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Malignant Lymphomas

A variant of ProMACE-CytaBOM chemotherapy for non-Hodgkin's lymphoma with threefold higher drug dose size but identical cumulative dose intensity. A pilot study of the Italian Lymphoma Study Group (GISL)

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ABSTRACT

Background and Objectives. **The positive results of high-dose chemotherapy followed by rescue with bone marrow progenitor cell transplantation are generally ascribed to the high dose size (DS) of the drugs given. However, a concomitant marked increase in dose intensity (DI) is always involved. With the aim of comparing the role of DS and DI in non-Hodgkin's lymphomas, a variant of Fisher's ProMACE-CytaBOM regimen was designed in which the projected cumulative drug DIs remained the same as in the original schedule but the DSs were tripled.**

Design and Methods. **Dosages in mg/m², route and days of administration were the following: cyclophosphamide 1,950 iv on days 1, 64; methotrexate 360 iv days 15, 78; vincristine 1.4 iv days 15, 78, 43, 106; etoposide 360 iv days 29, 92; epirubicin 120 iv days 29, 92; bleomycin 15 iv days 43, 106; cytarabine 900 iv days 50, 113. Thirty-six outpatients with intermediate- and high-grade non-Hodgkin's lymphomas entered the pilot study; 29 were untreated and 7 had relapse disease. Clinical stage was I in 1 patient, II in 7, III in 5 and IV in 23; 10 had B symptoms; the IPI score was 0-2 in 29 cases and ≥ 3 in the remaining 7.**

Results. **Of the 29 previously untreated patients, 16 achieved complete remission, 8 partial remission, 4 developed progressive disease and 1 was withdrawn early from the study because of acute viral hepatitis; subsequently 4 relapsed and 3 died (2 of disease progression, 1 of causes unrelated to the disease). In the pre-treated group 3 patients obtained complete remission, 2 partial remission and in 1 patient the disease progressed; 3 of these pre-treated patients died (1 of progressive disease, 1 of a new relapse, 1 of myocardial infarction during therapy). With a 20-month median follow-up, the 30-month overall and relapse-free survival were 0.58 and 0.70, respectively. G-CSF was administered to all but 2 patients, with median delivery throughout the whole regimen of 8,400 µg per patient. Actual cumulative DI was 0.82±0.11. Grade 3-4 hematologic toxicity consisted of anemia in 3 cases, of leukopenia in 8 and of thrombocytopenia in 2; the same grade of non-hematologic toxicity involved the liver in 2 cases, the heart in 1 (the above mentioned death), the digestive mucosa in 2 and the peripheral nerves in 1 patient.**

Interpretation and Conclusions. **The iso-DI sequential variant of the ProMACE-CytaBOM regimen can be considered feasibile, relatively non-toxic, and can be given on an out-patient basis. Limited use of G-CSF is required (about 3 vials after each drug administration). Thus, a randomized trial with the original ProMACE-CytaBOM regimen can be designed.**

Key words: non-Hodgkin's lymphoma, chemotherapy, dose intensity, dose size, toxicity

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The promising results recorded in the treatment of intermediate- and high-grade non-Hodgkin's lymphomas with high-dose chemotherapy followed by reinfusion of bone marrow or peripheral blood stem cells (PBSC) and/or administration of growth factors are generally ascribed to the higher dose size (DS) of the drugs given, which should saturate and overwhelm the cell resistance mechanisms, rather than to increased dose intensity (DI). However, the high DSs administered in myeloablative chemotherapy protocols generally correspond to a concomitant increase in the DI of these drugs. For example, the DIs of cyclophosphamide and methotrexate delivered in the high-dose sequential therapy with late intensification proposed by the Milan Group[1] in aggressive lymphomas are, respectively, 6 and 13 times higher than those in the MACOP-B schedule, and 5 and 31 times higher than those in the ProMACE-CytaBOM regimen. Thus, the true role of DS as compared with that of DI in determining response rate and survival parameters has not yet

been clarified, and this assessement could be crucial for the evolution of therapeutic strategies and the proper design of future clinical trials. For this purpose a comparison between conventional chemotherapy regimens – thus devoid of confounding factors such as late intensification, conditioning therapy or even drug doses for PBSC mobilization – which deliver the same drugs at the same cumulative dosages within the same time frame (i.e. with the same DI), but with substantially different DSs, should be fully convincing and decisive. The ideal comparison, if possible, would be between one of the most widely used conventional chemotherapy regimens and a properly modified version of the same which meets all the above requirements.

