COMMENTARY

TO THE EDITOR:

Clinical activity of axicabtagene ciloleucel in adult patients with Richter syndrome

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Aggressive lymphoma arising in the setting of underlying chronic lymphocytic leukemia (CLL), known as Richter syndrome (RS), is associated with poor outcomes with current standard-of-care therapies, particularly among patients with clonally related disease, prior ibrutinib treatment, and complex karyotype (CK).1,2 In our institutional experience, the median overall survival following RS diagnosis was only 5.9 months, with <40% of patients achieving an objective response to anthracycline-based chemoimmunotherapy.2 Two anti-CD19 chimeric antigen receptor (CAR) T-cell (CAR-T) therapies, axicabtagene ciloleucel (axi-cel) and tisagenlecleucel, are approved by the US Food and Drug Administration (FDA) for relapsed/refractory diffuse large B-cell lymphoma (DLBCL) or high-grade B-cell lymphoma. Both provide durable disease control in roughly 50% of patients, including cases of chemorefractory disease.3,4 Although anti-CD19 CAR-T therapy was first studied in CLL and achieves an antitumor response in some cases, response rates in CLL are lower compared with DLBCL, which may be explained by CLL-induced impairment in T-cell fitness and persistence.5,6 Owing in part to concerns related to CLL-induced immune dysfunction, patients with RS were excluded from the pivotal trials of axi-cel and tisagenlecleucel in DLBCL,3,4 and literature regarding the efficacy of approved CAR-T products in patients with RS is lacking. Herein, we describe the experience of our institution of treating patients with RS with commercial axi-cel.

After obtaining institutional review board approval, we identified 9 patients treated at our center for RS with axi-cel between 1 January 2019 and 15 May 2020. Baseline patient and disease characteristics along with subsequent clinical course were obtained from the electronic medical record by review of progress notes, pathology reports, and imaging studies. Cytokine release syndrome (CRS) and immune effector cell–associated neurotoxicity syndrome (ICANS) were graded and reported using American Society for Transplantation and Cellular Therapy (ASTCT) Consensus Grading as standard practice at our center7 and responses were assessed according to the 2014 Lugano Classification.8 The timing of response evaluation was in accordance with institutional practice: computed tomography (CT) imaging was performed ~30 days and positron emission tomography imaging ~90 days after axi-cel infusion. Commercial axi-cel was administered off-label.

Baseline patient characteristics (Table 1) included a median age of 64 years (range, 40-77 years) and a median of 4 (2-6) prior lines of therapy for CLL and/or RS. Eight patients had prior acalabrutinib or ibrutinib treatment: of these 8 patients who had received Bruton tyrosine kinase inhibitor (BTKi), 5 also received prior venetoclax, 1 patient had prior programmed cell death protein 1 inhibitor therapy, and 1 patient had previously received anti-CD19 CAR-T therapy in an investigational trial for CLL. Five patients were previously treated with anthracycline-based chemoimmunotherapy for RS. Five cases of RS were clonally related as assessed by IGH gene polymerase chain reaction testing; in the remaining cases, clonality was unable to be assessed. High-risk features included deletion 17p in 3 patients, CK in 6 patients, and MYC gene rearrangement in 4 patients. Molecular testing was available for 5 patients and revealed pathogenic TP53 mutations in 2 patients and a pathogenic NOTCH1 mutation in 1 patient.

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Table 1. Patient characteristics

| Pt no. | Age, y | Time: CLL Dx to RS, mo | Histology | Pertinent genetic aberrations by FISH | IGHV mutational status | Clonally related | Most recent prior line of Tx* | Time on BTKi prior to leuakapheresis, d | Time from RT diagnosis to leuakapheresis, d | Concurrent BTKi | Disease status at leuakapheresis | Max CRS grade | Max ICANS grade | Grade 3/4 events | Best response (Lugano) | Time to best response, d | Follow-up, d | Clinical status |
|--------|--------|------------------------|-----------|-------------------------------------|------------------------|---------------------|-----------------------------|----------------------------------------------|---------------------------------------------|----------------|-----------------------------|---------------|----------------|----------------|------------------------|------------------------|-----------------|-----------------|
| 1      | 50     | 24                     | Non-GCB   | Del(13q)                            | Yes                    | Unable to assess      | Unable to assess           | 3 RDHAP/RDHAX                            | N/A                                  | 1111           | No             | PR            | 1           | 4           | No            | CR              | 72                  | 345             | Ongoing CR     |
| 2†     | 46     | 38                     | Non-GCB   | Del(11q), MYC                        | Yes                    | Unmutated            | Unable to assess           | 6 BTKi                                    | 51                                      | 182            | Yes#           | PD            | 2           | 4           | No            | CR              | 92                  | 206             | Received consolidation with MUD PBSCT, with ongoing CR |
| 3      | 64     | 197                    | Non-GCB   | del(13q), del(17q), del(17p)         | Yes                    | Unmutated            | Yes                        | 5 BTKi                                    | 24                                      | 50             | Yes            | PR            | 2           | 0           | No            | CR              | 93                  | 210             | Ongoing CR, continues on BTKi |
| 4      | 76     | 89                     | HGBCL     | del(11q), del(13q), del(17q)         | Yes                    | Unable to assess      | Unable to assess           | 3 REPOCH                                  | 3                                      | 119            | Yes            | PD            | 1           | 0           | Yes           | PR              | 107                 | 210             | Relapsed disease at day 201 |
| 5      | 70     | 109                    | Non-GCB   | MYC                                 | Yes                    | Unmutated            | Yes                        | 3 BTKi                                    | 98                                      | 124            | Yes(§)         | PD            | 4           | 3           | Yes           | N/A             | N/A             | 49               | Died of infection |
| 6      | 72     | 36  Non-GCB             | del(11q)  | Not done                            | Mutated                | Yes                    | 2 BTKi                      | N/A                                      | 30                                      | 217            | Yes(§)         | SD            | 2           | 1           | Yes           | PR              | 64                   | 183             | Ongoing PR, continues on BTKi |
| 7      | 40     | 131                    | Non-GCB   | MYC                                 | Not done               | Mutated                | Unable to assess           | 5 REPOCH                                  | N/A                                      | 120            | Yes(§)         | SD            | 2           | 0           | No            | PR              | 37                   | 155             | Ongoing PR      |
| 8      | 63     | 157                    | GCB       | None                                | Not done               | Unmutated             | Yes                        | 4 REPOCH                                  | 120                                     | 143            | Yes            | PD            | 1           | 0           | No            | CR              | 81                   | 86              | Ongoing CR, continues BTKi |
| 9      | 69     | 117                    | HGBCL     | Del(17p)                            | Not done               | Unmutated             | Yes                        | 5 REPOCH                                  | N/A                                      | 215            | No            | PR            | 1           | 0           | No            | CR              | 92                   | 93              | Ongoing CR      |

