Malignant Lymphomas

Rituximab monotherapy is effective in patients with poor risk refractory aggressive non-Hodgkin's lymphoma

We report the results of rituximab monotherapy in 21 patients with refractory or relapsed aggressive non Hodgkin's lymphoma (NHL). The majority of the patients (16/21) were refractory to conventional treatment and not eligible for high dose chemotherapy. Responses (1 complete and 6 partial) were achieved in some of these patients and their median overall survival was 8 months.

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The prognosis for patients with refractory or relapsed aggressive non Hodgkin's lymphoma (NHL) is generally poor. The response rates to salvage therapy regimens range from 20-40%.[1] Patients who present with refractory disease have the worst prognosis, with a median survival of less than six months.[2-5] Only a minority of patients can be given high dose chemotherapy, the majority being ineligible due to disease progression during salvage therapy or extensive co-morbidity.

The efficacy of rituximab monotherapy has only been tested in a few patients with relapsed or refractory aggressive B-NHL with heterogeneic histology in a phase-I trial in the US and in a European multicenter phase-II study under controlled conditions.[6-8] We initiated a single arm phase-II study in 1996 to demonstrate the efficacy of rituximab in a series of patients, most of whom had refractory, aggressive NHL.

Between September 1996 and August 2001, 21 patients with refractory (n=16) or relapsed (n=5) aggressive NHL according to the REAL classification were entered into the study. Patients were eligible if they had histologically confirmed aggressive CD-20 positive B-cell NHL.

None of these patients could receive salvage therapy because of advanced age, co-morbidity or extensive prior treatment. Other inclusion criteria consisted of age 18-75 years, life expectancy of >3 months, ECOG performance status 0-3 and written informed consent. Exclusion criteria were an active second malignancy, clinically significant organ dysfunction, active uncontrollable infection and HIV-infection. Rituximab was administered at a standard dosage of 375 mg/m^2 once weekly for 4 weeks.

The study protocol was designed according to the declaration of Helsinki and had been approved by the ethics review board of the University of Cologne. Written informed consent was obtained from all patients before the start of treatment.

The patient´s characteristics are shown in Table 1. Twenty-one patients entered the study; 16 of these were refractory to their last treatment after having received a median of 2.5 prior chemotherapy regimens. Table 2 summarizes the response data. All patients (n=21) were evaluable. The overall response rate was 38.1% with one complete remission (CR) and seven partial remissions (PR). Four patients had stable disease (SD) (19%). Of 16 patients with refractory disease, one achieved CR and six had PR, resulting in an overall response rate of 43.8.%; two patients had SD (12.5%). Of the five relapsed patients one achieved a PR and two had SD. The median overall survival (OS) for all patients was 8.6 months. The median event-free survival was 3.8 months. The toxicity rate was very low. Adverse events were mild and restricted to allergic reactions such as fever, chills and skin rash during or after the first infusion of the antibody. In patients with progressive lymphoma treated with conventional salvage regimens the response rates are low and the duration of response is short. In an analysis of 64 patients with refractory NHL treated at our institution the overall response rate to various polychemotherapy salvage regimens

Table 1. Patients' characteristics.

Number of patients		*21*
Age (years)		
Mean	52.7	
Range	18- 74	
Gender		
Male	9	
Female	12	
Refactory patients		16
First relapse		3
Second or higher relapse		2
Stage at presentation		
I	–	
II	8	
III	6	
IV	7	
B symptoms		
yes	6	
no	15	
Extranodal disease		
yes	8	
no	13	
Prior chemotherapy regimens		
0	0	
1	8	
2	6	
3	2	
> 3	5	
Karnofsky index		
> 70		13
< 70		6
n.d.		2
Lactate dehydrogenase		
> 240 U/L		11
< 240 U/L		8
n.d.		2

Table 2. Response of patients with refractory or relapsed high-grade NHL treated with Mabthera.

