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High Dose-intensity Chemotherapy, with Accelerated Cyclophosphamide–Doxorubicin–Etoposide and Granulocyte–Macrophage Colony Stimulating Factor, in the Treatment of Small Cell Lung Cancer

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15 patients with small-cell lung cancer were treated with an "accelerated" chemotherapy consisting of standard-dose cyclophosphamide–doxorubicin–etoposide administered every 15 days (as opposed to the usual 21-day intervals) along with granulocyte–macrophage colony stimulating factor (10 μg/kg/day) administered prophylactically subcutaneously from day 4 to 13. The primary objective of this study was to examine the possibility of achieving a 50% dose-intensity increase by a shortening of chemotherapy intervals. 9 patients were not able to complete the planned six courses of chemotherapy owing to cumulative haematological toxicity. In fact, while leukopenia was acceptable and constant during treatment, both thrombocytopenia and anaemia progressively worsened with subsequent courses, becoming particularly severe after the 4th cycle when interruption of the treatment was often required. 13 patients who completed four courses of chemotherapy received a median of 96% of the planned dose-intensity. This corresponded with an average relative dose-intensity actually delivered of 1.44 compared with the planned dose-intensity of a standard cyclophosphamide–doxorubicin–etoposide every 21 days. In conclusion, acceleration of cyclophosphamide–doxorubicin–etoposide chemotherapy combined with granulocyte–macrophage colony stimulating factor can lead to a significant increase of dose-intensity but it is feasible only for a limited number of courses.
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INTRODUCTION

DESPITE ITS sensitivity to chemotherapy, small-cell lung carcinoma (SCLC) remains, for the majority of patients, an incurable disease. In fact, while an objective tumour regression is easily achievable, the long-term cure rate is still under 5% [1]. Attempts to improve these results have included the intensification of treatment, the rationale behind this being the observation that a dose–response relationship exists for drugs that are active in SCLC. A number of high-dose chemotherapy trials, mostly involving bone marrow transplant (BMT) support, have been performed. These studies show that the response to chemotherapy is indeed dose-dependent. Unfortunately, one or two courses of very high-dose chemotherapy seem to have no impact on the cure rate [2]. These results together with considerations related to costs, prohibitive toxicity and difficulties in repeating the procedure more than once, have led to the abandonment of high-dose chemotherapy studies with BMT in SCLC.

Recently, it has been found in several tumour types that not only is dose important but also the time in which it is given. The amount of chemotherapy delivered per unit time has been referred to as dose-intensity (DI) [3]. A number of retrospective studies in different tumour types has demonstrated that DI is significantly correlated with clinical outcome [4]. These observations have been partially confirmed in SCLC [5].

Haemopoietic growth factors are a family of glycoproteins which regulate proliferation, activation and differentiation of blood cell precursors [6]. Recent studies in SCLC have demonstrated that both granulocyte colony stimulating factor (G-CSF) [7, 8] and granulocyte–macrophage colony stimulating factor (GM-CSF) [9] are able to reduce the severity of neutropenia and its complications as well as speeding up haemopoietic recovery after CDE (cyclophosphamide, doxorubicin and etoposide) chemotherapy at standard dose and schedule. Moreover, these cytokines may allow DI of chemotherapy programs to increase without incurring the costs and the toxicity associated with BMT.

The present study was aimed at determining the feasibility of delivering standard dose CDE at intervals of 2 weeks (rather than the more conventional 3-week interval), with the support of GM-CSF, and to verify the possibility of obtaining a substantial DI increase through a shortening of chemotherapy intervals.

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PATIENTS AND METHODS

Entry criteria

Patients were considered eligible for entry into this phase II study if they had histologically or cytologically proven untreated SCLC. Additional entry criteria included: age ≤ 70 years, ECOG performance status ≤ 2 white blood cell (WBC) count ≥ 4.0 × 10^9/l, platelet (PLT) count ≥ 100 × 10^9/l, haemoglobin (Hgb) ≥ 11.0 g/dl, normal liver and renal function (serum bilirubin ≤ 2.0 mg/dl, serum creatinine ≤ 1.5 mg/dl), normal cardiac function (according to ECG and physical examination) and measurable disease. Patients with brain metastases, requiring continuous treatment with steroids, or patients with a history of previous malignancy were excluded.

