original research report

Addition of amifostine to the CHOP regimen in elderly patients with aggressive non-Hodgkin lymphoma: a phase II trial showing reduction in toxicity without altering long-term survival

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BACKGROUND AND OBJECTIVES: We report the 8-year follow-up of 34 patients aged ≥ 69 years old with NHL included in a phase IIb open-label randomized parallel groups study to evaluate the effectiveness of amifostine in preventing the toxicity of cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP regime) .

PATIENTS AND METHODS: Patients were randomized to receive classical CHOP (cyclophosphamide 750 mg/m^2, doxorubicin 50 mg/m^2, vincristine 1.4 mg/m^2 [maximum 2 mg] on day 1 and prednisone 100 mg/day for 5 days) or CHOP plus amifostine (6 cycles of amifostine 910 mg/m^2 on day 1). Efficacy (time to progression, TTP; disease-free survival, DFS; overall survival, OS) and toxicity endpoints were evaluated.

RESULTS: Thirty-four patients were randomized to A-CHOP (n=18) or CHOP (n=16). Patients with A-CHOP vs CHOP had significantly lower toxicity; neutropenia grade 4 ocurred in 13/92 (13%) vs 23/85 (27%, *P*=0.007) cycles, febrile neutropenia in 3/92 A-CHOP (3%) vs 8/85 (10%, *P*=.056) CHOP cycles, hospitalization for toxicity in 4/92 (4%) A-CHOP vs 11/85 (13%, *P*=.05) CHOP cycles. Median hospitalization stay for toxicity was 5 days with A-CHOP vs 8 days with CHOP (*P*=.05). There were no significant differences at 8 years in TTP (A-CHOP, 48.9% vs CHOP, 36.3%; *P*=.65), DFS (A-CHOP, 72.9% vs CHOP 55.6%; *P*=.50) and OS (A-CHOP, 44.3% vs CHOP, 54.4%). There was no long-term toxicity of clinical interest. The only prognostic factor identified to 8 years was the International Prognostic Index (IPI low/low intermediate risk vs high intermediate/high risk; HR=2.98; CI 95%:1.01-8.77; *P*=.048).

CONCLUSION: These results show that amifostine can be added to the standard CHOP treatment schedule with less acute toxicity and without influencing the outcome.

Treatment of elderly patients with aggressive non-Hodgkin lymphoma (NHL) remains a true challenge because of poor tolerance to standard-dose chemotherapy.[1] Amifostine is a selective cytoprotector that acts as a scavenger of free radicals and has a protecting activity over normal tissues.[2] Clinical trials evaluating amifostine in combination with chemotherapy in solid tumors have shown a reduction in chemotherapy-associated toxicity without modification of antineoplastic activity.[3,4] The same result was also observed in a previous single-arm trial of amifostine plus CHOP in elderly patients with aggressive NHL.[5] We evaluated the long-term outcome of the efficacy of amifostine in preventing toxicity to the CHOP regime in elderly patients with NHL.

PATIENTS AND METHODS

This was a randomized (1:1 ratio), parallel group, phase IIb trial to evaluate the effectiveness of amifostine in preventing chemotoxicity to CHOP in elderly NHL patients that was carried out in two hospitals in Lima, Perú (Instituto Nacional de Enfermedades

Neoplásicas and Hospital Edgardo Rebagliatti Martins). Accrual was from September 2000 to October 2001. CHOP (cyclophosphamide 750 mg/m^2, doxorubicin 50 mg/m2, vincristine 1.4 mg/m^2 [maximum 2 mg] on day 1 and prednisone 100 mg/day for 5 days) was given in 6 cycles of 3 weeks each. Amifostine (910 mg/m^2) was given in 6 cycles on day 1 (added to normal saline to a total volume of 100 mL, administrated intravenously 15 minutes before chemotherapy)

Inclusion criteria were age ≥69 years old, ECOG performance status 0-1, aggressive NHL of the following types according to the WHO classification: diffuse large B cell lymphoma, non-specific peripheral T-cell lymphoma, anaplastic T-cell lymphoma, grade II-III follicular lymphoma and mantle cell lymphoma (not blastoid), adequate bone marrow reserve (absolute neutrophil count ≥1.5×10^9/L, platelets ≥100×10^9/L), normal renal and hepatic function, and left ventricle ejection fraction greater than 50%. Patients taking chronic corticosteroid treatment discontinued it at least one week before inclusion. Exclusion criteria include previous chemotherapy, radiation therapy or modifiers of biological response, encephalic or meningeal infiltration by lymphoma, HIV infection, conditions that require continuous treatment between courses of chemotherapy, history of cardiac disease, active infections or illnesses that precluded the use of chemotherapy, concurrent malignancy or a history within 5 years (excluding non-melanoma skin cancer and early cervical uterine cancer treated for cure).