The *Italian Lymphoma Study Group* (GISL) has become very familiar with the ProMACE-CytaBOM[2] chemotherapy regimen (prednisone, cyclophosphamide, adriamycin, etoposide, cytarabine, bleomycin, vincristine, methotrexate) since in 1988 it began using this schedule to treat nearly 800 patients with intermediate-high-grade non-Hodgkin's lymphoma enrolled in three subsequent randomized trials: the first for a comparison with MACOP-B chemotherapy,[3,4] the second[5] and third[6] for comparisons of two distinct anthracyclines (which replaced adriamycin in the original scheme) at different dosages. With this regimen a 60-65% complete remission rate was generally achieved, with 50% long-term disease survival, low toxicity, a very low incidence of complications, and generally very good manageability on an out-patient basis.

As a logical consequence, GISL investigators chose the ProMACE-CytaBOM regimen to design suitable time and dose variations for a possible investigational treatment arm with identical projected DI but decidedly higher DS of each drug delivered with respect to the standard schedule. The most appropriate clinical target for this hypothetical comparison of treatments would be patients with low-risk, aggressive non-Hodgkin's lymphomas who are currently considered as being correctly treated with a second or third generation chemotherapy regimen or even with CHOP therapy.

We present here the results of a pilot study on the feasibility, toxicity and activity of a sequentially modified version of the ProMACE-CytaBOM regimen which delivers drug DSs three times those of the original schedule, while maintaining an identical projected mean cumulative DI.

Design and Methods

Based on the results of the most recent GISL trials on advanced, aggressive non-Hodgkin's lymphomas, we took as reference schedule that of the ProMACE-CytaBOM multiple drug chemotherapy in which epidoxorubicin 40 mg/m^2 substituted adriamycin 25 mg/m^2 (*ProMECE-CytaBOM*).[6]

Table 1 shows both the reference schedule and its modification, which is the regimen investigated in the present pilot study, with the projected threefold increase in the DS of each drug and the sequential timing of administration, which was considered more appropriate for better tolerance. Ten deliveries in all were scheduled within the same 113-day period as that needed for completion of the 6 cycles of the standard regimen. Fourteen-day intervals were planned between the first four administrations, while a 7-day rest was included between the fourth and the fifth; the delivery program from the sixth to the tenth cycle was identical to that of the first five. Only the DS of vincristine was not increased to avoid excessive neurotoxicity; 4 standard-dose administrations (1.4 mg/m^2) were planned to maintain cumulative doses and DI identical to those of the reference schedule. As a rule in GISL practice, single doses of vincristine were capped at 2 mg. Total prednisone dosage, which was the same as that given in the cyclic regimen, was refracted in four- to five-day administrations which started at each delivery of the antitumoral drugs. Nausea and vomiting were controlled with anti-H3 receptors (ondansetron, granisetron, tropisetron at standard dosages). The decision to administer growth factors was left to the clinicians' experience. The only recommendations given were to use G-CSF preferably on demand, in the case of either neutropenia $< 0.3\times10^9$/L granulocytes or fever of demonstrated or suspected infectious origin. The aim was to allow the patient's hematologic tolerance to be studied after the first drug administrations and to test his/her actual need for G-CSF with respect to

Table 1. Doses and times of administration of the original cyclic ProMACE-CytaBOM regimen (with the substitution of epidoxorubicin for adriamycin) and the sequential version which delivers three times greater dose sizes. Time for completion of both the original cyclic regimen and the entire sequentially modified schedule is the same, i.e. 113 days.

Drugs	*mg/m^2*	*Route*	*Days*
cyclic schedule			
cyclophosphamide	650	i.v.	1
epidoxorubicin	40	i.v.	1
etoposide	120	i.v.	1
prednisone	60	p.o.	1-14
cytarabine	300	i.v.	8
bleomycin	5	i.v.	8
vincristine	1.4	i.v.	8
methotrexate	120	i.v.	8
folinic acid	10	p.o.	9 (every 6 hrs for 5 doses)
sequential schedule			
cyclophosphamide	1950	i.v.	1, 64
mesna	600	i.v.	1, 64 (hr 0 and +6)
vincristine	1,4	i.v.	15, 43, 78, 106
methotrexate	360	i.v.	15, 78
folinic acid	20	p.o.	15, 78 (every 6 hrs for 5 doses)
etoposide	360	i.v.	29, 92
epidoxorubicin	120	i.v.	29, 92
bleomycin	15	i.v.	43, 106
cytarabine	900	i.v.	50, 113
prednisone	60	p.o.	1-5, 15-19, 29-33, 43-46, 50-54, 64-68, 78-82, 92-96, 106-109, 113-117

doses, duration of therapy and possible prophylactic use of the growth factor after subsequent administrations.

