Amifostine prevents secondary toxicity to CHOP chemotherapy in elderly patients with aggressive lymphoma: a randomized comparative study

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ABSTRACT

Background: The development of systemic chemotherapy regimens based on doxorubicin has been major therapeutic success in the treatment of lymphomas, however elderly patients have high morbidity and mortality related to this therapy. The aim of this work was to determine whether amifostine can effectively reduce chemotherapy-related side effects in non-Hodgkin's lymphoma (NHL patients).

Patients and methods: A randomized phase IIb trial was performed, comparing amifostine plus full-dose CHOP (A-CHOP) versus CHOP, in elderly patients (≥70 years) with aggressive NHL. Patients were randomized to receive 6 cycles of CHOP (cyclophosphamide 750 mg/m^2, doxorubicin 50 mg/m^2, vincristine 1.4 mg/m^2 on day 1 and prednisone 100 mg/day for 5 days, every 3 weeks) or A-CHOP (amifostine 910 mg/m^2 on day 1, plus CHOP).

Results: We included 34 previously untreated patients (18 A-CHOP, 16 CHOP). Demographic and disease characteristics, and prognostic factors were comparable between the two groups. Response rates were 89% (complete response [CR] 60%) for A-CHOP and 82% (CR 64%) for CHOP. A total of 73/92 (81%) planned cycles of A-CHOP and 69/85 (82%) of CHOP were administered with a median time of treatment delivery of 17.7 weeks (A-CHOP) and 19.9 weeks (CHOP) (p=0.05). Blood transfusion was required in 1/92 (1%) and 4/85 (5%) cycles of A-CHOP and CHOP respectively. Hospitalization for toxicity occurred in 4/92 (4%) A-CHOP cycles and 11/85 (13%) CHOP cycles (p=0.05). Febrile neutropenia occurred in 3/92 A-CHOP (3%) cycles and 8/85 (10%) CHOP cycles. The total durations of hospitalization due to chemotherapy toxicity were 21 days with A-CHOP and 76 days with CHOP.

Conclusion: Tolerance of the high dose CHOP regimen was significantly improved with amifostine in this elderly NHL population.

INTRODUCTION

Treatment of elderly patients with aggressive non-Hodgkin's lymphoma (NHL) It remains a true challenge to the medical oncologist due to the fact that many such patients are not candidates for standard dose chemotherapy, due to poor tolerance (1). With advancing age, the capacity of the bone marrow to respond to stimuli such as chemotherapy or cytokines is diminished (2). Likewise these patients have decreased kidney and liver functioning, which in turn may affect the pharmacokinetics and pharmacodynamics of cytostatic agents, resulting in the chemotherapy having a greater toxic impact (3, 4, 5, 6, 7). Nowadays, prevention of these toxicities has led to a new line of research, with the search for cytoprotector agents. As a result, novel agents are available for treatment, such as amifostine which provides cytoprotection against nephrotoxicity, neurotoxicity, ototoxicity and hematological toxicity induced by chemotherapy (8, 9, 10, 11, 12).

Amifostine is a selective broad-spectrum cytoprotector, which acts as a scavenger of free radicals, protecting normal tissues (13). This inactive pro-drug, is transformed to active thiol after dephosphorylation by alkaline phosphatase, which is found in the normal epithelium. In contrast, the absence of this enzyme in tumor tissue and the acidity of the tumoral environment, prevent the activation of the drug and cytoprotection of the tumoral cells, explaining the selectivity of the drug (14). In clinical trials, amifostine given in association with chemotherapy has been proven to reduce chemotherapy-associated toxicity, whilst the effectiveness of the antineoplastic drugs remains unaltered (15, 16, 17).

The influence of amifostine on toxicity of CHOP (cyclophosphamide, adriamycin, vincristine, and prednisolone) in elderly patients with aggressive NHL has been evaluated in a single arm study, suggesting that the use of amifostine was associated with a low level of toxicity, whilst not impairing the treatment outcome (16). The purpose of the current study was to evaluate the effectiveness of amifostine in a comparative trial, in elderly patients suffering of NHL receiving CHOP treatment with a curative intent.