The trial was designed to detect a difference of 20% in reduction, using amifostine, of grade 4 neutropenia events in cycles of chemotherapy, considering toxicity occurs in 43% of cycles in elderly patients with aggressive lymphoma treated with CHOP.[6] With a P=.05 and β=0.20, 83 cycles per group were needed (an estimated of 16 patients per arm). Toxicity was assessed according to CTCAE v2.0. Survival was estimated with the Kaplan-Meier method and the differences between groups were determined by the log rank test. Endpoints included hematological and biochemical toxicities and survival. Disease-free survival (DFS), time-to-progression (TTP) and overall survival (OS) were calculated by the Kaplan-Meier method and the log rank or Breslow (when appropriate) tests were used as methods of statistical inference between the two treatment groups. This study was conducted in accordance with the principles of the Declaration of Helsinki, Good Clinical Practice, and the current national rules for conducting clinical studies. The protocol was approved by the local hospital ethics committee (trial registration number INEN 00-18), and all patients signed an informed consent.

RESULTS

Thirty-four patients were randomized, 18 to the A-CHOP arm and 16 to the CHOP arm. Although the A-CHOP arm had stages III-IV cases (56% vs 32%, without statistical significance), the International Prognostic Index was similar in both arms. Other characteristics were balanced (**Table 1**).

CHOP administration

Eleven of the 18 (61%) A-CHOP patients and 12/16 (75%) CHOP patients completed six cycles of chemotherapy (P=.619). Five completed fewer than 4 cycles due to withdrawal of consent (one patient), disease progression (one patient) and toxicity (three patients: one A-CHOP and two CHOP). A total of 177 cycles were administered (92 in A-CHOP and 85 in CHOP), with a median of 6 cycles in both arms. Total chemotherapy dose (cumulative dose of cyclophosphamide or doxorubicin per square meter) was similar in both arms; however, the median treatment duration at the sixth cycle was significantly shorter in the A-CHOP arm (17.7 vs 19.9 weeks; P=.01); similarly, the median of relative dose intensity (RDI) at sixth cycle was higher in the A-CHOP arm (82% vs 72%, P=.03) (**Table 2**).

Efficacy

The overall response rate was 88% in A-CHOP patients (16/18) and 82% in CHOP patients 13/16; P=.2921 (**Table 1**). Seventeen A-CHOP and 15 CHOP patients finished treatment and were assessable. Response rates were 78.5% (60% complete responses) for A-CHOP and 81.1% (72% complete responses) for CHOP without statistical difference.

With a median of follow-up of 8.5 years, the median OS was 8.5 years for A-CHOP vs 8.7 for the CHOP arm (P=.496). A-CHOP was superior, but without significance in 8-year DFS (72.9% vs 55.6%; P=.50), and PFS (48.9% vs 36.3%; P=.652). The Cox-regression did not identify variables associated with DFS and PFS. The IPI was the only prognostic variable for OS (IPI low/low intermediate risk vs high intermediate/high risk; hazard ratio=2.98; 95% CI: 1.01-8.77; P=.048).

Toxicities

There were significant differences in leukopenia grade 4 (9% vs 18%; P=.031) and neutropenia grade 4 (13% vs 27%; P=.007). Febrile neutropenia was observed in 3/92 (3%) A-CHOP cycles and 8/85 (9%) CHOP cycles (P=.131). There was no requirement for platelet

Table 1. Patient and disease characteristics.

	A-CHOP		CHOP		*P*
	No.	%	No.	%	
Number of patients	18		16		
Age (Years)					
Median/range	74 (70-83)		73 (70-84)		.881[a]
Sex					
Female	11	61	9	56	
Male	7	39	7	44	.774[b]
Disease localization					
Nodal	15	83	14	88	
Extranodal	3	17	2	13	.732[b]
Clinical stage					
I-II	8	44	11	69	
III-IV	10	56	5	31	.154[b]
International Prognostic Index					
Low-intermediate low	9	50	9	56	
Intermediate high-high	9	50	7	44	.716[b]
Histology					
NHL DLBCL	14	78	12	75	
NHL peripheral T cell	1	6	1	6	
NHL mantle cell	2	11			
NHL malt high grade			1	6	
NHL follicular center grade III	1	6	1	6	
NHL unclassifiable			1	6	
Response					
Complete response	8	44	10	63	.535[b]
Partial response	8	44	3	19	
Disease progression			**1**	**6**	
Not evaluable	2	11	2	13	

[a]:t-student; [b]:chi-square test

transfusions. Red blood cell transfusion was required in 1 cycle of the A-CHOP group (1%) and in 4 cycles in the CHOP group (5%). Toxicity in 4/92 (4%) cycles led to hospitalization (median stay of 5 days) with A-CHOP and 11/85 cycles resulted in hospitalization (13%) with CHOP (median stay of 8 days, *P*=.05). Treatment delays (more than 28 days between chemotherapies) were reported in 22/92 (24%) and 26/85 (31%) cycles in A-CHOP and CHOP respectively (*P*=.317) and the main causes were neutropenia and severe asthenia (similar incidence in both arms). The only long-term toxicity consisted of two cardiac events—a ventricular extrasystole (A-CHOP arm) and an atrial fibrillation (CHOP arm).

