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References

1. Anonymous. A randomized double-blind placebo-controlled study with subcutaneous recombinant human erythropoietin in patients with low-risk myelodysplastic syndromes. Italian Cooperative Study Group for rHuEpo in Myelodysplastic Syndromes. Br J Haematol 1998; 103:1070-4.
2. Cascinu S, Fedeli A, Del Ferro E, Luzi Fedeli S, Catalano G. Recombinant human erythropoietin treatment in cisplatin-associated anemia: a randomized, double-blind trial with placebo. J Clin Oncol 1994; 12:1058-62.
3. Osterborg A, Boogaerts MA, Cimino R, Essers U, Holowiecki J, Juliusson G, et al. Recombinant human erythropoietin in transfusion-dependent anemic patients with multiple myeloma and non-Hodgkin's lymphoma: a randomized multicenter study. Blood 1996; 87:2675-82.
4. Negrin RS, Stein R, Doherty K, Cornwell J, Vardiman J, Krantz S, et al. Maintenance treatment of the anemia of myelodysplastic syndromes with recombinant human granulocyte colony-stimulating factor and erythropoietin: evidence for in vivo synergy. Blood 1996; 87:4076-81.
5. Thompson JA, Gilliland DG, Prchal JT, Bennett JM, Larholt K, Nelson RA, et al. Effect of recombinant human erythropoietin combined with granulocyte-macrophage colony-stimulating factor in the treatment of patients with myelodysplastic syndrome. Blood 2000; 95:1175-9.
6. Mazzella FM, Kowal-Vern A, Shrit MA, Wibovo AL, Rector JT, Cotelingam JD, et al. Acute erythroleukemia: evaluation of 48 cases with reference to classification, cell proliferation, cytogenetics, and prognosis. Am J Clin Pathol 1998; 110:590-8.
7. Estey EH. How I treat older patients with AML. Blood 2000; 96:1670-3.
8. Miyazaki E, Kohgo Y, Hirayama M, Kawanishi J, Kato J, Sakamaki S, et al. Remission after erythropoietin administration for erythroleukemia: a case study. Blood 1993; 82: 1378-80.
9. Takamatsu Y, Miyamoto T, Iwasaky H, Makino S, Tamura K. Remission induction by granulocyte colony-stimulating factor in hypoplastic acute myelogenous leukemia complicated by infection: a case report and review of the literature. Acta Haematologica 1998; 99:224-30.
10. Ferrara F, Di Noto R, Viola A, Russo C, Boccuni P, Costantini S, et al. Complete remission in acute myeloid leukaemia with t(8;21) following treatment with G-CSF: flow cytometric analysis of in vivo and in vitro effects on cell maturation. Br J Haematol 1999; 106:520-3.

A dexamethasone, vinblastine, cyclophosphamide, etoposide, methotrexate and bleomycin (D-VICEMB) protocol as first-line treatment of patients aged 70 years or older affected by intermediate / high grade non-Hodgkin's lymphoma

We treated 30 consecutive untreated patients aged > 70 years with advanced aggressive non-Hodgkin's lymphoma with 6 courses of cyclophosphamide, mitoxantrone, etoposide, bleomycin, vinblastine and dexamethasone (D-VICEMB). The global response was 93%. The 6-year overall survival and progression-free survival were 50%, and disease-free survival was 63%.