This trial was approved by the local ethical committee and by the Protocol Review Board of the Istituto Nazionale per la Ricerca sul Cancro of Genoa, and informed verbal consent was obtained from all patients prior to entry. This study was carried out under the auspices of the EORTC Lung Cancer Cooperative Group.

Staging

Before treatment all patients, having provided their clinical histories, underwent physical examination, biochemical analysis [complete blood count, serum creatinine and creatinine clearance, plasma urea and electrolytes, serum bilirubin, lactate dehydrogenase (LDH), alkaline phosphatase, serum glutamic oxaloacetic and pyruvic transaminases, total protein and albumin, coagulation tests, urine analysis, tumour markers (NSE and CEA], fiberoptic bronchoscopy with washing, brushing and biopsy of tumour, chest-X-ray, computer tomography (CT) of the thorax and brain, radionuclide bone scan, liver ultrasound or CT, ECG, bilateral bone marrow biopsy and aspiration.

Limited disease (LD) was defined as tumour confined to one hemithorax, including bilateral mediastinal and supraclavicular nodes; all the other conditions were considered as extensive disease (ED) category.

Treatment plan

The treatment plan consisted of six cycles of CDE chemotherapy, administered on an outpatient basis: cyclophosphamide 1000 mg/m^2 intravenous bolus on day 1, doxorubicin 45 mg/m^2 intravenous bolus on day 1 and etoposide 100 mg/m^2 intravenous 15 min infusion in 250 ml normal saline on days 1, 2 and 3. Recombinant human GM-CSF (Schering-Sandoz) 10 μg/kg/day subcutaneously was self administered by the patients from day 4 to day 13. Patients were advised to inject GM-CSF at bedtime. Paracetamol (tablets 500 mg three times a day) was prescribed to prevent constitutional symptoms. The CDE regimen was repeated on day 15, 48 h after the last GM-CSF administration, if WBC ≥ 3.0 × 10^9/l or absolute neutrophil count (ANC) ≥ 2.0 × 10^9/l, PLT ≥ 100 × 10^9/l and Hgb ≥ 9.5 g/dl. If on the 15th day these values were not reached, GM-CSF was restarted until haematological recovery, and then chemotherapy course was given, 48 h after the last GM-CSF administration. Chest radiotherapy was delivered, at the end of treatment, to LD responding patients and prophylactic brain radiotherapy was offered to LD patients in complete remission.

No dose reduction of CDE chemotherapy was foreseen. Early stopping rules for chemotherapy included: absence of response, grade IV non-haematological toxicity (excluding nausea, vomiting and fever), grade IV neutropenia associated with documented infection, grade IV thrombocytopenia associated with haemorrhage or any grade III/IV haematological toxicity lasting more than 2 weeks. Recombinant GM-CSF was stopped if any of the following events occurred: WBC ≥ 50 × 10^9/l, severe uncontrolled bone pain, life-threatening allergic reactions, cardiac arrhythmias, thromboembolic episode, first-dose reaction and any grade III/IV toxicity attributable to the drug. After the resolution of these side-effects, patients were retreated with a dose of GM-CSF reduced by 50%. Recurrence of any grade III/IV toxicity, despite the dose-reduction, required withdrawal from the study.

Prophylactic antibiotic treatment with quinolones was given to patients with WBC ≤ 1.0 and/or ANC ≤ 0.5 × 10^9/l. Patients with febrile neutropenia (fever ≥ 38.2°C and ANC ≤ 0.5 × 10^9/l) were given empiric parenteral antibiotics such as cefotaxim. Red blood cell (RBC) and PLT transfusions were administered when Hgb fell below 8 g/dl and PLT below 20 × 10^9/l.

Blood chemistries and chest-X-ray were repeated every two cycles of chemotherapy. During treatment a complete blood count was obtained on every other day of each cycle starting from the 5th day after the beginning of chemotherapy.

Tumour response was assessed with CT scan after at least four cycles of treatment.

Response criteria and dose-intensity calculation

Standard response criteria were used. A complete response (CR) required the complete disappearance of clinically detectable disease for at least 4 weeks. Partial response (PR) was defined as a 50% or greater decrease in the sum of the products of the two greatest perpendicular diameters of all measurable indicator lesions for at least 4 weeks. Stable disease (SD) was less than a 50% decrease or less than a 25% increase in total tumour size. Progressive disease (PD) was a 25% or greater increase in the sum of the products of the two greatest perpendicular diameters of all lesions or the appearance of new lesions.

