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# Epirubicin (CEOP-Bleo) versus idaurubicin (CIOP-Bleo) in the treatment of elderly patients with aggressive non-Hodgkin's lymphoma: dose escalation studies

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**One hundred and sixty nine untreated elderly patients (median age 69 years old; range 60–89 years old) with high or high-intermediate clinical risk non-Hodgkin's lymphoma were enrolled in a controlled clinical trial to evaluate escalated doses of epirubicin in a CEOP-Bleo regimen (cyclophosphamide, vincristine, epirubicin, prednisone and bleomycin), compared to escalated doses of idaurubicin in an CIOP-Bleo regimen (idaurubicin instead of epirubicin). Overall, 71% of the patients in the CEOP-Bleo arm achieved a complete response compared to only 48% in the CIOP-Bleo regimen ($p < 0.01$). At actuarial 3 year, 72% of the patients treated with the CEOP-Bleo regimen remained alive and free of disease, compared to 34% in the CIOP-Bleo arm ($p < 0.01$). Dose intensity was 0.86 in the epirubicin regimen, similar to 0.82 in the idaurubicin arm. Toxicities were more frequent and severe in the CEOP-Bleo regimen; however, no death-related treatment was observed in either groups. Cardiac toxicity was also similar in both arms. We conclude that treatment of elderly paitents with aggressive non-Hodgkin's lymphoma should be considered a curative attempt and not only palliative. The use of full doses of chemotherapy should be contemplated in elderly patients. Epirubicin, in escalating doses, is a drug with mild toxicity and improvement in outcome in this setting is observed. We cannot confirm the usefulness of idaurubicin, including escalating doses, in the treatment of patients with aggressive malignant lymphoma, because the complete response rate and survival were worse than other chemotherapy regimens. We feel that the CEOP-Bleo regimen with escalated doses of epirubicin is a useful option in the treatment of elderly patients with aggressive non-Hodgkin's lymphoma.**

*Key words*: Epirubicin, idaurubicin, non-Hodgkin's lymphoma, malignant lymphoma.

## Introduction

In recent years, prognosis of patients with aggressive non-Hodgkin's lymphoma (NHL) has changed dramatically. The introduction of anthracyclines in the late 1960s was one of the most important advances in the treatment of different human neoplasms. CHOP (cyclophosphamide, doxorubicin, vincristine and prednisone) was the first combination regimen with an anthracycline tested and today remains one of the best therapeutic approaches in these patients, including the so-called second- and third-generation programs.[1] However, long-term follow-up shows that only about 30% of patients can be considered cured.

The search for more successfull programs remains one of the more important goals in the treatment of patients with NHL.

Dose intensity of chemotherapeutic agents is an important variable in determining response to treatment in malignant disease. The use of more aggressive chemotherapeutic regimens has been proposed to achieve more complete response, and to increase the duration of remission and survival in these patients.[2] However, toxicities limit the use of this therapeutic approach in some patients.

Doxorubicin, the main drug in chemotherapy programs against NHL, cannot be used in increasing doses because non-hematological toxicities, especially gastrointestinal and cardiac, are not ameliorated by using hematopoietic growth factors.[3,4] The introduction of anthracyclines analogs, like epirubicin and idaurubicin, can avoid the presence of these toxicities, because epirubicin can be used in increasing doses with tolerable toxicities.[5–7]

In most clinical trials elderly patients are usually excluded because these are judged to have poor tolerance to chemotherapy and are more likely to die from toxicity to treatment.[8–16]

In a previous study we demonstrated that epirubicin can be safely increased in a CEOP-Bleo regimen (epirubicin instead of doxorubicin) with acceptable

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toxicity, high-rate complete responses and non-death-related treatment.[17] In the present study, 57% of the patients on the escalated arm were 60 years old. Idaurubicin, at standard doses (10 mg/m$^2$) has been introduced as an effective agent in the treatment of NHL.[17-19] This drug has been reported to have limited non-hematological toxicity and can be safely used in older patients. Thus far, no escalated studies have been performed to evaluate the role of this drug in dose-intensity programs.

For this reason we developed a randomized clinical trial to evaluate escalated doses of epirubicin compared to idaurubicin in older patients with aggressive NHL. The results are presented in this report.

## Materials and methods

Between June 1993 and December 1994, patients with NHL were considered candidates for entry in this study if they had the following criteria: diagnosis of NHL of intermediate or high grade according to the Working Formulation classification; no previous treatment; clinical high or high-intermediate risk according to the International Index Prognostic Factors Project;[20] age $> 60$ years old with no upper limit; acquired immunodeficiency virus test negative; ECOG performance status $< 3$; and normal renal, hepatic, pulmonary and cardiac function. Cardiac function was evaluated by left ventricular ejection fraction (LVEF). This evaluation was performed before starting chemotherapy, after three cycles of treatment and at the end of therapy and every year after treatment was finished. Normal values were above 50–75%. Abnormal values included a baseline decrease of more than 15% of LVEF to below 40%.