From August 1996 to March 1998, 29 consecutive previously untreated patients with non-Hodgkin's lymphomas of prevalently intermediate-high grade histology, were treated with the sequential ProMECE-CytaBOM regimen. Seven additional patients who had relapsed after first- (5 cases) or second-line (2 subjects) chemotherapy were included in the study. Exclusion criteria involved age < 15 or > 70 years, performance status (Karnofsky index) < 50, altered funtion of heart, lung, liver or kidney and HIV test positivity. Informed consent was obtained from each patient. The main clinical characteristics of the 36 treated subjects are shown in Table 2.

All the patients were clinically staged with routine laboratory tests, chest roentgenogram, computed tomography of the thorax and abdomen, abdominal ultrasound scan, and bone marrow biopsy. Every clinical, radiologic, or laboratory investigation that disclosed abnormalities at pre-treatment staging was repeated at the end of therapy to evaluate response. Prognostic evaluation was performed using the International Prognostic Index (IPI) score.[7]

Complete remission (CR) was defined as complete regression of measured lesions and disappearance of all other objective evidence of lymphoma for at least 3 months. Partial remission (PR) consisted of a decrease of more than 50% in the sum of the products of the diameters of the measurable lesions. No response (NR) was anything less than a 50% decrease in measurable lesions.

Toxicity was measured according to standard ECOG criteria.[8] Dose intensity was calculated according to the criteria reported by Hryniuk[9] and to examples and suggestions offered by DeVita *et al.*[10]

Median follow-up was 20 months (8-33). Overall survival (OS) was computed from the start of treatment to death from any cause. Relapse-free survival (RFS) for complete responders was measured from the date of therapy completion to the date of last observation or relapse. Survival curves were calculated using the method of Kaplan and Meier.[11]

Table 2. Clinical characteristics of the patients who entered the pilot study

Characteristics	*previously untreated* *No.*	*pre-treated* *No.*
Age		
< 45 years	10	1
≥ 45 years	19	6
Gender		
Male	18	3
Female	11	4
Histology (Working Formulation)		
A	0	1
C	1	0
D	3	1
E	0	1
F	3	0
G	18	3
H	2	0
J	0	1
K	1	0
Uncertain	1	0
Stage		
I	1	0
II	6	1
III	5	0
IV	17	6
B symptoms	8	2
IPI score		
0-2 (low)	23	6
3-5 (high)	6	1
Performance Status		
≥ 80	27	7
< 80	2	0

Results

Twenty-eight of the 29 previously untreated patients were evaluable for response. Sixteen achieved CR (57%), 8 only a PR (29%), while 4 (14%) did not respond to therapy or suffered disease progression. Four of the 16 complete responders subsequently relapsed. Three patients in this group died: 1 of disease progression during chemotherapy, 1 of disease progression in relapse and 1, aged 67, of an ischemic cerebrovascular accident, presumably unrelated to therapy, after the 64th day of drug administration.

In the group of patients refractory to or relapsed after other previous treatments, 3 reached CR, 3 PR and one did not respond. Three of these patients died: 1 of disease progression after a null response to treatment, 1 of myocardial infarction during the course of therapy, to which he was responding partially, and the third of uncontrolled disease in second relapse after CR.

The average cumulative DI for all the drugs delivered, except prednisone, was 0.82±0.11. The mean cumulative DI of each drug is reported in Table 3, which shows that all the drugs (except the capped vincristine) were given with comparable dose intensities, from 0.80 to 0.87, which is sufficiently near to that which was projected.

The ECOG grades of hematologic toxicity record-

Table 3. Mean dose intensities (± 1 standard deviation) of each drug given.

