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Clinical report

Influence of amifostine on toxicity of CHOP in elderly patients with aggressive non-Hodgkin's lymphoma—a phase II study

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Due to concerns about toxicity, many elderly patients with aggressive non-Hodgkin's lymphoma (NHL) are not considered candidates for standard chemotherapy with cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP). The cytoprotective agent amifostine has the potential to reduce toxicity when added to chemotherapy. The purpose of the current study was to examine the toxicity of CHOP combined with amifostine in elderly patients with aggressive NHL. A prospective phase II study was performed in patients aged 60 years and older. Patients with stage I/II disease received 4 cycles of CHOP followed by involved-field irradiation. Patients with stage III/IV received 6–8 cycles of CHOP. Amifostine (740 mg/m^2) was administered as a 15-min i.v. infusion immediately before chemotherapy. Forty-one (median age 69.5 years, range 60–87) of 49 consecutive previously untreated patients, aged 60 years and older, with aggressive NHL seen in our center were included in the study. Twenty-one patients had stage I/II disease and 20 had stage III/IV disease. The patients received a total of 207 cycles of amifostine–CHOP. Infusion of amifostine caused mild to moderate transient side effects, including a drop of systolic blood pressure >20 mmHg in 54 cycles and nausea/vomiting in 36 cycles. Hematotoxicity of CHOP consisted of leukopenia grade 4 in only 15.4% of cycles. There were two cases of grade 3 anemia. No thrombocytopenia higher than grade 2 occurred. Febrile neutropenia was rare, occurring in 4.3% of cycles. One patient died after the first CHOP administration because of anthracycline-related acute cardiomyopathy (corresponding to a toxic death rate of 2.4%). The complete response rates were 85 and 75% in stage I/II and stage III/IV patients, respectively. After median follow-up of 33 months (range 17–50 months) the median overall survival was not reached in patients with stage I/II and was found to be 32 months in patients with stage III/IV. At 2 years, 76% of patients with stage I/II and 70% with stage III/IV were alive. Twelve of the 15 patients who died were aged older than 70. Amifostine pre-treatment was associated with a low toxicity of CHOP in elderly patients with aggressive NHL treated with curative intent. Treatment outcomes appeared not to be impaired by the addition of amifostine to CHOP. This schedule merits further testing in a randomized trial. [© 2002 Lippincott Williams & Wilkins.]

Key words: Aggressive non-Hodgkin's lymphoma, amifostine, CHOP, elderly, toxicity.

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Introduction

A high percentage of aggressive non-Hodgkin's lymphomas (NHL) occur in patients older than 60 years.[1] Due to demographic changes and the rapid increase in incidence rates of aggressive NHL, more and more old and very old people will be diagnosed with these lymphomas.[2,3] During the last decade progress has been made in defining treatment standards, but treatment outcomes are still unsatisfactory, especially in elderly patients.

Advanced age is an adverse prognostic factor for patients with aggressive NHL.[4,5] Many factors may contribute to the poorer outcomes of elderly patients. Differences in the biology of the disease in elderly people in comparison to their younger counterparts may be the reason for the different prognosis. However, except for large cell anaplastic lymphoma, no clear age-related difference in the biology of aggressive NHL has been described so far.[3,6] Co-morbidity and poor functional status are factors with a negative impact on treatment results in elderly patients with aggressive NHL.[1,7] Co-morbidity and poor functional status may influence outcome in elderly patients in different ways, e.g. through a

higher rate of lymphoma-unrelated death, higher treatment-related toxicity and suboptimal or in some cases no treatment.[7–11] Suboptimal treatment has been suggested as being the main reason for inferior outcomes in a significant subset of patients older than 60 years with aggressive NHL. Suboptimal treatment may arise from the physician's judgment or patient's or family's choice, fear of higher treatment-related toxicity being the main motivating factor.[3,10] Thus, if fear of toxicity is a major obstacle to administration of standard treatment, then attempting to reduce the toxicity of standard antineoplastic therapy seems to be a reasonable approach to adopt.

