Treatment of Small Cell Lung Cancer in the Elderly

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ABSTRACT
Small cell lung cancer (SCLC) accounts for approximately 20% of lung carcinomas. Chemotherapy is the cornerstone of treatment for SCLC. In limited disease, the median survival time is about 12–16 months, with a 4%–5% long-term survival rate; in extensive disease the median survival time is 7–11 months. More than 50% of lung cancer patients are diagnosed when they are over the age of 65, and about 30% are over 70. Elderly patients tolerate chemotherapy poorly compared with their younger counterparts, because of age-related progressive reductions in organ function and comorbidities. The standard therapy for limited disease is combined chemoradiotherapy, followed by prophylactic brain irradiation for patients achieving complete responses. In the elderly, the addition of radiotherapy to chemotherapy must be carefully evaluated, considering the slight survival benefit and potential for substantial toxicity incurred with this treatment. The best approach is to design clinical trials that specifically include geriatric assessment to develop active and well-tolerated chemotherapy regimens for elderly SCLC patients. Survival improvement for SCLC patients requires a better understanding of tumor biology and the subsequent development of novel therapeutic strategies. Several targeted agents have been introduced into clinical trials in SCLC, but a minority of these new agents offers a promise of improved outcomes, and negative results are reported more commonly than positive ones. This review focuses on the main issues in the treatment of elderly SCLC patients. The Oncologist 2005;10:399–411

INTRODUCTION
Lung cancer is a major cause of mortality worldwide. It was estimated that 171,900 new cases of lung cancer would be diagnosed in the U.S. in 2003, and that 157,200 men and women would die of this disease [1]. Small cell lung cancer (SCLC) accounts for approximately 20% of primary lung cancers and is rarely cured with the currently available therapies. This tumor is characterized by a rapid doubling time, high growth fraction, and the early development of widespread metastases [2]. According to the two-stage system of the Veterans Administration Lung Cancer Group (VALG), more than two-thirds of patients have extensive disease (ED-SCLC) at diagnosis, that is, a tumor not confined to one hemithorax or with malignant pleural effusion; the remainder present with limited disease (LD-SCLC), that is, with a tumor confined to one hemithorax comprising ipsilateral, mediastinal, or supraclavicular lymph nodes [3]. Because of its sensitivity to chemotherapy, in both LD- and ED-SCLC, chemotherapy is the cornerstone of treatment; but despite this relative chemosensitivity, the long-term prognosis is poor. Overall response rates with chemotherapy are 70%–80% for LD-SCLC and 60%–70% for ED-SCLC, unequivocally improving the survival of patients. In LD-SCLC, the median overall survival (OS) time is about 12–16 months, with 4%–5% of long-term survivors considered cured. However, in ED-SCLC, the
median OS time is 7–11 months, with virtually no patients surviving after 5 years [4].

More than 50% of lung cancer patients are diagnosed when they are over the age 65, and about 30% are over 70. More than two-thirds of patients who die from lung cancer in the U.S. are over 65 years old [5]. In current practice, the elderly, who are usually excluded from participation in clinical trials, receive untested or inadequate treatment based on a long-held, but completely undocumented, notion that cancers in older people are less aggressive [6].

Elderly cancer patients often present with medical and physiological characteristics that make the selection of their optimal treatment more challenging. Unfortunately, because of this, these patients are at risk for being under-treated [7]. Lung cancer is no exception to this observation; in fact, data show that it can be considered the paradigm of elderly under-representation in clinical research [8–10].

To confirm this, a recent survey analyzed trials for cancer drug registration conducted over 7 years (from 1995–2002) and showed a great disparity between the percentage of elderly patients in the general population and the percentage in clinical trials for lung cancer: 67% versus 35% [11]. Under-representation was particularly notable for patients older than 75 years. This phenomenon can significantly affect the generalizability of trial results, which depend largely upon whether participants in clinical trials are fully representative of the entire spectrum of patients suffering from the disease.

Moreover, the disparity between the apparently decreased cancer aggressiveness in individual elderly patients and the high rate of cancer mortality in older age groups of patients may be because the survival data are confounded by special problems common to geriatric populations (e.g., comorbidity, polypharmacy, physician or family bias regarding diagnosis and treatment of the elderly, age-associated life stresses). These factors may increase death rates and counteract any primary influence that aging might have on reducing tumor aggressiveness [12].

