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Research Letter

Combining Obinutuzumab With Radiation for Refractory DLBCL: Retrospective Safety and Efficacy Analysis

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Purpose: Approximately 30% of patients with diffuse large B cell lymphoma (DLBCL) will develop relapsed or treatment-refractory disease after primary chemotherapy. Patients unable to undergo aggressive chemotherapy and stem cell transplant or chimeric antigen receptor T-cell (CAR T-cell) therapy have limited treatment options. Here, we investigated the safety and efficacy of combining obinutuzumab with cytoreductive radiation to all areas of disease in patients with relapsed DLBCL.

Methods and Materials: A retrospective review of patients with treatment refractory DLBCL was performed. All patients were treated with external beam radiation to all sites of refractory disease with concurrent and adjuvant obinutuzumab. Toxicities were evaluated based on Common Terminology Criteria for Adverse Events v5.0 criteria. Kaplan-Meier analysis was used to calculate progression-free survival and overall survival.

Results: Between 2016 and 2022, 7 patients with refractory DLBCL were treated with concurrent radiation and obinutuzumab. No grade 3 or greater treatment-related toxicity was observed. Four of the 7 patients had a complete response at the radiated site on first postradiation imaging. The median progression-free survival and overall survival were 30 months.

Conclusions: In this small cohort of treatment-refractory patients with DLBCL, the combination of radiation and obinutuzumab was well tolerated without excessive treatment-related toxicity. The combination resulted in durable disease control with a prolonged overall survival without additional treatment in a subset of patients.

Introduction

Approximately 30,000 new cases of diffuse large B cell lymphoma (DLBCL) are diagnosed annually in the United States.[1] Between 30% to 40% of these patients will relapse after chemotherapy or will develop treatment-refractory disease to primary chemotherapy.[2] Treatment options for these patients include salvage chemotherapy with stem cell transplantation or chimeric antigen receptor T-cell (CAR T-cell) therapy.[3-7] However, survival outcomes for these patients remain poor, with 5-year overall survival (OS) of 20% to 40%.[8,9] Radiation therapy can be employed to bridge patients to systemic salvage treatments. Alternatively, radiation to areas of active residual disease can be combined with salvage chemotherapy before stem cell transplant (SCT) to improve response to

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therapy.[10-12] A significant proportion of patients with relapsed or refractory disease are not eligible for SCT, and CAR-T cell therapy can be used in these patients.[2,13] The process of collecting and preparing CAR-T therapy involves a 2- to 5-week window. Radiation also may be used as a bridging therapy in these patients to minimize risk of further progression and cytoreduce the overall bulk of disease before CAR-T administration.[14,15]

Obinutuzumab is a glycoengineered type II anti-CD20 antibody.[16] It builds upon the success of rituximab, a type I CD20 antibody approved for first-line treatment of CD20-positive malignancies. Type II antibodies induce cell death via direct cell death pathways outside of those used by type I antibodies.[17] Therefore, obinutuzumab has been employed for rituximab-refractory disease and as first-line therapy for indolent non-Hodgkin lymphomas, with prospective trials showing a significant improvement in progression-free survival (PFS) compared with standard of care in these patients.[18,19] However, the role of obinutuzumab in treatment of refractory DLBCL is less clear. A small phase II study showed a best overall response rate of 37% for obinutuzumab in rituximab-refractory or relapsed DLBCL.[16] The median response duration was 9.8 months in this study. Overall, obinutuzumab was well tolerated in this study, with 13 of 40 patients experiencing any grade 3+ toxicity and no treatment-related deaths.[16] Data combining radiation and obinutuzumab in this patient population are lacking, and the safety of concurrent radiation and obinutuzumab has not been reported. Here, we present a small case series of patients treated with combined obinutuzumab and radiation for treatment-refractory DLBCL.

Methods and Materials

After institutional review board approval, a retrospective review of patients with treatment- refractory DLBCL was performed. All patients were treated with external beam radiation to all sites of refractory disease with concurrent and adjuvant obinutuzumab. Patients were treated with obinutuzumab every 21 days, with 1600 mg on days 1 and 8 of cycle 1, followed by 800 mg on day 1 for 8 total cycles or until progression.

