Malignant Lymphomas

Adapted CHOP plus rituximab in non-Hodgkin's lymphoma in patients over 80 years old

Treatment of very old patients with non-Hodgkin's lymphoma remains controversial. Indeed, patients over 80 years old are usually not included in trials. We show here that addition of rituximab to reduced-dose CHOP chemotherapy seems to be a good compromise between toxicity and efficacy, allowing clinicians to treat very elderly patients with a curative intent.

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The study of cancer and aging is emerging as a critical issue in oncologic care. Although approximately one third of the cases of non-Hodgkin's lymphoma (NHL) occur in patients older than 75 years of age,[1] very few data are available concerning the optimal treatment in this age group. Indeed, the number of very elderly patients in published trials is small and patients over 80 years old are not usually included.

The value of the cyclophosphamide, adriamycin, vincristine and prednisone (CHOP) plus rituximab (R-CHOP) combination therapy in both aggressive and indolent B-cell lymphoma has been demonstrated in several clinical trials.[2-4] This study was designed to retrospectively assess the safety and the efficacy of R-CHOP in patients over 80 years old. The medical records of all NHL patients more than 80 years old who were treated with R-CHOP between March 2001 and November 2003 at two French hematology departments were retrospectively analyzed. The diagnosis of NHL was made according to the World Health Organization classification.[5] All slides from tissue biopsies were reviewed by an experienced hematologic pathologist. Response was classified according to the International Workshop criteria.[6] Radiographic studies, including scans were reviewed by a reference radiologist blinded to the previously reported response data. Overall survival (OS) was defined as the interval from the start of therapy to the time of death or the last follow-up. Event-free survival (EFS) was calculated from the beginning of therapy to the time of disease progression or death due to any cause. According to our department's policies, patients over 80 years old without unstable cardiac disease or any detectable sign of heart failure (e.g., reduced left ventricular ejection fraction on echocardiography) at the time of diagnosis are eligible for treatment with an anthracycline-containing regimen.

During the study period, 29 over 80-year olds with B-cell NHL were referred to our departments. Two patients were treated with radiotherapy only (localized follicular lymphoma) and three with a CVP regimen (systolic congestive heart failure). The study population consisted of 24 patients. Their main characteristics are listed in Table 1. All these patients were treated with a CHOP regimen plus concurrent rituximab, delivered on day 1, every 21 days. The standard doses of 50 mg/m^2 of doxorubicin and 750 mg/m^2 cyclophosphamide were reduced in 22 patients (92%) and 3 patients (12.5%), respectively. The median relative dose intensities calculated for doxorubicin and cyclophosphamide were 63% and 86%, respectively.

Table 1. Patients' characteristics.

No. of Patients	*Age, years*	*%*
Median (Range)	83 (80-88)	
Sex		
Male	10	41.5
Female	14	58.5
Performance status (ECOG)		
0	2	8.3
1	12	50
2	8	33.3
3	2	8.3
Histological diagnosis		
Diffuse large B-cell lymphoma	19	79
Mantle-cell lymphoma	3	12.5
Follicular lymphoma	2	8.5
Disease status at initiation of therapy		
Newly diagnosed	18	75
Relapsed/refractory	6	25
Stage		
I	2	8.5
II	5	21
III	8	33
IV	9	37.5
No. of extranodal sites		
0	12	50
1	7	29
≥ 2	5	21
Bone marrow involvement		
Yes	5	21
No	6	25
Unknown	13	54
Age-adjusted IPI score		
0	1	4
1	5	21
2	2	8.5
3	3	12.5
Not available	13	54