We must consider that it is very difficult to establish a maximum age for chemotherapy in the elderly. Within the epidemiological literature, the age of 65 is usually considered as the cutoff point for the elderly population. In contrast, in clinical trials, the age of 70 is frequently used as the lower limit for patient selection, while a cutoff age of 75 years is less common. Obviously, indirect comparison of trials that include patients aged 65–70 with those that do not may be biased. In clinical practice, biological age instead of chronological age should be considered. Unfortunately, to date, laboratory tests and geriatric evaluations are inadequate to define aging; therefore, at present, chronological age should be used as a frame of reference for clinical trials. A cutoff of 70 years of age seems to be the most appropriate. In fact, 70 years of age may be considered as the lower boundary of senescence, because the incidence of age-related changes starts to increase after the age of 70 [13].

Improving the survival rate of patients with SCLC requires a better understanding of tumor biology and the subsequent development of novel therapeutic strategies. Targeted therapies include treatment strategies that focus on cell signaling and other biological pathways involved in tumorigenesis. Several targeted agents have been introduced into clinical trials in SCLC, and some phase III studies have already produced definitive results [14]. This review focuses on the main issues of treatment of elderly SCLC patients.

**Biological Changes Associated with Aging**

The increasing risk of cancer in the aging population can be attributed mainly to two processes: A) DNA damage as a result of cumulative exposure to carcinogenic chemicals, radiation, and viruses and B) progressive decline in host defenses against tumor growth as a result of decreasing production and activity of protective enzymes and hormones that repair or bypass damaged DNA [13].

In the general population, aging alters the demographics of cancer, but in the individual, it alters the biology of cancer through its influence on normal metabolism. Physiological changes in body composition in elderly people are characterized by an increase in fat that is proportional to a decrease in intracellular water and lean body mass [15]. Elderly patients tolerate chemotherapy poorly because of progressive organ failure related to age and comorbidities. Decreased hepatic, renal, and bone-marrow functions have a negative impact on the degree of toxicity resulting from chemotherapy, in particular, cisplatin (Platinol®; Bristol-Myers Squibb, Princeton, NJ, http://www.bms.com) toxicity [16, 17]. As a consequence, older patients handle chemotherapy differently.

Preliminary observations of cancer patients confirm the coexistence of other diseases in elderly cancer patients [18]. Comorbidities are serious medical conditions that are not directly related to the cancer itself and mainly involve metabolism or the cardiovascular, respiratory, renal, and hepatic systems. These conditions are usually chronic and can also adversely affect patient functional status. It has been reported that, among individuals aged 65–74 years, the mean number of chronic diseases is six. The prevalence of these comorbid conditions is about twice as high in the elderly as in the general population [19]. Preliminary observations of cancer patients also confirm the coexistence of other diseases in elderly lung cancer patients [20]. The most important coexisting pathologies in lung cancer patients are cardiovascular and pulmonary diseases, common among heavy smokers.

Another important issue is the definition of frail elderly persons. Frailty can be defined as a condition in which most
functional reserve is exhausted, making the person susceptible to even minor stresses. Frail patients are those who depend on others for the activities of daily living, often because of physical and cognitive dysfunction. With the expansion of the older population, the number of frail elderly people and the number of frail elderly people with cancer are expected to rise. According to a conservative estimate, approximately 400,000 frail elderly people in the U.S. are affected by some form of cancer at any given time [21, 22]. Generally, in these groups of patients, chemotherapy should be avoided. For SCLC, however, chemotherapy provides significant survival improvement.

**Chemotherapy for Elderly Patients**

Many elderly lung cancer patients are undertreated, probably because their primary care physicians assume that the elderly are less tolerant of chemotherapy and have a limited life expectancy compared with their younger counterparts [23]. Moreover, many authors have demonstrated that some oncologists do not feel that the potential survival benefits of chemotherapy outweigh the possible side effects [24–26].

Usually, elderly patients are excluded from participation in clinical trials [8], and in clinical practice they are untreated or receive untested or inadequate treatment [7]. Chronological age should not be a barrier to the use of potentially curative therapy or palliative, life-prolonging treatment; studies have shown that, with appropriate supportive care, otherwise-healthy older patients can obtain the same benefit from standard treatment as younger patients [27–30].

For SCLC in particular, the feeling should be different, considering that chemotherapy provides significant survival improvement. In SCLC there is a different starting point: chemotherapy improves survival dramatically [4] and the only question concerns what kind of chemotherapy to use.

