Increasing Chemotherapy in Small-Cell Lung Cancer: From Dose Intensity and Density to Megadoses

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ABSTRACT
The hypothesis that increasing cytotoxic dose intensity will improve cancer cure rates is compelling. Although supporting evidence for this hypothesis has accrued for several tumor types, including lymphomas, breast cancer, and testicular cancers, it remains unproven. Small-cell lung cancer is extremely chemo- and radiosensitive, with a response rate of 80% achieved routinely, but few patients are cured by chemoradiotherapy. In this setting, increased cytotoxic dose intensity might improve cure rates. The finding that response rates in small-cell lung cancer correlate with received cytotoxic dose intensity merely confirms that “less is worse” and “more is better.” Within conventional ranges, dose intensity can be increased with the support of hematopoietic growth factors and/or by shortening treatments intervals; however, dose intensity could be increased by only 20%–30%, and a survival advantage has not been clearly demonstrated. Given its high chemosensitivity, small-cell lung cancer was one of the first malignancies deemed suitable for increasing dose intensity and even for the use of a megadose with the support of autologous bone marrow transplantation. Some interest is emerging again due to improvements in supportive care, such as the availability of hematopoietic growth factors and peripheral blood progenitor cells. The Oncologist 2007; 12:79–89

INTRODUCTION
The principal elements that determine the success of a chemotherapy regimen, in addition to biochemically mediated drug resistance, are tumor bulk, growth rate, and dosage of the chemotherapy regimen given, because there is a dose-response curve for chemotherapeutic drugs. Human tumors are frequently polyclonal rather than monoclonal with regard to treatment sensitivity, so theoretically we have to use full dose levels of all drugs to which tumor cells are sensitive.

In the mid-1980s, Goldie and Coldman and Goldie et al. [1, 2] used a mathematical argument to suggest that a strict alternation of agents would be superior when concurrent administration of full-dose chemotherapy was not feasible. For drug-sensitive cancers, the factor limiting the capacity to cure is often proper dosing. In fact, there is a parallelism of toxicity with dose, because beyond a certain dose above the conventional ranges, toxicity increases more than the response. So diminishing the dose or increasing the interval between cycles of treatment could avoid acute toxicity. But as Cohen et al. [3] demonstrated, increasing the dose from a suboptimal level to a standard dose is accompanied by a benefit in terms of response and survival. In 1984, Hryniuk and Bush [4] demonstrated the importance of dose intensity for metastatic breast cancer, but this concept has been applied to many other tumors.
Dose intensity (DI) is defined as the chemotherapy dose per unit of time over which the treatment is given and is expressed as mg/m² per week. DI is generally used as a relative DI, that is, the ratio of an experimental versus standard regimen or the delivered versus planned DI of a specific regimen.

**SMALL-CELL LUNG CANCER**

**Epidemiology**

Lung cancer is the leading cause of death from cancer in both men and women and is epidemic throughout the world due to increased tobacco consumption. Approximately 15%–25% of all bronchogenic carcinomas are small-cell lung cancer (SCLC). In the United States, there are 30,000 new cases per year. It was estimated that the number of lung cancer-related deaths worldwide in 2000 was 1,000,000. Approximately 200,000 of those deaths were attributable to SCLC, and 98%–99% were caused by cigarette smoking.

**TREATMENT OF SCLC**

The median survival for limited-stage disease (LD) SCLC is 14–20 months, and the 2- and 5-year survival rates are approximately 20%–30% and 10%, respectively. The median survival for extensive stage disease (ED) is 9–12 months, but survival after 2 years is rare (<5%) [5–7]. If untreated, a patient with extensive disease has a median survival of 5 weeks. So a patient with SCLC has to be treated. The correlation between disease stage and survival rate could be biologically explained by the fact that SCLC has a large growth fraction, with a rapid growth rate and early metastases.

Chemotherapy is presently the cornerstone of treatment of SCLC, and it is routinely recommended for patients with good performance status. Preclinical tumor models in SCLC suggest a steep dose-response curve for most chemotherapeutic drugs. It is therefore hypothesized that drug resistance might be overcome by escalating the dose intensification of the drugs. This could be possible by increasing DI in different ways:

- Increasing the dose per cycle, such as by increasing the dose of chemotherapy for one or more cycles;
- Shortening the interval between cycles (increasing dose density);
- Combining of these two modalities (different number of cycles at different dosages and/or at different treatment intervals);
- Using megadose chemotherapy with peripheral blood progenitor cell (PBPC) rescue.

**Increased Dose of Chemotherapy for One or More Cycles**

Several randomized trials evaluated the impact of chemotherapy dosage on survival. The same drugs were delivered at the same interval and for the same number of cycles, with the only variable being the dose in one or more cycles (Table 1).

The Southeastern Cancer Study Group [8] evaluated higher doses of cyclophosphamide and doxorubicin in the cyclophosphamide, doxorubicin, and vincristine (CAV) regimen (1,200 mg/m² cyclophosphamide, 70 mg/m² doxorubicin, and 1 mg/m² vincristine) compared with a standard dose of CAV (1,000 mg/m² cyclophosphamide, 60 mg/m² doxorubicin, and 1 mg/m² vincristine) in patients with extensive disease. The overall response rate (higher-dose CAV, 63%; and standard-dose CAV, 53%; with a complete response [CR] rate, 22% vs. 12%) and median survival time (higher-dose CAV, 8 months; standard-dose CAV, 6.8 months) did not differ significantly between the two arms, but the higher-dose arm demonstrated higher toxicity.

