pre-treated and elderly population, the duration of remission was limited. The strengths of this study include demonstrating the feasibility of

administering a chemotherapy-free regimen in an elderly population, and importantly, these data contribute to an area where prospective data have been limited and are much-needed. The median age of 78 years for the patients in this trial particularly makes this a challenging patient population due to the potential for toxicities. Additionally, the only known curative modality for RT, namely allo-SCT, is not feasible for the majority of patients in this age group.

These findings should be interpreted in the setting of the emerging data with non-chemotherapy treatment options for patients with RT (Table 1). A recent phase II study evaluated pirtobrutinib, venetoclax and obinutuzumab in 15 patients (median age, 70 years) with RT who were either previously treated for CLL or RT. With this regimen, the overall response rate (ORR) per Lugano was 80%. The 12-month PFS and OS rates were 80% and 86%, respectively. The safety of this regimen was comparable to other triplet combination regimens. Notably, all 12 responding patients had ongoing remission at 12 months.[8]

While cross trial comparisons are fraught with significant limitations, these data may suggest that while chemotherapy-free strategies are feasible, their success may not be uniform. Additional emerging data further supports the growing efforts to explore chemotherapy-free and immunotherapy-based approaches in RT. The combination of the PD-1 inhibitor tiselizumab and zanubrutinib demonstrated an ORR of 58% with a median PFS of 10 months in a cohort of 48 predominantly frontline RT patients.[5] Similarly, the PD-L1 inhibitor atezolizumab in combination with venetoclax and obinutuzumab led to an ORR of 68% and median PFS of 10 months in 28 patients in the frontline setting.[6] A recently published analysis of duvelisib, an oral PI3K- δγ inhibitor, plus venetoclax in patients with either R/R CLL or RT demonstrated an ORR of 50% in 4 of the 8 evaluable patients with RT, a median PFS of 2.6 months, and median OS of 9.2 months.[9] Additional agents, including epcoritamab, a CD3xCD20 bispecific antibody, are being explored, with the EPCORE-CLL-1 trial demonstrating ORR of 48% in 42 patients receiving epcoritamab monotherapy as either frontline or salvage therapy, with a median PFS of about 3 months.[10] Glofitamab, another CD3xCD20 bispecific antibody was investigated in 11 patients with R/R Richter with 64% ORR and median PFS of 3.5 months.[11] Lastly, chimeric antigen receptor (CAR) T-cell therapy has also been explored in patients with R/R RT, where in a multicenter, retrospective analysis, the ORR was 63% with a median PFS of 4.7 months; modest in comparison to outcomes seen in de novo large B-cell lymphomas.[6] Lastly, a Center for International Blood and Marrow Transplant Research (CIBMTR) registry study demonstrated 2-year PFS and OS rates of 33% and 47%, respectively, in a cohort of 140 patients with R/R RT treated with commercial CAR T-cell therapy.[12]

Ultimately, the present study by Tadmor et al supports the use of a chemotherapy-free approach for patients with RT, especially in older adults where chemoimmunotherapy

may not be well tolerated, demonstrating tolerability and the ability to lead to early remissions. While the durability of response remains a major challenge, more potent, emerging regimens may hopefully bridge this gap. Continued efforts are needed to develop and optimize chemotherapy-free regimens in a manner which will maximize both tolerability and efficacy for patients with historically poor outcomes and limited treatment options.

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Table 1. Chemotherapy-Free Regimens in Richter Transformation

Trial/Regimen	N	Median age (range)	ORR (%)	% allogeneic Transplanted	PFS median or PFS %	OS median or OS %
GIVe-RS (Obinutuzumab, ibrutinib, venetoclax	12 (frontline RT, n=8; R/R RT, n=4)	78 (62-87)	70	8	4.4 months	7.8 months
Pirtobrutinib, venetoclax, obinutuzumab	15 (frontline RT, n=5; R/R RT, n=10)	70 (48-81)	80	20	80% (12-month)	86% (12-month)
Nivolumab and ibrutinib	24 (frontline RT=14; R/R RT n=10)	65 (47-88)	42	17	NR (median DOR 15 months for responding patients)	13 months
Tislelizumab and zanubrutinib	48 (frontline RT, n=38; R/R RT, n=10)	67 (45-82)	58	19	10 months	75% (12-month)
Atezolizumab, venetoclax, obinutuzumab	28 (all frontline RT)	70 (32-81)	68	11	43% (12-month)	64% (12-month)
Duvelisib and venetoclax	9 (both frontline and R/R RT included)	65 (55-72)	50	13	2.6 months	9.2 months
Pirtobrutinib	82 (frontline RT n=8; R/R RT n=74)	67 (59-72)*	50	10	3.7 months	12.5 months
Epcoritamab	42 (frontline RT, n=21; R/R RT, n=21)	69 (50-80)	48	17	3 months	13 months
Glofitamab	11 (R/R RT)	71 (48-77)	64	NR	3.5 months	3.5 months

*reported as IQR

ORR: Overall response rate; PFS: Progression-free survival; OS: Overall survival; DOR: Duration of response; NR: Not reported