Duration of response was calculated from the first day of treatment. Dose-intensity was expressed in mg/m^2/day. The standard reference CDE regimen chosen to calculate average relative dose-intensity (ARDI), according to the method of Hryniuk and Bush [3], was that used by the EORTC Lung Cancer Cooperative Group [10]. Patients who did not receive at least four cycles of chemotherapy were excluded for DI calculation.

Statistical considerations

The present protocol was designed to allow a 50% DI increase over the standard CDE. This increment is achievable by reducing the interval from one cycle to the following one: 2 weeks of interval between cycles instead of the more conventional 3 weeks.

All patients who started the therapy were considered evaluable from a statistical point of view. It was arbitrarily decided that patients stopping the treatment before the 6th cycle or patients receiving less than 68% of the planned DI should be considered as failures. Minimax design was employed [11]. The design is based on testing a null hypothesis (HO = 60%). If the null hypothesis is true, then we require that the probability is less than 10% of concluding that the combination regimen is sufficiently promising to be accepted for further testing in other clinical trials. It also requires that if a specified alternative hypothesis H1 = 80% is true (i.e. true success probability is at least 80%) then the probability of rejecting the regimen for further studies should be less than 10%. 27 patients were

required in the first step of the trial. If 18 or less patients are successes the study is terminated; otherwise accrual continues to a total of 35 patients. 25 successes have to be observed in 35 patients in order to conclude that further studies are warranted.

RESULTS

15 male patients were entered into the study from May 1990 to August 1991. Patients' characteristics are listed in Table 1. 4 patients had extensive disease; of these no. 4 had liver, no. 1 bone marrow, no. 3 and no. 4 liver and bone involvement. Overall, 69 courses of chemotherapy, with a median of five cycles per patient (range 1–6), were given. All patients were assessed for response and toxicity. The mean chemotherapy interval was 17 days (range 13–22). 1 patient died at home after the first course of chemotherapy while febrile. Another patient died after two courses due to disease related respiratory failure. These 2 patients were recorded as failures but excluded from DI calculation. 5 patients received four courses and 2 patients five courses. 1 of these patients had to discontinue therapy because of a lack of response and 6 others because of haematological toxicity: 1 due to neutropenic infection, 1 to persistent severe anaemia and thrombocytopenia and 4 patients due to thrombocytopenia associated to bleeding. 6 patients completed the planned six courses of chemotherapy.

Haematological toxicity was evaluated across 67 cycles. Grade IV and III leukopenia were recorded in 15 (22.4%) and 23 (34.3%) courses, respectively. The mean WBC nadir was mild and constant during the treatment: 1.993 (range 0.6–4.7); 2.988 (0.5–7.7); 2.107 (0.3–6.9); 1.966 (0.1–6.8); 1.686 (0.5–4.2); 4.366 (1.2–8.7) × 10^9/l during the 1st, 2nd, 3rd, 4th, 5th and 6th cycle, respectively (Fig. 1). The WBC nadir occurred, as an average, 9 days (range 5–16) after the start of treatment; this did not change in subsequent cycles. Thrombocytopenia grade III and IV observed in 22.4% of courses (2 and 13 episodes, respectively), was the main reason for stopping chemotherapy prematurely. The mean PLT nadir progressively worsened with subsequent courses: 175 (69–279), 166 (79–371), 106 (12–224), 62 (5–186), 75 (12–144), 68 (4–114) × 10^9/l (Fig. 1). In the first three cycles (accounting for a total of 40 courses) only three (7.5%) episodes of grade IV thrombocytopenia were observed. On the contrary, 10 (37%) episodes of grade IV thrombocytopenia occurred in the following three cycles (total of 27 courses). The 11th day (range 7–16) was the median day of PLT nadir.