Figueredo et al. [9] conducted a randomized study that evaluated drug escalation in the CAV regimen (1,500 mg/m² cyclophosphamide, 60 mg/m² doxorubicin, and 1 mg/m² vincristine vs. 1,000 mg/m² cyclophosphamide, 50 mg/m² doxorubicin, and 1 mg/m² vincristine), and they observed results similar to those obtained by the Southeastern Cancer Study Group.

Ihde et al. [10] explored dose escalation of etoposide and cisplatin (EP) in patients with extensive-stage disease. Patients received higher doses in the first two cycles (27 mg/m² cisplatin for 5 days and 80 mg/m² etoposide for 5 days), whereas in the third and fourth cycles all patients received standard-dose EP (80 mg/m² cisplatin on day 1 and 80 mg/m² etoposide for 3 days) at 3-week intervals. There was no difference in the two arms with respect to the response rate (85% and 81%) or median survival (11.4 months and 10.7 months), but considerable excess toxicities, in particular hematologic toxicity, were observed in patients who received high-dose EP.

Arriagada et al. [11] reported a prospective study in 105 limited-stage disease patients randomized to higher versus lower doses of cisplatin and cyclophosphamide in the first cycle only (100 mg/m² cisplatin on day 1 and 300 mg/m² cyclophosphamide for 4 days). All patients received the lower doses of cisplatin and cyclophosphamide (80 mg/m² cisplatin on day 1 and 225 mg/m² cyclophosphamide for 4 days) and the same doses of doxorubicin (40 mg/m²) and etoposide (225 mg/m²) from the second through the sixth cycle of chemotherapy at 4-week intervals, alternating with thoracic irradiation. Enrollment was prematurely closed af-
Densification of Chemotherapy

The following trials were designed in such a way that cumulative doses were planned to remain the same, whereas DI was increased in the experimental arm due to the shorter treatment duration. This was made possible with the discovery and subsequent introduction in clinical practice of granulocyte colony-stimulating growth factors such as granulocyte colony-stimulating factor (G-CSF) (Table 2).

Woll et al. [12] conducted a trial in which 65 patients were randomized to six cycles of vincristine, ifosfamide, carboplatin, and etoposide (V-ICE) alone or with G-CSF. There was no fixed dose interval, and in both arms retreatment was given as soon as blood counts had recovered. The G-CSF arm received a small but significantly higher DI than the control group. Despite the small difference in DI (a relative increase of 6%), the 2-year survival rate was higher for the G-CSF arm (32% vs. 15%).

Fukuoka et al. [13] conducted a trial with weekly chemotherapy. Sixty-three patients with ED were randomized either to six cycles of cyclophosphamide, vincristine, doxorubicin, and etoposide (CODE) alone or with G-CSF. With G-CSF, chemotherapy could be delivered more frequently at the time the next cycle was planned, resulting in an increased delivered DI over all cycles (84% vs. 72% of the planned DI) with a significant improvement in 2-year survival rate of 31% versus 7% ($p = .00014$).

In the trial by Steward et al. [14], patients were randomized to six cycles of V-ICE at fixed intervals, either every 3 weeks or every 4 weeks. In this study, survival was a secondary endpoint. Furthermore, patients in CR were offered prophylactic cranial and/or thoracic radiotherapy at the end of chemotherapy. The every-3-weeks regimen resulted in a 26% increase in DI actually delivered. There was no significant difference in the total dose of chemotherapy delivered in the two arms. The densified treatment resulted in an improvement of 15% in 2-year survival rate and 3 months in median survival ($p = .0014$). Furthermore, the magnitude of the difference was comparable for LD and ED patients.

The British Medical Research Council [15] reported a large randomized trial in which the impact of a shorter therapy interval on survival was assessed. A total of 403 patients were randomized either to six cycles of cyclophosphamide, doxorubicin, and etoposide chemotherapy given over 3 days at 2-week intervals with G-CSF or to the same chemotherapy but at 3-week intervals and without G-CSF. Patients with LD were offered thoracic irradiation after chemotherapy. The DI actually received was 34% higher in the intensified arm, whereas the total amount of chemotherapy delivered was similar in the two arms. CR rates were 40% versus 28% in favor of the intensified arm, and there was a survival benefit with an increase of 8% in survival at 1 year, 5% at 2 years, and a median survival of 0.6 month ($p = .04$). A subgroup analysis showed that the survival advantage for ED patients was as large as it was for LD patients.

The European Organisation for Research and Treatment of Cancer (EORTC) [16] evaluated dose intensification with weekly multiagent chemotherapy (doxorubicin, etoposide, cyclophosphamide, vincristine, cisplatin, and methotrexate) compared with doxorubicin, etoposide, and cyclophosphamide given every 3 weeks. There was no difference in the median or overall survival.

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**Table 1. Increased dose of chemotherapy for one or more cycles**

<table>
<thead>
<tr>
<th>Reference</th>
<th>Patients (n)</th>
<th>Dose per cycle (mg/m²)</th>
<th>Cycles at high dose</th>
<th>Relative increase in dose (%)</th>
<th>Response rate (standard vs. experimental)</th>
<th>Median survival time (months)</th>
<th>2-Year survival rate (%)</th>
<th>$p$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Johnson et al. [8]</td>
<td>247</td>
<td>Ctx 1,000 + A 40 vs. Ctx 1,200 + A 70</td>
<td>3</td>
<td>Ctx 16 A 18</td>
<td>53 vs. 63</td>
<td>8 vs. 6.8</td>
<td>2 vs. 2</td>
<td>$&gt;.05$</td>
</tr>
<tr>
<td>Figueredo et al. [9]</td>
<td>103</td>
<td>Ctx 1,000 + A 50 vs. Ctx 1,500 + A 60</td>
<td>4</td>
<td>Ctx 56 A 18</td>
<td>60 vs. 71</td>
<td>12 vs. 13</td>
<td>ND</td>
<td>.36</td>
</tr>
<tr>
<td>Ihde et al. [10]</td>
<td>90</td>
<td>E 80 × 3 + P 80 vs. E 80 × 5 + P 27 × 5</td>
<td>2</td>
<td>E 68 P 68</td>
<td>85 vs. 81</td>
<td>10.7 vs. 11.4</td>
<td>13 vs. 10</td>
<td>.68</td>
</tr>
<tr>
<td>Arriagada et al. [11]</td>
<td>105</td>
<td>Ctx 225 × 4 + P 80 vs. Ctx 300 × 4 + P 100</td>
<td>1</td>
<td>Ctx 33 P 25</td>
<td>54 vs. 67</td>
<td>14 vs. 18</td>
<td>26 vs. 43</td>
<td>.02</td>
</tr>
</tbody>
</table>