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Increasing age has a negative impact on the outcome of patients with aggressive non-Hodgkin's lymphoma (NHL). In scientific literature people aged 60 years and older are defined as elderly patients. In reality, the condition of elderly people depends on biological age, namely on previous or concomitant diseases and their degree of aging. Patients aged >70 years usually have a poorer outcome.[1-3] Anthracycline-containing regimens, such as CHOP, seem to be more effective than others.[4] However, treatment-related mortality increases up to 15% in elderly patients. In the last decade, weekly regimens, such as P-VEBEC, and VNCOP-B, have been used with the aim of reducing chemotherapy toxicity.[5-9] The D-VICEMB protocol was conceived for day-hospital administration and to facilitate treatment compliance in elderly patients reluctant to depart from their family-environment or to modify life practices. Our regimen, a combination of 6 myelotoxic and non-myelotoxic drugs, was specifically tailored to treat patients aged >70 years. The treatment consisted of six courses, every 21 days, of cyclophosphamide (600 mg/m^2 iv), mitoxantrone (10 mg/m^2 iv), etoposide (60 mg/m^2 iv) on day 1; etoposide (60 mg/m2 orally) on day 2; bleomycin (6 mg/m^2 iv) and vinblastine (6 mg/m^2 iv) on day 7; dexamethasone (12 mg/m^2 orally) on days 1,2,3,5, and 7. Radiotherapy (36 Gy) to residual masses was programmed. The use of granulocyte colony- stimulating factor (G-CSF) at the dose of 5 μg/kg/day for 4-6 days was employed in case of neutropenia < 500/mL. Patients received bacterial and fungal oral prophylaxis with ciprofloxacin (500 mg) and fluconazole (100 mg). Informed consent was provided. From January 1996 to April 2001, 30 consecutive untreated patients received this D-VICEMB regimen. Inclusion criteria were: age >70 years, histologic diagnosis of intermediate/high grade NHL according to the Working Formulation, stages II-IV. The patients' characteristics and outcome are described in Table 1. After chemotherapy administration we recorded 18 (60%) complete remissions (CR), 10 (33%) partial remissions (PR) and 2 (7%) cases of progressive disease (PD). Four patients in PR received additional radiotherapy and 2 of them obtained CR. Overall survival (OS) and progression-free survival (PFS) rates at 72 months (median 28, range 7-77) were 50%. The rate of disease-free survival (DFS) of the 20 patients in CR was 63% (Figure 1). Patients with good performance status (PS) (> 80%) or with an age-adjusted international prognostic index (Aa IPI) score of 0-1 had an evident survival advantage; there was no difference between patients below 75 and those 75 or over (Table 1). One hundred and sixty-one of the planned 180 courses were administered. Four patients in CR suspended treatment after five courses; 4 patients in PR refused further therapy after four or five courses as a result of their improvement; 2 patients received only two courses due to PD. Neutropenia < 500 /mL occurred in 36 of the 161 courses (22%). No relevant infections occurred and no admissions to hospital were required. The incidence of thrombocytopenia was minimal. Only 2 packed red cell transfusions were

Table 1. Characteristics and outcome of the 30 patients.

Age (years)	*median 74* *>75 12*	*(range 70-85)*
Age adjusted IPI	0-1 10	(33%)
	2-3 20	(67%)
Bulky tumor (≥ 6 cm)	4	(13%)
Bone marrow involvement	7	(23%)
Extranodal sites	15	(50%)
Elevated lactate dehydrogenase	11	(36%)
Sex (male/female)	14/16	
B symptoms (No/Yes)	17/13	
Performance status < 80% ≥ 80%	19/11	
(Karnofsky index) <60	11	
Disease stages		
II	5	(16%)
IIE	8	(27%)
III-IV	17	(57%)
Histologic subtypes		
(Working Formulation)		
E	1	
F	6	
G	23	
Overall survival		
Age adjusted IPI		
0-1	71%	
2-3	18%	*p* <.02
Performance status		
≥ 80%	71%	
< 80 %	30%	*p* .08
Age		
≤ 75 years	51%	
>75 years	47%	*p* .8

