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Review paper

Dose intensification of chemotherapy and the role of granulocyte colony stimulating factor and granulocyte macrophage colony stimulating factor in small cell lung cancer

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The natural history of small cell lung cancer (SCLC) is characterized by early dissemination. Despite the high responsiveness to chemotherapy, the disease remains ultimately fatal in the majority of patients. One of the strategies to improve final outcome is the administration of intensified chemotherapy, either by dose escalation or by chemotherapy given at shortened intervals. By now, in only one randomized study, in which cyclophosphamide and cisplatin dosage was escalated by 30% in the first course only, a survival advantage was demonstrated in limited disease patients. The different ways of achieving intensification of chemotherapy are highlighted. The addition of growth factors in current dose-escalated or accelerated schedules seems to result in a relative dose intensity of no more than 150% when compared to optimally delivered conventional regimens. Whether such a moderate degree of dose intensification will improve survival rates has to be awaited from phase III trials.

Key words: Chemotherapy, dose intensification, hematopoietic growth factors, small cell lung cancer.

Introduction

Without treatment, median survival in small cell lung cancer (SCLC) is poor at 5–12 weeks. In 1969 it was reported that cyclophosphamide prolonged the survival of patients with advanced SCLC.[1] In the 1970s several combination chemotherapy regimens were evaluated, and appeared to give higher response rates and longer survival than single drug therapy. Nowadays, cyclophosphamide/adriamycin/vincristine (CAV), cyclophosphamide/adriamycin/etoposide (CDE), cisplatin/etoposide (PE) and (vincristine/)ifosfamide/carboplatin/etoposide (VICE or ICE) are the most frequently used combinations. At standard dose these combinations are considered to be more or less equipotent, although this is not proven by randomized trials. In limited disease (LD) an overall response (OR) rate of 80–95% and a complete response (CR) rate of at least 50–60% with a median survival between 12 and 16 months can be achieved. Corresponding numbers in extensive disease (ED) are an OR rate of 60–80% and a CR rate of 15–30% with a median survival between 7 and 12 months. Thus, despite the high responsiveness to chemotherapy, the disease remains ultimately fatal in the majority of patients with a 2-year disease-free survival of 15–40% in LD and 0–5% in ED patients.[2]

Initially, chemotherapy for SCLC was often administered until death or disease progression occurred. In the 1980s it had been questioned whether maintenance chemotherapy could indeed prolong survival. Comparisons between five or six to eight and 12 or 28 courses demonstrated that five to six courses of chemotherapy gave the same results as prolonged treatment, therefore six courses should be accepted as a maximum.[3–9] Two other large randomized trials reported that three or four courses of chemotherapy are probably too short to produce long-term disease-free survival.[10,11]

Goldie and Coldman postulated a mathematical model concerning genetic resistance at the cellular level and argued that non-cross-resistant drug combinations should be used in an attempt to circumvent the development of drug resistance.[12] Several large randomized trials evaluated the impact of alternating regimens, but could not show any major survival advantage.[13,14] However, in these trials only partial non-cross-resistant drugs were used and this may be insufficient to test the hypothesis.[15]

There is still an on-going debate on the importance of dose in SCLC treatment. Skipper and

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Schabel showed a clear dose–response relationship for cyclophosphamide and other anticancer drugs in animal tumor models, suggesting that dose is critical to tumor cell kill.[16] The concept of dose intensification has been tested in patients with SCLC. Dose intensification can be achieved by delivering a higher dose per course and/or by shortening intervals between courses. Higher doses per course can be delivered in the first course(s), i.e. early intensification, or last course(s), i.e. late intensification, or during all courses. In the first part of this paper, we will discuss dose intensification studies performed in the pre-growth factor period, with attention focussed on randomized trials. In the second part we will review the role of granulocyte colony stimulating factor (G-CSF) and granulocyte macrophage colony stimulating factor (GM-CSF) as adjuncts to standard-dose and intensified chemotherapy.

Before discussing the individual studies, some general remarks concerning definitions have to be made. The amount of anticancer drugs given during a certain time period (mg/m^2 per week or day) is referred to as dose intensity (DI).[17] Projected (planned) DI is obviously not the same as actually delivered DI, but the latter, more important, information is seldom reported. Another frequently used term is relative DI (RDI), i.e. the ratio of the DI of the investigated regimen and the DI of another usual standard regimen. The average DI for combination chemotherapy is calculated by the sum of DIs of each individual agent divided by the number of agents in that combination, with the assumption that the different drugs are equivalently active. It is important to note that the reported DI is often calculated only for those cycles that are indeed delivered. This may be misleading, when for example a substantial number of patients have discontinued treatment prematurely, because in these patients the DI may be high, although the delivered total dose is actually low. The delivered total dose is therefore valuable additional information, but this is often not separately reported.

Dose intensification without growth factors

Dose–response relationship and schedule dependency for single agents in SCLC

Cyclophosphamide is a commonly used agent in SCLC. Single-agent cyclophosphamide at conventional dose (1000 mg/m^2) produces a response rate of 30–40% in SCLC patients, while complete responses are seldom seen.[19] Souhami and colleagues showed that in untreated LD patients 160–200 mg/kg cyclophosphamide, administered during one course, produced an OR rate of 84% and a CR rate of 56%, indicating that there is a clear dose–response relationship.[20] These promising results could not be improved by giving a second cycle of high-dose cyclophosphamide, implying that there was a quick emergence of drug resistance.[21] Etoposide in a conventional dose has shown response rates of 40–60% in previously untreated SCLC patients.[22] When given at a higher dose conflicting data have been reported.[23–25] Other agents that do have antitumor activity in SCLC have not been studied for a dose–response correlation, when given as a single agent at a megadosage. For etoposide a schedule dependency has been shown, with increasing activity when given over several consecutive days,[26] which may also be the case for cyclophosphamide.[27]

Early intensification studies

In a meta-analysis it was concluded that the DI of the first two courses was not consistantly correlated with response and survival in SCLC.[28] However, in this analysis studies in both chemonaive and relapsed patients were taken together. Dose intensification studies were excluded, because the first two courses would not be representative for the whole treatment period. When having a closer look at the tables, it shows that the majority of trials had a RDI of smaller than 1 (compared to a reference regimen), indicating that in the majority of trials standard versus low dose was compared. Moreover, the range of RDIs was small and it may have been difficult to assess any correlation at all. The validity of this kind of retrospective analysis has also been questioned by others.[29] The results of this analysis may therefore not be used as an argument against dose intensification studies.