**Abbreviations:** A, doxorubicin; Ctx, cyclophosphamide; E, etoposide; ND, not determined; P, cisplatin.
Murray et al. [17] reported encouraging results from a pilot study of a weekly CODE regimen. Based on these results, the National Cancer Institute of Canada and the Southwest Oncology Group conducted a study comparing the CODE regimen with alternating CAV/EP in patients with ED SCLC. A twofold increase of DI was achieved in the CODE arm, as patients received slightly higher cumulative dosages of the four drugs, and the treatment was complete in 9 weeks instead of 18 weeks. The overall survival was no better in the CODE arm, and 10 patients died during chemotherapy in the CODE arm compared with one death in the control arm. The Japan Clinical Oncology Group [18] conducted a similar study but included G-CSF in the CODE arm. Again, there was no difference in survival.

The EORTC [19] conducted a study in which the experimental arm had both a higher DI and a greater dose density. The standard arm received cyclophosphamide, doxorubicin, and etoposide at the standard dose every 3 weeks, whereas the experimental arm had about a 25% increase in the dosage of all three drugs, which were administered every 2 weeks with the use of G-CSF. The dose intensification actually delivered was 70% higher in the experimental arm. Despite greater toxicity in the dose-intensified arm, there was no difference in survival.

Lorigan et al. [20] conducted a randomized phase III trial in which they studied 318 patients who were randomized to receive six cycles of ifosfamide, carboplatin, and etoposide (ICE) chemotherapy with either a 4-week (standard arm) or 2-week (dose-dense arm) interval between cycles. Patients in the dose-dense arm received G-CSF and support with autologous whole-blood hematopoietic progenitors. In the dose-dense arm, a relative dose intensity of 1.82 was achieved. Overall response rates were 80% in the standard arm and 88% in the dose-dense arm. Median overall survival was 13.9 months in the standard arm and 14.4 months in the dose-dense arm; the 2-year survival rates were 22% and 19%, respectively.

The dose-dense regimen has been validated in terms of safety, deliverability, and acceptability, so this regimen could be applied to other tumor types in which dose intensity may have a great impact on survival, but further attempts at dose intensification in SCLC are not justified.

**Chemotherapy for Different Number of Cycles at Different Dosages and/or at Different Treatment Intervals**

James et al. [21] reported a randomized trial in which 167 patients were treated by alternating cisplatin and EP/CAV chemotherapy. In the control arm, patients received standard-dose chemotherapy for six cycles at 3-week intervals,

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**Table 2. Densification of chemotherapy**

<table>
<thead>
<tr>
<th>Reference</th>
<th>Patients (n)</th>
<th>Regimen</th>
<th>Interval</th>
<th>Relative increase in dose (%)</th>
<th>Response rate (standard vs. experimental)</th>
<th>Median survival time (months)</th>
<th>2-Year survival rate (%)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Woll et al. [12]</td>
<td>65</td>
<td>V-ICE</td>
<td>Not fixed</td>
<td>100 vs. 106</td>
<td>93.5 vs. 94.1</td>
<td>15 vs. 15.9</td>
<td>15 vs. 32</td>
<td>&lt;.05</td>
</tr>
<tr>
<td>Fukuoka et al. [13]</td>
<td>63</td>
<td>CODE</td>
<td>1 week</td>
<td>100 vs. 117</td>
<td>84 vs. 97</td>
<td>7.4 vs. 13.6</td>
<td>7 vs. 31</td>
<td>.00014</td>
</tr>
<tr>
<td>Steward et al. [14]</td>
<td>299</td>
<td>V-ICE</td>
<td>4 vs. 3</td>
<td>100 vs. 126</td>
<td>78 vs. 88</td>
<td>11.5 vs. 14.2</td>
<td>18 vs. 33</td>
<td>.0014</td>
</tr>
<tr>
<td>Thatcher et al. [15]</td>
<td>403</td>
<td>CAE</td>
<td>3 vs. 2</td>
<td>100 vs. 134</td>
<td>79 vs. 78</td>
<td>10.9 vs. 11.5</td>
<td>8 vs. 13</td>
<td>.04</td>
</tr>
<tr>
<td>Sculier et al. [16]</td>
<td>233</td>
<td>Multiagents vs. CAE</td>
<td>1 vs. 3</td>
<td>NR</td>
<td>61 vs. 67</td>
<td>11.3 vs. 10.2</td>
<td>7.9 vs. 8.5</td>
<td>NS</td>
</tr>
<tr>
<td>Murray et al. [17]</td>
<td>219</td>
<td>CODE vs. CAV/EP</td>
<td>1 vs. 3</td>
<td>100 vs. 120</td>
<td>70 vs. 87</td>
<td>10.9 vs. 11.7</td>
<td>18 vs. 18</td>
<td>NS</td>
</tr>
<tr>
<td>Furuse et al. [18]</td>
<td>227</td>
<td>CODE (+G-CSF) vs. CAV/EP</td>
<td>1 vs. 3</td>
<td>100 vs. 88</td>
<td>77 vs. 84</td>
<td>10.9 vs. 11.6</td>
<td>8.5 vs. 11.7</td>
<td>NS</td>
</tr>
<tr>
<td>Ardizzoni et al. [19]</td>
<td>244</td>
<td>CDE</td>
<td>3 vs. 2</td>
<td>100 vs. 170</td>
<td>79 vs. 84</td>
<td>12 vs. 12.5</td>
<td>15 vs. 18</td>
<td>.885</td>
</tr>
<tr>
<td>Lorigan et al. [20]</td>
<td>318</td>
<td>ICE</td>
<td>4 vs. 2</td>
<td>100 vs. 182</td>
<td>80 vs. 88</td>
<td>13.9 vs. 14.4</td>
<td>22 vs. 19</td>
<td>.67</td>
</tr>
</tbody>
</table>

