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CASE REPORT

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Immunotherapy beyond cellular therapy in follicular lymphoma: A case of complete remission after failure of two CAR-T

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Abstract

Patients with relapsed follicular lymphoma who do not respond to CAR-T have a poor outcome. We present a case of refractory follicular lymphoma who relapsed after two CAR-T infusions and achieved a complete remission after treatment with obinutuzumab and lenalidomide. This represents a promising treatment option in the post-CAR-T setting.

KEYWORDS

CAR-T, follicular lymphoma, immunotherapy, lenalidomide, obinutuzumab

1 | INTRODUCTION

Follicular lymphoma is the most common indolent non-Hodgkin lymphoma, which is known for its relapsing-remitting disease course with 20% of patients developing progression of disease within 2 years of chemoimmunotherapy.[1] The treatment for relapsed follicular lymphoma includes combinations of chemoimmunotherapy, immune modulators, and hematopoietic stem cell transplant. More recently, chimeric antigen receptor T-cell therapy (CAR-T) has demonstrated impressive activity in the relapsed/refractory setting leading to the FDA approval of axicabtagene ciloleucel in February 2021 for relapsed or refractory follicular lymphoma.[2] Patients not responding to CAR-T or relapsing soon after treatment have a poor outcome.[3] The optimal treatment for such CAR-T treatment failure remains unclear. Here, we present a case of relapse refractory follicular lymphoma who relapsed after multiple lines of chemoimmunotherapy including two CAR-T infusions, who then achieved a complete remission after treatment with obinutuzumab and lenalidomide.

2 | CASE REPORT

The patient is a 73-year-old woman who was diagnosed with stage IVA follicular lymphoma in 2000. Over a period of 20 years, she received the following treatments with variable responses (Table 1), including: cyclophosphamide, vincristine, and prednisone, followed by multiple rounds of rituximab, targeted radiation, a clinical trial with everolimus, single agent lenalidomide, an oral PI3K

TABLE 1 Treatment history demonstrating duration of treatment, progression-free survival and best treatment response

Treatment	Duration of treatment	Progression-free survival (months)	Treatment response
CVP	6 cycles	16	Partial response
Rituximab (start 8/9/2001)	8 cycles	31	Complete response
Rituximab (start 4/2004)	5 cycles	15	Partial response
Radiation therapy	2000 cGy in 10 fractions	1	Stable disease
Everolimus trial (start 1/2007)	12 months	12	Stable disease
Lenalidomide start 9/27/2010)	5 months	5	Partial response
Rituximab (start 2/2011)	8 cycles	11	Stable disease
Lenalidomide (start 1/2012)	28 months	28	Complete response
PI3K delta Inhibitor trial (6/2014)	6 months	6	Partial response
Gemcitabine and Oxaliplatin (start 12/30/2014)	7 cycles	19	Partial response
Axicabtagene ciloleucel (9/2018)	N/A	20	Complete response
Axicabtagene ciloleucel (6/2020)	N/A	2	Partial response
BCL-2 inhibitor trial	2 weeks	0	No response
Obinutuzumab and Lenalidomide	5 cycles	Ongoing (>6)	Complete response
Lenalidomide maintenance	Ongoing	Ongoing (>6)	Complete response

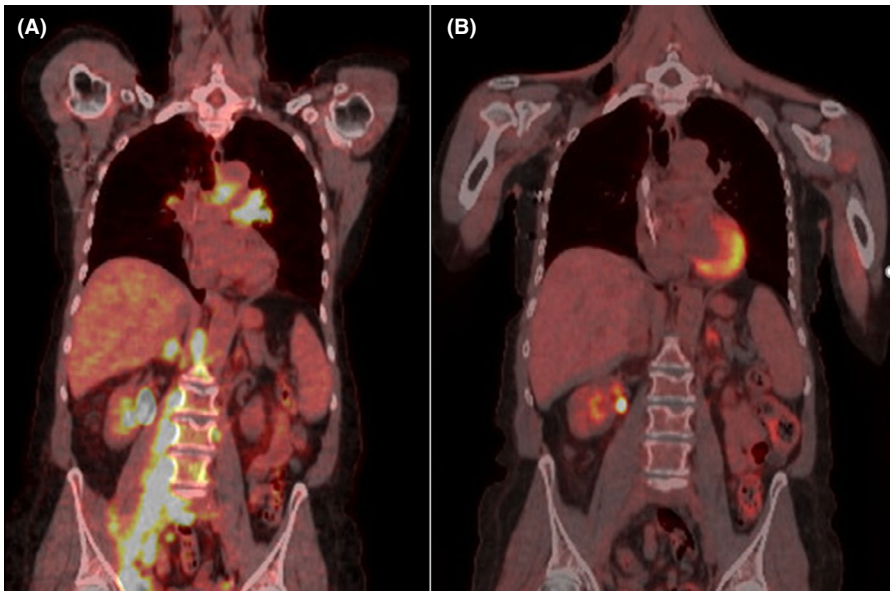

FIGURE 1 (A) FDG-PET scan demonstrating extensive hypermetabolic soft tissue activity involving the mediastinal bilateral hilar node chains with extensive confluent mesenteric, retroperitoneal, pelvic and inguinal lymph node disease. (B) Post-treatment FDG-PET demonstrating complete remission