Sequential cycles of chemotherapy resulted also in an anaemia

Table 1. Patients' characteristics

Patient	Age	PS	Stage	No. of cycles	Response	Response duration (days)	Site of relapse	Survival (days)
1	59	1	ED	5	PR	308	CNS	332
2	61	1	ED	1	EaD	—	—	14
3	50	1	ED	6	PR	334	CNS	586+
4	63	0	ED	6	PR	213	CNS	224
5	62	0	LD	6	PR	334	Liver	454
6	62	0	LD	4	PR	311	NA	311
7	63	1	LD	4	CR	228	Lung	249
8	48	1	LD	6	CR	795+	—	795+
9	56	0	LD	4	NR	—	Lung	681+
10	58	1	LD	4	CR	171	CNS	219
11	58	1	LD	6	CR	304	CNS	387
12	51	0	LD	6	CR	273	Lung	350
13	57	0	LD	4	CR	170	CNS	203
14	48	1	LD	5	PR	365	CNS	426
15	61	1	LD	2	EaD	—	—	30

EaD = early death; PR = partial response; CR = complete response; NR = no response; + = still continuing; PS = performance status according to ECOG; NA = not assessable, ED = extensive disease; LD = limited disease.

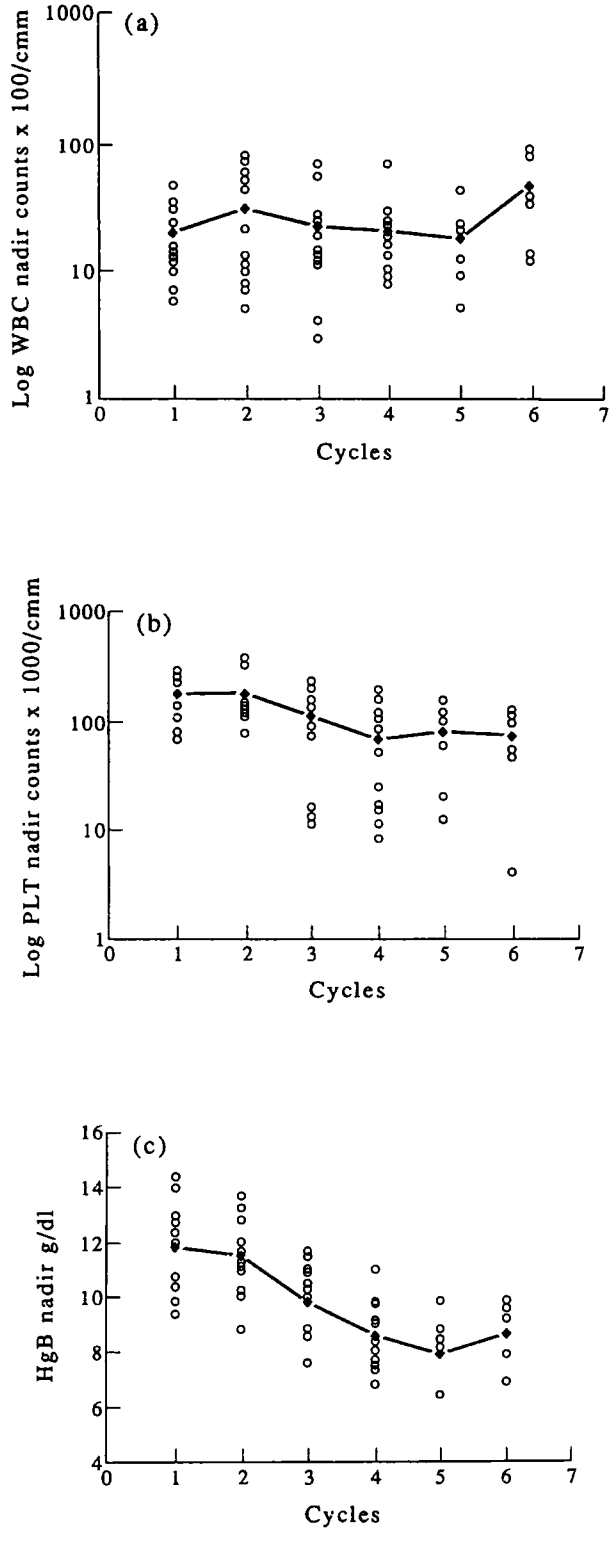

Fig. 1. Scatter plot of (a) WBC, (b) PLT and (c) HGB nadirs.

of increasing severity. The mean Hgb nadir fell from 11.8 g/dl at the first cycle to 7.9 g/dl at the sixth cycle (Fig. 1). After the fifth cycle most patients required to be transfused.

Among 13 patients who completed four courses of chemotherapy, 10 (76.9%) patients required at least one transfusion: 5 patients had PLT transfusion with a mean of 7 units (range 2–22) and 9 patients RBC transfusion with a mean of 7.7 units (range 2–26). 1 patient suffered from clinically documented bacterial infection, and 3 other patients had febrile neutropenia.

