original article

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The role of dose size in a chemotherapy regimen (ProMECE-CytaBOM) for the first-line treatment of large B-cell lymphomas: a randomized trial by the Gruppo Italiano Studio Linfomi (GISL)

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Background: It is still unclear the actual contribute of dose intensity (DI), dose size (DS) and dose density (DD) in the conventional chemotherapy of large, B-cell non-Hodgkin lymphomas.

Methods: A prospective, randomized trial compared the cyclic schedule of ProMECE-CytaBOM chemotherapy (cyc-PC, 6 cycles) with a modified version of it, which administered the same drugs sequentially (seq-PC), with the same planned cumulative DI and an 83% DD, within the same time frame (113 days), but with three times higher DS of all the drugs except vincristine.

Results: Fifty-six patients received cyc-PC and 52 seq-PC. The actual mean cumulative DI was 0.79 ± 0.15 with cyc-PC, 0.78 ± 0.17 with seq-PC. Response was complete in 59% and 52%, partial in 20% and 21%, null in 5% and 6%, respectively. There were four toxic deaths (two per arm). Relapses occurred in 36% and 37%, respectively. Toxicity was similar in both arms. Overall, failure-free, progression-free and disease-free survival (median follow-up: 54 months) were statistically indifferent.

Conclusions: The very similar DI actually delivered in both arm seems to be the main common determinant of the indifferent results recorded. Increasing DS – at least within the limits clinically attainable without stem cell rescue – does not improve results.

Key words: chemotherapy, large B-cell lymphoma, dose intensity, dose size, dose density

original article

introduction

Many efforts have been performed to improve the results of conventional chemotherapy for aggressive non-Hodgkin lymphomas. However, it is still unclear whether better results can be achieved by increasing the dose intensity (DI) rather than the dose size (DS) of the active drugs or by shortening the schedules of drug administration, thus pursuing a higher dose density (DD).

The addition of new drugs to those included in the historical standard regimens (CHOP, BACOP) seemed to strictly comply with the Goldie and Coldman's theory [1, 2], according to which tumor cell kill would benefit by the early exposure to the highest number of active drugs. However, clinical results of randomized trials failed to demonstrate clear advantages for the so-called second- and third-generation chemotherapy regimens (ProMACE-CytaBOM, m-BACOD, MACOP-B) [3, 4]. Moreover, the comparison of these regimens with CHOP seemed to question the concept itself of dose intensity that Hryniuk [5, 6] derived from the basic assumptions of the Goldie-Coldman model, since the new regimens have a clearly higher average dose intensity than CHOP (in particular, that of MACOP-B and ProMACE-CytaBOM is approximately two-fold higher). It is well-known that some investigators tried to explain this conceptual failure by advocating the reduction in cyclophosphamide and doxorubicin—considered as more active than others—determined by the addition of many other less active drugs [7].

However, drug DI may be only one of the many variables potentially able to explain the clinical results of chemotherapy. The favorable results of high-dose chemotherapy with stem cell support in many [8, 9]—but not in all—clinical settings of

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non-Hodgkin's patients should suggest that the amount of dose (DS) can overcome the multidrug resistance. Actually, the DS of drugs administered in the most common myeloablative regimens are 10 to 30 times higher than those given in the conventional chemotherapy programs, though a contemporary true increase in their DI is contemporarily achieved. So the true, individual role of DS and DI in determining therapeutic results is still to be clarified.

Now, the research for escalated dose in conventional chemotherapy regimens has become very active, mainly by the help of growth factor support. While in some trials the increase of DI has been approached through direct escalation of drug doses, in others it has been reached through the administration of standard doses on shortened intervals. In these last cases a third parameter of chemotherapy is exploited, the so-called dose density (DD) [10], i.e. the frequency of effective drug dose administration. This concept complies with the Norton and Simon's assumption on tumor heterogeneity [11], according to which the most efficient therapy should be the most dose–dense therapy, giving as much drug as possible over as short a period as possible. Probably, this ideal pattern of therapy should be better accomplished by sequential than alternating treatments.