In phase II studies of up-front early intensification, megadoses of cyclophosphamide (up to 7.0 g/m^2) and/or etoposide (up to 1.5 g/m^2) were prescribed, with or without autologous bone marrow support.[30–34] These regimens were very toxic and, despite promising high CR rates, survival seemed not to be improved.

Direct comparisons of chemotherapeutic agents at different dosages have seldom been reported in SCLC. An old randomized study showed a benefit of an increased dose of cyclophosphamide, methotrexate and lomustine,[35] but in this study a comparison

between low and standard dose was made and the pivotal question is not whether standard dose is better than low dose, but whether high dose is better than standard dose. To address this question, four randomized studies have assessed the impact of early intensification of commonly used agents (see Table 1).[36–39] These trials differ in selection of patients, choice of regimen and degree of intensification. Patients were randomized to receive a number of initial courses (1–4) at either intensified or standard dose. In the subsequent cycles all patients received courses at standard dose. The increase in delivered total dose was relatively larger than the increase in dose intensity. As can be expected, toxicity was in general more severe in the intensified cycles, although this was manageable. A significantly better CR rate by early intensification was achieved in only one study, but this was not translated into a better survival.[37] The French trial was the only trial that showed an improved survival (2-year survival 43 versus 26% in favor of the intensified arm; $p = 0.02$), with a nearly significant difference in median duration of CR (540 versus 358 days; $p = 0.06$).[38] This trial was based on a retrospective analysis in 131 consecutive treated LD patients, which showed that a 20% increase in initial doses of cyclophosphamide and cisplatin, produced an increase of 2-year survival of 20%.[40] The survival benefit seen in the French trial is encouraging, but may be due to chance, as the difference in dose intensity between both arms is remarkably small. On the other hand, it may be a fact that dose escalation is especially worthwhile in LD patients (low volume disease) and this may also explain the lack of any benefit in the other early intensification studies. Another explanation for these disappointing results may be the number of patients, that may have been too small to draw definite conclusions in three of four trials. Furthermore, the doses of a number of drugs were increased, although the phase II data of these drugs are often incomplete when looking for a dose–response relationship in SCLC. Moreover, the degree of intensification may be still too low and megadoses as used in some phase II studies may still be worthwhile to evaluate in a randomized setting.

Late intensification studies

Norton and Simon proposed a mathematical model, in which they argued that small tumors may be less sensitive to chemotherapy due to a reduced growth fraction.[41] Therefore, they suggested to administer intensified chemotherapy of a relative brief duration, in case a CR by the induction therapy had been obtained. To test their theory a number of small phase II trials were conducted.[42–51] In most of these

Table 1. Randomized trials comparing identical induction regimens at different dosages in SCLC

No. of patients	Standard regimen (mg/m^2)	No. of HD/ total courses[a]	RDI in HD course[b] (%)	Relative total dose (%) in HD course[c]	Grade IV neutropenia CD/HD (% of courses)[d]	CR CD/HD (%)	MST CD/HD (months)	Reference
103 LD/ ED	C 1000 A 50 V 1	4/4	C + 47 A + 12 V − 10	C + 56 A + 18 V − 6	45/75*	22/21	12/13	36
298 ED	C 1000 A 40 V 1	3/6	AC + 27	C + 16 A + 68	40/79**	12/22**	8/7	37
105 LD	C 900 P 80 A 40 E 75 × 3	1/6		C + 33 P + 25	23/39	54/67	14/18***	38
90 ED	P 80 E 80 × 3	2/4	PE + 46	PE + 68	2/32****	22/23	11/11	39

Abbreviations: C = cyclophosphamide, A = adriamycin, V = vincristine, P = cisplatin, E = etoposide, HD = high dose, CD = conventional dose, RDI = relative dose intensity, CR = complete response, MST = median survival time.
[a]In both arms four to six courses in total: all courses either CD or the first one to four courses HD followed by CD courses.
[b]Actually delivered increase in DI in the HD course when compared to CD course (CD = 100%), reported per agent or per regimen.
[c]Actually delivered increase in dose in the HD course when compared to CD course (CD = 100%), reported per agent or per regimen.
[d]Only compared for those courses in which HD chemotherapy was prescribed.
* $p < 0.003$, ** $p < 0.05$, *** $p = 0.02$, **** $p < 0.0001$.

trials only one high-dose cycle was given with cyclophosphamide (4.0–7.0 g/m^2) and/or etoposide (1–3.5 g/m^2). In 20–50% of patients with a partial response (PR) after induction therapy, a CR after late intensification was achieved, although in general of short duration. In this highly selected patient population long-term disease-free survival varied from 5 to 20% and therefore seems not superior to conventional regimens.