Furthermore, selected, fit older patients are as able as younger patients to tolerate chemotherapy, but their management may require more attention to supportive care. For these reasons, there should be no maximum age for receiving chemotherapy, but frail patients should receive only best supportive care, even though frailty is not equivalent to “near death.” In fact, the average life expectancy of a frail person is in excess of 2 years [21, 22].

Moreover, a better understanding of the effects of chemotherapeutic agents on older patients and increased knowledge of pharmacokinetic data will help to determine their appropriate use in the elderly [17].

The correct assessment of an elderly cancer patient is a key step in the treatment process. Data indicate that the clinical outcome for each type of cancer is predicted not by age itself but by the degree of comorbidity and functional decline that may be present. Reliable information regarding patient comorbid health problems is mandatory to planning an appropriate treatment. However, to date, a standard, fully satisfactory way to assess comorbidity has not been defined [31].

**Multidimensional Assessment**

Although advanced age is one of the most important risk factors for cancer, elderly patients tend to be excluded from clinical trials purely on the basis of chronological age. Performance status (PS) has been used widely to select adult patients for participation in clinical trials, but it does not include a comprehensive evaluation of various age-related factors in the elderly. Many people reach old age without any measurable loss of functional capacity and are free from severe medical problems [32]. It is clear that elderly patients comprise a heterogeneous population in which different outcomes are more probably related to different degrees of deterioration in organ function than to the type of therapy itself. To plan medical treatment in elderly patients, and to further individualize treatment choice, it is mandatory to use not only the patient’s basic medical history and the standard cancer staging system, but also a comprehensive geriatric assessment (CGA). CGA includes the assessment of comorbiditides, socioeconomic conditions, functional dependence, and emotional and cognitive conditions, along with an estimate of life expectancy and the recognition of frailty. All these various facets of the patient’s health and environment may interfere with therapy. The choice of drug should be based on both the evaluation of the toxicity profile of each drug and the patient CGA. The basic components of a CGA are presented in Table 1 [33].

A CGA may be too lengthy for a busy clinical practice; therefore, a number of screening instruments have been developed to select those older patients who may benefit from a full CGA. Of these, the evaluation proposed by the Cardiovascular Health Study, which allows the classification of elderly patients into three groups (fit, prefrail, frail) according to five items (unintentional weight loss, self-reported exhaustion, weakness, walking speed, and level of physical activity) [34] has gained particular prominence, because it is well correlated with mortality and risk for functional dependence. This classification has been proposed as a standard language for the classification of older individuals. Another simple screening instrument is the Vulnerable Elderly Survey 13 (VES-13), which includes 13 simple questions, the answers to which are scored and totaled; a patient whose total score is four or higher may benefit from a full CGA [35].

Also, a patient’s self-reported quality of life (QoL) evaluation can add significant prognostic information. When the prognostic role of baseline QoL, as measured by the European Organization for Research and Treatment of Cancer EORTC
Table 1. Elements of a comprehensive geriatric assessment

<table>
<thead>
<tr>
<th>Parameter assessed</th>
<th>Elements of the assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Function</td>
<td>Performance status, Activities of daily living, Instrumental activities of daily living</td>
</tr>
<tr>
<td>Comorbidity</td>
<td>Number of comorbid conditions, Severity of comorbid conditions (comorbidity index)</td>
</tr>
<tr>
<td>Socioeconomic conditions</td>
<td>Living conditions, Presence and adequacy of a caregiver</td>
</tr>
<tr>
<td>Cognition</td>
<td>Folstein mini-mental state evaluation, Other tests</td>
</tr>
<tr>
<td>Emotional conditions</td>
<td>Geriatric depression scale</td>
</tr>
<tr>
<td>Pharmacy</td>
<td>Number of medications, Appropriateness of medications, Risk for drug interactions</td>
</tr>
<tr>
<td>Nutrition</td>
<td>Mini-nutritional assessment</td>
</tr>
<tr>
<td>Geriatric syndromes</td>
<td>Dementia, Delirium, Depression, Falls, Neglect and abuse, Spontaneous bone fractures</td>
</tr>
</tbody>
</table>

C30 global QoL score, was evaluated in elderly patients diagnosed with non-small cell lung cancer (NSCLC). QoL score was a strong and independent prognostic factor for survival in patients undergoing first-line treatment [36]. These results confirm the strong prognostic role of self-assessed QoL in elderly patients with advanced lung cancer [37] and show that a simple, self-reported questionnaire may add useful information to baseline evaluation of the patient.