As expected, the design of investigational trials able to test these chemotherapy parameters separately is not easy in clinical practice. Here we describe a multicentric, randomized, clinical experiment in diffuse large B-cell non-Hodgkin's lymphoma patients, in which the role of DS was selectively explored under the same conditions of DI and minimal variation of DD.

patients and methods

eligibility criteria and staging

Between October 1997 and November 2001 112 patients participated in this multicenter, randomized trial (GISL, LA-04). The following criteria had to be fulfilled for inclusion into the study: newly diagnosed patients with diffuse large B-cell lymphoma with exclusion of cases either derived from previous indolent lymphoma or presenting one of the following variants: anaplastic, plasmoblastic, T-cell rich B-cell, primary mediastinal B-cell lymphoma; clinical stage I with bulky mass, stage II with more than three involved sites or with bulky mass, stage III or IV; age 15–70 years; performance status (PS) 0–3 according to the European Cooperative Oncology Group [12]; no serious cardiac, renal, pulmonary and hepatic co-morbidity; negativity of the serologic test for human immunodeficiency virus.

Pre-treatment staging procedures included physical examination, complete blood count, biochemical analyses, bone marrow core biopsy, chest X-ray and computed tomography scan of chest and abdomen. Initial bulky disease was defined—in the mediastinum—as lymphoma masses with maximum width larger than 1/3 of transverse diameter of the thorax at the level of T5/6, and—outside the mediastinum—as masses with the largest dimension greater than 10 cm. The prognostic evaluation allowed by the score of the International Prognostic Index (IPI) [13] was considered for each patient. Written informed consent was obtained from all patients before randomization.

After randomization, four patients were excluded for revised histology (three were defined as high-grade B-cell, Burkitt-like lymphomas, and one as anaplastic large T-cell lymphoma). So, 108 patients were eligible for the study, and all are evaluable for the end-points of the study.

treatments

Patients were randomly assigned to receive either six cycles of ProMECE-CytaBOM chemotherapy or a sequential variant of it which administered higher doses of the same drugs of the cyclic schedule within the same time frame.

The cyclic ProMECE-CytaBOM (cyc-PC) was a simple modification of the original regimen proposed by Fisher et al. [14] in which doxorubicin (25 mg/m^2) was replaced by epidoxorubicin (40 mg/m^2). This epidoxorubicin-based variant had been preferred by the GISL in a previous randomized trial [15] due to its better effectiveness/toxicity balance.

The sequential variant of the ProMECE-CytaBOM (seq-PC) was specifically designed to administer single drug doses three times higher than those delivered in the cyclic schedule, but with total doses of each drug and total length of the whole treatment fully identical. A GISL pilot study verified both feasibility and tolerability of a such a schedule [16]. Only for vincristine the threefold single dose increase was judged potentially neurotoxic when combined with higher doses of the other antitumoral agents and its standard dose was repeated no more than four times in the seq-PC (instead of six times as in the cyc-PC). Oral prednisone administration paralleled and followed every antitumoral delivery in the seq-C-P as in the cyc-PC but with a total dose lower (3000 vs. 5040 mg/sqm). Mesna was given only in the seq-PC, after the two high doses of cyclophosphamide, while the rescue with folinic acid was provided in both regimens after methotrexate infusion. The decision to administer growth factors was left to the experience of each clinician, with the recommendation of using them strictly on demand, e.g. in case of neutropenia $<0.5 \times 10^9$/l (drug dose intensification had not to be pursued in any of the two regimens). Table 1 details the schedules of both cyc-PC and seq-PC.

Dose intensity was calculated according to the criteria reported by Hryniuk [5] and to the examples and suggestions offered by de Vita et al. [17]. Steroids are generally considered of minor importance in relation to the final clinical outcome of these calculations [17], thus the dose intensity of prednisone was not taken into account.

Radiotherapy was given after the end of chemotherapy either on those lymphomatous lesions evaluated as bulky at initial staging or on partially responsive lesions after chemotherapy. Doses of 36 Gy were recommended to areas with no signs of disease at the end of chemotherapy and 44 Gy to sites with partially persisting disease.

response and toxicity

Clinical response was assessed about 1 month after the end of chemotherapy and after the subsequent radiotherapy, if any. Complete (CR), partial (PR), null response (NR) and progressive disease (PD) were evaluated according to the International Workshop criteria [18].