In the one randomized late intensification study that has been reported by Humblet *et al.*, it was assessed whether after five induction cycles (of six different drugs) a last intensified cycle would produce better results than an additional standard-dose cycle.[52] Patients were eligible for randomization in case after induction a CR or PR was obtained in LD and a CR in ED. This was the case in only 40 of 101 registered patients; an additional five ED patients with PR were abusively also randomized. The last standard-dose cycle consisted of cyclophosphamide 750 mg/m^2, etoposide 120 mg/m^2 × 5 orally and BCNU 60 mg/m^2. In the intensified cycle the doses of these three agents were increased by 700, 67 and 4900%, respectively, with autologous bone marrow rescue. After the intensified cycle, the CR rate increased from 39 to 79%, while in the standard arm the response rate did not increase after the last conventional dosed cycle. Although median relapse-free survival after randomization was significantly better in the intensified arm (28 versus 10 weeks, $p = 0.002$), there was no more than a trend toward improvement in median overall survival (68 versus 55 weeks, $p = 0.13$). This disappointing result may be explained by the small size of the study, the inclusion of ED patients and by the fact that during late intensification drugs were used that were also part of the induction regimen. Patients with a partial remission are unlikely to be cured by a last dose escalation; however, in this study among four long-term survivors two were partial responders to the induction regimen. Despite the support of autologous bone marrow infusion 17% toxic deaths were seen during aplasia in the intensified arm, compared to no toxic deaths in the standard treatment arm, and this may also have contributed to the final bad outcome. Lastly, no thoracic irradiation was given and this appeared to be the primary site of relapse in the majority of patients.

Acceleration studies

A third way to increase the DI is delivering chemotherapy at shortened intervals. In three phase II trials, four to seven drugs were administered weekly in an alternating fashion over a total of 9–16 weeks.[53–55] In these regimens, most drugs were delivered at an increased DI per course, but in comparison with conventional schedules sometimes at the cost of total dose. The regimens appeared to be feasible in the majority of patients and promising high response rates were reported. Only two phase III trials testing this concept have been reported.[56,57] In the first, 223 patients were randomized to receive either the weekly regimen (cyclophosphamide 500 mg/m^2, doxorubicin 25 mg/m^2 and etoposide 120 mg/m^2 in week 1, cisplatin 60 mg/m^2 and vindesine 3 mg/m^2 in week 2, vincristine 2 mg and methotrexate 100 mg/m^2 in week 3; 6 times repeated) or six three-weekly courses of CDE (1000, 50, 3 × 80 mg/m^2, respectively).[56] Response rates and survival showed no significant differences. Toxicity was tolerable in both arms. Grade III and IV neutropenia occurred more frequently in the standard arm (59 versus 76% of patients, $p = 0.03$). In another randomized trial, 438 patients received either weekly chemotherapy (12 alternating cycles of ifosfamide 2 g/m^2/doxorubicin 25 mg/m^2 and cisplatin 50 mg/m^2/etoposide 2 × 75 mg/m^2) or six three-weekly alternating cycles of standard dose CAV/PE (600, 50, 2 and 60, 3 × 120 mg/m^2, respectively).[57] Again, no differences in response nor in survival could be demonstrated. The weekly schedule was less feasible and more often treatment had to be reduced or delayed, with the consequence that only 74% of planned DI could be delivered, while 93% of planned DI of the standard regimen could be given. In these randomized studies different agents were used in the different arms. Therefore, no exact comparisons concerning delivered dose and DI can be made. The results of a collaborative trial conducted by the Eastern Cooperative Oncology Group the Southwest Oncology Group, and the National Cancer Institute of Canada have to be awaited. In their study the weekly regimen consisting of cisplatin, vincristin, doxorubicin and etoposide (CODE)[55] is compared with standard dose CAV/PE.

Role of growth factors in chemotherapy for SCLC

Growth factors and chemotherapy-induced myelosuppression

Colony stimulating factors are physiologically occurring glycoproteins that control proliferation

and differentiation of multipotent and lineage-restricted hematopoietic progenitor cells and, furthermore, promote the functional activation of mature cells.[58–62] G-CSF administered s.c. or i.v. at a dose of 0.3–60 μg/kg/day produces a 1.6- to 12-fold increase in absolute neutrophil count.[63–65] This increase is dose dependent, although there is a considerable overlap. After discontinuation a rapid fall in circulating neutrophils to pre-treatment levels is seen within 2–4 days. G-CSF primarily affects the peripheral counts of neutrophils. GM-CSF produces a similar dose-dependent increase in neutrophils and produces also a significant increase in monocytes and eosinophils.[66–68] Both growth factors produce an increased bone marrow cellularity with increased myeloid–erythroid ratio.[60,67,68] G-CSF is associated with only minimal toxicity, even at 60 μg/kg/day, essentially limited to bone pain.[59,69] In contrast, GM-CSF often induces fever, musculoskeletal pain, malaise and anorexia. Capillary-leak syndrome and thrombosis have been observed at dose levels of 30 μg/kg/day or higher.[59] *In vitro* analyses have shown specific high-affinity binding sites of G-CSF and GM-CSF to certain SCLC cell lines and sometimes colony forming stimulation,[70,71] but *in vivo* a significant effect on tumor cell growth has never been reported.