Abbreviations: CAE, cyclophosphamide, doxorubicin, etoposide; CAV/EP, cyclophosphamide, doxorubicin, vincristine/etoposide, cisplatin; CODE, cyclophosphamide, vincristine, doxorubicin, etoposide; G-CSF, granulocyte colony-stimulating factor; ICE, ifosfamide, carboplatin, etoposide; NR, not reported; NS, not significant; V-ICE, vincristine, ifosfamide, carboplatin, etoposide.
whereas in the experimental arm the dose was reduced to 50%, and the number of cycles was doubled and delivered at a 10–11-day interval. The delivered dose and DI were similar in both arms. There was no significant survival difference.

In the randomized trial by Pujol et al. [22], the impact of an increased dose per cycle for a reduced total number of cycles delivered at the same interval was evaluated. High-dose chemotherapy of cyclophosphamide, epirubicin, etoposide, and cisplatin with granulocyte-macrophage colony-stimulating factor support for four cycles was compared with a standard-dose regimen with the same drugs given for six cycles, both at 4-week intervals. Planned cumulative doses of the drugs were the same in both arms (except for cisplatin, which was 80% in the high-dose arm), but DI was planned to be increased by 50% due to the shorter treatment duration. The cumulative doses of chemotherapy actually delivered were significantly lower in the high-dose arm (84% of planned in the standard-dose arm vs. 75% of planned in the high-dose arm). The DI actually delivered was not reported. The CR rate was 38% for the standard-dose arm and 22% for the high-dose arm. Patients in the high-dose arm had a significantly reduced time to progression with a shorter median survival time of 2 months and a reduced 2-year survival rate of 10%.

The EORTC [23] conducted a trial in which patients were randomized either to standard-dose cyclophosphamide, doxorubicin, and etoposide (CDE) chemotherapy given at 3-week intervals for five cycles or to intensified CDE chemotherapy given at 125% of the standard dose at 2-week intervals for four cycles with G-CSF support. The increase in DI actually delivered was about 70%, whereas the cumulative dose was comparable in the two arms. Dose intensification of CDE chemotherapy by dose escalation and treatment densification did not result in improved survival, with a median survival time of 12.5 months for the standard arm and 12 months for the intensified arm, possibly due to a reduced number of cycles (Table 3).

Megadose Chemotherapy
One of the limiting factors in dose-intensification strategies is that very few patients achieve greater than a twofold increase in dose intensity, due primarily to hematologic toxicity. With the assistance of autologous bone marrow transplantation (ABMT), myeloablative chemotherapy was proposed as early as 1972 for the treatment of relapse or resistant SCLC. Half of all patients could obtain a clinical remission. Even if of short duration, these remissions supported the concept of dose-response relationship in the disease and prompted the development of intensification programs, either in untreated patients as initial intensification or in patients already responding to standard chemotherapy as late intensification.

Early Intensification
The early intensification approach offers the theoretical advantage that drug resistance has not been induced by exposure to previous conventional doses of chemotherapy. Souhami et al. [24, 25] carried out two studies on high-dose chemotherapy supported by ABMT. In the first study, they treated 25 patients (21 LD and 4 ED) with 160–200 mg/kg cyclophosphamide. In the second study, 26 patients with LD were treated with cyclophosphamide twice, and 800–1,200 mg/m² etoposide was also added in 8 patients. Thoracic radiotherapy at 40 Gy was given after chemotherapy in both studies. Despite the higher dose and the addition of etoposide, the CR rates were similar in the two studies (56% and 57%, respectively), and the 2-year survival rate was even lower in the second trial than in the first (11.5% vs. 30%). Using a mathematical model, the authors estimated the tumor volume on thoracic computed tomography (CT) scans and found that nearly all patients had a dramatic reduction only with the first of the two cycles of high-dose chemotherapy. So this strategy reduced the sensitive component of the tumor but not the resistant clones. In fact, despite radiotherapy, the primary tumor was the most frequent site of relapse.

Farha et al. [26] treated 14 patients with two cycles of 4.5 g/m² cyclophosphamide, 600 mg/m² etoposide, 3 mg/m² vincristine, with or without 80 mg/m² doxorubicin, ABMT rescue, and brain irradiation. Maintenance chemotherapy was then administered with or without radiotherapy to the chest. Two patients died from pneumonitis, and at 2 years, only one patient was disease-free.

Littlewood et al. [27] treated seven patients (two LD and five ED) with 1,400–2,400 mg/m² etoposide followed by ABMT and obtained five partial responses (PRs) and no CRs. Leyvraz et al. [28] achieved an actual threefold increase in DI in nine patients (five LD and four ED) using 5 g/m² cyclophosphamide, 900 mg/m² etoposide, and 150 mg/m² cisplatin administered for a median of three cycles. The CR rate was 66%, and the median progression-free survival and overall survival were 13 months and 17 months, respectively. Toxicity was manageable.