11 out of 15 patients required at least one course of antibiotics, either as prophylaxis or as therapy of febrile neutropenia. 6 patients needed hospitalisation due to PLT transfusion requirement (5 patients) or infection (1 patient).

Non-haematological toxicities were mild. Particularly mucositis was never observed and only 5 patients developed grade I epithelial toxicity.

GM-CSF related toxicity was mild: 5 patients experienced grade III toxicity (mainly constitutional symptoms). 1 patient, with a history of chronic obstructive lung disease, developed a first-dose reaction (severe dyspnoea and bronchospasm) and refused further GM-CSF therapy, but remained on study. No patients required GM-CSF dose reduction.

The worst toxicities seen per each patient are listed in Table 2. At the 4th cycle the median percentage of actually delivered versus planned DI was 96% (range 81%–102%). The median ARDI, actually delivered, compared with a planned one of a standard CDE every 21 days, was 1.44 (range 1.21–1.54). The values of DI for each patient are reported in Table 3.

9 out of 15 patients failed to achieve the desired DI at the 6th cycle (Table 3). According to its statistical premise (less than 9 failures in 27 patients were required for continuing patients' accrual), the study was hence interrupted.

Response, time to progression, site of relapse and survival of each patient are reported in Table 1.

Table 2. Toxicity

Grade	0 (%)	I (%)	II (%)	III (%)	IV (%)
Fatigue	4 (28.6)	3 (21.4)	6 (42.9)	1 (7.1)	
Flu-like syndrome	9 (64.3)	3 (21.4)	1 (7.1)	1 (7.1)	
Fever†	5 (35.7)	2 (14.3)	5 (35.7)	2 (14.3)	
Disgeusia	13 (92.8)			1 (7.1)	
Skin	9 (64.3)	5 (35.7)			
Bone Pain*	11 (73.3)	2 (13.3)	2 (13.3)		
Neurological	12 (85.7)	1 (7.1)	1 (7.1)		
Weight loss*	11 (73.3)	4 (26.7)			
Hypotension	11 (78.6)	1 (7.1)	2 (14.3)		
Infection	13 (92.8)				1 (7.1)
Diarrhoea	12 (85.7)		2 (14.3)		
Nausea*	10 (66.7)	3 (20.0)	2 (13.3)		
Vomiting*	13 (86.6)	2 (13.3)			
Leukopenia			1 (7.1)	5 (35.7)	8 (57.1)
Thrombocytopenia	3 (21.4)	2 (14.3)	1 (7.1)	1 (7.1)	7 (50.0)
Anaemia	1 (7.1)	2 (14.3)	7 (50.0)	3 (21.4)	1 (7.1)
Haemorrhage	10 (71.4)	2 (14.3)	1 (7.1)	1 (7.1)	
Anorexia	11 (78.6)	1 (7.1)	2 (14.3)		
Liver (enzyme)	12 (85.7)	2 (14.3)			

*On all 15 patients; † relative to GM-CSF.

Table 3. Dose-intensity results

PTS	No. of cycles	DI delivered vs. planned at 6th cycle (%)	Outcome	DI delivered vs. planned at 4th cycle (%)	Outcome
3	6	99	Success	101	Success
5	6	88	Success	102	Success
8	6	97	Success	98	Success
4	6	94	Success	102	Success
11	6	87	Success	89	Success
12	6	87	Success	81	Success
14	5	—	Failure	99	Success
1	5	—	Failure	102	Success
9	4	—	Failure	96	Success
7	4	—	Failure	85	Success
13	4	—	Failure	82	Success
10	4	—	Failure	82	Success
6	4	—	Failure	85	Success
15	2	—	Failure	—	Failure
2	1	—	Failure	—	Failure

DISCUSSION

A conclusive demonstration of a direct correlation between DI and clinical outcome still requires randomised prospective trials. Our present knowledge on this subject is based only on retrospective data and on an "intended", and therefore theoretical, DI rather than on one which is "actual", i.e. really delivered. Moreover, whether the possible correlation between DI and clinical results is linear or sigmoid remains unknown. A low DI could prove less effective in comparison with the standard [12], however this does not necessarily mean that higher dose-intensities produce better results [13]. Whereas for breast cancer and lymphoma the available data suggesting a correlation between DI and clinical outcome are consistent, the few data on SCLC are less certain [5, 14]. Therefore, when testing the impact of DI on this disease, one should deal with a sufficiently large DI increase which is likely to produce some detectable improvement. The recent availability of haemopoietic growth factors, specifically GM-CSF and G-CSF, might allow such an increase of chemotherapy DI to be obtained.