delta inhibitor on a clinical trial and rituximab plus gemcitabine with oxaliplatin. Despite all these therapies, she continued to progress. She was enrolled in ZUMA-5 clinical trial for treatment with axicabtagene ciloleucel CAR-T and obtained a complete remission that lasted for approximately 1.5 years. At relapse, she underwent a second CD19 CAR-T in June 2020 and had florid progression of disease just 2 months later in August 2020 (Figure 1A). She briefly enrolled on a clinical trial with a novel BCL-2 inhibitor but had rapid disease progression within few days. In October 2020, she was started on obinutuzumab and lenalidomide. The dose of lenalidomide had to be reduced from 20 mg (days 1–21) to 5 mg (days 1–14) due to thrombocytopenia. A PET scan was obtained to assess response to treatment after 2 months and revealed radiologic complete remission. Ongoing surveillance, PET scan (Figure 1B) in April 2021, showed continued remission, consistent with a 6-month durable radiologic complete remission after 5 cycles of obinutuzumab and lenalidomide two weeks on one week off.

3 | DISCUSSION

Relapsed follicular lymphoma can be treated with a variety of modalities including chemoimmunotherapy,

immune modulators, hematopoietic stem cell transplant and CAR-T (Table 2). Rituximab has been studied in heavily pretreated and in patients who had previously responded to rituximab and resulted in overall response rate (ORR) 40% and complete response (CR) in 11% of patients.[4] Chemotherapy can also be added to monoclonal antibodies in patients with untreated and relapsed follicular lymphoma to achieve an improved overall survival compared to patients with chemotherapy alone.[5] In the GADOLIN trial, rituximab refractory indolent non-Hodgkin lymphoma was treated with obinutuzumab plus bendamustine. In the intention-to-treat group the median progression-free survival was 25.8 months and 14.1 months, in the combination and monotherapy arms, respectively.[6] Combination was given for 6 cycles followed by maintenance obinutuzumab every 2 months for 2 years until progression. Immune modulators have also been incorporated into these regimens. Lenalidomide can be combined with rituximab or obinutuzumab for early or late relapse. In the AUGMENT trial, patients received lenalidomide or placebo for 12 cycles plus rituximab weekly.[7] The median PFS was improved from 14 months to 39 months. Obinutuzumab was combined with lenalidomide after rituximab-containing therapy in a phase Ib trial with 63% of patients achieving a response, as seen in this patient.[8] While these regimens have a higher toxicity profile, combining these agents in patients with a good performance status appears to be beneficial.

The recent approval of axicabtagene ciloleucel for the treatment of relapsed or refractory follicular lymphoma after two prior lines of therapy was based on the results of a ZUMA-5, which demonstrated 80% complete response rate and 12 month durable response of 72%.[2] This offers an effective treatment option for patients who develop refractory disease. However, treatment after disease progression following CAR-T is unclear and provides an opportunity for further investigation. With the CAR-T FDA approval occurring after two lines of treatment, patients with relapsed follicular lymphoma will be receiving this therapeutic modality earlier in their disease course, which opens the door for re-treatment with previous used regimens or unused combinations guided by mechanisms of treatment failure. The mechanisms of CAR-T treatment failure have been divided into three categories including tumor intrinsic factors (i.e., loss of CD19 epitope), other host factors (i.e., negative regulatory pathways, high tumor burden) and inadequacies of the CAR-T cell.[9] Clinical trials are ongoing to overcome these mechanisms of treatment failures including targeting programmed death-ligand 1/programmed cell death protein 1. A phase I/II trial is underway using pembrolizumab in patients failing to respond to CD19 CAR-T or relapse after CAR-T.[10]

TABLE 2 Response rates and outcomes for the treatment of relapsed or refractory follicular lymphoma

Regimen	Overview	Overall response rate	Survival outcomes
Single agent Rituximab[4]	Low tumor burden, poor performance status, slowly progressive	66% (initial) 40% (re-treatment)	mPFS: 21 months (initial) mPFS: 18 months (re-treatment)
Rituximab + Chemo[a] [5]	First relapse, or late relapse	RR 1.28 favoring R-chemo	HR for mortality: 0.63 2 years OS: 90%
Obinutuzumab + Bendamustine[6]	Rituximab refractory	57%	mPFS: 25.8 months
Anti-CD20 + lenalidomide[7,16]	Late or early relapse	65%–77%	mPFS: 39 months mTTP: 24 months
Lenalidomide[16]	Late or early relapse	53%	mTTP: 13.2 months
Idelalisib[17]	After two prior therapies	57%	mPFS: 11 months
Tazemetostat[18]	EZH2 mutation in first relapse	69%	mPFS: 11 months
Autologous HSCT[19]	Early treatment failure	78%	5 years OS 73%
Axicabtagene ciloleucel[2]	After two prior therapies	95%	12 month DOR: 71.7%
Pembrolizumab[b] [10]	After failed CAR-T	27%	n/a
Lenalidomide +/-anti-CD20[b] [15]	After failed CAR-T	63.6% (within 15 days of CAR-T infusion) 18.8% (15 days after CAR-T infusion)	n/a

Abbreviations: DOR, duration of response; HR, hazard ratio; mPFS, median progression-free survival; mTTP, time to progression; n/a, not available.