Van de Velde et al. [29] used a 12-week regimen. Thirty-five patients were treated with radiotherapy on the primary tumor every 21 days concomitantly with 4 g/m² ifosfamide on days 1–3, and 30 mg/m² epirubicin on days 1–3 during cycles 1 and 3, and with carboplatin to an area under the concentration–time curve (AUC) of 5 on days 1 and 2; and 120 mg/m² etoposide during cycles 2 and 4. G-CSF was given during each cycle, and PBPCs were col-
lected during the first cycle and rein infused on cycles 2, 3, and 4. The CR rate was 66%, and median time to progression and survival were 15 months and 24.6 months, respectively. An actuarial 2-year survival rate of 51% was reported. No toxic deaths occurred, and 83% of patients completed the planned treatment.

The European Group for Blood and Marrow Transplantation (EBMT) [30] conducted a phase II study in which 69 patients were enrolled; 39 patients (56%) had ED with multiple metastatic sites. Mobilization of PBPCs was obtained by 150 mg/m² epirubicin and G-CSF. High-dose chemotherapy consisted of 10 g/m² ifosfamide, 1.2 g/m² carboplatin, and 1.2 g/m² etoposide (ICE regimen) and was repeated three times every 4 weeks. This regimen allowed a DI of approximately 3 times that of standard ICE. Chemotherapy was completed in 72% of the cases. CR and PR rates were 51% and 35%, respectively; the CR rate was significantly higher in LD (70% vs. 36%). Overall median survival was 13.5 months (11 months in ED and 18 months in LD), with a 2-year survival rate of 32% in the LD group. Multivariate analysis demonstrated that the only significant prognostic factor was disease extent.

A preliminary report of a randomized phase II study with intensified chemotherapy with ICE with sequential re-infusion of hematopoietic progenitor cells was presented in 2003. Of the 70 patients (66 LD and 4 ED) enrolled, half were treated with standard-dose ICE, half with intensified ICE. The overall response rate was 100% in the intensified arm. The study reported a statistically significantly better median survival (29.8 months for intensified ICE and 17.4 months for standard ICE) and 2-year survival rate (62% vs. 36%, respectively; \( p = .0466 \)) for the dose-dense arm than for the standard arm [31].

Past experience as well as this last study suggest that the determination of the role of intensification in the treatment of SCLC will need large-scale and collaborative trials. For this reason, in 1996 the EBMT started a multicentric phase III randomized trial of sequential high-dose chemotherapy versus standard chemotherapy for the treatment of SCLC [32]. Six cycles of standard ICE were compared to three cycles of high-dose ICE supported by PBPCs collected after two courses of 150 mg/m² epirubicin and 175 mg/m² paclitaxel.

Due to low accrual, a formal stopping rule was introduced. Since June 1997, 145 patients have been accrued, of which 140 were evaluable (71 in the standard arm and 69 in the high-dose arm). CR rates were 32% and 37% for the standard and high-dose arms, respectively (\( p = .188 \)). With a median follow-up of 4.9 years, median overall survival times were 15 months and 19.1 months (\( p = .659 \), unadjusted) for the standard and high-dose arms, respectively. At 3 years, 19% of the patients were alive in both arms. The authors concluded that there is no evidence that the treatment of SCLC can be improved by increasing the dose intensity, the peak dose, or the total dose of ICE and that such an intensification strategy should probably be abandoned. The results of the above-mentioned studies are reported in Table 4.

Despite an impressive high rate of CR (approximately 40%), the relapse-free, 2-year, and overall survival rates are comparable with those for patients treated with conventional chemotherapy. Moreover, bone marrow transplantation as initial therapy for SCLC patients is difficult, because these patients are very likely to have impaired performance status and cardiovascular function due to smoking history, resulting in high mortality rates and limiting the applicability of this treatment. In addition, patients are more likely to have contamination of their bone marrow with tumor cells.

### Late Intensification

In the late-intensification approach, it is hypothesized that minimal residual tumor cells, still responding to standard chemotherapy, may be more sensitive to an intensification strategy. Thus, the complete response rate could be almost

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**Table 3. Chemotherapy for different number of cycles at different dosages and/or intervals**

<table>
<thead>
<tr>
<th>Reference</th>
<th>Patients (( n ))</th>
<th>Dose per regimen (mg/m²)</th>
<th>Cycles (( n ))</th>
<th>Intervals</th>
<th>Median survival time (months)</th>
<th>2-Year survival rate (%)</th>
<th>( p ) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>James et al. [21]</td>
<td>167</td>
<td>P 60 + E 120/Ctx 600 + A 50 + VCR 2 vs. 50%</td>
<td>6 vs. 12</td>
<td>3 vs. 1.5</td>
<td>5.8 vs. 6.4</td>
<td>3 vs. 4</td>
<td>NS</td>
</tr>
<tr>
<td>Pujol et al. [22]</td>
<td>125</td>
<td>Ctx 1,200 + Epi 40 + E 225 + P 100 vs. 150%</td>
<td>6 vs. 4</td>
<td>4 vs. 4</td>
<td>11 vs. 8.9</td>
<td>13 vs. 3</td>
<td>.0005</td>
</tr>
<tr>
<td>Tjan-Heijen et al. [23]</td>
<td>90</td>
<td>Ctx 1,000 + A 45 + E 300 vs. 125%</td>
<td>5 vs. 4</td>
<td>3 vs. 2</td>
<td>12.5 vs. 12</td>
<td>15 vs. 18</td>
<td>.9113</td>
</tr>
</tbody>
</table>

Abbreviations: A, doxorubicin; Ctx, cyclophosphamide; E, etoposide; Epi, epirubicin; NS, not significant; P, cisplatin; VCR, vincristine.
doubled by intensive chemotherapy following standard chemotherapy.