The present study was therefore undertaken in order to assess the possibility of obtaining a DI increase of at least 50% and to verify the short and long term feasibility of this programme. The CDE regimen was chosen for two reasons. Firstly, it is one of the most active regimens in the treatment of SCLC. In addition, the data suggesting a correlation between DI and clinical outcome, refer mainly to CDE and there is no suggestion of a similar correlation for other regimens such as the combination of cisplatin and etoposide [13, 14].

Of the two possible approaches for increasing DI (i.e. increase of the doses and reduction of the time) we chose the latter. This was based on the observations that both G-CSF [7, 8] and GM-CSF [9] allow complete haemopoietic recovery after 14 instead of 21 days, from CDE chemotherapy. On the other hand, the severity of nadir neutropenia is reduced only partially by the prophylactic use of GM-CSF. It seemed, therefore, easier to attain a 50% increase of the DI through a 1/3 (one week) reduction of the time interval between cycles than through a corresponding increase of the dose. Moreover, acceleration of chemotherapy is also supported by the rapid growth rate of SCLC and the positive results reported with the use of weekly chemotherapy [15, 16].

Our study clearly demonstrates that accelerated chemotherapy with GM-CSF is feasible only for a limited number of courses. In fact, both anaemia and thrombocytopenia progressively wors-

ened with increasing cycles of treatment. Grade IV thrombocytopenia occurred in 50% of the patients (19% of evaluable cycles) and was the major reason for hospitalisation and treatment discontinuation. Severe thrombocytopenia associated with the use of full-dose chemotherapy and GM-CSF has been reported also by others [8, 17, 18]. More than one reason could account for this toxicity. Aglietta *et al.* [19] found that GM-CSF increases the birth rate of cycling haemopoietic precursors lasting for a few days after GM-CSF suspension. Therefore, if chemotherapy is applied in this period, it could produce excessive damage of the precursor cells compartment. Bishop *et al.* [20] observed that the degree of thrombocytopenia is related to the duration of GM-CSF; the longer the GM-CSF treatment, the higher the severity of thrombocytopenia. In this respect the duration of GM-CSF used in our study might have been too long and the rest period before chemotherapy repetition too short. Alternatively, thrombocytopenia as well as anaemia could be simply the result of the higher chemotherapy DI on committed haemopoietic precursors not sustained by GM-CSF.

On the contrary, leukopenia was not a major reason for treatment failure in our trial: the mean nadir remained above 1.0×10^9/l and constant along the treatment. Despite the fact that 57% of the patients developed grade IV leukopenia sometime during treatment (22% of evaluable cycles), this was always of short duration and caused infection, with consequent treatment suspension, in only 1 patient after the 4th cycle.

In contrast to this, Hoekman *et al.* [21] found that repeated cycles of dose-intensive chemotherapy including high-dose doxorubicin and cyclophosphamide at standard intervals, with GM-CSF, produced cumulative haematological toxicity not only for PLT and Hgb but also for neutrophils. This difference might be related, at least in part, to the different type of dose-intensity increase used in the two studies (i.e. dose intensification vs. acceleration). In fact GM-CSF is probably more effective in accelerating leucocyte recovery than in abrogating their nadir.

Bronchud *et al.* [22] in a similar accelerated chemotherapy study were able to deliver doxorubicin at rather high doses (75–150 mg/m^2) every 2 weeks for a maximum of three courses combined with G-CSF. In contrast to our study, they did not find prohibitive haematological toxicities but unexpected marked epithelial toxicity. In a previous study, we were able to administer accelerated cyclophosphamide–doxorubicin–vincristine alternated to cisplatin–etoposide, combined or not with GM-CSF, without encountering life-threatening haematological toxicity [18]. The higher haematological toxicity found in the present study could be related to differences as to the type and schedule of either the growth factor or the chemotherapy employed.