MATERIAL AND METHODS

Study design

This prospective trial was performed in two hospitals, in Lima, Perú, including patients from September 2000 to October 2001. It was a randomized phase IIb clinical trial in elderly patients with aggressive NHL. Inclusion criteria were: older than 69 years of age, performance status 0-1 (ECOG scale), diagnosis of aggressive NHL of the following types (WHO classification): diffuse large B cell lymphoma, non specific peripheral T-cell lymphoma, anaplastic T-cell lymphoma, grade II follicular lymphoma and mantle cell lymphoma (not blastoid); adequate bone marrow reserve as measured by absolute neutrophil count of at least 1.5 x 10^9/L and platelets over 100 x 10^9 /L; normal renal and hepatic function; and left ventricle ejection fraction greater than 50% (isotopic ventriculography). Exclusion criteria were: previous chemotherapy, radiation therapy or modifiers of biological response, patients with encephalic or meningeal infiltration by lymphoma, HIV infected patients, those receiving chronic corticosteroids treatment discontinued at least one week before inclusion or that require continuous treatment between courses of chemotherapy, history of cardiac disease, active infections or illnesses that preclude 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 protocol was approved by the local hospital ethics committee, and all patients signed a written informed consent.

Patients were randomized to two treatment arms; A-CHOP: 6 cycles of amifostine 910 mg/m^2 on day 1 plus a standard dose of CHOP (cyclophosphamide 750 mg/m^2, doxorubicin 50 mg/m^2, vincristine 1.4 mg/m^2 on day 1 and prednisone 100 mg/day for 5 days) every 3 weeks or CHOP: 6 cycles of standard CHOP without amifostine, every 3 weeks. The calculated dose of amifostine was added to normal saline to a total volume of 100 ml and given intravenously in a 15-minute continuous infusion before the chemotherapy (doxorubicin as the first drug).

Parameters used to assess the efficacy of amifostine in preventing secondary effects of chemotherapy were: incidence of febrile neutropenia and infections requiring parenteral antibiotics and other adverse events, the need to postpone or reduce the chemotherapy dose or to suspend the treatment because of severe toxicity, number of cycles resulting in hospitalization due to toxicity and duration of hospitalization and requirements of red blood cells and/or platelet transfusions.

The Total Dose is the sum of each single dose of cyclophosphamide and doxorubicin per square meter. Relative dose intensity (RDI) was calculated according to the Hryniuk and Bush method (18) and is expressed as mg/m²/week.

Statistical analysis

The statistical analysis included descriptive tabulations of the clinical characteristics of patients in both arms of the study and the comparison between them. The statistical methods used were t-student, Chi-square or the exact Fisher test to assess the homogeneity and comparability of the groups of treatment.

We performed evaluations of total dose and relative dose intensity of cyclophosphamide and doxorubicin and the duration of receipt of six cycles of treatment in both arms, by Mann-Whitney U test using the simulation method of Monte Carlo.

All statistical evaluations were performed at a level of significance of 5% and data were processed using SPSS version 9.0.

RESULTS

A total of 34 patients with a diagnosis of aggressive NHL were enrolled in the study between September 2000 and October 2001. Eighteen of the 34 patients

were randomized to receive CHOP with amifostine and 16 to receive CHOP only.

Patient and Disease Characteristics

Patient characteristics were well balanced between the two arms, as shown in Table 1. Patients ranged in age from 70 to 84 years, with a median of 74 and 73 years in the A-CHOP and CHOP arms respectively (p = 0.8). Sixty-one percent of patients were male in the A-CHOP arm and 56% in CHOP (p = 0.7). Ten of the 18 (55%) A-CHOP patients had a clinical stage III-IV and five of 16 (32%) in the CHOP arm (p = 0.1). According to the international prognostic index, the distribution was intermediate-high to high in nine of 18 (50%) patients in A-CHOP and seven of 16 (44%) patients in CHOP arm (p = 0.7).

Treatment Administration

Eleven of the 18 (61%) A-CHOP patients completed six cycles of chemotherapy and 12 of the 16 (75%) CHOP patients (Table 2). Fifteen of the 18 (83%) A-CHOP patients, and 14 of 16 (88%) CHOP patients received at least four chemotherapy cycles. The five patients who did not complete at least 4 cycles of chemotherapy withdrew from the study due to withdrawal of consent, disease progression (one patient each) and toxicity in three patients (one A-CHOP, two CHOP). A total of 177 cycles were administered and all were included in the analysis, with 92 and 85 cycles administered in A-CHOP and CHOP, respectively, thenad a median of 6 cycles in both arms.