Klastersky et al. [33] reported on 13 of 36 patients (36%) who entered an intensification program with one or two cycles of intensified chemotherapy with 120 mg/m² cisplatin, 90–135 mg/m² doxorubicin, and 720–1,080 mg/m² etoposide. Two partial responders were converted to complete responders, and there were two toxic deaths. Median survival from initial therapy was 10 months (range, 2–22).

Stewart et al. [34] performed ABMT in 10 patients (7 with ED) after conventional chemotherapy. At the time of transplant, only three patients were in CR. The intensification consisted of 120 mg/kg cyclophosphamide and single-agent total-body irradiation. Six patients with ED received additional nitrosoureas (150 mg/m² carmustine, 500–600 mg/m² etoposide, and 1,000 mg/m² etoposide). Two partial responders were converted to complete responders, and there were two toxic deaths. Median survival from initial therapy was 10 months (range, 2–22).

Stahel et al. [35] conducted a small study in which four patients were intensified with 120 mg/kg cyclophosphamide, 400 mg/m² carmustine, and 1,000 mg/m² etoposide. Two achieved CR, but there were two toxic deaths.

Smith et al. [36] treated 36 patients with 7 g/m² cyclophosphamide, but only the first 17 underwent ABMT. Median survival of the 14 LD patients who had already achieved CR with conventional chemotherapy was 20 months.

Cunningham et al. [37] treated 22 patients (16 LD), 50% of whom were in CR after conventional chemotherapy. The intensification consisted of 180 mg/kg cyclophosphamide and 1,000 mg/m² etoposide followed by radiotherapy to the primary tumor. Of the 11 patients in PR, 2 achieved a CR (18%). There were no treatment-related deaths, but only one patient survived beyond 16 months.

Sculier et al. [38] conducted a study with 15 patients (11 LD) intensified with 200 mg/kg cyclophosphamide and 1–3 g/m² etoposide. There were five new complete responders, but they were of very short duration (<1 year), and one toxic death occurred.

Ihde et al. [39] found that only 8 of 29 ED patients (27.5%) could be treated with late-intensive combined modality therapy consisting of radiation therapy to the chest followed by 120 mg/kg cyclophosphamide, 600 mg/m² etoposide, and ABMT. Median relapse-free survival was very short (4 months), and there were two treatment-related deaths.

Spitzer et al. [40] treated 32 patients with two consecutive autotransplants (4.5 g/m² cyclophosphamide, 600–750 mg/m² etoposide, with or without 40–60 mg/m² doxorubicin, and 0.5–1.5 g/m² methotrexate). The intensification therapy increased the CR rate from 41% to 69%, and six patients remained off therapy for more than 4 years.

In a subsequent report [41], Spitzer et al. found fewer long-term disease-free patients in a group of matched patients receiving standard therapy. The conclusion was that long-term benefit is more likely in patients with minimal disease (i.e., CR or near-CR) at the time of intensification therapy and in those completing the full schedule of treatment.

Pico et al. [42] reported intensification in 13 patients responsive to conventional therapy and in 6 with progressive disease (300 g/m² carmustine, 1.6 g/m² procarbazine, 800 mg/m² etoposide, and 180 mg/m² melphalan). In the group of responders, 10 patients were already in CR at the time of

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**Table 4. Early intensification**

<table>
<thead>
<tr>
<th>Reference</th>
<th>Patients (n)</th>
<th>Regimen + support</th>
<th>CR (%)</th>
<th>MST (months)</th>
<th>2-Year survival rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Souhami et al. [24]</td>
<td>25</td>
<td>Ctx + ABMT</td>
<td>56</td>
<td>NA</td>
<td>30</td>
</tr>
<tr>
<td>Souhami et al. [25]</td>
<td>26</td>
<td>Ctx + Vp16 + ABMT</td>
<td>57</td>
<td>NA</td>
<td>11.5</td>
</tr>
<tr>
<td>Fahra et al. [26]</td>
<td>14</td>
<td>Ctx + Vp16 + VCR + ABMT</td>
<td>54</td>
<td>NA</td>
<td>7</td>
</tr>
<tr>
<td>Littlewood et al. [27]</td>
<td>7</td>
<td>Vp16 + ABMT</td>
<td>0</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Leyvra et al. [28]</td>
<td>9</td>
<td>Ctx + Vp16 + C + PBPCs</td>
<td>66</td>
<td>17</td>
<td>NA</td>
</tr>
<tr>
<td>Van de Velde et al. [29]</td>
<td>35</td>
<td>Ifo + Epi/Cb + Vp16 + PBPCs</td>
<td>66</td>
<td>24.6</td>
<td>51</td>
</tr>
<tr>
<td>Leyvra et al. [30]</td>
<td>69</td>
<td>Ifo + Cb + Vp16 + PBPCs</td>
<td>49</td>
<td>13.5</td>
<td>32 (LD group)</td>
</tr>
<tr>
<td>Buchholz et al. [31]</td>
<td>70</td>
<td>ICE + PBPCs</td>
<td>48.5</td>
<td>29.8</td>
<td>49</td>
</tr>
<tr>
<td>Leyvra et al. [32]</td>
<td>140</td>
<td>ICE + PBPCs</td>
<td>37</td>
<td>19.1</td>
<td>19 (3 years)</td>
</tr>
</tbody>
</table>

Abbreviations: ABMT, autologous bone marrow transplantation; C, cisplatin; CR, complete response; Ctx, cyclophosphamide; Epi/Cb, epirubicin/carboplatin; ICE, ifosfamide, carboplatin, etoposide; Ifo, ifosfamide; LD, limited-stage disease; MST, median survival time; NA, not applicable; PBPC, peripheral blood progenitor cell; VCR, vincristine; Vp16, etoposide.
high-dose chemotherapy, and a new CR was achieved in 2 of 3 patients in PR. Of the six patients with progressive disease, short-lasting CR (median, 2 months) was achieved in three; one toxic death occurred.

