Review Article

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Rituximab and prednisone with or without radiotherapy in elderly frail patients with diffuse large B-cell lymphoma

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Abstract

Treating elderly and frail patients with DLBCL is a unique therapeutic challenge since standard chemotherapy is not applicable. We report the outcome of nine patients deemed unable to tolerate chemotherapy who were treated with rituximab plus prednisone with or without radiotherapy at our institute between 2012 and 2021. Median age was 82 years (range 75 - 93). While four of our patients had no clinical benefit, three patients profited notably from therapy and another two achieved a mixed response. Median OS was 7.0 months and median PFS was 3.2 months. Median PFS in responders and non-responders was 25.1 months and 2 days, respectively. Positive outcomes were associated with ECOG performance status < 4, non-severe comorbidities, mainly localized disease, IPI non high risk and those who received radiation to the main tumor mass. Our data suggests that selected frail patients may benefit from therapy with rituximab plus prednisone.

Keywords: Rituximab; frail; elderly; diffuse large B-cell lymphoma.

Introduction

Treating elderly and frail patients with diffuse large B-cell lymphoma (DLBCL) is a unique therapeutic challenge since standard chemotherapy is not applicable. In patients who are considered fit enough to receive cytotoxic chemotherapy, current treatment standards are modifications of the R-CHOP (rituximab, cyclophosphamid, doxorubicin, vincristin and prednisone) protocol and rituximab plus bendamustine. Patients unable to tolerate any cytotoxic chemotherapy due to severely reduced performance status and/or comorbidities are usually treated with best supportive care (BSC). The results of this study were presented as digital poster at the 2021 virtual annual congress of the austrian society of medical oncology.

Method

We performed a retrospective chart review of patients with DLBCL who were treated at our institute between 2012 and 2021. Patients who received rituximab and prednisone without any additional cytotoxic chemotherapy were included in this analysis. Data cut-off was December 31th, 2021.

Patient characteristics

Nine patients were identified. Median age was 82 years (range 75 - 93) and Eastern Cooperative Oncology Group (ECOG) performance status ranged between 2 and 4. Five patients were classified as severely comorbid which was defined by having multiple clinically significant cardiopulmonary diseases (e.g. heart insufficiency, chronic pulmonary obstructive disease). The other four patients had one or more non-severe well controlled chronic conditions. Five patients had activated B-cell type and two patients germinal center B-cell type DLBCL (the cell of origin was not determined due to lack of tissue samples in the other two patients). Most patients (six) presented with ann arbor stage IV disease. In most patients, prognosis was poor according to the international prognostic index. Detailed patients characteristics are listed in (**Table 1**).

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Table 1: *We can see here strabismus and gaze dedication.*

Baseline characteristics		
Median age (range) - yr		82 (75 - 93)
ECOG performance status - no.	*2*	4
	3	2
	4	2
	missing data	1
Comorbidities - no.	*mild to moderate*	4
	severe	5
Cell of origin - no.	*germinal center B-cell*	2
	activated B-cell	5
	missing data	2
Ann Arbor stage - no.	*I*	1
	II	2
	III	0
	IV	6
International prognostic index - no.	*low-intermediate (2 points)*	2
	high-intermediate (3 points)	3
	high (4 or 5 points)	3
	missing data	1

Comorbidities: severe: multiple clinically significant cardiopulmonary diseases. Mild to moderate: well controlled chronic conditions (non-severe).

Treatment

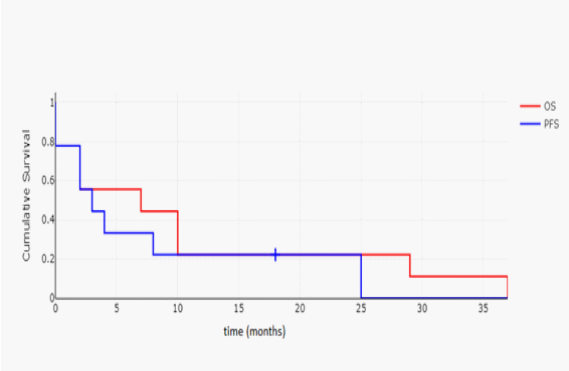
Patients received 3-weekly intravenous rituximab dosed 375mg/m² on day 1 combined with oral prednisone 100mg on days 1 to 5. Rituximab plus prednisone was given for 6 cycles in the absence of disease progression in most patients. However, one patient even received 9 treatment cycles. The median number of administered rituximab plus prednisone cycles was 6 (range 1 - 9). Radiotherapy was applied to five patients.