The augmentation of circulating neutrophils by G-CSF and GM-CSF suggested a role in improving recovery of myelopoiesis after chemotherapy. In a phase II study in SCLC patients, G-CSF was given to each patient for 14 days on alternate (odd or even) cycles of three-weekly chemotherapy. G-CSF doses varied from 1 to 40 μg/kg/day and was commenced 24 h after the last chemotherapy dose.[63] While on G-CSF, the duration of chemotherapy-induced neutropenia was reduced considerably with normalization of neutrophil count within 2 weeks after day 1 of chemotherapy. This resulted in a significant reduction in infectious episodes. GM-CSF was evaluated by a similar study design.[72] Despite partial abrogation of chemotherapy induced neutropenia, GM-CSF failed to reduce the frequency of febrile episodes. In general 5–10 μg/kg/day G-CSF or GM-CSF is advised when prescribed for standard-dose chemotherapy. The efficacy of G(M)-CSF depends not only on dose but also on schedule of administration. At standard chemotherapy, a 7–10 day administration starting 1 day after the end of chemotherapy is optimal in reducing both degree and duration of leukopenia. A later onset is less effective, an earlier one aggravates leuco- and thrombocytopenia.[73–75]

Growth factors as adjunct to standard-dose chemotherapy

The combination of fever and neutropenia is a life-threatening complication of chemotherapy. Despite immediate administration of broad-spectrum i.v. antibiotics, mortality remains approximately 10% among patients with documented infections and 2% for all cases of fever.[76] The most important prognostic factor for the risk of infection is the recovery of neutrophil counts.[77] In view of the influence of G-CSF and GM-CSF on neutropenia its impact on febrile neutropenia has been evaluated in six randomized trials in SCLC, four with G-CSF and two with GM-CSF (see Table 2).[78–83]

In the first, 199 patients were treated by six courses of three-weekly CDE.[78] Treatment with G-CSF or placebo was given on days 4–17, at a dose of 230 μg/m^2. Both severity and duration of neutropenia were significantly reduced and, concommitantly, a nearly 50% reduction in incidence of febrile neutropenia, in i.v. antibiotic use, hospitalization and culture confirmed infections was observed. The duration of individual episodes of antibiotic use and hospital stay were similar in both treatment groups. The confirmatory trial demonstrated comparable results.[79] G-CSF in the weekly CODE regimen showed also a protective effect on number of febrile patients and episodes.[80] The incidence of infection was not reduced during another weekly chemotherapy regimen supported by G-CSF, despite higher white blood cell counts.[81]

GM-CSF was studied at different dose levels in 238 SCLC patients.[82] Hematopoeises was stimulated at all dose levels, but only patients who received 10 μg/kg GM-CSF required less i.v. antibiotics compared with the observation group. Overall fever occurred more frequently in both the 10 and 20 μg/kg GM-CSF groups, and this was considered to be a major side-effect of GM-CSF at these dose levels. This and other toxicities were the reason for more patients in the GM-CSF group than in the observation group to drop out of the study. In the second GM-CSF trial, the incidence of grade IV neutropenia was not significantly different, despite higher neutrophil nadirs in the GM-CSF arm.[83] More important, patients on GM-CSF spent significantly more days in the hospital, and had a higher incidence of fever, i.v. antibiotic usage, life-threatening thrombocytopenia, transfusions, toxic deaths and non-hematologic toxicities.

In conclusion, there is a remarkable difference in the results obtained with G-CSF compared to GM-CSF: in three out of four G-CSF studies the incidence

Table 2. Phase III trials with standard-dose chemotherapy evaluating the impact of G(M)-CSF support

No. of patients	Regimen	Support	Febrile neutropenia (%)[a]	RDI (%)	Total dose (%)	Reference
199	CDE	G-CSF	40*			78
		without G-CSF	77			
129	CDE	G-CSF	26**	96		79
		without G-CSF	53	88		
63	CODE	G-CSF	44***	66[b]		80
		without G-CSF	77	35		
40	PE/ID	G-CSF	NS	84	88	81
		without G-CSF		82	88	
238	CDE	GM-CSF 5 μg/kg	21			82
		10 μg/kg	11***			
		20 μg/kg	29			
		without GM-CSF	29			
215	PE	GM-CSF	39****	75		83
		without GM-CSF	22	85		

Abbreviations: CDE = cyclophosphamide, doxorubicin, etoposide; CODE = cisplatin, vincristine, doxorubicin, etoposide; PE/ID = cisplatin, etoposide, ifosfamide, doxorubicin; PE = cisplatin, etoposide. RDI = relative dose intensity (percent of planned DI). Total dose = percent of planned total dose.

[a]For references 78–80: percent of patients with at least one episode of fever; for references 82 and 83: percents of patients requiring i.v. antibiotics through all cycles.

[b]Not RDI, but percent of patients whose treatment was completed within 10 weeks ($p < 0.05$).

* $p < 0.001$, ** $p < 0.002$, *** $p < 0.01$, **** $p = 0.04$

of febrile neutropenia was reduced by almost 50% when compared to no support, while conflicting results were reported with GM-CSF. The absence of any benefit in the trial of the Southwest Oncology Group[83] may be explained by the concurrent use of GM-CSF with chest radiotherapy, although, on the other hand, ameloriation of radiotherapy-induced neutropenia by growth factors has also been reported.[84] Another explanation may be that the occurrence of fever was not infection related but a side-effect of GM-CSF, because the incidence of fever seemed to be GM-CSF dose dependent.[82]

The incidence of febrile neutropenia is important as it is the critical factor influencing cost effectiveness: the probability of hospitalization would have to exceed 40% before the prophylactic use of a growth factor will be cost effective.[85] Febrile neutropenia after conventional CDE doses is reported to occur in 6–56% of all cycles.[86] The high rate of episodes of febrile neutropenia in the first study may reflect the unusual vigilant monitoring, a stricter definition of febrile neutropenia (i.e. temperature of 38.2°C or greater and absolute neutrophil count below 1.0×10^9/l) and the higher than usual chemotherapy dosage (cyclophosphamide 1000 mg/m^2, doxorubicin 50 mg/m^2 and etoposide 3×120 mg/m^2). The somewhat lower incidence in the second study may be due to different patient characteristics (younger, more often limited disease with a better performance status). The incidence of fever in the observation arm in the GM-CSF study was only 29%, probably due to the lower CDE dosage (doxorubicine 20% and etoposide 33% lower when compared with the other two CDE studies).[82]

An alternative for prophylactic administration of growth factors may be delayed administration of growth factors, i.e. not until fever has already occurred. The advantage is that overtreatment of patients that will never have fever will be prevented. In the few studies that have investigated this concept, both G-CSF and GM-CSF produced a slightly accelerated neutrophil recovery, but this did not result in a reduction in duration of fever and hospitalization.[87–90] A second alternative may be the prophylactic use of antibiotics. In SCLC patients prophylactic co-trimoxazole resulted in a reduced overall incidence of documented infections of 60% when compared with placebo, especially in case neutrophil count was less than 100×10^6/l.[36,91] It may be worthwhile to compare directly the protective value of growth factors with that of antibiotics, especially from an economic point of view.