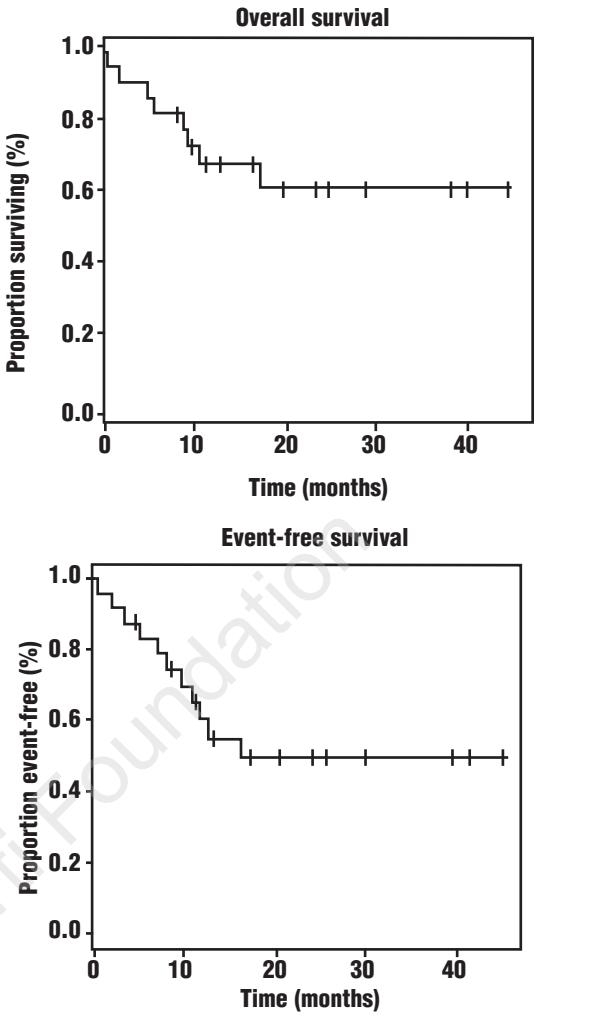

Figure 1. Kaplan-Meier plot of overall survival and event-free survival for all patients (N=24)

Doses were reduced in all cases from the first cycle, on the basis of the clinician's decision. A total of 125 cycles were administered with a mean of 5.2 courses (range 1–8) per patient. Eight patients (33%) received at least one course of granulocyte colony-stimulating factors during their treatment. The overall response rate was 79% with 15 patients (62.5%) achieving a complete or unconfirmed complete response and four (16.5%) a partial response. After a median follow-up of 23 months, the 2-year OS and EFS were 63% and 50%, respectively (Figure 1). Considering only newly diagnosed patients with diffuse large B-cell lymphoma (n=15), the 2-year OS and EFS were 76% and 62.5%, respectively. The toxicity, mainly hematologic, was manageable, febrile neutropenia occurred in 6% of the courses and there were no toxic deaths. No significant adverse events related to infusion of the rituximab were noted. Twenty-two patients (92%) in our study received reduced doses of doxorubicin (mean dose reduction, 30%). Analyzing the reasons for these dose reductions revealed that old age was the sole cause in 20 cases and poor performance status was the cause in the other two cases.

Several studies have reported that elderly patients are able to tolerate full-dose doxorubicin-containing regimens.[7-8] However none of these studies has focused on very elderly patients (≥80 years). Moreover, although granulocyte colony-stimulating factor may allow completion of therapy in elderly NHL patients, and may reduce the duration and severity of neutropenia, significant differences in hospitalization, infections, and in particular, survival, have not been clearly demonstrated in this population.[9] So, dose reduction, especially for doxorubicin given its hematotoxicity, seems to be a reasonable option. The 2-year OS of 63% in our study population was much higher than the 30% in an unselected group of NHL patients more than 80 years old in whom treatment was considered as optimal by the authors in only 17% of the cases.[10] This suggests that poorer outcome in older patients with NHL, as previously reported, is at least partially due to inadequate treatment.

Despite the usual limitations of retrospective analyses, our study shows that addition of rituximab to reduced-

dose CHOP chemotherapy seems to be a good compromise between toxicity and efficacy, allowing clinicians to treat very elderly patients with a curative intent.

This underscores the fact that age alone should not be used as a reason to deny patients with NHL an adapted and potentially curative treatment. Thus, at the time of writing, the Groupe d'Etudes des Lymphomes de l'Adulte (GELA) is considering a prospective phase II study of an attenuated R-CHOP regimen in patients over 80 years old.

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