Despite this severe nadir haematological toxicity, haemopoietic recovery almost always occurred promptly within 2 weeks from the previous chemotherapy course: the mean chemotherapy interval was 17 days and this interval did not increase with continuation of treatment. Therefore, GM-CSF does allow a shortening of chemotherapy intervals but cumulative haematological toxicity (mainly anaemia and thrombocytopenia) precludes the administration of many accelerated courses. From this study, it cannot be clear whether GM-CSF is really needed to attain such a modest acceleration. In fact, as we have previously shown, chemotherapy acceleration can also be obtained in the absence of haemopoietic growth factors use, at least when less myelosuppressive agents are used [18]. However, a recent randomised study conducted in patients with advanced breast cancer clearly demonstrates that cyclophosphamide–epidoxorubicin–fluorouracil chemotherapy cannot be accelerated without the use of GM-CSF [23].

In designing the statistics of this study it was decided to stop the accrual as soon as the H1 hypothesis (true proportion of success = 80%) could be rejected. This was in fact the case after 15 patients. Therefore, we conclude that six courses of accelerated CDE with a 50% DI increase are not feasible, even in the presence of the growth factor.

However, if the data of the present study are analysed at the 4th cycle, a completely different picture emerges. Only three episodes (7.5% of 40 evaluable cycles) of grade IV thrombocytopenia occurred and 13 out of 15 patients (86.7%; 95% confidence interval 58.4–97.7%) were able to reach this point, and could therefore be considered as successes according to the statistical premise. Since, at the 4th cycle we were able to administer 96% of the planned DI, it is likely that three courses of accelerated chemotherapy are feasible with a consequently 50% increase of the projected dose intensity over a standard every 21 days CDE.

Several randomised studies [24] in SCLC have shown that duration of chemotherapy does not significantly influence survival and one very recent study [25] indicates that three courses of standard dose chemotherapy are as effective as six courses. Therefore, it might well be that 3–4 courses of accelerated chemotherapy could be a reasonable treatment for SCLC and the comparison of this approach with standard DI chemotherapy would allow a definitive answer to the question of the importance of DI in the treatment of SCLC.

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Curability of Advanced Burkitt's Lymphoma in Children by Intensive Short-term Chemotherapy

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The treatment programme (regimen I) we designed in 1982 for advanced Burkitt's lymphoma was modified in 1986 as regimen IIA and IIB for patients presenting without or with bone marrow (BM) and/or nervous system involvement, respectively. Following a 5-week course of cytoreductive chemotherapy, including vincristine (VCR), cyclophosphamide (CPM), doxorubicin (DXR), high-dose methotrexate (HDMTX) and intrathecal methotrexate and cytarabine (ARAC), high-dose ARAC and cisplatin were given as a 4-day continuous infusion. Regimen I continued with an additional 3-week course including VCR, CPM, DXR and HDMTX, which was omitted in regimen IIA. In regimen IIB the initial cytoreductive chemotherapy was complemented by adding etoposide and increasing HDMTX doses, and by modifying the high-dose ARAC administration modality and was followed, once the bone marrow had recovered, by ifosfamide that concluded the programme. A total of 44 children (22 in regimen I and 22 in regimens IIA and IIB) were treated, with an overall response rate of 98%. 4 patients died as a result of treatment related complications. Survival, progression-free and event-free survival rates were 73, 70 and 63%, respectively, for regimen I, and 82, 90 and 82%, respectively, for regimen IIA and IIB. A short chemotherapeutic regimen, using alternating phase-specific and non-specific agents, is able to cure the majority of patients with advanced Burkitt's lymphoma.
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INTRODUCTION

BURKITT'S LYMPHOMA (Bu-L) is a highly malignant lymphoma resulting from a transformed B-cell monoclonal expansion, occurring mostly in children and in patients with congenital or acquired immunodeficiencies [1–3]. It was first recognised and described in equatorial Africa, where it still represents one of the most common malignancies in children [4]. In countries outside Africa Bu-L occurs less frequently, but represents a large proportion of childhood non-Hodgkin lymphoma [5, 6]. It has a typical clinical picture of rapidly growing masses within the abdomen involving the gastrointestinal tract, the lymph nodes, the kidney and/or the liver, often associated with malignant peritoneal effusion. Extra-abdominal lesions may occur anywhere such as skeleton, central nervous system (CNS), bone marrow (BM), subcutaneous tissue, lymph nodes and may or may not be associated with abdominal involvement [1].