Prospective randomized trials have clarified that aggressive NHL in the elderly should be treated with full-dose CHOP or CHOP-like regimens whenever possible.[12–15] Patients with localized aggressive NHL should receive 3–4 cycles of CHOP followed by involved-field radiotherapy.[16–18] In patients with advanced disease, 6–8 cycles of CHOP should be administered.[12,19] The value of additional radiation is not clear in this situation.[9]

Myelotoxicity is the most common complication of cytotoxic chemotherapy. The risk of grade 3 and 4 myelosuppression increases with age.[20] In one recent study in patients with aggressive NHL aged 70 years or older receiving full-dose CHOP, grade 4 neutropenia was in excess of 70%, which was 3 times as high as in the group of patients aged 61–69 years.[21] The complications of severe neutropenia are particular devastating in older individuals. In a retrospective study in patients 60 years of age or older with aggressive NHL who received CHOP there was a toxic death rate of 13% and infections accounted for 82% of the toxic deaths.[22] Since infectious complications, mainly associated with neutropenia, represent a prominent cause of morbidity and mortality among elderly patients treated with CHOP, the use of hematopoietic growth factors is considered an attractive option in these patients.[20] Two randomized trials evaluated the benefit of granulocyte colony stimulating factor (G-CSF) in elderly patients with aggressive NHL receiving CHOP.[15,23] Both trials yielded similar findings. G-CSF added to CHOP results in less infectious complications. In one study this was associated with decreased use of antibiotics and less mitigation of CHOP chemotherapy.[23] Unfortunately this does not result in improved survival rates in aggressive NHL in elderly patients.

Further aspects of toxicity have to be considered. Growth factors do not afford protection against other toxicities associated with CHOP, especially cardiotoxicity from doxorubicin and neurotoxicity from vincristine. The incidence of anthracycline-related cardiotoxicity increases with age.[24,25] Neurotoxicity from vincristine seems to be more common in elderly patients.[26] Therefore, an agent that protects against myelotoxicity, cardiotoxicity and neurotoxicity would be particularly valuable in elderly patients receiving CHOP.

Amifostine (WR-2721), an aminothiol, is a broad-spectrum cytoprotective agent.[27] Amifostine provides protection against cyclophosphamide-induced myelosuppression.[28,29] Preclinical studies have demonstrated that amifostine is cardioprotective, possibly by scavenging reactive oxygen species produced by doxorubicin.[30,31] Finally, clinical observations suggest that amifostine has neuroprotective properties.[32,33] These findings provided the basis for a phase II trial of amifostine given before every cycle of CHOP chemotherapy in elderly patients with aggressive NHL.

Patients and methods

Forty-one (median age 69.5 years, range 60–87) of 49 consecutive previously untreated patients, aged 60 years and older, with aggressive NHL seen in our center from January 1997 through December 1999 were included in the study and given amifostine–CHOP. Written informed consent was obtained from all patients. Eligibility criteria included age $\geqslant$60 years and aggressive NHL, i.e. a confirmed histologic diagnosis of diffuse large B cell lymphoma, anaplastic large cell lymphoma or peripheral T cell lymphoma according to the REAL classification;[1,34] WHO performance status 0–3; echocardiographically estimated left ventricular ejection function (LVEF) $\geqslant$40%. Patients with prior indolent lymphoma, or human immunodeficiency infection were excluded. Patients were also excluded if they had other illnesses that precluded the use of CHOP, such as polyneuropathy (vincristine). The staging work-up included a physical examination, a computed tomography scan of the supraclavicular region, thorax and abdomen, and a bone marrow biopsy in all patients. Cerebrospinal fluid was analyzed if clinically indicated. Bulky disease was defined as a tumor mass $\geqslant$10 cm. All patients were assessed for toxicity according to the common toxicity criteria (CTC). Cardiac function was monitored echocardiographically. LVEF was measured before treatment and then every other cycle. Biochemical and hematologic examinations (complete blood count) were performed before each cycle, additional blood cell

counts were performed on days 7 and 14 of each cycle. Use of hematopoietic growth factors in case of neutropenia was not permitted and no patient received such treatment.

With respect to assessment of co-morbidity, chronic obstructive pulmonary disease, hypertension and diabetes were only recorded if the patient received current medical treatment during admission. Cardiovascular, cerebrovascular and other vascular diseases were also included after a circulatory event or vascular surgery.[35]

Treatment

The CHOP regimen was administered as follows: cyclophosphamide 750 mg/m^2 given i.v. on day 1, vincristine 2 mg given i.v. on day 1, doxorubicin 50 mg/m^2 given i.v. on day 1 and prednisone 100 mg given orally on days 1–5. A new course was repeated every 21 days. Treatment was delayed by 1 week in case of grade 3 and 4 toxicity (CTC) at day 21, except for alopecia. Vincristine was stopped in the event of grade $\geqslant 2$ neurotoxicity. A 33% dose reduction was initiated for cyclophosphamide and doxorubicin if the neutrophil count was between 1.0 and 1.5×10^9/l, or if the platelet count was less than $100\,000 \times 10^9$/l on day 28.