Routine staging procedures included a complete blood count, and differential, liver and renal function tests. A serum determination of immunoglobulins, lactic dehydrogenase and $\beta_2$-microglubulin; a chest radiograph, a computed tomography (CT) of abdomen and pelvis; and aspirate and threpine bone marrow biopsy. Other studies, including biopsies, were carried out when necessary to clarify staging and facilatate treatment decisions. Bulky disease was defined as a tumor mass greater than 10 cm in diameter.

After staging procedures, all patients received a preinduction phase with low doses of methotrexate to avoid the development of acute tumor lysis syndrome, as previously reported.[21]

After this, the patients were randomly assigned to receive escalated doses of CEOP-Bleo regimens, as follows: cyclophosphamide 750 mg/m$^2$, i.v., day 1; vincristine 1.4 mg/m$^2$ (maximum dose 2 mg), i.v., day 1; prednisone 40 mg/m$^2$, p.o., daily, days 1-5 and bleomycin 10 mg/m$^2$, i.v., day 14; epirubicin was escalated to cycle 1 70 mg/m$^2$, i.v., day 1; cycle 2 90 mg/m$^2$; cycle 3 115 mg/m$^2$; cycle 4 145 mg/m$^2$; cycle 5 145 mg/m$^2$ and cycle 6 145 mg/m$^2$. Patients assigned to the CIOP-Bleo regimen received cyclophosphamide, vincristine, prednisone and bleomycin at the same doses and schedule as the CEOP-Bleo arm. Idaurubicin was escalated as follows: cycle 1 10 mg/m$^2$, cycle 2 12.5 mg/m$^2$, cycle 3 15 mg/m$^2$; cycle 4 17.5 mg/m$^2$; cycle 5 17.5 mg/m$^2$ and cycle 6 17.5 mg/m$^2$. The planned doses of epirubicin were 710 mg/m$^2$ and idaurubicin 90 mg/m$^2$.

Both chemotherapy programs were administered at 21 day intervals if blood count and patient condition permitted. If the absolute granulocyte count was below $1.8 \times 10^9$ or the platelet count below $100 \times 10^9$ on day 22 (when the next scheduled course of therapy was initiated) treatment was delayed 1 week to the time the absolute granulocyte count was above $1.8 \times 10^9$ and platelet count above $100 \times 10^9$. The program did not involve dose reduction. If after 2 weeks of delay the patients did not show hematological recovery, they were excluded from the study and considered toxic failures.

The criteria for response evaluation were as follows. Complete response (CR) was defined as the absense of all signs and symptoms of the disease for at least 6 months. Partial response was considered when a reduction of greater than 50% of all measurable disease was observed for at least 6 months. Failure was considered when there was a lack of reduction of measurable disease. Progression was the increase of measurable disease at a new localization. Response evaluation was performed after the planned six cycles of chemotherapy. All patients were considered elegible to assess response and toxicity if they received at least one cycle of chemotherapy.

Time to treatment failure (TTF) was calculated from the date the patient achieved CR until the first clinical or radiological evidence of relapse. Histological relapse was confirmed whenever possible. The overall survival was measured from the date of diagnosis to the date of death, secondary to tumor progression of the complication of treatment or the last follow-up (September 1996).

All elegible patients were analyzed on a intention-to-treat basis.[22] The $\chi^2$ test was used to compare the two groups in terms of remission and survival.[23] Actuarial TTF and overall survival were calculated by the life-table method of Kaplan and Meier[24] and compared by the log rank test.[25] Confidence intervals for 3-year TTF and overall survival were constructed with standard errors determined with Grenwood's formula.[26]

Because all patients had the same prognostic factors, multivariate analysis to validate the influence was not performed.

The intensity of dose actually received by each patient was defined as the total amount (mg) of drug actually delivered during the entire study, divided by the patient body surface area, divided again by the total number of weekly therapies received.

Toxicity was graded according to the common criteria formulated by the World Health Organization. The protocol was approved by the Institutional Board of Ethics and informed consent was given by each patient.

## Results

One hundred and ninety patients were considered candidates for inclusion in the study. Twenty-one were excluded: 12 were low-intermediate clinical risk; two were lymphoblastic lymphoma; two were positive for acquired immunodeficiency syndrome; and five refused treatment. The demographic characteristics of the 169 evaluable patients can be seen in Table 1. No statistical differences were observed between the two arms. Sixty-one (71%) of the patients treated with the CEOP-Bleo regimen achieved CR; total response was achieved in 67 out of 86 patients (77%) which is statistically different to 48 and 54%, respectively, in the CIOP-Bleo program (Table 2), the number of progression cases was higher in the CIOP-Bleo regimen: 17 (20%) than the five (6%) in the CEOP-Bleo regimen. After a median follow-up of 31.6 months, 16 out of 45 patients in the CIOP-Bleo regimen relapsed, compared to only five out of 67 in the CEOP-Bleo regimen.