Cyclophosphamide	0.86 ± 0.10
Vincristine	0.68 ± 0.17
Methotrexate	0.86 ± 0.13
Etoposide	0.85 ± 0.15
Epidoxorubicin	0.80 ± 0.17
Bleomycin	0.81 ± 0.20
Cytarabine	0.87 ± 0.09

Table 4. ECOG grades of the recorded hematologic toxicity.

ECOG grades	*1*	*2*	*3*	*4*
Anemia	8	5	2	1
Leukopenia	5	6	5	3
Thrombocytopenia	6	2	1	1

Table 5. List of the non-hematologic side effects.

	No. of patients
Renal toxicity	2
Mucositis	9
Constipation	4
Paresthesias	8
Dyspnea (after etoposide delivery)	1
Hematuria (without mesna after cyclophosphamide)	1

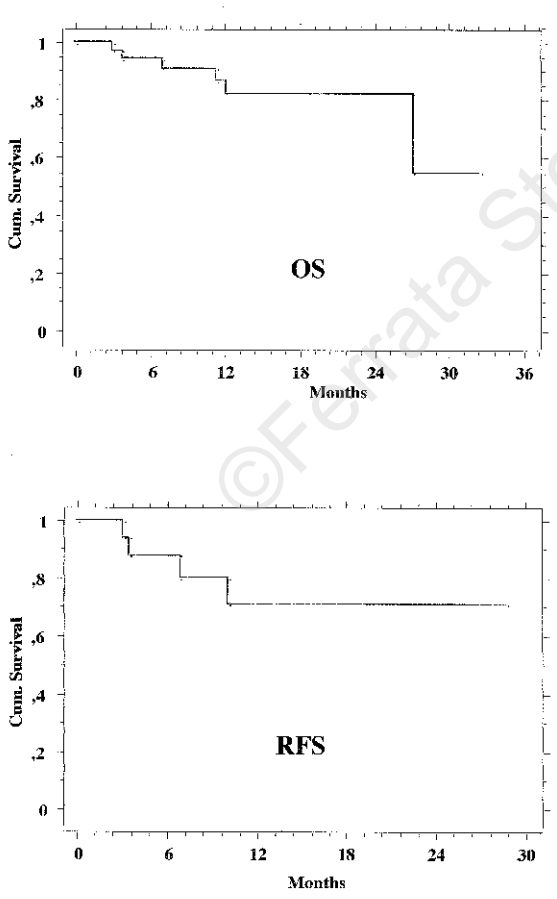

Figure 1. Overall survival (OS) of the whole study population and relapse-free survival (RFS) of all 19 complete responders (3 of whom had been previously treated).

ed in the whole study population are given in Table 4. Severe (grade 3-4) anemia and thrombocytopenia were rare since they occurred in only 3 and 2 cases, respectively. Severe leukopenia was more frequent in spite of the use of G-CSF; however, the growth factor was given according to rather discretional criteria as dictated by the investigators' experience and the tolerance shown by each individual patient after the first drug administration. Thus, while the median cumulative G-CSF dose per single drug administration can overall be considered low – 780 µg – as expected, there was great variability in this dose (SD: 480 µg). At one extreme of this range were two patients who completed the entire program with full drug doses and within the scheduled intervals without any G-CSF and, at the other extreme, 1 patient who received 300 µg/day for 10 days after each antitumoral drug administration.

Non-hematologic toxicity was moderate. Table 5 reports all such side effects recorded in this study. None of them, however, deserves any specific comment. The sequential ProMECE-CytaBOM regimen did not necessitate hospitalization in the great majority of cases. Only 4 patients in this series had to be hospitalized for complications.

In spite of the short follow-up, the 30-month projected overall survival of all 36 patients (both previously untreated and pre-treated) is 0.55 (with a 95% confidence interval of 0.14), as shown in Figure 1, which also illustrates the 0.70 (±0.29) RFS at 30 months of the 19 complete responders (of whom 16 were previously untreated and 3 pre-treated).

Discussion

The purpose of this study was to evaluate the toxicity, feasibility and activity of a newly devised sequential and iso-DI ProMECE-CytaBOM chemotherapy regimen. Hematologic toxicity on the whole can be considered tolerable and comparable to that which is generally experienced with one of the third generation regimens currently used in the treatment of aggressive non-Hodgkin's lymphomas. This evaluation takes into account the nearly unavoidable need for G-CSF to allow sufficient compliance with projected drug doses and scheduled intervals between cycles. However, in the light of the results of this pilot study we conclude that the need for G-CSF is rather low, and that, as a rule, suitable prophylaxis would consist of about 300 µg/day for 3 days, preferably from day 8 to 10 of any 14-day interval (the two intervals that are one-week long do not need growth factors since they are preceded by the administration of non-myelotoxic drugs).