Amifostine 740 mg/m^2 was administered as a 15-min i.v. infusion before chemotherapy. Patients received ondansetron 8 mg i.v. and 250 ml of 0.9% saline before amifostine. Heart rate and blood pressure were monitored every 2–5 min during amifostine infusion. In the event of hypotension, administration was modified according to the guidelines provided by Kemp *et al.*[32] The patient's routine medication (e.g. antihypertensive drugs) was continued on the day of chemotherapy.

Patients with stage I/II disease received 4 cycles of amifostine–CHOP followed by involved field irradiation if response to chemotherapy was 'no change' or remission. The radiotherapy doses ranged from 4000 to 5500 Gy. The radiotherapy ports included all visible sites of disease determined before biopsy and treatment with CHOP. Patients with stage III/IV disease received 6–8 cycles of amifostine–CHOP. Response was assessed after the second and fourth cycle in all patients, and again after 6 cycles in stage III/IV patients. Two additional cycles were given to patients with stage III/IV if 6 cycles were required to achieve a complete response. Patients with evidence of progressive disease during therapy were withdrawn from the protocol and treated at the discretion of the attending physician. These patients have been retained in the analysis.

Assessment of response

Responses were assessed and progression-free survival as well as overall survival were indicated according to the guidelines provided by Cheson *et al.*[36]

Analysis and statistics

Received dose intensity of doxorubicin and cyclophosphamide was calculated by dividing the total received dose of each drug by the number of weeks of treatment. The number of treatment weeks was defined as the time required to complete all cycles of therapy and was measured from the day chemotherapy commenced until the day when a hypothetical additional cycle of therapy would have been given. One patient who died after the first administration of CHOP was excluded from this analysis.

The survival curves are depicted in accordance with the Kaplan–Meier method. All calculations were performed using SPSS for Windows.

Results

Forty-one of 49 consecutive previously untreated patients, aged 60 years and older, with recently diagnosed aggressive NHL (83.7%) were included in the study. Reasons for exclusion from the study were an ECOG grade 4 performance status (n=2), cardiac disease with LVEF < 40% (n=2), polyneuropathy (n=1), dementia (n=1) or patient choice (n=2 refused any chemotherapy). The median age of the patients included in the study was 69.5 years (range 60–87). According to the REAL classification 40 patients had diffuse large B cell lymphoma and one patient had peripheral T cell lymphoma. The results are analyzed for the total group and for two age subgroups: 60–69 years of age (n=21) and 70 years of age or older (n=20). The characteristics of the patients are depicted in Table 1.

Amifostine side effects

The most significant side effects during the amifostine infusions were transient hypotension and nausea/vomiting (Table 2). Amifostine infusion had

Table 1. Patient characteristics

	All patients (n=41) [no. (%)]	60–69 years (n=21)	70–87 years (n=20)
Sex			
female	19 (46.3)	9	10
male	22 (53.7)	12	10
ECOG performance status			
0	8 (19.5)	6	2
1	16 (39.0)	11	5
2	14 (34.2)	3	11
3	3 (7.3)	1	2
Ann Arbor stage			
I/II	21 (51.2)	12	9
III/IV	20 (48.8)	9	11
B symptoms	11 (26.8)	4	7
Extranodal involvement	20 (48.8)	10	10
Elevated LDH level	22 (53.7)	9	13
Bulky disease	12 (29.3)	6	6
International Index			
low	8 (19.5)	6	2
low/intermediate	15 (36.6)	9	6
high/intermediate	8 (19.5)	3	5
high	10 (24.4)	3	7
Co-morbidity			
0	15 (36.6)	10	5
1	9 (22.0)	5	4
$\geqslant$2	17 (41.5)	6	11

Table 2. Side effects of amifostine (percent of cycles)