The prophylactic use of growth factors may facilitate the delivery of planned chemotherapy dose due

to less dose reductions and delays, and this was indeed demonstrated in two out of four G-CSF studies, but only to a moderate degree (see Table 2).[79,80] Crawford *et al.* reported no data concerning delivered dose or dose intensities.[78] For GM-CSF conflicting observations have been made. Hamm reported that more patients on GM-CSF were able to receive full-dose cycles (more than 55% of patients treated during cycles 2 and 3 with either 5 or 10 μg/kg GM-CSF compared with 36% of the observation patients). On the other hand, more patients in the observation arm were able to complete all six cycles (66 versus 60, 42 and 33% of patients with 5, 10 and 20 μg/kg GM-CSF, respectively).[82] In the trial of concurrent use of GM-CSF and chemoradiotherapy, delivered total dose was even 10% lower in the GM-CSF arm as compared to the control arm.[83]

In none of these studies were significant differences in response or survival found, but as these were not primary end-points, sample sizes may have been too small to detect small differences and this outcome may also be explained by the inclusion of ED patients.

Growth factors as adjunct to high-dose chemotherapy

It has been attempted to increase the maximum tolerated dose (MTD) by the support of growth factors (see Table 3). In the study of Katakami *et al.*[94] the MTD was not determined without G-CSF and therefore studies with the same chemotherapy regimen have been reported in Table 2.[92,93] Although direct comparison is difficult, a moderate dose escalation of carboplatin seems possible with the addition of G-CSF. Luikart tried to escalate etoposide dose besides a constant carboplatin dose, but this was hardly possible with GM-CSF 10 or 20 μg/kg/day.[95] The Cancer and Acute Leukemia Group B reported two separate phase I studies, one without and one with the addition of G-CSF.[97,98] Despite the use of G-CSF, the MTD was the same due to the occurrence of febrile neutropenia as the major toxicity. On the other hand, with G-CSF the duration of neutropenia was in general brief and recycling at a three-weekly interval was, therefore, mainly possible in G-CSF-treated patients. The study reported by Paccagnella *et al.*[99] had an interesting design. The MTD of epirubicin was determined during the first cycle. In the first group of patients the MTD was determined without GM-CSF and in the next group of patients it was attempted to increase the MTD by the addition of GM-CSF. The MTD could only be moderately increased with the addition of GM-CSF, i.e. from 60 to 70 mg/m^2. All patients were subsequently evaluated for feasibility during the next five cycles. Although this was not a randomized study, comparisons were made between patients treated at a lower epirubicin dose (45–

Table 3. Dose-finding studies with and without the addition of G(M)-CSF

Regimen	MTD without G(M)-CSF (mg/m^2)	MTD with G(M)-CSF (mg/m^2)	DLT with G(M)-CSF	Reference
Carboplatin Etoposide	500 3 × 100			92
Carboplatin Etoposide	350 3 × 100			93
Carboplatin Etoposide		450/650[a] 3 × 100	thrombocytopenia	94
Carboplatin Etoposide	3 × 125 3 × 200	3 × 125 3 × 250	thrombocytopenia	95
Cisplatin VM-26	80 5 × 60	80 5 × 120	leukopenia/diarrhoea	96
Cisplatin Etoposide	3 × 25 3 × 200	3 × 25 3 × 200	febrile neutropenia	97, 98
Cisplatin Etoposide Epirubicin	60 3 × 120 60	60 3 × 120 70	neutropenia	99

Abbreviations: MTD = maximum tolerated dose, DLT = dose-limiting toxicity.
[a]450 at age 70 or older, 650 at age below 70 years.

60 mg/m^2, without GM-CSF) and at a higher epirubicin dose (60–70 mg/m^2, with GM-CSF). It was demonstrated that the higher dose with GM-CSF was not only feasible, but that GM-CSF also had reduced significantly the severity of neutropenia when compared to patients treated at a lower epirubicin dose without GM-CSF (grade IV neutropenia 26 versus 57%, $p < 0.01$). In patients on GM-CSF, neutropenia in the first course (in which MTD was determined) was more severe than in the next five courses. Due to less dose reductions and delays for hematological toxicity, the actually delivered DI of epirubicin over six cycles was in the GM-CSF-treated patients substantially increased by 63% when compared to patients treated without GM-CSF. This resulted also in an increase of relative dose intensity for cisplatin and etoposide of about 30%, despite the same planned dose for these two agents. Moreover, only 73% of planned cycles could be delivered in the control arm versus 86% of cycles supported by GM-CSF. Patients treated at lower dose levels had an OR rate of 72% (CR 24%), compared to an OR rate of 95% (CR 40%) in patients treated at higher dose levels.

In conclusion, in these few studies in SCLC it was shown that the MTD could not or only modestly be increased by the addition of G(M)-CSF. Nevertheless, due to less dose reductions and delays, the total RDI over all courses could be increased by 30–60% in one phase II study. More studies are warranted in order to assess the exact role of growth factors in chemotherapy dose.