Humblet et al. [43] conducted a randomized trial in which 101 patients received conventional chemotherapy; 45 of these patients were randomized with 23 included in the intensification arm (6 g/m² cyclophosphamide, 300 mg/m² carmustine, and 500 mg/m² etoposide). As a result of intensification, 9 of the 12 patients in PR after induction therapy achieved CR. Median relapse-free survival of the intensification group was 28 weeks, versus 10 weeks for the control arm. The difference was especially apparent in LD patients: relapse-free survival was 35 weeks after intensification versus 10 weeks in the controls. Three patients with LD receiving high-dose chemotherapy became long-term survivors versus none in the standard arm; however, overall survival did not differ between the two groups. Of note, there were four toxic deaths in the high-dose arm.

Wilson et al. [44] conducted a small study in which five patients (three LD) were treated with 200 mg/m² cisplatin, 400 mg/m² etoposide, and 140 mg/m² melphalan. There was one toxic death and three new complete responders, but all patients died within 2 years.

In a study conducted by Souhami et al. [45], 15 LD patients were given one cycle of high-dose cyclophosphamide following two cycles of conventional chemotherapy. The CR rate was 40%; the 2-year survival rate was 13%. There was an additional CR obtained after high-dose therapy, but it was of short duration.

Marangolo et al. [46] treated 15 patients (10 with LD) responsive to conventional chemotherapy with single-agent etoposide (1,800 mg/m²). Three of the seven partial responders before high-dose therapy were converted to complete responders before high-dose therapy. As a result, three toxic deaths occurred.

Table 5. Late intensification

<table>
<thead>
<tr>
<th>Reference</th>
<th>Patients (n)</th>
<th>Regimen and support</th>
<th>New CR (%)</th>
<th>MST (months)</th>
<th>2-Year survival rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Klastersky et al.</td>
<td>25</td>
<td>CAV + ABMT</td>
<td>25</td>
<td>10</td>
<td>NA</td>
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<tr>
<td>Stewart et al.</td>
<td>10</td>
<td>Ctx + TBI + ABMT</td>
<td>29</td>
<td>NA</td>
<td>10</td>
</tr>
<tr>
<td>Stahel et al.</td>
<td>4</td>
<td>Ctx + BCNU + Vp16 + ABMT</td>
<td>33</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Smith et al.</td>
<td>36</td>
<td>Ctx + ABMT</td>
<td>33</td>
<td>20</td>
<td>NA</td>
</tr>
<tr>
<td>Cunningham et al.</td>
<td>22</td>
<td>Ctx + Vp16 + ABMT</td>
<td>18</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Sculier et al.</td>
<td>15</td>
<td>Ctx + Vp16 + ABMT</td>
<td>42</td>
<td>&lt;12</td>
<td>NA</td>
</tr>
<tr>
<td>Ihde et al.</td>
<td>8</td>
<td>Ctx + Vp16 + ABMT</td>
<td>0</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Spitzer et al.</td>
<td>32</td>
<td>Ctx + Vp16 ± A ± Mtx × 2 + ABMT</td>
<td>28</td>
<td>NA</td>
<td>12.5</td>
</tr>
<tr>
<td>Pico et al.</td>
<td>13</td>
<td>BCNU + Pro + Vp16 + Mel + ABMT</td>
<td>66</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Humblet et al.</td>
<td>23</td>
<td>Ctx + BCNU + Vp16 + ABMT</td>
<td>60</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Wilson et al.</td>
<td>5</td>
<td>C + Vp16 + Mel + ABMT</td>
<td>60</td>
<td>&lt;24</td>
<td>0</td>
</tr>
<tr>
<td>Souhami et al.</td>
<td>15</td>
<td>Ctx + ABMT</td>
<td>31</td>
<td>NA</td>
<td>13</td>
</tr>
<tr>
<td>Marangolo et al.</td>
<td>15</td>
<td>Vp16 + ABMT</td>
<td>27</td>
<td>NA</td>
<td>20</td>
</tr>
<tr>
<td>Lange et al.</td>
<td>16</td>
<td>Ctx + Vp16 ± BCNU + ABMT</td>
<td>25</td>
<td>NA</td>
<td>10</td>
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<tr>
<td>Elias et al.</td>
<td>36</td>
<td>Ctx + C + BCNU + ABMT ± PBPCs</td>
<td>69</td>
<td>NA</td>
<td>57</td>
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<tr>
<td>Jennis et al.</td>
<td>10</td>
<td>Mtx + Vp16 + PBPCs</td>
<td>0</td>
<td>4</td>
<td>NA</td>
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<tr>
<td>Fetscher et al.</td>
<td>30</td>
<td>Vp16 + Ifo + Cb + Epi + PBPCs</td>
<td>23</td>
<td>8 (ED)</td>
<td>53 (LD)</td>
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<tr>
<td>Bessho et al.</td>
<td>8</td>
<td>Ifo + Cb + Vp16 + PBPCs</td>
<td>25</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

Abbreviations: A, doxorubicin; ABMT, autologous bone marrow transplantation; BCNU, bischloroethyl nitrosourea; C, cisplatin; CAV, cyclophosphamide, doxorubicin, vincristine; Cb, carboplatin; CR, complete response; Ctx, cyclophosphamide; ED, extensive-stage disease; Epi, epirubicin; Ifo, ifosfamide; Mel, melphalan; MST, median survival time; Mtx, methotrexate; PBPC, peripheral blood progenitor cell; Pro, procarbazine; TBI, total body irradiation; Vp16, etoposide.
plete responders but relapsed within 14 months. Three patients remained disease-free beyond 4 years.