Overall survival (OS) was calculated from the start of therapy to death from any cause. Failure-free survival (FFS) was measured for all patients from the start of therapy to the date of treatment failure, disease progression, relapse or death related to the disease or to the treatment. Relapse-free survival (RFS) was calculated for complete responders from the end of treatment to the date of relapse or death from the disease [19].

Toxicity was evaluated according to the standard ECOG grades [12].

statistics

The main endpoint of the study was the 5-year failure-free survival, while additional endpoints were response rate, 5-year relapse-free survival and overall survival. Sample size was calculated taking into account that the study had to be able both to evaluate a possibly more active and toxic treatment and to pick up a hypothetical advantage, or equivalent, of the conservative therapy compared. To this aim we chose the formula of Makuch and Simon [20], which can test the effectiveness of conservative treatments, too, with the correction of Fleiss [21] for samples of possibly

Table 1. Doses and schedules of administration of the two regimens compared, the original cyclic ProMECE-CytaBOM and its sequential variant

Drugs	mg/m^2	Route	Days
Cyclic P-C			
Cyclophosphamide	650	iv	1
Epidoxorubicin	40	iv	1
Etoposide	120	iv	1
Prednisone	60	po	1–14
Cytarabine	300	iv	8
Bleomycin	5	iv	8
Vincristine	1,4	iv	8
Methotrexate	120	iv	8
Folinic acid	10	po	9 (every 6 h for 5 doses)
To be repeated every 21 days for 6 cycles (planned duration 113 days)			
Sequential P-C			
Cyclophosphamide	1950	iv	1, 64
Mesna	600	iv	1, 64 (h 0 and +6)
Methotrexate	360	iv	15, 78
Folinic acid	20	po	15, 78 (every 6 h for 5 doses)
Vincristine	1, 4	iv	15, 43, 78, 106
Epidoxorubicin	120	iv	29, 92
Etoposide	360	iv	29, 92
Bleomycin	15	iv	43, 106
Cytarabine	900	iv	50, 113
Prednisone	60	po	1–5, 15–19, 29–33, 43–46, 50–54, 64–68, 78–82, 92–96, 106–109, 113–117.

Planned cumulative relative dose intensity with respect to the cyclic schedule: 0.95 for all drugs, 1.00 for the six drugs after the exclusion of vincristine.

unequal size. For these calculations we assumed that a 0.10 difference in 5-year FFS might be probable between the sequential and the cyclic regimen (0.60 versus 0.50), and chose a two-sided significance level of 0.05 with a similarly two-sided power of 0.80. Calculations indicated that the whole sample size should have included 86 evaluable patients, 43 per treatment arm. Actually, the GISL decided to protract patient accrual and randomization until the start of a new subsequent protocol, and the prolonged discussion of the new program allowed 36 additional patients to be randomized and treated.

Randomization was performed at the GISL Trial Office with communications by telephone. Patients were stratified on the basis of IPI score (≤1 versus ≥2) and participating center.

results

Of the 108 eligible patients, 56 were randomized to the treatment with the cyc-PC schedule, 52 with the seq-PC one. Table 2 reports the main clinical and prognostic characteristics of the two groups of patients and demonstrates the good comparability of the two treated groups. The slight, statistically not significant, prevalence of constitutional symptoms in the cyc-CP arm is counterbalanced in the seq-PC arm by a slightly higher proportion of bone marrow involvement and abnormality of serum albumin concentration, β2-microglobulin and erythrocyte sedimentation rate.

Table 2. Clinical characteristics of the 108 eligible patients of the study, subdivided per treatment arm (per cent in italic)