Symptom	All patients (% of n=207 cycles)	60–69 years (% of n=108 cycles)	70–87 years (% of n=99 cycles)
Drop in systolic blood pressure			
$\leqslant$20 mmHg	58.9	60.2	57.6
$>$20 mmHg	26.1	23.2	29.3
Nausea/vomiting	17.4	16.2	20.2
Feeling of warmth	24.6	27.8	21.2
Sneezing	9.2	11.1	7.1
Dry mouth	3.9	4.6	3.0

to be interrupted in 20 of 207 courses (12 times in patients aged 70 years or older; 8 times in patients under 70 years) due to hypotension but was restarted in all but 3 cases after blood pressure had returned to baseline levels. Hypotension did not result in medical sequelae in any of the patients. Side effects were similarly frequent in the patients under 70 and over 70 years old.

Dose delivery

All patients with stage I/II disease received the scheduled 4 cycles of chemotherapy. In four of 20 patients with advanced disease, one cycle of chemotherapy had to be postponed for more than 1 week due to toxicity. Four of these patients were older than 70 years. In two patients with advanced disease (older than 70 years) chemotherapy was stopped prematurely after 5 cycles due to toxicity. Except for 3 cycles, chemotherapy was administered without dose reduction for doxorubicin and cyclophosphamide. These dose reductions were carried out in two patients older than 70 years. Nine patients did not receive the planned dose of vincristine due to neurotoxicity. Seven of these patients were older than 70 years. Treatment was stopped after 4 cycles in one patient with advanced disease due to disease progression

The mean ($\pm$SD) dose per week was 15.3 ± 1.4 mg/m^2 for doxorubicin and 230.2 ± 20.3 mg/m^2

Table 3. Worst hematotoxicity and mucositis (CTC)

Symptom	All patients (% of *n*=207 cycles)	60–69 years (% of *n*=108 cycles)	70–87 years (% of *n*=99 cycles)
Leukopenia			
grade 3	42.5	41.7	43.4
grade 4	15.4	13.9	17.2
Anemia			
grade 2	9.2	3.4	12.1
grade 3	1.0	0.9	1.1
Thrombocytopenia			
grade 2	1.9	0	4.0
Febrile neutropenia	4.3	3.7	5.1
Mucositis (grade 1/2)	4.8	3.7	6.1

for cyclophosphamide. The mean weekly dose for doxorubicin and cyclophosphamide tended to be lower in the patients aged 70 years and older compared with the younger patients, but the difference was not statistically significant.

Toxicity of chemotherapy

There was one toxic death (2.4% toxic death rate) which occurred in a 73-year-old women who developed acute anthracycline-associated cardiomyopathy after her first course of CHOP.

Grade 4 leukopenia occurred in 15.4% of cycles (Table 3). The respective figures are 13.0 and 16.9% in patients with I/II and patients with stage III/IV disease. Febrile neutropenia was rare occurring in 4.3% of cycles. Febrile neutropenia was seen in 14.3% of patients aged 60–69 years and 25.0% of patients older than 69 years. Only two patients with localized NHL experienced febrile neutropenia compared with six patients with advanced NHL. There were only seven hospitalizations due to febrile neutropenia. No life-threatening infection was seen. Two patients once required transfusion of red blood cells. There was no clinically significant thrombocytopenia (Table 3).

The incidence of mucosal damage was low, and no patient showed grade 3 or 4 mucosal toxicity.

A 10–5% asymptomatic decline in left ventricular ejection fraction occurred in two patients. Three patients experienced a decline of more than 15%. In one patient this happened after 5 cycles of CHOP and led to cessation of treatment. In the other patients the worsening of left ventricular ejection fraction occurred after the last cycle of CHOP. Only one of these five patients was younger than 70 years. This patient had myositis. His left ventricular ejection fraction recovered completely after treatment with prednisone. All of the remaining four patients had coronary heart disease, and three of them also had hypertension.

Nine patients developed neurotoxicity of grade 2 or more. Although vincristine was stopped in these patients, polyneuropathy progressed temporarily to grade 3 in four patients, of whom three were older than 70 years.

Response to treatment; survival

In patients with stage I/II disease, 13 of 20 (65%) had complete remission (CR)/CRu, six had partial remission (PR) and one had stable disease after 4 cycles of chemotherapy. After radiotherapy the remission rate increased to 100% , and the CR rate increased to 85%.

We observed 11 CRs, four CRus (CR/CRu rate 75%), four PRs (20%) and one progression during chemotherapy in patients with stage III/IV disease.