Lange et al. [47] treated 16 patients (12 LD) with 7 g/m² cyclophosphamide alone (6 patients), 7 g/m² cyclophosphamide and 1.5–2 g/m² etoposide (9 patients), or 7 g/m² cyclophosphamide, 900 mg/m² etoposide and 500 mg/m² carbamustine (1 patient). New CRs were not achieved in the group receiving the single agent compared, with a 20% CR rate in the group receiving the combination treatment. The 2-year survival rate was approximately 10%.

Elias et al. [48–50] studied 36 patients with LD responsive to conventional therapy. Patients received high-dose chemotherapy with 5,625 mg/m² cyclophosphamide, 165 mg/m² cisplatin, and 480 mg/m² carbamustine with the support of ABMT alone or associated with PBPCs. Of the 29 patients with a CR or near-CR prior to high-dose chemotherapy, 14 (48%) experienced actuarial 2- and 5-year survival rates of 57% and 53%, respectively.

In a small study by Jennis et al. [51], 10 responsive patients with ED were treated with 8 g/m² methotrexate and 2 g/m² etoposide supported by PBPCs. Six patients achieved a PR, but all relapsed with a median time of 4 months.

Fetscher et al. [52] treated 100 patients with two cycles of standard-dose chemotherapy. Thirty (19 LD) were intensified with the V-ICE protocol (1,500 mg/m² etoposide, 12 g/m² ifosfamide, 750 mg/m² carboplatin, and 150 mg/m² epirubicin) and PBPC support. This protocol allowed a DI approximately three times that of conventional schedules. There were four treatment-related deaths (13%). New complete responders were obtained in 35% of the cases, mainly in LD patients. Median survival of ED patients, from the end of the last treatment, was 8 months, whereas the 2-year survival rate in LD patients was 53%; 10 of the 19 patients with LD were in CR prior to the high-dose chemotherapy.

Bessho et al. [53] used high-dose ICE (15 g/m² ifosfamide, 1,500 mg/m² carboplatin, and 1,500 mg/m² etoposide) in 8 of 11 patients. Toxicity was manageable without mortality, and three of four patients were converted to complete responders.

From all these studies, results of which are reported in Table 5, we can conclude that the probability of achieving a CR was 2–3 times higher in LD patients than in those with ED. But at this time there is no interest in either early or late intensification because the increase of complete responses is counterbalanced by the increase in toxicity and especially toxic mortality. With the exception of very few studies, there was no result in an increased survival, and the only randomized study performed is negative [43]. In general, like early megadoses, late intensification is too toxic, and even if more CRs are observed, they are, for no clear reason, of short duration, with an overall survival not different from, or even shorter than, that observed with conventional doses.

DISCUSSION
The high response rates observed with chemotherapy in SCLC led to expectations of producing high cure rates in this disease; however, many attempts to improve the outcomes of SCLC patients with traditional chemotherapy agents and radiation therapy have failed. Within conventional ranges, dose intensity can be increased with the support of hematopoietic growth factors, autologous bone marrow transplantation, and/or shortening treatment intervals by only 20%–30%, and a survival advantage is not definitely obtained.

In their prospective study, Arriagada et al. [11] reported a statistically significant advantage in survival for LD patients treated with a higher dose of cisplatin and cyclophosphamide only during the first cycle, showing that within conventional ranges of dose there may be an interest in early intensification. The dose-dense regimens have been validated in terms of safety, deliverability, and acceptability. Lorigan et al. [20] conducted the only randomized phase III trial and concluded that, in SCLC, survival rates have reached a plateau and further attempts at dose intensification are not justified. Moreover, high-dose chemotherapy does not seem to have modified the pattern of relapse/progression compared with conventional chemotherapy.

Leyvraz et al. [30] conducted a phase II study in which patients were treated with a high-dose ICE regimen, and the multivariate analysis demonstrated that the only significant prognostic factor was disease extent. The probability of achieving CR with high-dose chemotherapy is 2–3 times higher in LD patients, and this could result in an increasing survival for LD patients. The EBMT study [32], the only randomized phase III trial, demonstrated that there were no such differences in terms of response rate and overall survival between the standard and high-dose arms.

CONCLUSION
The lesson we have learned is that the current literature indicates that there is no evidence that the treatment of SCLC can be improved by increasing the dose intensity, peak dose, or total dose of chemotherapy, and survival rates have reached a plateau, so intensification strategy should probably be abandoned. Advances in molecular biology over the last few years have led to the recognition of certain molecular abnormalities in SCLC that contribute to the progression of this disease. It is possible that agents that target these molecular abnormalities might improve upon the current
standards of SCLC treatment without causing significant toxicity. New chemotherapeutic agents such as irinotecan, topotecan, vinorelbine, and gemcitabine, have been proven to be effective agents against SCLC, but response rate and overall survival are not improved. New strategies and drugs are required to overcome resistant clones and to obtain a more effective cell killing, as demonstrated by the fact that only one third of the patients in PR after conventional chemotherapy could be converted to complete responders with high-dose chemotherapy.

**Disclosure of Potential Conflicts of Interest**
The authors indicate no potential conflicts of interest.