Characteristics	cyc-PC		seq-PC		Total	
Age yrs						
Median	56		55		56	
Range	26–70		22–68		22–70	
Gender						
Male	29	*52*	30	*58*	59	*55*
Female	27	*48*	22	*42*	49	*45*
Histologic variants*						
Centroblastic	50	*89*	47	*90*	97	*90*
Immunoblastic	6	*11*	5	*10*	11	*10*
Stage						
I	9	*16*	5	*10*	14	*13*
II	17	*30*	14	*27*	31	*29*
III	12	*22*	12	*23*	24	*22*
IV	18	*32*	21	*40*	39	*36*
Extranodal involvement						
(E stages I–III)	12	*21*	9	*17*	21	*19*
B symptoms	19	*34*	12	*23*	31	*29*
Bulky disease	17	*30*	17	*33*	34	*31*
Bone marrow involvement	14	*25*	16	*31*	30	*28*
Performance status						
ECOG						
0	38	*68*	39	*75*	77	*71*
1	13	*23*	7	*13*	20	*18*
2	2	*4*	3	*6*	5	*5*
3	3	*5*	3	*6*	6	*6*
IPI score						
0–1	28	*50*	26	*50*	54	*50*
2	21	*38*	22	*42*	43	*40*
3	5	*9*	2	*4*	7	*6*
4–5	2	*3*	2	*4*	4	*4*
Alb < 35 g/L	15	*27*	16	*31*	31	*29*
ESR > 50 mm/1st hr	13	*23*	15	*28*	28	*26*
β2-m > 3 mg/L	19	*34*	22	*42*	41	*38*

IPI: International Prognostic Index. Alb: serum albumin concentration. ESR: erythrocyte sedimentation rate. β2-m: serum β2-microglobulin concentration.

Both regimens were administered with very similar DI for each drug, except vincristine which had the planned 1/3 reduction in the sequential schedule (Table 3). The lower DI of vincristine was counterbalanced by a slight higher one of the other drugs, so that the average cumulative dose intensity is nearly superimposable in both regimens (0.79 ± 0.15 with cyc-PC, 0.78 ± 0.17 with seq-PC). Therefore, the two treatments can be really considered iso-DI, in spite of the very different DS of each drug. Granulocyte colony stimulating factors (G-CSF) were given only when requested either by neutrophil count below 0.5×10^9/l or by neutropenia even above this limit if associated with fever or signs of infections. In the seq-PC arm the mean G-CSF dose was 300 μg/day for 3–4 days after every drug administration (three cases did not need G-CSF support at all, seven cases requested G-CSF support for 6 days after some antitumoral drug administration). In the cyc-PC the use of G-CSF was only occasional.

Clinical response rate was very similar in both treatment groups as well as per cent of refractory cases, relapses and death from any cause as shown in Table 4. In particular, complete response, progression and relapse rate were 61%, 14 and 25% in the cyc-PC arm and 58%, 13% and 19% in the seq-PC, respectively. Among the total number of deaths during the subsequent follow-up, 20 in the cyc-PC arm and 23 in the seq-PC one, there was a slight excess of deaths from the disease in the investigational arm (20 versus 14) and of deaths due to toxicity or complications in the group with standard therapy.

Thirty-two patients received radiotherapy after chemotherapy, 18 in the cyc-PC arm, 14 in the seq-PC one. Response rate did not differ in the two treatment groups related to administration of local RT according to the criteria adopted.

Median follow-up for the whole population of the study was 46 months (range 2–81), 54 months for patients alive (range 24–81). Projected 5-year FFS, RFS and OS show slight and statistically not significant differences between treatments (Figure 1), though with a constant slight advantage in favor of the cyc-PC arm (FFS: 44 versus 34%; RFS: 75 versus 65%; OS: 63 versus. 53%). No substantial differences of FFS, RFS and OS were found between patients with favorable (IPI 0–1) and unfavorable (IPI ≥2) prognostic score of the two treatment arms.

Toxicity was moderate in both groups of patients (see Table 5). Four patients, two per arm, died of infections or septic shock during chemotherapy despite a powerful antibiotic and G-CSF therapy. Hematologic toxicity was comparable as far as anemia and thrombocytopenia are concerned, while neutropenia was more frequent and heavy with seq-PC. Nonhematologic toxicity was mainly related to reactivation of HBV infections in the liver at the end of chemotherapy

Table 3. Planned and actually delivered dose intensity (DI) of each drug in the 108 patients treated with one of the two ProMECE-CytaBOM regimens. Calculations were made in relation to the doses of the cyclic regimen, taken as reference schedule

	Planned DI		Delivered DI	
Drugs	cyc-PC	seq-PC	cyc-PC	seq-PC
Cyclophosphamide	1	1	0.82±0.17	0.84±0.19
Epidoxorubicin	1	1	0.78±0.14	0.82±0.19
Etoposide	1	1	0.82±0.15	0.80±0.22
Cytarabine	1	1	0.83±0.17	0.85±0.12
Bleomycin	1	1	0.82±0.20	0.83±0.14
Vincristine	1	0.67	0.66±0.16	0.49±0.11
Methotrexate	1	1	0.83±0.16	0.82±0.18
Mean	1	0.95	0.79±0.15	0.78±0.17