**Table 1.** Patients characteristics

| | CEOP-Bleo | CIOP-Bleo |
|---|---|---|
| No. | 86 | 83 |
| Age (years) | | |
| median | 69.3 | 68.7 |
| range | 60–89 | 60–84 |
| Sex: male/female | 39/47 | 40/43 |
| Histology | | |
| diffuse large cell | 60 | 62 |
| small cells not cleaved | 5 | 2 |
| Immmunoblastic | 17 | 15 |
| anaplastic Kyl+ | 4 | 4 |
| Clinical risk | | |
| high-intermediate | 26 | 24 |
| high | 60 | 59 |
| Bulky disease | 42 (48%) | 38 (45%) |
| $\beta_2$-Microglobulin (>5.0 $\mu$g/ml) | 31 (36%) | 26 (31%) |
| Bone marrow positive | 21 (24%) | 29 (34) |

Figure 1 shows the actuarial TTF. Statistical differences were observed between the two arms ($p < 0.01$). All patients with progression or failure were treated with different salvage regimens. However, at this time only four patients are alive and free of disease (two of both groups).

Figure 2 shows the actuarial survival. Statistical differences were observed: 72% of the patients were alive and free of disease in the CEOP-Bleo regimen, compared to only 34% in the CIOP-Bleo regimen (<0.01).

**Table 2.** Response [*n* (%)]

| | CEOP-Bleo | CIOP-Bleo |
|---|---|---|
| Complete response | 61 (71) | 40 (48) |
| Partial response | 6 (5) | 5 (5) |
| Failure | 15 (17) | 21 (25) |
| Progression | 5 (6) | 17 (20) |
| Total response | 67 (77) | 45 (54) |
| Total failures | 20 (23) | 38 (45) |

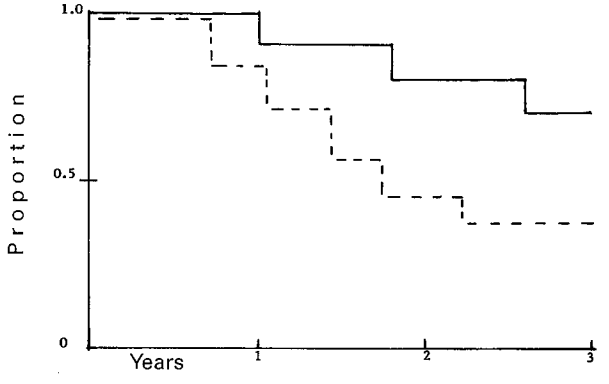


**Figure 1.** Actuarial curve for time to treatment failure.

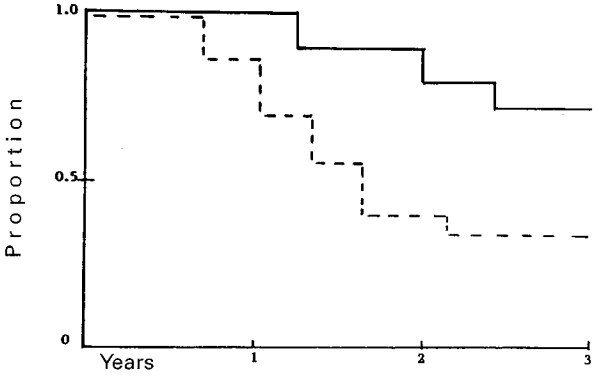


**Figure 2.** Actuarial curve for overall survival.

The CEOP-Bleo regimen called for a total dose of epirubicin of 710 mg/m$^2$ to be administered over a period of 18 weeks (dose intensity 39.4 mg/m$^2$/week) as compared to 90 mg/m$^2$ (dose intensity 5 mg/m$^2$/week). The mean received dose intensity of epirubicin was 36.4 mg/m$^2$/week (95% confidence interval 30.8–43.2 mg/m$^2$) and for idaurubicin was 4.6 mg/m$^2$ (95% confidence interval 3.9–5.1 mg/m$^2$).

### Toxicity

Table 3 shows the most frequent acute side effects. Although these were more frequent and severe in patients who received the CEOP-Bleo regimen, the differences were not statistically significant. Hematological toxicity, delays on treatment and cardiac toxicity were similar in both groups. No death-related treatment was observed in this study.