DISCUSSION

Although the older population is growing, they are often excluded from clinical trials. Elderly patients are treated

Table 2. Chemotherapy treatment exposure.

	Cycle	Ideal level	A-CHOP		CHOP		*P* [a]
			n	Median	n	Median	
Dose (mg/m²)							
Cyclophosphamide							
	2nd	1500	17	1472[b]	16	1472[b]	.35
	4th	3000	15	2921[b]	14	2909[b]	.39
	6th	4500	11	4346[b]	12	4326[b]	.46
Doxorubicin							
	2nd	100	17	96.5[b]	16	96.4[b]	.46
	4th	200	15	190.5[b]	14	190.7[b]	.46
	6th	300	11	281.9[b]	12	285.9[b]	.32
Relative dose intensity (%)							
CHOP							
	2nd	100%	17	88%[c]	16	83%[c]	.07
	4th	100%	15	79%[c]	14	74%[c]	.08
	6th	100%	11	82%[c]	12	72%[c]	.03
Treatment duration (weeks)							
	2nd	6	17	6.4[d]	16	7[d]	.07
	4th	12	15	13.6[d]	14	14.8[d]	.07
	6th	18	11	20.7[d]	12	22.9[d]	.01

[a]P (1-tailed): Mann-Whitney U; [b]Median dose in mg/m²; [c]Median of percentage of ideal dose; [d]Median of duration period in weeks.

with suboptimal doses of chemotherapy due to fear of toxicity and comorbidities. A previous study from our group shown that in patients older than 60 years (61-69 vs ≥70 years old), there was no difference in the efficacy of chemotherapy, but there was in toxicity.[1,6]

The standard CHOP dose improves survival in patients with malignant lymphomas and a 20% to 30% dose reduction is associated with lower complete response rates and shorter OS. Although a relative dose intensity (RDI) ≥80% is a favorable factor for an increased OS; these patients are 2.7 times more likely to experience a hospitalization due to febrile neutropenia.[7] Unfortunately, there are few studies evaluating RDI effect of CHOP in patients >70 years old. Pfreundschuh et al suggested a new standard regimen of chemotherapy with CHOP-14 and G-CSF in patients >60 years with an ideal RDI of 150; however only 20% of the patients included were >70 years old.[8] In our study, the group receiving amifostine achieved a significantly higher RDI.

Balducci et al evaluated nine studies in elderly patients with aggressive lymphoma and found that the risk of severe hematologic toxicity in patients >70 years was about 40%. The risk of developing septic neutropenia was 21% to 47%, and the risk of death from infection was 5% to 30%.[9] In our study, grade 4 neutropenia was observed in 13% of A-CHOP cycles versus 27% in the control group. Likewise, febrile neutropenia was observed in 3% of all cycles with amifostine versus 10% in the group without amifostine. Finally, there were no deaths related to chemotherapy, which is probably the result of the low observed RDI.[9] Späth-Schwalbe et al evaluated amifostine plus CHOP in elderly patients with aggressive lymphoma. Patients over the age of 70 received a total of 207 cycles with amifostine and, in a pattern similar to our results, they reported grade 4 leukopenia in 15% of cycles, two cases of grade 3 anemias and febrile neutropenia in 4.3% of cycles, suggesting the efficacy of amifostine in reducing CHOP toxicity in elderly patients.[5]

Evaluating 177 cycles administered, we observed that

Table 3. Hematologic and non-hematologic toxicities.

	A-CHOP (92 Cycles)				CHOP (85 cycles)			
Events	**1**	**2**	**3**	**4**	**1**	**2**	**3**	**4**
Hematologic Toxicities								
Anemia	23	3			25	7		
Leukopenia[a]	9	25	42	9	8	22	40	18
Neutropenia[a]	32	18	37	13	22	12	32	27
Thrombocytopenia	23		1		22	4	1	
Non hematologic toxicities								
Emesis	8	1			1			
Diarrhea	4	5	1					
Fatigue	2	1			5			
Neuropathies	3							
Elevated SGOT	12			1	5		2	
Elevated SGPT	7	1		1	6	1		
Elevated Creatinine	8				16	2		

Values are percent. [a]Grade 4: *P*=.031, [b]Grade 4: *P*= .007

in >69 year-old NHL patients, CHOP plus amifostine was tolerated better than CHOP. A reduction in adverse events also reduced the number of hospitalizations during the treatment without modify the long-term outcome, but this should be studied with a larger sample size. We observed in both cohorts longer survivals than reported by Coffier et al (median OS of 3.5 years) for elderly patients treated with only CHOP.[10] In conclusion, amifostine allows use of CHOP in a programed schedule and prevents short-term toxicities without influencing statistically the treatment result in elderly patients with aggressive NHL treated with CHOP.

Author contributions

Data collection: HLG; FC; CSV; LV; LC; JL; FHM; CAC; JAP; data analysis: HLG; CF; JAP; manuscript preparation: all authors; manuscript approval: all authors.

Conflict of interest

The authors declared no conflict of interest.

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