Data analysis

Follow-up imaging was reviewed to assess disease response at the irradiated site. Radiographic response was assessed on first postradiation computed tomography or positron emission tomography-computed tomography imaging. All imaging was obtained within 1 to 3 months of completing radiation and before additional therapy. PFS and OS were calculated from date of radiation completion to time of progression or death by Kaplan-Meier method. Patients were censored at last follow-up. Planned CAR-T or stem cell transplant was not considered progression if treatment was planned before initiating radiation. Toxicities were evaluated based on Common Terminology Criteria for Adverse Events v5.0 criteria. Statistical analysis was performed in Prism and JMP software.

Results

Between 2016 and 2020, 7 patients were treated with concurrent obinutuzumab and radiation for treatment-refractory DLBCL. Patient characteristics are shown in Table 1. The median age was 67 (range, 52-82). All patients had DLBCL, with 2 patients having transformed disease from prior follicular lymphoma. One patient had double hit DLBCL (BCL2 and MYC rearrangements), and 1 patient had triple hit DLBCL (BCL2, BCL6, MYC rearrangements). The median number of prior systemic therapies was 2 (range, 1-4). Four patients initially were

Table 1 Patient and treatment characteristics

Age	Median	67
	Min	52
	Max	82
Number of obinutuzumab cycles	Median	4
	Min	2
	Max	8
Radiation dose (Gy)	Median	44
	Min	30
	Max	50
Prior lines of systemic therapy	Median	2
	Min	1
	Max	4
Initial systemic treatment		
R-CHOP	N	4
R-CVP	N	1
R-DA EPOCH	N	2
Prior autologous stem cell transplant		
No		6
Yes		1
Prior CAR-T therapy		
No		6
Yes		1

Abbreviations: CAR-T cell = chimeric antigen receptor T-cell; R-CHOP = Rituximab - cyclohposhamide, doxorubicin, vincristine, prednisone; R-CVP = Rituximab - cyclophosphamide, vincristine, prednisone; R-DA EPOCH = Rituximab - dose adjusted etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin.

Table 2 Radiation target sites

Patient #	Target site
1	Cervical neck and sternum
2	Abdomen
3	Abdomen
4	Supraclavicular and axillary nodes
5	Iliac and para-aortic nodes
6	Posterior thigh muscle compartment
7	Jejunal wall

Table 3 Acute radiation-related toxicities

Adverse event	Grade 1		Grade 2	
	Number of patients	%	Number of patients	%
Fatigue	3	43	0	0
Nausea	1	14	0	0
Dermatitis	1	14	1	14
Bloating	0	0	1	14
Dyspepsia	0	0	2	28
Diarrhea	0	0	1	14

treated with Rituximab - cyclohposhamide, doxorubicin, vincristine, prednisone (R-CHOP), 2 patients initially were treated with dose adjusted etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin - Rituximab (DA-EPOCH-R), and 1 patient initially received Rituximab - cyclophosphamide, vincristine, prednisone (R-CVP). Treatment for refractory disease varied, with 1 patient undergoing autologous stem cell transplant and 1 patient undergoing CAR-T cell therapy for refractory disease before radiation and obinutuzumab.

Radiation was delivered to all sites of fludeoxyglucose (FDG) positron emission tomography avid disease. The median dose of radiation was 44 Gy (range, 30-50 Gy) (Table 1). Radiation target sites are shown in Table 2. No grade 3 or greater acute or late radiation-related toxicity was observed. Six patients experienced 10 acute grade 1 to 2 radiation-related toxicities, with the most common toxicity being radiation- related fatigue (3/7 patients) (Table 3). No late radiation-related toxicity was observed. Four patients had a complete radiographic response at the treated site, and the other 3 patients had a partial response on first postradiation imaging, before starting any new therapy. Only 1 patent experienced subsequent recurrence within the radiation field, 6 months after completion of radiation therapy in the setting of widespread disease recurrence. Four patients survived at least 30 months without evidence of recurrent disease, including 1 patient who had progressed after prior autologous SCT before starting obinutuzumab and radiation. Three patients completed 8 cycles of obinutuzumab. One patient completed 2 cycles of obinutuzumab before proceeding with planned CAR-T cell therapy. The other 3 patients developed progressive distant disease before completing 8 cycles of obinutuzumab. Median PFS and OS were 30 months for the 7 patients (Fig. 1). Two patients died of unrelated disease at 60 and 30 months postradiation therapy without evidence of DLBCL recurrence without additional therapy. Two patients are alive without evidence of recurrence 60 and 34 months postradiation, including the patient who had a planned CAR-T cell therapy immediately after radiation and obinutuzumab.