Total Dose, Relative Dose Intensity and Response to Treatment

Comparison of the total chemotherapy dose, in all cycles and every two cycles, showed no statistical difference between arms (Table 2 and 4). Median treatment duration in patients receiving 6 cycles was significantly shorter for A-CHOP compared to CHOP (17.7 versus in relation to 19.9 weeks respectively; p= 0.01), Similarly, median relative dose intensity, showed a favorable difference with A-CHOP , being significant from the fourth cycle.

The overall response rate was 88% in A-CHOP patients (16 out of 18) and 82% in CHOP patients (13 out of 16; Table 1). Response rates were not statistically different (p= 0.2).

Toxicity

Febrile neutropenia was observed in 3 of the 92 (3%) A-CHOP cycles and 8 of the 85 (9%) CHOP cycles. Toxicity in 4 of the 92 cycles led to hospitalization (4%) in A-CHOP treated patients with a median stay of 5 days (table 03). Eleven of the 85 (13%) CHOP cycles resulted in hospitalization with a median stay of 8 days. This tendency was reflected clinically, with significant differences in rates of toxicity by cycle between the two treatments. Red blood cell transfusion was required in 1 cycle of A-CHOP (1%) and 4 in CHOP (5%). There was no requirement for platelet transfusions. There was no statistical significant difference between arms in relation to hematological and biochemical laboratory tests.

Treatment delays (more than 28 days between chemotherapies) were reported in 22/ 92 (24%) and 2/ 85 (31%) cycles in A-CHOP and CHOP respectively. The main causes of these delays were neutropenia and severe asthenia, and were similar in the two arms.

DISCUSSION

In the middle of the last century, aggressive malignant lymphoma was a uniformly fatal disease. However the development of systemic chemotherapy regimens based on the cytotoxic doxorubicin, has been major therapeutic success, further improved by the more recent addition of monoclonal antibodies to chemotherapeutic regimens (19). Nonetheless, many studies in elderly patients report high morbidity and mortality associated with the successful chemotherapy. Moreover, elderly patients are often excluded from clinical studies due to poor tolerance to chemotherapy, an inadequate performance status and presence of co-morbid diseases. The elderly are rarely proportionally represented in clinical studies due to their inclusion criteria, leading us to question conclusions made about this population.

Our group has previously studied the biological characteristics and clinical reality of NHL in a local population of elderly patients. Thirty percent of our population of elderly patients with this malignancy do not receive treatment for it. Furthermore, the proportion of elderly NHL patients receiving treatment with anthracycline-based regimens is lower than in other age groups. We showed that the principal prognostic factors for treatment success are ECOG performance status and clinical stage at diagnosis (20).

Some authors have suggested that chemotherapy with standard dose CHOP improves survival of patients with malignant lymphoma, rather the 20-30% reduced dose which is associated with a lower complete response rate and a shorter overall survival. An RDI of at least 80% is recognized to be a favorable factor for increased overall survival in patients with malignant lymphoma. Morrison et al. (2001) evaluated the relationship between age and dose intensity of CHOP. An RDI of 80% or less was observed in 24.3% of patients over 75 years compared to only 9% in patients under 60 years. Furthermore, the risk of hospitalizations due to chemotherapy-associated toxicity was higher in the elderly than in younger patients (21).

Unfortunately there are very few studies evaluating the RDI of CHOP in patients over 70 years. Pfreundschuh et al. (2004), suggest a new standard regimen of chemotherapy with CHOP-14 and G-CSF in patients over 60 years with an ideal RDI of 150%, however in their study, only 20% of the patients were over 70 years old and is very difficult to apply their findings to the subgroup of older patients (22). In our current comparative study, all patients were older than 70 years and treated with CHOP at standard doses, the group receiving amifostine achieved an RDI of 80%, with a significant difference compared to the control group, which reached an RDI of 72%. It is clear from our results that patients over 70 years receiving chemotherapy require cytoprotective support in order to achieve an acceptable RDI and thus improve their survival.

Chemotherapy-related toxicities are the most frequent adverse events in elderly NHL patients who receive treatment for their disease, and often limit the administration of full dose chemotherapy. Morrison et al. (2001), found that patients receiving an RDI of at least 80% were 2.7 times more likely to experience a hospitalization due to febrile neutropenia (21). Recently, research has been aimed at preventing chemotherapy-related toxicity, including evaluation of these agents in association with amifostine. In the update of the American Society of Clinical Oncology (2002), for the use of protective drugs against chemotherapy side effects, the panel recommended that amifostine should be considered in order to reduce episodes of neutropenia in patients receiving chemotherapy based on alkylating agents (23). However, the usefulness of amifostine to prevent toxicity has not been evaluated in depth in elderly patients.