Table 4. Clinical response to and evolution after Cyc-P-C and Seq-P-C regimens

	cyc-PC		seq-PC		Total	
	No.	%	No.	%	No.	%
Complete response	34	*61*	30	*58*	64	*59*
Partial response	11	*20*	12	*23*	23	*21*
Null response	3	*5*	3	*6*	6	*6*
Progression	8	*14*	7	*13*	15	*14*
Relapse	12	*21*	10	*19*	22	*20*
Death from disease	14	*25*	19	*36*	33	*31*
Death from toxicity or complications	6	*11*	4	*8*	9	*9*

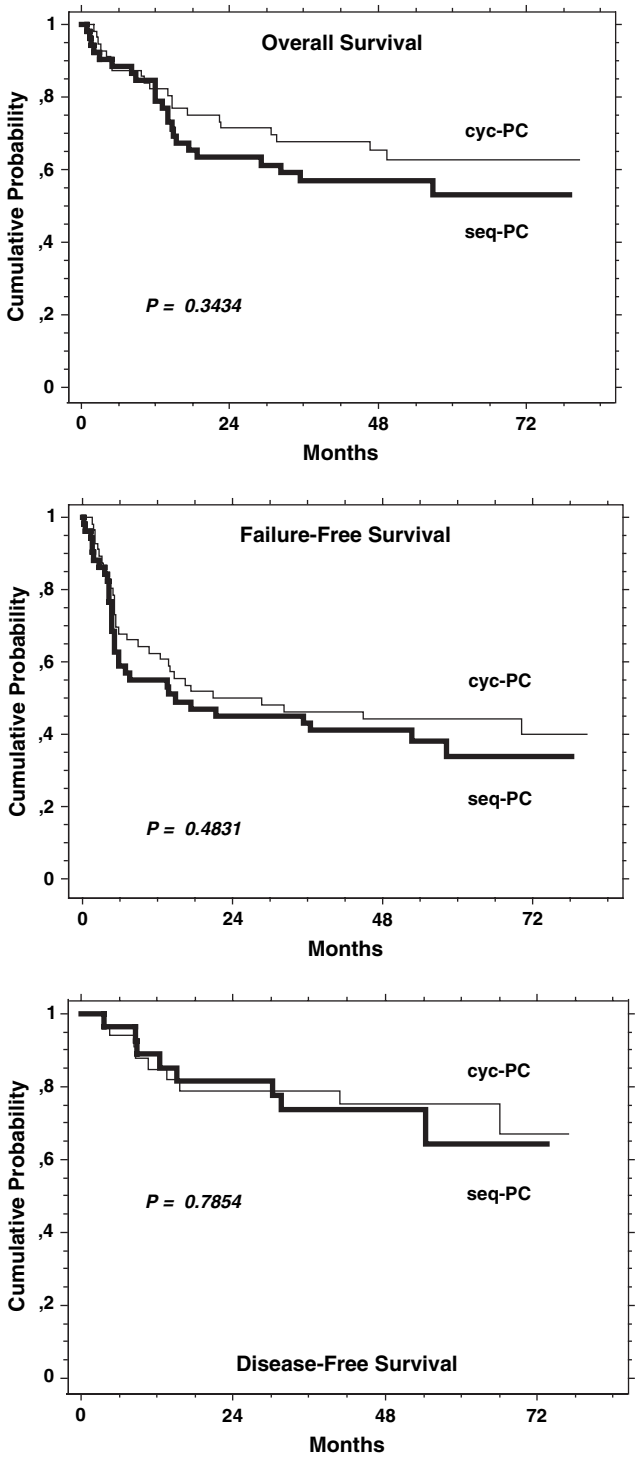

Figure 1. Overall survival, failure-free survival and disease-free survival recorded in the 56 patients treated with the original, cyclic ProMECE-CytaBOM schedule (cyc-PC) and in the 52 treated with the sequential modification of the same regimen (seq-PC), administering three-fold higher drug dose sizes, with equivalent cumulative dose intensity.