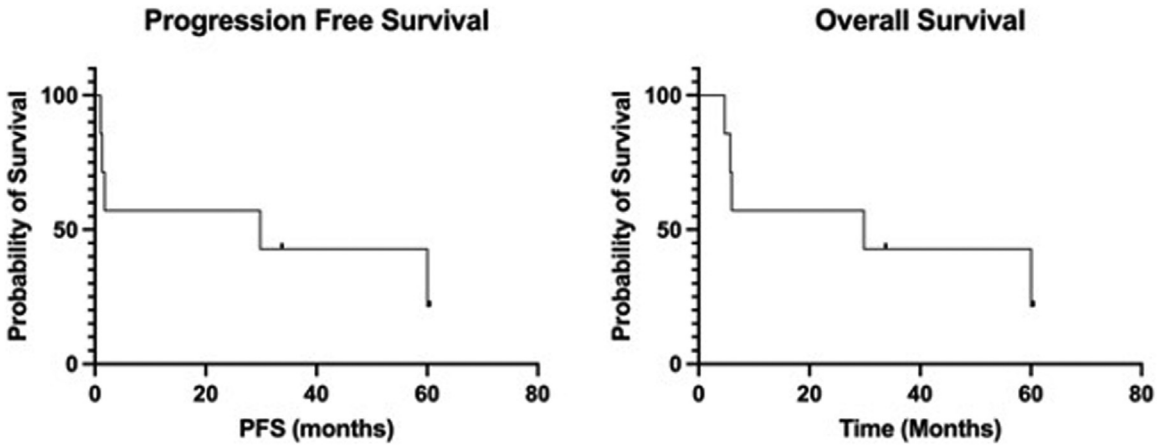

Figure 1 Progression-free and overall survival after obinutuzumab and radiation therapy for refractory diffuse large B cell lymphoma. Prolonged progression-free survival (A) and overall survival (B) of 30 months observed in this patient cohort. Two patients remain alive without evidence of disease at 34 and 60 months postradiation, and 2 patients died of unrelated disease without evidence of progression.

Discussion

In this small retrospective cohort of patients with refractory DLBCL, we evaluated the combination of radiation and obinutuzumab as a salvage treatment option. The combination therapy was well tolerated and associated with durable treatment response with a median OS of 30 months.

To our knowledge, this study represents the first report showing outcomes of combined radiation therapy and obinutuzumab for relapsed or treatment-refractory DLBCL. Interestingly, our results showed a sharp divide in response. Although 6 of the 7 patients had no evidence of recurrence within the radiation field, 3 of the 7 patients developed rapidly progressive disease outside of the irradiated site. However, the other 4 patients responded to treatment and did not go on to develop further disease, with only 1 patient receiving any additional therapy (planned CAR-T cell therapy). This includes the patient who had double hit DLBCL, who received no further therapy after completing radiation and 8 cycles of obinutuzumab. These results suggest a possible window for the combination of radiation and obinutuzumab as a salvage treatment before widespread dissemination of refractory DLBCL.

The study does have significant limitations, including the small sample size and retrospective nature. Patients had undergone a variety of previous treatments, including, in some cases, SCT or CAR-T therapy. Patients had to have disease that could be targeted with radiation, excluding patients with widespread, multifocal disease. Moreover, it is difficult to predict who would respond to treatment with such a small sample size. Finally, 1 of the long-term survivors had planned CAR-T therapy after completing radiation. It is unclear how the disease would have responded without CAR-T treatment. However, this may suggest a role for radiation therapy and obinutuzumab as a bridging therapy before CAR-T or SCT to help minimize disease burden. Indeed, these results compare favorably to a small 14 patient cohort receiving radiation and chemotherapy after SCT failure.[20]

In this small retrospective study, the combination of radiation and obinutuzumab was associated with prolonged OS in a subset of patients compared with obinutuzumab or radiation alone.[16,20] The data presented warrant further prospective evaluation as a stand-alone treatment option for refractory DLBCL or as a bridging therapy before CAR-T cell therapy.

Disclosures

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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