The risk of severe hematologic toxicity from chemotherapy in patients over 70 years is about 40%, as reported in a review by Balducci et al. evaluating nine trials in elderly patients with aggressive lymphoma. They determined that the risk of developing septic neutropenia was between 21% and 47%, and the risk of death from infection was between 5% and 30% (24). In our study, in 13% of cycles with CHOP plus amifostine, patients developed grade 4 neutropenia 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 a result of the low RDI.

Späth-Schwalbe et al. (2002) evaluated the use of four amifostine plus CHOP cycles in elderly patients with aggressive lymphoma. Patients over the age of 70 received a total of 207 cycles with amifostine. The reported grade 4 leucopenia in 15% of cycles, two cases of grade 3 anemia and febrile neutropenia in 4.3% of cycles, are similar to our data, supporting our conclusion that amifostine plays a role in reducing CHOP toxicity in elderly patients. The authors recommend this be further studied in a randomized trial.

There are several studies evaluating the use of G-CSF plus chemotherapy in elderly patients with NHL, which suggest a significant reduction in the incidence of neutropenia, complications from infections, antibiotic use and duration of hospitalizations. Ozer, based on recent recommendations for the use of hematopoietic colony-stimulating factors, recommends that any chemotherapy regimen exceeding 40% febrile neutropenia should receive primary prophylaxis with hematopoietic growth factors as standard treatment (25). Repetto et al., moreover, based on "Use of Growth Factors in the elderly patient with cancer: a report from the Second International Society for Geriatric Oncology (SIOG) 2001 meeting, recommended that elderly patients with cancer should not be denied the administration of a curative chemotherapy when appropriate palliative chemotherapy was not available for this group of patients, and prophylactic therapy should be provided with appropriate growth factors, to avoid complications (26).

We thus suggest that amifostine has a role in the prevention of hematological and renal toxicity caused by CHOP. Further studies to determine the cytoprotective activity of amifostine as compared to hematopoietic growth factors are required.

In our study, the results obtained during administration of chemotherapy, in terms of febrile neutropenia events, number and length of hospital stays and transfusions of red blood cells, were lower in patients who received amifostine.

Conclusion

The results obtained in this study show that patients over the age of 69 treated with the CHOP regimen in association with amifostine, better tolerate chemotherapy than those treated only with CHOP alone. This improved tolerance is reflected in the reduction of hematologic, non-haematological toxicity, along with the frequency of febrile neutropenia events. The reduction of adverse events in patients treated with amifostine also reduced the number of hospitalizations during the course of treatment.The addition of amifostine decreases the number of related adverse events with CHOP therapy and allows a high dose intensity, which would be expected to have a direct impact, not yet demonstrated, on the treatment outcome.

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Tables

Table 1: Patient and disease characteristics

	A-CHOP		CHOP		
	No.	**%**	**No.**	**%**	**p**
Patients	18		16		
Age (years)					
Median / range	74 / (70 - 83)		73 / (70 - 84)		0.881[t]
Sex					
Female	11	61%	9	56%	
Male	7	39%	7	44%	0.774[x]
Disease Localization					
Nodal	15	83%	14	88%	
Extranodal	3	17%	2	13%	0.732[x]
Clinical Stage					
I- II	8	44%	11	69%	
III-IV	10	56%	5	31%	0.154[x], /1
Index international prognosis					
Low-intermediate low	9	50%	9	56%	
Intermediate high - high	9	50%	7	44%	0.716[x], /2
Histology					
NHL DBLCL	14	78%	12	75%	
NHL Peripheral T	1	6%	1	6%	
NHL Mantle	2	11%			
NHL Malt high grade			1	6%	
NHL CF grade III	1	6%	1	6%	
NHL Unclassifiable			1	6%	
Response					
Complete response	8	44%	10	63%	
Partial response	8	44%	3	19%	
Disease progression	-		1	6%	
Not evaluable	2	11%	2	13%	

t: t-student, x: Chi-squared., /1: I-II vs III-IV y /2: Intermediate-high and high vs Intermediate-low and low
CF: DBLCL : diffuse B large cell lymphoma ; NHL: non-Hodgkin lymphoma;