After a median follow-up period of 33 months (range 17–50 months) the median overall survival was not reached in patients with stage I/II, and overall survival was 32 months in patients with stage III/IV (Figures 1 and 2). At 2 years, the progression-free survival rate was 67% in stage I/II and 61% in stage III/IV, and the overall survival rate was 76% in stage I/II and 71% in stage III/IV. The most frequent cause of death was lymphoma (11 of 15 deaths). One patient died of pneumonia in CR. One patient died of a cardiac event shortly after cranial radiation for relapse. One patient died of an unknown cause and, as already mentioned, one patient died during treatment. Notably, 12 of the 15 patients who died were older than 70 years.

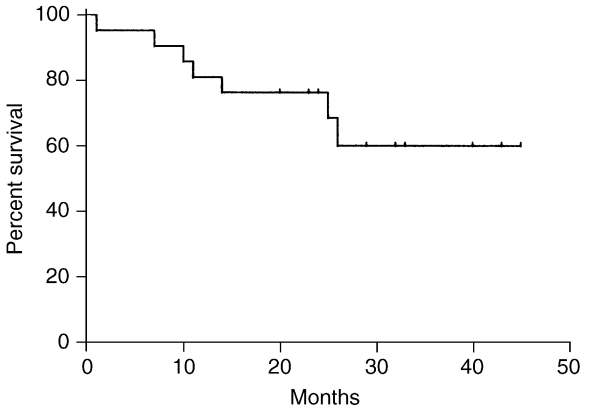

Figure 1. Kaplan–Meier estimates of survival in elderly patients with non-Hodgkin's lymphoma in stage I/II treated with amifostine–CHOP followed by involved-field irradiation.

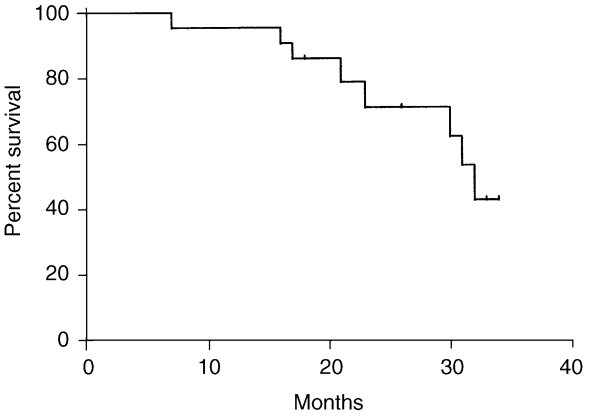

Figure 2. Kaplan–Meier estimates of survival in elderly patients with non-Hodgkin's lymphoma in stage III/IV treated with amifostine–CHOP.

Discussion

Prospective randomized trials have established CHOP as gold-standard chemotherapy for aggressive NHL in patients 60 years and older.[12–15] Nevertheless, it appears that many, if not most elderly patients with aggressive NHL are still given suboptimal treatment.[3,5,37] There may be different reasons for not administering standard treatment to elderly patients with aggressive NHL, including poor performance status, co-morbidity, but also doctor's, patient's or family bias. Frequently the fear of toxicity is the major obstacle for treatment with CHOP. Therefore, it appears important to demonstrate that, by using effective supportive measures, optimal dose chemotherapy can be administered without excess toxicity, even in elderly patients.

In this phase II study we tried to achieve this goal by using amifostine. The reason for choosing amifostine was its broad-spectrum cytoprotective activity which, so far, appears to be restricted to normal tissues.[32,38] The most striking observation in our study was the low incidence of severe hematotoxicity during treatment with CHOP in our elderly patients with aggressive NHL. This was associated with a low rate of febrile neutropenia and during 207 cycles of CHOP we did not observe life-threatening infections in this group of elderly patients. This is encouraging because infectious complications represent a prominent cause of morbidity and mortality in elderly patients receiving CHOP.[39] Moreover, only two patients had to be transfused once with packed red cells and not a single episode of severe thrombocytopenia occurred. Several studies have investigated the impact of hematopoietic growth factors on the toxicity of CHOP.[15,21,23,40,41] In two randomized studies patients receiving G-CSF experienced fewer infections than patients without G-CSF.[15,23] As far as CHOP-related hematotoxicity is concerned, our data compare favorably with these studies which used either G-CSF or granulocyte macrophage colony stimulating factor (GM-CSF) as supportive measure in elderly patients with aggressive NHL. Although we lumped patients with localized and advanced disease together, it is not very likely that our results are very distorted with respect to hematotoxicity. As far as toxicity is concerned, we felt it was acceptable to lump all patients together because the risk of life-threatening toxicity is highest during the first courses of CHOP in elderly patients.[20,22]