Growth factors as adjunct to accelerated chemotherapy (dose-densified)

The feasibility of reducing intervals between full-planned-dose chemotherapy courses by the addition of G(M)-CSF has been tested in a few phase II studies (see Table 4). Ardizzoni *et al.* reported such an 'accelerated' chemotherapy regimen of CAV and PE, which was planned to be alternated weekly for a total of six courses (cyclophosphamide 1000 mg/m^2, doxorubicin 50 mg/m^2, vincristine 2 mg on day 1; cisplatin 60 mg/m^2 and etoposide 150 mg/m^2 on days 8 and 9).[100] In the first five patients GM-CSF was given as soon as grade IV leukopenia developed, while in five additional patients the same regimen was given without GM-CSF. Although not one patient was indeed able to receive the planned weekly regimen, the average number of days required to recycle was substantially reduced when compared to the standard interval of 21 days (10 days with and 13 days without GM-CSF). As a consequence treatment duration was limited to 57 days with GM-CSF and 73 days without GM-CSF (standard projected 107 days), resulting in an almost 2- and 1.5-fold increase in dose intensity, respectively. Although the decrease in treatment duration in patients treated with GM-CSF was larger than without GM-CSF, it was disappointing that the absolute benefit of GM-CSF was not as large as expected. The authors suggested, that the 'prophylactic' use of growth factors may be more suitable instead of 'on-demand' use. Over all cycles, the

Table 4. Standard-dose chemotherapy delivered at shortened intervals with the addition of G(M)-CSF

Regimen	No. of patients	Mean interval (range) (days)	Percent of patients that completed four/six cycles	Grade IV WBC (% of cycles)	Grade IV platelets (% of cycles)	RBC[a] (no. of patients)	PLT[b] (no. of patients)	Reference
CAV/PE GM-CSF	5	10 (6–19)	80/80			3	2	100
CAV/PE	5	13 (6–23)	100/100			3	0	100
CDE GM-CSF	15	17 (13–22)	87/40	22	19	9	5	101
CDE G-CSF	32	17 (14–30)	81/63			21	5	102
CDE G-CSF	20	17 (14–42)	65/60	40	25	17	12	103

Regimen: see text
[a]Number of patients that received red blood cell transfusions
[b]Number of patients that received platelet transfusions

mean white blood cell count and platelet nadirs were 0.60 and 46×10^9/l in the GM-CSF group versus 0.84 and 105×10^9/l in the controls, probably reflecting the higher DI in the GM-CSF-treated patients. The increase in DI was not associated with a worsening of non-hematological side-effects. In a subsequent trial, the same group tried to accelerate standard CDE (cyclophosphamide 1000 mg/m^2, doxorubicin 45 mg/m^2, etoposide 3×100 mg/m^2) by giving it every 2 weeks with prophylactic GM-CSF 10 μg/kg/day from day 4 to 13.[101] The Medical Research Council (MRC) Lung Cancer Working Party performed two comparable studies with CDE, but the chemotherapy was administered at a moderate higher dose for two agents (doxorubicin 50 mg/m^2 and etoposide 3×120 mg/m^2).[102,103] Moreover, they prescribed G-CSF instead of GM-CSF (filgrastim 300 μg/day day 4–14 in 32 patients[102] and lenograstim 5 μg/kg/day day 4–14 in 20 patients[103]). The mean chemotherapy interval was 17 days for all three studies. Ardizzoni calculated that the delivered RDI was 1.44 per cycle. It must be remembered that RDI and intervals can only be calculated over cycles that are actually delivered. Approximately 80% of patients were able to receive at least four cycles, but only 55% were able to complete all six cycles. Premature discontinuation in all three studies was mainly due to progressive thrombocytopenia and anemia, particularly severe after the fourth cycle. This was also the main reason for delays, which were concentrated towards the end of the treatment period. In the MRC studies grade IV neutropenia occurred more often than in the study of Ardizzoni, probably due to the higher doses per course. Nevertheless, neutropenia had almost invariably resolved by the end of the 14 day period in all three studies and there was no evidence of increasing risk of neutropenia following subsequent cycles. Non-hematologic toxicity was in general mild and manageable. Toxic deaths occurred in approximately 10% of patients in all three studies. Response rates in the MRC studies seemed similar to conventional regimens. In conclusion, accelerating CDE is feasible but only for a limited (four) number of cycles, thereby compromising delivery of total cumulative dose as projected in standard three-weekly regimens of six courses. A fifth acceleration study has been reported only in abstract form.[104] The authors concluded that the combination of epirubicin 80 mg/m^2 and ifosfamide 5 g/m^2 could be given at two-weekly instead of three-weekly intervals due to the addition of G-CSF. No details concerning actual mean interval were given.

These phase II studies support the feasibility of delivering chemotherapy at shortened intervals. However, the exact role of growth factor addition should preferably be determined in a randomized fashion and for this reason 65 patients were randomized to receive VICE (ifosfamide 5 g/m^2, carboplatin 300 mg/m^2, etoposide 120 mg/m^2 on day 1 and 2, and 240 mg/m^2 on day 3 orally, vincristine 2 mg) with or without G-CSF.[105] There was not a fixed treatment interval planned to maximize DI in both treatment arms in order to determine the exact contribution of G-CSF. Retreatment was possible as soon as WBC count was 3.0×10^9/l or greater and platelet count was 100×10^9/l or greater. No dose reductions were allowed. It was demonstrated that in both arms dose intensity could be increased compared to the conventional four-weekly schedule; over the first three cycles RDI was 1.34 for the G-CSF arm and 1.17 for the control arm ($p = 0.001$). Over all six cycles the average RDI was 1.25 and 1.18 per cycle, respectively ($p = 0.03$). When both arms were compared among each other, it was shown that only the first two intervals were shortened by 2–3 days in the G-CSF arm. Thus, the contribution of G-CSF to dose intensity was rather disappointing, despite its statistical significance ($1.25/1.18 \times 100\% = +6\%$). Fifty-five percent of patients completed six cycles in both arms. Neutrophil counts were consistently higher in G-CSF patients, but in both arms 70% of patients had at least one period of febrile neutropenia. There were more toxic deaths in the G-CSF arm (6 versus 1). Response rates were similar, but 2-year survival was better in the G-CSF arm (32 versus 15%), although 32% is not better than usually reported in good prognosis patients.