Table 5. Number of patients of both treatment arms in whom severe toxicity grades were recorded (ECOG grades 3 and 4)

	cyc-PC		seq-PC	
	Grades		Grades	
	3	4	3	4
Hemoglobin	1	2	2	0
Neutrophils	7	6	11	9
Platelets	0	1	2	0
Liver function tests	1	1	2	1
Renal function tests	0	1	0	0
Mucosytis	2	0	3	1

(two grade four cases, one per arm) or to transient increased serum creatinine and urea concentration (one case, treated with cyc-PC), probably due to insufficient liquid infusion. Mucosytis was more frequent in the seq-PC arm.

discussion

The therapeutic efficacy of conventional therapy is still unsatisfactory for patients with large B-cell non Hodgkin's lymphoma and new strategies are warranted in this clinical setting. The administration of high-dose chemotherapy with autologous stem-cell transplantation has been the main major clinical progress since the introduction of CHOP about 30 years ago. Even though its use in first-line patients remains controversial, the large amount of results obtained as second-line therapy contributed to strengthen the hypothesis that a high dose of an antitumoral drug is better than a standard one. Possible explanations of higher effectiveness of increasing doses might be (a) prolonged exposure time to greater than a cytotoxic threshold, (b) penetration of sanctuary sites, (c) producing cytotoxicity through alternative mechanisms. More probably high-doses can more successfully interfere with the active processes of either extracellular extrusion of the drug or sequestration of it into the cytoplasm, away from the nuclear targets, that characterize the multidrug resistance. As a matter of fact, the idea that increasing drug DI can be a reliable way to improve clinical outcome has been prevalent in clinical studies with conventional chemotherapy. Now, however, it is still unproven whether it is more useful to simply escalate drug doses administered at the standard time intervals or to shorten the time intervals while maintaining the DS unmodified, or even to pursue both aims simultaneously. Many modifications of the current chemotherapy schedules have been proposed to simultaneously increase DS and DI or this last and DD. The purpose of the present study was to explore the actual contribute of DS in the therapy of large B-cell lymphomas in an experimental condition with equal DI and as similar DD as possible. This would be a clinical test, without confounding effects of time, of the Goldie and Coldman's model [1], which predicts an inverse relationship between DS and development of drug resistance, The results can help to correctly direct the next clinical efforts towards either dose escalation or time shortening (or both).

The choice of ProMECE-CytaBOM as test bench for investigational schedule manipulations is simply justified by the fact that all the GISL centers were very familiar with this third-generation regimen [15, 22, 23]. This was the only reason why it was preferred to CHOP which was developed more than 30 years ago [24] and is still considered a very effective conventional treatment for aggressive lymphomas and a simple experimental tool for clinical investigation [25].

Our results indicate that in two prognostically comparable subsets of patients with large B-cell lymphoma two iso-DI regimens, one of which with drug threefold higher doses, have very similar rates of response, relapse, specific death and toxic death. Actually, FFS, RFS and OS curves do not show statistically significant differences. The slightly higher hematological toxicity observed with the regimen delivering escalated doses can be considered to have been partially mitigated by the larger use of growth factors. Thus, a first level of conclusion should be that DI is the truly important parameter in the treatment of lymphomas and that the increase of DS or of the number of drugs administered are not sufficient devices to give appreciable clinical results.

A comparison with the findings from other clinical experiments testing modifications of doses and time of drug administration in lymphoma therapy can be made with a few studies mainly dealing with CHOP.

The Southwest Oncology Group (SWOG) [26] reported on cohort of 88 intermediate- or high-grade lymphoma patients treated with a 2 week CHOP schedule in which cyclophosphamide was given at a dose of 1600 mg/m^2 and doxorubicin at a dose of 65 mg/sqm. The study demonstrated the feasibility of such intensification and, though the 2-year progression-free survival was lower than expected (51% versus 60%), the estimated overall survival at 5 years was 14% better than that of patients treated with standard CHOP in an earlier SWOG study. In this trial a clear-cut intensification was reached through both escalating doses and shortening intervals among cycles.