Response	*All patients (n=21)*	*Refractory patients (n=16)*	*Relapsed patients (n=5)*
CR	1 (4.8%)	1 (6.3%)	
PR	7 (33.3%)	6 (37.5%)	1
SD	4 (19%)	2 (12.5%)	2
PD	9 (42.9%)	7 (43,8%)	2
RR (CR+PR)	8 (38.1%)	7 (43.8%)	1

CR: complete remission; PR: partial remission; PD: progressive disease; RR: response rate.

was only 15% with a mean overall survival of 6.8 months.[9]

Coiffier *et al.* reported on 54 patients with relapsed or refractory NHL treated with two different doses of rituximab;[8] 31% achieved a response with the time to treatment progression (TTP) being 8 months. The CR rate was 9% and the PR rate 22%. The limitation of this study is that only half of the patients (30/54) had diffuse large B-cell lymphoma according to the REAL-classification and in 10 patients the disease could not be precisely categorized. Given the heterogeneity of the histologic subtypes, evidence on the efficacy of rituximab in the treatment of refractory or relapsed aggressive NHL could not be considered conclusive. Meanwhile, a Japanese phase-II pharmacokinetic study demonstrated an overall response rate of 37% in patients with relapsed aggressive NHL.

In accordance with the above mentioned studies, in our study 38.1% of patients with refractory or relapsed aggressive NHL responded to rituximab monotherapy. Interestingly, patients who were refractory to prior treatment by the time of inclusion, showed a higher response rate of 43.8%. Rituximab was associated with very little toxicity and symptoms were generally mild. The median EFS of 3.8 months was relatively short and the median overall survival was 8.6 months. It is an open question whether prolonging rituximab treatment up to 8 weeks, as reported by Coiffier *et al.*,[8] may increase EFS.

Our study confirmed the efficacy of rituximab as single agent therapy for aggressive NHL in patients with a poor prognosis who are ineligible for high dose chemotherapy. It is, however, important to mention the high costs of rituximab monotherapy in this setting, taking into account the relatively short EFS. The whole treatment is applicable in an outpatient setting without the toxicity commonly observed with combination chemotherapy regimens. We, therefore, consider that CD20 monoclonal antibody is a well tolerated treatment option for patients with very poor prognosis NHL in a palliative setting.

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Monoclonal Gammopathy

Malignant evolution of monoclonal gammopathy of undetermined significance: analysis of 633 consecutive cases with a long term follow-up

In 633 consecutive patients with monoclonal gammopathy of undetermined significance (MGUS) the probability of malignant evolution was 9, 17 and 51% at 5, 10 and 15 years, respectively, after diagnosis. The values of monoclonal component, Bence-Jones proteinuria and erythrocyte sedimentation rate were associated with malignant transformation.

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Monoclonal gammopathy of undetermined significance (MGUS) is an asymptomatic disorder characterized by the presence in the serum of a homogeneous monoclonal immunoglobulin (M-component, MC) without any evidence of lymphoproliferative disorders.[1,2] The incidence of MGUS increases with age, from 2, 3 and 4% in patients older than 50, 70 and 80 years, respectively.[3,4] In some cases this condition is stable over the years, while in others it evolves into multiple myeloma (MM or, rarely, into another malignant lymphoproliferative disorder. In the largest study so far published the probability of malignant transformation was 12, 25 and 30% at 10, 20, and 25 years after diagnosis, respectively.[5]

From January 1974 to December 1997, 976 consecutive MGUS patients were followed at our department. Of them, 633 patients (306 males, 327 females, median age 62 years, range 27-87 years) with a minimum follow-up of 1 year were evaluated. The diagnosis of MGUS was made using standard criteria.[2] In each patient, we evaluated the following data: hemoglobin, leukocyte and platelet counts, erythrocyte sedimentation rate (ESR), C reactive protein (CRP), lactate dehydrogenase (LDH), serum protein electrophoresis, quantification of polyclonal and monoclonal immunoglobulins (MC), presence of Bence Jones (BJ) proteinuria, β2-microglobulin, serum creatinine and calcium. In patients with ≤ 5 g/L MC, laboratory tests were monitored every year; in patients with 5-15 g/L MC, laboratory tests were monitored every six months for 3 times and thereafter every year in the case of a stable MC level. Bone marrow aspirate and