The hepatotoxicity manifested by two cases could have been related to pre-existing positivity for hepatitis B virus markers. It was accompanied by slight elevation of renal function tests and occurred after the first administration of methotrexate and vincristine, on the 15th day of the schedule. These manifestations could be interpreted for both patients as a toxicity excess due to insufficient hydration, possibly related to a series of concomitant transitory causes: fever, reduced intake of fluids as a result of severe mucositis, hyperhydrosis due to great heat. As already

observed,[12] it is possible that a first phase of heavy toxicity and immunosuppression induced by the first day administration of cyclophosphamide could have enhanced viral replication. The subsequent interval between cycles might have resulted in partial restoration of immunocompetence with consequently more rapid destruction of hepatocytes. At this point, it is possible that the 15th day delivery of methotrexate with vincristine was carried out when hepatocyte lysis had already started; then possible fever and/or mucositis consequent to methotrexate, perhaps combined with the heat, might have also reduced circulating body fluids, with transitory elevation of renal function tests. Patients positive for hepatitis B virus markers should probably be excluded from the sequential therapy or at least treated with great caution, especially regarding the possibility of gradually restoring their immunocompetence.

The patient who died of myocardial infarction had just been admitted to hospital because of recent jaundice and a slight increase in renal function tests; death occurred 8 days after the administration of methotrexate and vincristine on the 78th day, i.e. 35 days after the first dose of epidoxorubicin. Thus, it is likely that cardiac toxicity can be ascribed to multiorgan damage due to a higher and more protracted serum concentration of these drugs and their metabolites than is usually encountered. The possible role of epidoxorubicin seems indirect and non-specific. In this regard, we feel the administration of dexrazoxane is unneccessary; moreover, the projected cumulative dose of epidoxorubicin, expressed in terms of doxorubicin equivalents, is far from the threshold of 300 mg/m^2 above which cardioprotection may be useful.[13]

Our experience has shown that great attention must be paid to proper hydration both during administration of the drugs and in the following 2-3 days, especially after the delivery of methotrexate and vincristine (15th and 64th days), and especially on an outpatient basis (for example, with the additional infusion of 1,000 mL of saline after the drug-containing solutions, and with the recommendation to drink at least 2 liters of water or light liquids at home). No further cases of hepatoxicity and nephrotoxicity were recorded after investigators began focusing on this aspect of patient management.

The case of moderate hemorrhagic cystitis due to a single administration of cyclophosphamide neither accompanied nor followed by mesna medication confirms both the necessity of this precaution and the effectiveness of the dosages of mesna employed, (somewhat lower than that currently suggested for the doses of cyclophospamide delivered; moreover, the second dose was given orally, so that expected absorption was even lower). Although evaluation of therapeutic activity was not the principal aim of this pilot study, the results obtained demonstrate satisfactory effectiveness, at least not inferior to what can be expected with the original chemotherapy schedule in the GISL experience.

In conclusion, we consider the sequential formulation of the ProMECE-CytaBOM regimen to be quite feasibile without patient hospitalization, with controllably low toxicity, especially if the proper preventive countermeasures suggested by the pilot study are adopted. Therefore this can be used without intolerable risks in possible future comparisons with the original ProMACE-CytaBOM schedule, with respect to which it can actually deliver three times the DS of each drug (except for vincristine) with the same average cumulative DI.

Contributions and Acknowledgments

PGG, PA and VS planned and designed the study; PGG, MLG and CB drafted the article; LB, GQ, CS, CL were the principal contributors to collection, statistical analysis and interpretation of the data; VS and EA critically revised and finally approved the article.

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Potential implications for clinical practice

- Sequential variation of the ProMECE-CytaBOM chemotherapy regimen for aggressive non-Hodgkin's lymphomas is feasible on an outpatient basis, shows acceptable toxicity and gives results at least comparable with those of the best third generation regimens; thus, it can be employed in a randomized trial projected to test the distinct role of drug dose size and dose intensity in the results of treatment of patients with non-Hodgkin's disease.

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