Table 2: Chemotherapy treatment exposure

		A-CHOP		CHOP		
	Cycles	**N patients (N=18)**	**Median**	**N patients (N=16)**	**Median**	**p-value**
Median total dose (mg/m²)						
Cyclophosphamide	2nd	17	2260	16	2325	0.218
	4th	15	4505	14	4462	0.401
	6th	11	6700	12	6713	0.412
Doxorubicin	2nd	17	150	16	150	0.305
	4th	15	300	14	298	0.406
	6th	11	440	12	443	0.484
Median N treatment weeks	2nd	17	3.4	16	4.0	0.079
	4th	15	11.3	14	12.3	0.093
	6th	11	17.7	12	19.9	0.010
Median dose intensity (mg/m²)						
Cyclophosphamide	2nd	17	220	16	211	0.125
	4th	15	416	14	406	0.360
	6th	11	213	12	181	0.028
Doxorubicin	2nd	17	15	16	14	0.110
	4th	15	27	14	27	0.346
	6th	11	13	12	12	0.028

P (2-tailed): Mann - Whitney U

Table 3. Neutropenia and hospitalizations during the treatment, by cycle

	A-CHOP		CHOP		
	N	%	N	%	p
Total N of Cycles	92		85		
Febrile Neutropenia	3	3%	8	9%	0.056
N cycles with hospitalization due to neutropenia	4	4%	6	7%	0.524
N cycles with hospitalization due to chemotherapy	12	13%	15	18%	0.521

Table 4. Cyclophosphamide dose administered in each cycle

	Equality of variances Levene´s test		Equality of means		
Cycle	**F**	**p**	**t**	**df**	**p**
1	1.044	0.315	-0.178	32	0.860
2	0.820	0.372	-0.203	31	0.841
3	5.556	0.025	0.498	20	0.624
4	2.116	0.158	0.530	26	0.600
5	0.303	0.587	0.226	24	0.823
6	1.200	0.286	0.247	20	0.808

Trends of Cyclophosphamide dose (CTX) between two treatment arms

F- approximate of Wald's statistics p = 0.177.

Table 5. Changes in hematological parameter values, by cycle

		Baseline		Cycle 1		Cycle 2		Cycle 3		Cycle 4		Cycle 5		Cycle 6	
	Arm	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Hb (g/dl)	A-CHOP	12.97	1.60	11.83	1.23	11.39	1.58	11.18	1.06	10.91	1.26	10.53	1.14	10.75	1.64
	CHOP	12.49	1.66	11.33	1.51	10.64	1.26	10.60	1.15	10.35	1.15	10.40	1.40	10.29	1.37
	p	0.404		0.293		0.143		0.153		0.233		0.799		0.489	
WBC cells/mL	A-CHOP	6257.22	1760.01	2242.22	1167.31	1898.82	1127.26	2022.35	783.58	2352.67	1478.33	2801.43	1564.13	2835.45	1645.43
	CHOP	6016.25	2161.32	1857.50	1234.98	1655.63	1298.94	2090.71	1059.81	1890.77	1107.60	1992.50	1031.13	1800.00	1089.04
	p	0.723		0.358		0.569		0.838		0.364		0.140		0.097	
ANC cells/mL	A-CHOP	4452.89	1510.93	1206.56	979.66	1002.53	940.25	1166.82	727.54	1167.53	858.39	1392.64	778.04	1568.36	1034.31
	CHOP	4248.69	1979.00	807.06	870.86	839.06	792.62	1245.36	869.24	988.23	624.06	1130.75	852.18	1126.60	1011.16
	p	0.736		0.220		0.594		0.786		0.539		0.421		0.336	
Platelets cells/mL	A-CHOP	302.78	111.36	206.11	91.78	212.82	97.10	185.47	51.71	240.67	96.22	223.64	89.60	190.55	67.86
	CHOP	286.94	80.51	210.88	109.23	184.63	69.20	216.00	80.77	204.69	56.75	193.00	67.37	195.82	94.42
	p	0.642		0.891		0.347		0.212		0.234		0.341		0.882	

SD, standard deviation, P, t-student.
ANC: absolute neutrophil count; Hb: hemoglobin; WBC: white blood cells