BTKi, Bruton tyrosine kinase inhibitor; CR, complete response; del/Del, deletion; Dx, diagnosis; FISH, fluorescent in situ hybridization; GCB, germinal center B; HGBCL, high-grade B-cell lymphoma; IGHV, immunglobulin heavy chain variable region; Max, maximum; MUD PBSCT, matched unrelated donor peripheral blood stem cell transplant; MYC, MYC gene rearrangement; N/A, not applicable; PD, progressive disease; PR, partial response; Pt, patient; RDHAP, rituximab, dexamethasone, cytarabine, cisplatin; RDHAX, rituximab, dexamethasone, cytarabine, oxaliplatin; REPOCH, rituximab, etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin; SD, stable disease; Tx, treatment.

*Denotes prior line of therapy immediately preceding leukapheresis.
†Patient received prior CAR T therapy for CLL before developing RS.
‡Stopped BTKi when patient received MUD PBSCT.
§Stated BTKi 5 days after ari-cel due to toxicity.
¶Stopped on BTKi after leukapheresis and continued.
||Started on BTKi after leukapheresis stopped prior to ari-cel infusion.
The patient ultimately died due to complications of acute respiratory and bacteremia, and subsequent acute respiratory distress syndrome.

The hospital course was complicated by ICANS requiring repeated tocilizumab administration and developed grade 3 ICANS on day 16 requiring high-dose corticosteroids. This patient’s hospital course was complicated by Enterococcus faecalis pneumonia and bacteremia, and subsequent acute respiratory distress syndrome. The patient ultimately died due to complications of acute respiratory distress syndrome on day +49 with no formal assessment of response to therapy. Chest CT scans performed on day +31 demonstrated resolution of prior lymphadenopathy including a large (previously 6 x 4 cm) retrocrural lymph node conglomerate. On autopsy, the largest visible lymph node measured 3 cm in diameter; on histopathologic examination of the lymph node, necrotic tissue without viable lymphoma cells was seen.

Eight patients underwent formal response assessment. All evaluable patients achieved an objective response including 5 patients with complete response (CR) and 3 patients with PR as best response (Figure 1). Response assessment was by positron emission tomography in 7 patients; 1 evaluable patient was assessed by CT scan only (patient 6, classified as PR). The median follow-up was 6 months (range, 2.8-11.3 months). One case of disease progression was observed (patient 4), with the remaining 7 patients in remission at last follow-up. One patient (patient 2) whose CLL was refractory to ibrutinib and venetoclax, and whose recent relapse occurred following CAR-T infusion, and when performed was not done in a uniform manner. Hence, CLL response to therapy could not be determined.

Data regarding the efficacy of anti-CD19 CAR-T therapy in RS are limited and with commercially available agents are very limited. A study reported by Cruz et al included 2 patients with RS treated with allogeneic (donor-derived) CAR-Ts; 1 PR was observed with progression within 2 months of treatment. In an early study of axi-cel at the National Cancer Institute, 1 patient with RS was included and achieved a PR but progressed after 1 month. Finally, Turtle et al conducted a study of the anti-CD19 CAR-T product JCAR017 in 24 patients with relapsed/refractory CLL, including 5 patients with
RS. Of the 5 patients with RS, best response was CR in 2 patients, PR in 1 patient, and progressive disease in 2 patients.12

To our knowledge, this is the largest published cohort of patients with RS treated with a commercial anti-CD19 CAR-T therapy. Prior reports on the efficacy of anti-CD19 CAR-T therapy in RS, although limited by small numbers, suggest either lack of response or brief duration of response. We observed encouraging response rates with axi-cel in patients with RS, including 1 case of deepening response with ongoing follow-up; however, the short duration of follow-up limits evaluation of long-term durability of response. In our series, 7 patients received a BTKi concurrent with axi-cel therapy. Preclinical evidence supports enhanced ex vivo CAR-T expansion in CLL patients receiving BTKi treatment, and improved CAR-T engraftment and tumor clearance with BTKi continuation after CAR-T infusion in murine models; prospective clinical data support the safety of this combination.13-16 Whether concurrent BTKi treatment contributed to successful CAR-T manufacturing and/or efficacy in our study cannot be determined due to heterogeneity in this series regarding the administration of BTKi. Prospective study is warranted to determine the optimal timing of BTKi treatment in the context of CAR-T therapy for RS and to develop strategies to mitigate potential toxicity. In conclusion, further study is warranted to evaluate the efficacy of anti-CD19 CAR-T treatment in RS given these promising results and the lack of effective standard therapies.

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