In conclusion, standard chemotherapy can be accelerated both with and without growth factor support, simply by giving chemotherapy as soon as blood counts are recovered. The magnitude of acceleration depends on the degree of myelosuppression produced by a specific regimen. G-CSF seems to improve DI by no more than 10–30% when compared to a maximalized standard-dose regimen. It should be noted that increased DI seems only feasible for the first four courses due to cumulative thrombocytopenia and anemia. As a consequence total dose in a intensified regimen may even be lower than in a conventional regimen. At present it is unclear whether total dose or DI is the most important parameter for final outcome. For this reason several collaborative groups have initiated a number of randomized trials. The EORTC has started a study, in which three-weekly CDE is compared with two-weekly CDE which is supported with G-

CSF. In this study standard CDE is given for five courses, while the accelerated CDE is given for only four courses at an approximately 25% higher dose per course. By this design the total dose will be equal in both arms, while in the accelerated arm the treatment will be delivered in half the time in comparison with the standard arm. The influence of the 100% dose increase on survival and response will be evaluated.

Growth factors and peripheral blood progenitor cells

We have discussed the influence of G(M)-CSF on peripheral neutrophil counts. An additional effect is a pronounced dose-related increase in peripheral blood progenitor cells (PBPC), not only including granulocyte macrophage colony forming clones (CFCs), but also erythroid and megakaryocyte CFCs.[106,107] The mechanisms by which cytokines increase PBPC are not well understood. Proliferation resulting in expansion of the population of progenitor cells, differentiation of stem cells into circulating progenitor cells and an alteration in adhesion molecules on the cell membrane that regulate the release of cells from the marrow into the peripheral blood may all play a role.[108] Initially, PBPC were only used together with AMBT. It was demonstrated before that the application of growth factors after ABMT resulted in an accelerated neutrophil recovery, when compared to ABMT alone.[109] The addition of PBPC could not further accelerate neutrophil recovery, but platelet recovery was remarkably faster than in controls.[110] The use of PBPC may therefore facilitate much larger dose-intensifications than achieved by G(M)-CSF or by ABMT. Another theoretical advantage of PBPC over ABMT may be the lower risk for tumor cell contamination, although concomitant tumor cell recruitment upon mobilization of PBPC has been demonstrated in ED SCLC patients.[111] The biologic relevance of this observation is not completely understood. To mobilize PBPC, G(M)-CSF can be used either alone or in combination with high-dose cyclophosphamide or disease-specific chemotherapy. By the combination of a growth factor and chemotherapy an even higher number of PBPCs can be collected, thereby reducing the number of necessary leukaphereses.[112,113] Not all regimens are equally effective in mobilizing PBPC. It was demonstrated that PE produced a 10-fold increase of PBPC, 3–5 weeks after treatment, while no rebound phase occurred after CAV treatment.[114] In a phase II study in 18 LD patients, G-CSF plus two conventional-dose chemotherapy cycles were prescribed (etoposide, ifosfamide, cisplatin and epirubicin) followed by one 2 h leukapheresis procedure after the second course.[115] Subsequently one high-dose course (300% of the conventional schedule, with the replacement of cisplatin by carboplatin) was administered and this showed to be feasible with PBPC infusion. However, if cure is the goal to be achieved, more than one high-dose cycle is probably needed. Shea *et al.* demonstrated that multiple courses of high-dose chemotherapy were feasible by the repeated administration of PBPC.[116] In SCLC one study has reported the sequential administration of PBPC.[117] Twenty-five SCLC patients were treated with six cycles of ICE with G-CSF 300 μg on days 4–15. PBPC were collected during each cycle on day 15, by leukapheresis in cohort 1 (cryopreservation) and 2 (stored at 4°C), and by venasection in cohort 3 (500–750 ml whole blood stored at 4°C), and reinfused on day 3 of the next cycle. Patients in cohort 1 were treated every 3 weeks, and in cohorts 2 and 3 every 2 weeks. ICE chemotherapy with G-CSF was effective in mobilizing blood progenitors, with a median of 120-fold above baseline. The planned DI was 134% for cohort 1 and 200% for cohort 2 and 3. This could indeed be delivered in the first three cycles, but only half of patients in cohorts 2 and 3 completed all six courses, compared to two-thirds in cohort 1. Toxicity was not significantly different between the three cohorts. The authors concluded that PBPC collected in whole blood without cryopreservation is a practical and attractive procedure in chemotherapy regimens of short duration, using drugs of short half-life that are effective in mobilizing blood progenitors and have low toxicity for blood stem cells. The group has opened a phase III study with the cohort 3 schedule as the investigational arm.

Discussion

It is apparent that we need better chemotherapy for SCLC, considering the fact that the majority of patients will ultimately die of their disease. One approach to improve outcome may be the delivery of chemotherapy at increased dose intensity, either by dose escalation for one or more cycles or by giving chemotherapy at shortened intervals. Both concepts have been evaluated in SCLC patients. By giving chemotherapy at shortened intervals the delivery of total dose may be compromised. At present, it is unclear whether dose intensity or total dose is the most important parameter for final

outcome and both factors should therefore be evaluated separately in future trials.

