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Combined treatment with anti-CD20 (rituximab) and CHOP in relapsed advanced-stage follicular lymphomas

We studied the safety and efficacy of combined treatment with rituximab plus CHOP in 16 patients with relapsed advanced-stage follicular lymphomas. The intent-to-treat overall response rate (ORR) was 88%, 75% complete remissions (CR) and 13% partial remissions (PR). At a median follow-up of 18 months, 63% of the patients are alive (50% CR). The combination of rituximab and CHOP in relapsed advanced-stage follicular lymphomas achieves high ORRs and CRs, with low toxicity except for in previously autografted patients.

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Non-Hodgkin's lymphomas (NHLs) are a diverse group of lymphoid neoplasms that range from indolent malignancies to rapidly growing and highly aggressive tumors. Follicular lymphomas (FL) represent the second most frequent type of B-cell NHLs, which usually present as a disseminated disease with an indolent course. Although a high initial response rate is achieved, repeated relapses occur with progressively lower response rates and shorter durations. The efficacy and safety of rituximab as single-agent therapy[1-4] or in combination with interferon-α 2[5] has been demonstrated in patients with either relapsed or refractory low grade lymphomas, as well as first-line therapy in this type of lymphomas.[6,7] Only one study has been reported[8] of combined treatment with rituximab and CHOP in low grade lymphomas, achieving higher response rates than rituximab as single agent therapy.

The current study is an open-label non-randomized multicenter phase II study designed to investigate the toxicity and efficacy of rituximab plus CHOP in the treatment of patients with relapsed advanced follicular lymphoma. We included patients with CD20 positive relapsed follicular lymphoma according to the REAL classification, whatever the cell type, between 18 and 70 years of age. They had disease stage III or IV according to the Ann-Arbor classification, ECOG <2 and adequate renal and hepatic functions.

The treatment schedule consisted of six intravenous infusions of rituximab (375 mg/m^2) on days 1, 8, 78, 85, 155, 162 (2 initial infusions to reduce tumor mass and 2 final infusions to end up with minimal residual disease), and six standard cycles of CHOP on days 15, 36, 57, 92, 113, 134. Treatment was discontinued if disease progression was observed or if a severe adverse therapy-related event appeared. Patients were evaluated for disease status at base line, after the third cycle of CHOP, at the end of treatment and every three months thereafter. Response was evaluated following the criteria of Cheson et al.[9] Response categories consisted of complete response (CR), partial response (PR) and no response (NR) or progressive disease (PD). Toxicity was evaluated according to the WHO criteria.

Table 1. Patient's characteristics at the time of inclusion in the trial, treatment response and status.

Pat.	*Sex*	*Age*	*Num*	*Time*	*Response*	*Status*
1	M	46	2 (ASCT)	11m	Withdrawn toxicity PR	Died progression +16m
2	F	66	6	38m	PR	Died progression +10m
3	M	64	2	85m	CR	CR +11m
4	M	69	3	65m	CR	Relapse +3m Died progression +12m
5	M	63	1	27m	Progression	Died progression +10m
6	M	59	3	64m	CR	CR +2m
7	M	66	2	143m	CR	CR +13m
8	M	43	2 (ASCT)	60m	Withdrawn toxicity Progression	Died progression +14m
9	M	62	2	31m	CR	CR +10m
10	M	63	1	13m	CR	CR +6m
11	M	49	1	15m	CR	CR +18m
12	F	48	2	92m	CR	CR +18m
13	M	39	1	5m	CR	Relapse +3m. PR +5m
14	F	39	2 (ASCT)	41m	Withdrawn VHB reactivation. CR	Relapse +16m. PR +4m
15	M	66	2	8m	CR	Relapse +7m Died progression +9m
16	F	45	1	11m	CR	CR +17m

F= female; M= male; ASCT= autologous stem cell transplant. CR: complete remission; PR: partial remission.

Results of the descriptive analysis are expressed as median and range for continuous data and number of cases with their proportion for qualitative data. Survival analysis was performed at the univariate level by means of Kaplan-Meier techniques. Sixteen patients were enrolled in this study in 4 centers from July 1998 to August 2000. The median age was 61 years (range: 40-70 years) and 12 (75%) were males. All of them had received at least one prior therapy (median 2; range 1-6) and three cases (19%) had been previously submitted to an autologous bone marrow transplant. The median time between diagnosis and inclusion in the study was 35 months (range: 8-143 months) (Table 1).

Infusional toxicity of rituximab appeared in 50% of the patients, usually mild and in all cases this only occurred with the first infusion. It was managed by adjustments of the infusion rate and was not a cause of treatment withdrawal. CHOP toxicity was observed in 8 patients (50%), mainly hematologic, with grade IV neutropenia in 5 patients. All three patients who had previously undergone a peripheral stem cell transplant did not complete treatment, two due to hematologic toxicity and one due to viral hepatitis B reactivation.

The intent-to-treat analysis showed 12 (75%) CR and 2 (13%) PR with an 88% ORR (Table 1). Of the 12 patients in CR, 4 (33%) patients relapsed (mean duration of CR of 14 months) (Figure 1). With a median follow-up of 18 months, 10 patients (63%) are alive, 8 (50%) in CR and 2 (13%) in PR.

We report a trial evaluating the clinical efficacy and safety of combined treatment with rituximab and CHOP in relapsed advanced-stage follicular lymphomas.

Rituximab has been used as single-agent therapy[1-4] or in combination with interferon-α 2a[5] in relapsed or refractory follicular lymphomas achieving ORRs of approximately 50% (15% CR), as well as a single agent in first line low grade lymphomas[6,7] with 70% ORRs (20% CR).

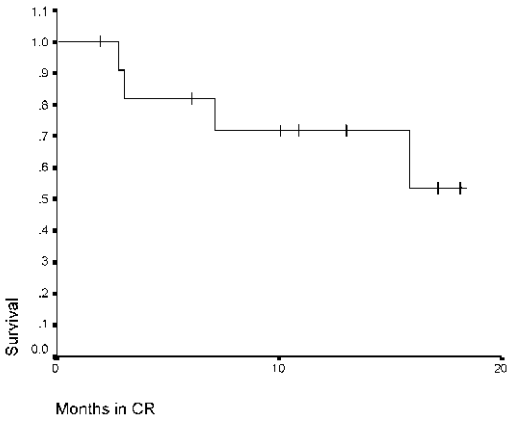

Figure 1. Disease free survival curve of patients who achieved a CR. The mean duration of CR is of 14 months.

These response rates, together with the fact that rituximab enhances the *in vitro* efficacy of conventionally used cytotoxic drugs,[10] led to the use of combined treatment using anti-CD20 with conventional chemotherapy. Czuczman *et al.*[8] included 40 patients with low grade or follicular lymphomas (31 untreated and 9 previously treated lymphomas) with an intent-to-treat ORR of 95% (55% CR) (89% ORR in the previously treated patients (56% CR)).

In our group of previously treated follicular lymphomas the intent-to-treat ORR was 88% (75% CR), similar to that obtained by Czuczman *et al.*,[8] which significantly improves the response rates obtained with conventional chemotherapy.

Rituximab in combination with CHOP chemotherapy in patients with relapsed advanced-stage follicular lymphomas is associated with high ORRs and high CRs, together with low toxicity, except for in previously transplanted patients. These results encourage the use of rituximab as first-line therapy in combination with other effective agents.

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