## Discussion

The prognosis of patients with aggressive NHL identified as high or high-intermediate clinical risk is generally poor. Recently, the introduction of very intensive chemotherapy has been reported to enhance the prognosis with an increase in the CR rate and improvement in duration of complete remission and overall survival.[2] However, elderly patients (above 60 years old) are generally excluded from these studies because it has been supposed that intolerance to chemotherapy in elderly patients is poor, and toxicities are frequent and severe. This consideration is based on non-controlled studies using doxorubicin-based regimens. Generally doxorubicin cannot be used in increasing doses, including younger patients, because the toxicities (hematological, cardiac and gastrointestinal) limit its use.[4] The introduction of epirubicin in escalating doses has been proven to be possible, because this drug had acceptable hematological and gastrointestinal toxicity. Cardiac toxicity has not been evaluated in larger populations and long-term follow-up, but acute toxicity even in higher doses has been acceptable.[7] Nevertheless, in some non-controlled studies, elderly patients have been treated with full doses of the planned chemotherapy programs with adequate tolerance and mild toxicity. So, the idea that elderly patients with aggressive NHL should be treated with attenuated doses of cytotoxic drugs is incorrect.

**Table 3.** Toxicity [*n* (%)]

| | CEOP-Bleo | CIOP-Bleo |
|---|---|---|
| Number of cycles | 510 (100) | 473 (100) |
| Nausea/vomiting | 263 (51) | 108 (23) |
| grade I | 182 (35) | 108 (23) |
| grade II | 81 (16) | – |
| Mucositis | 31 (6) | 21 (4) |
| grade I | 31 (6) | 21 (4) |
| Granulocytopenia | 92 (18) | 62 (13) |
| grade I | 57 (11) | 40 (8) |
| grade II | 21 (4) | 18 (4) |
| grade III | 4 (1) | 4 (1) |
| Thrombocytopenia | 19 (3) | – |
| grade I | 19 (3) | – |
| Infection-related treatment | 14 (3) | 11 (2) |
| Delays on treatment (days) (median) | 3.1 | 4.0 |
| Cardiotoxicity | | |
| LEVF > 0.15 | 4 (4) | 2 (2) |
| LEVF < normal values | 3 (3) | 2 (2) |
| Clinical congestive heart failure or arrythmias | 0 | 0 |
| Death-related treatment | 0 | 0 |

In a previous study with escalating doses of epirubicin, a subset of elderly patients (above 60 years old) was treated with high doses of epirubicin (total dose 710 mg/m$^2$). Toxicity was mild, CR was higher and similar to that in younger patients; follow-up showed that duration of response and survival were better than compared to standard doses.[17] Thus, we considered that if elderly patients can be treated with adequate doses of chemotherapy, an improvement in outcome should be possible.[27,28] However, the risk of late cardiac toxicity cannot be ruled out. Idaurubicin is an anthracycline analog that in some studies, using standard doses, has been reported to be useful in the treatment of malignant lymphoma.[18,19] Martinelli *et al.* reported in a clinical trial that idaurubicin can be used at higher doses of 25 mg/m$^2$ every cycle (150 mg/m$^2$ total dose) without severe hematological or cardiac toxicity.[29] Thus, controlled studies with standard versus escalating doses of idaurubicin were mandatory to explore the possibility that this drug can be used in higher doses without hematological and cardiac toxicities.

In the present study we demonstrate that escalating doses of idaurubicin in the CIOP-Bleo regimen can be tolerated, because hematological and acute cardiac toxicity were mild. However, the CR rate, TTF and overall survival were worse when compared to the escalating doses of epirubicin in the CEOP-Bleo regimen used as control. Although, side effects were more frequent and severe in the CEOP-Bleo regimen compared to the CIOP-Bleo regimen, these toxicities were not life threatening and recovery was observed

in all cases. Cardiac toxicity was observed with both drugs without clinical impairment. It is evident that long-term follow-up is necessary to define the presence or absence of late cardiac side effects in an older population. To our knowledge there are no reports on the presence of these types of side effects in this setting.

In most programs treating elderly patients, a reduction of doses of chemotherapy is considered because an older population is assumed not to tolerate adequate regimens of chemotherapy.[4,7] However, this therapeutic approach should be considered palliative, because the CR is small and the duration of remission is very short. Only a few patients will be considered cured with these types of treatments. It seems possible that in some elderly patients with severe intercurrent disease, the use of chemotherapy will be complicated with severe and probably lethal side effects. However, older patients should be considered candidates for an adequate treatment program that provides a chance to achieve a CR without a worsened quality of life.

The CEOP-Bleo regimen with escalated doses of epirubicin appears to be one of these treatment options. The CR rate in patients with aggressive NHL in patients older than 60 years is excellent, and the impact in duration of remission and survival appears to be superior to other chemotherapeutic programs without excessive toxicity.

We cannot confirm the usefulness of idaurubicin in the treatment of NHL. The CIOP-Bleo regimen was well tolerated but the complete response rate was worse than with other regimens.

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