[a]CHOP, CNOP, CVP, FCM, MCP.

[b]Includes multiple subtypes of lymphoma including DLBCL, primary B-cell lymphoma, transformed follicular.

Of the 11 patients, 2 patients had partial response and 1 CR suggesting benefit that could be the result of altering CAR-T-cell exhaustion, or immunosuppressive tumor microenvironment.

Lenalidomide has been investigated for the treatment of lymphoma based on its direct antineoplastic effects on malignant B-cells, and cytotoxicity mediated by T cells and NK cells.[11] The malignant B-cell effects of lenalidomide are shown through its ability to regulate cyclin dependent kinases decreasing cellular proliferation, down regulation of programmed death-ligand 1, and AKT inhibition all resulting in antineoplastic and antiproliferation. Lenalidomide combats cancers ability to evade the immune system, a key defensive mechanism. While lymphoma cells induce impaired immune synapse formation and effector function impacting antigen presentation, lenalidomide has been shown to repair this immune synapse formation in an Ex vivo model,[12] thereby enhancing T-cell-mediated cytotoxicity. Additional improvement in cellular cytotoxicity can be seen with lenalidomide's impact on NK cell activity. In patients treated with lenalidomide, NK cell number and activity were increased resulting in enhanced antibody dependent cellular cytotoxicity (ADCC) and NK cell induced cytotoxicity.[13] With understanding the mechanisms of action, lenalidomide has been combined with other agents to achieve synergistic activity. When the anti-CD20 monoclonal antibody, rituximab, is used as an antineoplastic agent it results in the direct induction of apoptosis and ADCC. When lenalidomide is combined with rituximab it results in enhanced apoptosis via upregulation of c-Jun N-terminal protein kinase phosphorylation and activating the mitochondrial derived apoptotic pathway.[14] This combined therapy was performed in mantle cell lymphoma mouse models and resulted in synergistic activity causing decrease tumor burden by two fold and improved survival time compared to single agents.[14]

Lenalidomide success in the post-CAR-T setting has been demonstrated in a small cohort of patients presented at the 2020 American Society of Hematology by Dr. Thieblemont et al. Eleven patients with varying lymphoma subtypes who progressed within 15 days post-CD19 CAR-T infusion were treated with lenalidomide with or without rituximab or with obinutuzumab.[15] An ORR of 63.6% was observed with a CR of 36.4%. Response rates with lenalidomide were also seen in patients who progressed/relapsed after 15 days from CAR-T infusion with an ORR of 18.8% and CR of 10.4%. In addition to response, patient's receiving lenalidomide also had a higher CAR-T expansion in the blood. These results with lenalidomide are promising based on its antitumor response and immunomodulatory impact, mechanisms which are necessary as patient's progress after CAR-T. The response rate in this cohort as well as our case presented here is likely the combined result of the synergistic activity of lenalidomide plus anti-CD20 monoclonal antibody in addition to lenalidomides immune modulatory effects, which aid in cellular cytotoxicity and achieving a durable response.

4 | CONCLUSION

The complete remission seen in this patient suggests the use of lenalidomide with obinutuzumab could be used in follicular lymphoma in the post-CAR-T setting, analogous to published data with other lymphoma subtypes. With CAR-T being an approved third line option for follicular lymphoma, further research is warranted to determine appropriate sequencing of agents leading up to CAR-T and post-CAR-T failure in order to optimize survival outcomes. With lenalidomide's T-cell and antitumor effects, begs the question of where this agent should be in the sequence of treatments? Whether it is included as therapy pre-CAR-T, maintenance post-CAR-T, or salvage post-CAR-T, still requires further investigation. While confirmation in a large clinical trial is needed, lenalidomide plus obinutuzumab could be considered as a treatment option in patients with follicular lymphoma who progress/relapse post-CAR-T.

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CONFLICT OF INTEREST
The authors have no conflicts of interests.

AUTHOR CONTRIBUTIONS
Adam Kase contributed to conceptual design and drafting the manuscript; Mohamed Kharfan-Dabaja provided critical analysis and revisions; Andrew Donaldson provided revisions; Jamie Elliott provided revisions; Taimur Sher provided conceptual design of manuscript, critical analysis, and revisions.

ETHICAL APPROVAL
Patient consent was obtained for the publication of this case report.

CONSENT
Written informed consent was obtained from the patient to publish this report in accordance with the journal's patient consent policy.

DATA AVAILABILITY STATEMENT
The data that support the findings of this study are not publicly available due to privacy or ethical restrictions.

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