The Japan Clinical Oncology Group [27] conducted an interesting randomized trial in aggressive lymphoma patients. Thirty-two patients were assigned to receive eight cycles of standard CHOP (cyclophosphamide 750 mg/m^2, doxorubicin 50 mg/m^2, vincristine 1.4 mg/m^2 and prednisone 100 mg for 5 days) every two weeks or six cycles of dose-escalated CHOP (cyclophosphamide 1500 mg/m^2, doxorubicin 70 mg/m^2, vincristine 1.4 mg/m^2 and prednisone 100 mg for 5 days) every 3 weeks. Hematological toxicity was higher in the escalated-dose arm, despite the prophylactic use of lenograstim, but response rate and progression-free survival were lower. This trial tested the efficacy of a 150% dose densification (in this case corresponding also to 150% dose intensification) versus a dose escalation of 200% for cyclophosphamide and 140% of doxorubicin (with a 147% mean cumulative intensification). According to this trial, under condition of nearly equal mean dose intensity (150 versus 147%), administrating standard doses with higher frequency was more effective than escalating doses at standard intervals.

Balzarotti et al. [28] reported very promising results (74% complete remission rate) with a modified biweekly CHOP—both dose-intense and dose-dense—escalating the dose of cyclophosphamide and doxorubicin at 1750 and

75 mg/m^2, respectively. In this study, dose escalation was 233% for cyclophosphamide and 150% for doxorubicin, and dose densification was, again, 150%, with a resulting average dose intensification for the whole regimen of 240%.

Another very instructive study was performed by the German High-Grade Non-Hodgkin's Lymphoma Study Group separately in patients younger than 60 [29] and in those older than 61 years of age [30]. In both trials three treatments were compared to standard CHOP (CHOP 21), a biweekly (CHOP 14), an etoposide added CHOP at standard intervals (CHOEP 21) and a biweekly version of this last (CHOEP 14). Among young patients, and in comparison with CHOP 21, CHOP 14 was significantly better only with respect to 5-year overall survival, CHOEP 21 improved 5-year event-free survival only, whereas CHOEP 14 significantly increased complete response rate, reduced disease progression under therapy and improved both overall and event-free survival. CHOP 14 was also more toxic and required obligatory use of growth factors. In older patients cycle shortening (CHOP 14) had a more favorable impact on complete response rate, 5-year time to treatment failure, and 5-year overall survival, than did the inclusion of etoposide. Attempting both cycle shortening and etoposide addition (CHOEP 14) markedly reduced dose intensity (83% versus > 93% of the other regimens) and led to the relatively poorest clinical results. The message should be that dose densification is a practicable and effective way to increase the performances of chemotherapy, whereas the addition of a new drug, such as etoposide, can further increase efficacy but with a raise of toxicity that can be intolerable by frail and elder patients and detrimental to the clinical outcome. These results seem to disagree with those of Fisher et al. [4] who failed to demonstrate any advantage over CHOP for three regimens (m-BACOD, ProMACE-Cyta-BOM and MACOP-B) that have to be considered as actually intensified, densified and enriched with one or more drugs with respect to CHOP (specifically also with etoposide in the case of ProMACE-CytaBOM).

However, taking clear lessons from these clinical experiences is difficult since we are still using imperfect clinical tools, and are able to only partially explain what happens in the treatment of our patients. The assumptions which are inherent in the basic concepts of DI, DS and DD probably represent an oversimplication of the biological reality (i.e. the equivalent activity of empirically defined 'standard' doses of different drugs, the expected proportionality of cell killing activity of a drug to the dose administered). We need to take into account further information on individual drug activity, such as the actual synergism existing among chemotherapeutic agents (and among these and radiotherapy), the role of scheduled time and sequence of administration of drugs, the area under the concentration-time curve of each drugs.

At present, from the results of both this study and some recent others it appears that speeding up the sequence of administration of the drugs of a current and effective chemotherapy regimen is the most simple and safe way to increase DI and to improve clinical results in large, B-cell lymphoma patients. This conclusion seems to be consistent with that drawn by the Norton and Simon's theory on heterogenous tumor cells with different growth speed [31]. Within the wide range of doses which can be delivered now with support of growth factors—but without stem-cell rescue—the increase of DI through an increase of DS can variably improve effectiveness sometimes, but it constantly raises toxicity, often with an opposite effect on survival. In both cases the prophylactic use of growth factors is needed.

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