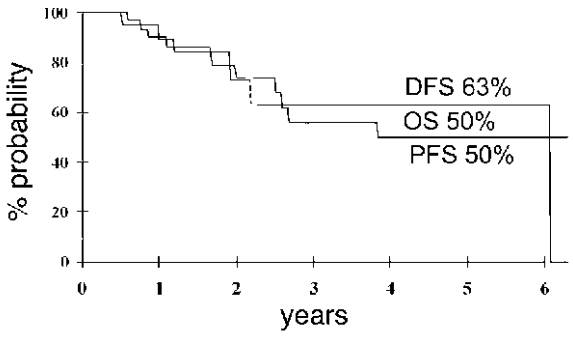

Figure 1. Overall survival and progression-free survival among all patients. Disease-free survival among the 20 patients in complete remission.

needed. Two treatment-unrelated deaths occurred off-therapy; the first patient in PR, affected by hypertension died of a cerebral ictus 7 months after the diagnosis of NHL; the second died in CR after 10 months, because of surgical complications of an adhesiotomy. In conclusion, our protocol is well-tolerated and effective in treating very elderly patients with aggressive NHL since the patients in CRs had a sustained DFS. The lack of difference between two age-subgroups suggests that age in itself is not a poor prognostic factor in elderly patients treated with the D-VICEMB regimen. In contrast, the presence of co-morbidity, especially diabetes, hypertension and cardiovascular diseases in our patients with a PS< 60 limited the treatment's feasibility. For these patients additional supportive means are needed. Finally, with the aim of ameliorating the efficacy of D-VICEMB we planned the association of rituximab in patients with an Aa-IPI score of 2-3.

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References

1. Armitage JO, Potter JF. Aggressive chemotherapy for diffuse histiocytic lymphoma in the elderly: increased complications with advancing age. J Am Geriatr Soc 1984; 32:269-73.
2. Hoskins PJ, Ng V, Spinelli JJ, Klimo P, Connors JM. Prognostic variables in patients with diffuse large-cell lymphoma treated with MACOP-B. J Clin Oncol 1991; 9:220-6.
3. Coiffier B, Gisselbrecht C, Herbrecht R, Tilly H, Bosly A, Brousse N. LNH-84 regimen: a multicenter study of intensive chemotherapy in 737 patients with aggressive malignant lymphoma. J Clin Oncol 1989; 7:1018-26
4. O'Reilly SE, Klimo P, Connors JM. Low-dose ACOP-B and VABE: weekly chemotherapy for elderly patients with advanced-stage diffuse large-cell lymphoma. J Clin Oncol 1991; 9:741-7.
5. Martelli M, Guglielmi C, Coluzzi S, Avvisati G, Amadori S, Giovannini M, et al. P-VABEC: a prospective study of a new weekly chemotherapy regimen for elderly aggressive non-Hodgkin's lymphoma. J Clin Oncol 1993; 11:2362-9.
6. Bertini M, Freilone R, Vitolo U, Botto B, Pizzuti M, Gavarotti P, et al. P-VEBEC: a new 8-weekly schedule with or without rG-CSF for elderly patients with aggressive non-Hodgkin's lymphoma (NHL). Ann Oncol 1994; 5:895-900.
7. Zinzani PL, Storti S, Zaccaria A, Moretti L, Magagnoli M, Pavone E, et al. Elderly aggressive-histology non-Hodgkin's lymphoma: first-line VNCOP-B regimen experience on 350 patients. Blood 1999; 94:33-8.

8. Bastion Y, Blay JY, Divine M, Brice P, Bordessoule D, Sebban C, et al. Elderly patients with aggressive non-Hodgkin's lymphoma: disease presentation, response to treatment, and survival: a Groupe d'Etude des Lymphomes de l'Adulte study on 453 patients older than 69 years. J Clin Oncol 1997; 15: 2945-53.
9. Tirelli U, Errante D, Van Glabbeke M, Teodorovic I, Kluin-Nelemans JC, Thomas J, et al. CHOP is the standard regimen in patients ≥ 70 years of age with intermediate-grade and high-grade non-Hodgkin's lymphoma: results of a randomized study of the European Organization for Research and Treatment of Cancer Lymphoma Cooperative Study Group. J Clin Oncol 1998; 16:27-34.

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).