We observed a very low incidence of mucositis which was in the range of 5%. Mucositis is seldom reported in CHOP studies in elderly patients. In the study by Gomez *et al.* using GM-CSF together with CHOP in elderly patients, the mucositis rate (29%) was remarkable, although no severe mucosal toxicity was observed.[21] The very low mucositis rate in our study may have contributed to the low rate of fever/infections during neutropenia. According to our observations, and in comparison with the above-mentioned data from the literature, it seems that amifostine protects the mucosa to some degree against chemotherapy-induced damage, which is in line with findings in patients who received high-dose melphalan.[42]

It is not clear whether amifostine has clinically relevant cardioprotective properties in patients receiving anthracyclines. Preclinical studies suggest that this is the case, but our data cannot confirm whether the preclinical findings can be transposed to

the clinical setting.[30] Sonneveld *et al.* described a reduction in left ventricular ejection fraction of more than 15% in 10 of 22 elderly patients receiving 3 cycles of CHOP, who were serially monitored by multiple-gated acquisition scanning.[12] In our echocardiographically monitored patients only three of 40 patients receiving 4 cycles of CHOP experienced a decline in left ventricular ejection fraction of more than 15%. A cardioprotective effect of amifostine may have contributed to this favorable result, but this remains speculative. The four patients who developed a decline in their left ventricular ejection fraction and were older than 70 years had at least two further known risk factors for doxorubicin-induced cardiomyopathy.[25] Further studies are needed to clarify whether such patients fare better with alternative chemotherapy, e.g. VNCOP-B, which according to the experience of Zinzani *et al.* is associated with virtually no risk of cardiotoxicity.[43]

From our results we conclude that amifostine has no protective effect on vincristine-induced neuropathy. In the study of Tirelli *et al.*, 15 out of 60 (25%) elderly patients who received a median of 6 cycles of CHOP developed grade 2 neurotoxicity.[14] In the present study, nine out of 40 (22.5%) patients who received 4–8 cycles (median 4) developed grade 2–3 neurotoxicity.

In general, toxicity in patients 70 years and older tended to be higher than in the patients aged 60–69 years, but with amifostine we did not observe such a large difference in treatment-related toxicity in these two age subgroups as Gomez *et al.* who used GM-CSF in addition to CHOP.[21] Accordingly, in our study, eight out of 10 patients with advanced disease aged 70 years and older completed treatment in contrast to only 55% in the Gomez study and 65% in another trial.[14,21]

When the present trial was started experience with amifostine in elderly patients was sparse. The present results support our recent observation[44] that amifostine is well tolerated by elderly patients including those with co-morbidities. Nevertheless, patients who receive amifostine need careful monitoring during the infusion.

From our data thus far, there is no evidence that antitumor efficacy of CHOP is not fully maintained in elderly patients with aggressive NHL receiving amifostine. Nevertheless, CHOP treatment outcomes in elderly patients with aggressive NHL are still unsatisfactory. Preliminary results with rituximab added to CHOP are promising.[45] Whether amifostine would have a favorable impact on the toxicity of this combination is unknown.

We cannot completely exclude a referral bias allowing us to include a substantially higher percentage of our elderly patients with aggressive NHL in our study than has been reported recently from other studies.[13,46,47] Unfortunately, most reports on chemotherapy in elderly patients with aggressive NHL do not state the number of patients not included as a percentage of all patients seen at the participating center(s) nor is it stated why these patients are not treated within the study. As far as our patients are concerned, we would like to emphasize that more than 40% had ECOG performance status 2 or 3 and more than 60% had at least one significant co-morbid condition. This indicates that our study population was not highly pre-selected.

Conclusion

CHOP accompanied by amifostine can be administered with acceptable toxicity to the majority of elderly patients, even in the subset of patients who present with co-morbid disease. In elderly patients receiving CHOP, amifostine appears to be a valuable alternative to hematopoietic growth factors in the effort to reduce toxicity and merits further evaluation in randomized trials.

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