Despite promising phase II data concerning megadose chemotherapy, a survival benefit was seen in only one out of four randomized early-escalation studies (in LD patients).[36–39] In the one randomized late-escalation trial in SCLC, the relapse-free survival after randomization was significantly better after one high-dose cycle, but there was no more than a trend toward improved median overall survival.[52] In two reported phase III acceleration studies no survival benefit was demonstrated; however, in both studies dose intensity was not the sole variable, which precludes definite conclusions.[56,57] One explanation of these disappointing results may be the relative small size of most of these trials. Furthermore, a survival advantage in some patients may not have been demonstrated due to the inclusion of patients likely to have a less favorable outcome (like ED patients). Moreover, the schedules investigated may not have been the most suitable ones, i.e. type of intensification, number of intensified cycles and choice of agents.

It is important to reconsider the two ways to achieve intensification: (1) escalation and (2) acceleration. Although these two approaches may seem comparable as they are both being used to increase dose-intensity, the underlying mechanisms of their action are probably quite different. This distinction is often not recognized and both approaches are frequently mixed up in the literature.

Significant dose escalation may overcome intrinsic drug resistance, which can be proven by a response after high-dose chemotherapy, not seen after the same chemotherapy at standard dose. The efficacy of high-dose chemotherapy was initially demonstrated in patients with acute myeloid leukemia. High-dose chemotherapy was not yet able to increase survival in SCLC, but the doses in the phase III trials were substantially lower than the megadoses in the earlier (promising) phase II trials. In more recent years high-dose chemotherapy has been increasingly used with the support of PBPC and growth factors, in different solid tumors like breast cancer and germ cell tumors. By now, it is not known how many high-dose cycles are needed, but it is in general believed that it should be more than one cycle. The use of very high-dose chemotherapy is only logical for those agents that have a S-shape dose–response curve of which the plateau level has not yet been reached. Cyclophosphamide has been demonstrated to produce a 3-fold increase in response rate at a 7-fold increase in dose above standard. Ifosfamide is at an approximately 4 times higher dose equivalent in activity to cyclophosphamide. In soft tissue sarcoma high-dose ifosfamide was demonstrated to circumvent the resistance to standard-dose ifosfamide, while at this dose treatment was still manageable using routine clinical support.[118] For etoposide the dose–response data are conflicting.[23–25] Few clinical studies have related exposure of doxorubicin to antitumor effect.[119] A major problem for significant dose-escalation is cardiotoxicity, which is the most important chronic dose-limiting toxicity. The analog epirubicin, when compared with doxorubicin, causes less myelo- and cardiotoxicity, thus allowing dose intensification. Such dose-intensive regimens of epirubicin have produced high response rates in a number of malignancies including SCLC.[99,120] Cisplatin is another important drug in SCLC. The dose of cisplatin can be increased to 200 mg/m^2 every 4 weeks, but further dose escalation is limited by cumulative neurotoxicity.[121] Although high-dose cisplatin seemed promising in several phase II studies, it was recently demonstrated that with 200 mg/m^2 per course no survival advantage was seen in non-SCLC and poor-risk germ cell tumors.[122,123] As noted earlier, in a randomized trial in SCLC dose escalation of both cisplatin and cyclophosphamide with approximately 30% for one course only, resulted in a significant survival benefit.[38] This observation remains difficult to interpret and needs to be confirmed before any conclusion can be made. Carboplatin is the most important cisplatin analog, and is less nephro-, neuro- and ototoxic when given at a conventional dose. The major side-effect is myelosuppression, especially thrombocytopenia. It is one of the most frequently used agents in high-dose schedules, often in combination with high-dose cyclophosphamide and thiotepa, of which the phase II results are encouraging. However, in patients with advanced (relapsed and previously untreated) ovarian carcinoma, it was demonstrated that, although the likelihood of tumor response increased with higher carboplatin dose, this relationship was nonlinear and did not increase significantly above a carboplatin area under the curve (AUC) of 7 mg/ml × min (more or less comparable with 560 mg/m^2).[124,125] Methotrexate and 5-fluorouracil are both antimetabolites with increased activity at a higher dose, but these two agents do not play a major role in the treatment of SCLC. Significant dose escalation of vincristine is restricted by cumulative neurotoxicity. Adequate high-dose studies with new antineoplastic agents, like the taxanes and topoisomerase I inhibitors, have to be awaited.

By the second approach, i.e. giving chemotherapy

at shortened intervals, efficacy may be increased by preventing tumor regrowth during the intervals and also by preventing the development of intrinsic drug resistance during the interval. This approach may be especially worthwhile for tumors like SCLC, that are characterized by rapid growth and marked chemosensitivity. This application may also be useful for drugs that are already at their maximum response level.

It is obvious that substantial dose intensification is only possible for those anti-cancer drugs that have myelosuppression as main side-effect. In the older intensification studies autologous bone marrow transplantation was used as rescue, but this procedure was still accompanied with a significant degree of morbidity and mortality. Because G-CSF and GM-CSF are able to reduce duration and severity of neutropenia, it was suggested that the delivery of intensified chemotherapy supported by these factors might be more feasible. However, the addition of growth factors in current dose-escalated or accelerated schedules seems to result in a relative dose intensity of no more than 150% when compared to optimally delivered conventional regimens. At this point cumulative thrombocytopenia becomes a major problem. With the sequential administration of peripheral blood progenitor cells repeated cycles at 200% RDI can be delivered; at this level both hematologic and non-hematologic toxicity become dose limiting. Whether such a degree of dose intensification will improve survival rates has to be awaited from phase III trials. However, when reduction of neutropenia and/or febrile neutropenia will remain the most important effects of these hematopoietic growth factors, prophylactic administration of antibiotics as adjunct to standard-dose chemotherapy or application of chemotherapy dose reductions or delays may be more appropriate.

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