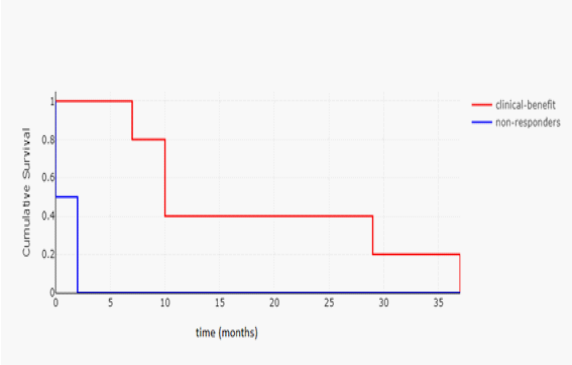
Results

Until now, all patients had died. Four of our patients had no clinical benefit with two of them dying a few days after initiation of therapy. In contrast, three patients profited substantially from therapy (two partial remissions and one complete remission) while the remaining two patients achieved a mixed response (**Table 2**). The complete remission was observed in a patient with localized primary cutaneous DLBCL. Median overall survival (OS) was 7 months (range 1 day - 3 years) and the 1-year survival rate was 22% (**figure 1**). Median OS in patients who derived benefit from therapy (including the two patients with mixed response) was 10.3 months as opposed to 2 days in non-responders (**figure 2**). Median progression free survival (PFS) was 3.2 months. Median PFS in the 3 responders and 4 non-responders was 25.1 months and 2 days, respectively. As expected, therapy was well tolerated without any observed higher grade toxicities. Positive outcomes were associated with ECOG performance status < 4, non-severe comorbidities, mainly localized disease with the application of radiotherapy to the main tumor mass and intermediate risk by IPI (as opposed to high risk). Two patients received second line therapy (rituximab plus prednisone reintroduction and lenalidomide, respectively) unfortunately without clinical benefit.

Table 2: *Therapy and outcome data.*

Therapy and outcome		
Median number of rituximab cycles (range)		6 (1 -9)
Radiotherapy - no.	*yes*	5
	no	4
Best response - no.	*complete remission*	1
	partial remission	2
	mixed response	2
	progressive disease or death	4





Discussion

The current standard therapy for elderly and/or frail patients with DLBCL represents variations of the R-CHOP protocol. One widely used therapy regimen is R-miniCHOP, which achieved a median OS of 29 months in the original phase 2 trial [1]. Other options are cutting out the anthracycline and reducing the dose of cyclophosphamide and vincristine. Rituximab plus bendamustine is another well tolerated treatment regimen with a reported median OS of 30 months in a phase 2 trial published in 2018 [2]. However, for patients unable to tolerate any chemotherapeutic substance due to frailty, current practice suggests a seven day trial of prednisone. If the performance status (PS) increases during this week, rituximab in combination with chemotherapy is given. For patients with-

out PS improvement, a BSC strategy is followed. Despite the small number of patients in this sample; the surprisingly positive results with approximately half of the patients profiting from therapy encourages this treatment approach. Given the good therapy tolerance of rituximab and prednisone, there are basically no toxicity related negative outcomes. Rituximab and prednisone used in patients with DLBCL is anecdotally mentioned in the literature. The largest patient collective is described in a retrospective cohort analysis of the Humedica database of which 70 patients are reported to have received rituximab monotherapy [3]. However, no specific patient characteristics nor therapy outcomes are described.

Radiotherapy was applied to five patients and probably has played a substantial role in the overall treatment success in two patients where radiation was targeted at the main tumor mass; thus confounding the positive results of this retrospective analysis. Although the small number of patients in this case series limits its expressiveness, it seems that selected frail and elderly patients with DLBCL who are unable to tolerate any chemotherapy potentially profit from therapy with rituximab plus prednisone.

Conflict of interest:

The author reports that there are no competing interests to declare.

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