TREATMENT

Currently, the standard treatment for LD-SCLC for unselected patients consists of four to six cycles of a platinum-based chemotherapy regimen combined with thoracic radiotherapy (RT) of the tumor region and the mediastinum, which is followed by prophylactic cranial irradiation (PCI) in cases of complete remission [38–40]. The concurrent (versus sequential) approach seems to offer better survival [38, 41]. Chemotherapy remains the only treatment for patients affected by ED-SCLC because RT has only a palliative role.

Three options can be identified for the treatment of elderly SCLC patients: A) use the same chemotherapy as in younger patients; B) empirically reduce drug doses (usually by about 25%); and C) design active and well-tolerated regimens specifically for the elderly.

Same Chemotherapy as Younger Patients

Several retrospective studies analyzed data related to elderly patients treated with standard chemotherapy regimens and showed substantial toxicity with this therapy, making it inadvisable [42–50]. Many authors [42–50] found that older patients (≥70 years) treated with optimal chemotherapies had response rates (RRs) and OS rates similar to those in younger patients, although the elderly received less chemotherapy than the planned protocol dose and experienced more toxicity. Table 2 summarizes the main retrospective studies in elderly SCLC patients compared with their younger counterparts and the main retrospective chart reviews.

A meta-analysis of Pignon et al. [38] showed that thoracic RT moderately improved survival (5.4% ± 1.4% at 3 years) for SCLC patients, but this effect was lost in patients ≥70 years of age. Two recent meta-analyses, evaluating the timing of thoracic RT combined with chemotherapy, showed a small but significant improvement in the 2-year OS rate for early RT versus late RT, and a greater difference was evident for hyperfractionated RT and platinum-based chemotherapy [51, 52]. A large phase III trial of once-daily versus twice-daily thoracic RT plus concurrent chemotherapy reported better results for the twice-daily approach with a median survival time (MST) of 23 months and a 5-year survival rate of 26% [53]. RT, especially when administered concurrently with chemotherapy, may cause substantial esophageal and bone marrow toxicity in the elderly. A retrospective study, with data from 1,208 patients treated with thoracic RT in six trials, showed that advanced age (>70) had no impact on acute and late toxicity [54]. However, only one of the trials included SCLC patients treated with combined chemoradiotherapy. Regarding PCI, the meta-analysis of Auperin et al. [40] showed a slight increase in survival (5.4% at 3 years), not influenced by age. However, clinical trials have shown neuropsychological impairments and abnormalities on brain computed tomography scans that were potentially related to PCI [55]. Specific neurological examinations and the use of tools to evaluate mental status could be useful. Therefore, the use of PCI should be carefully evaluated and not generally advised.

Considering the low number of elderly patients analyzed in most retrospective trials and looking at these data, we can conclude that standard treatment is not always safe for use in clinical practice. In fact, the problem with all retrospective subgroup analyses is the high risk for selection bias. Elderly patients treated with more aggressive treatment are usually selected by PS and organ function both in clinical trials and in clinical practice [56].

Several prospective trials designed specifically for elderly patients were performed. Carboplatin (Paraplatin®; Bristol-Myers Squibb, Princeton, NJ, http://www.bms.com) plus etoposide (Etopophos®; VePesid®; Bristol-Myers Squibb) is the most investigated regimen in elderly SCLC patients. In three phase II trials, this regimen, including oral etoposide, showed good activity but substantial myelotoxicity [57–59].
Five other phase II studies tested carboplatin plus etoposide given i.v., with an RR ranging from 59%–81% and an MST ranging from 7.9–11.6 months [60–64]. Again, the most frequent toxicities were hematological. Recently, Kasahara et al. [65] added vincristine (Oncovin®; Eli Lilly and Company, Indianapolis, IN, http://www.lilly.com) to the combination of carboplatin plus oral etoposide in the treatment of 31 elderly or unfit SCLC patients and reported interesting results but increased toxicity. Further investigations have been conducted using carboplatin plus teniposide (Vumon®; Bristol-Myers Squibb) [66, 67]. Goss et al. [66], in a phase II trial including 39 patients, reported a 72% RR with considerable toxicity. Michel et al. [67] observed a 66% RR and a 9-month MST with moderate toxicity. The analysis of

<table>
<thead>
<tr>
<th>Study</th>
<th>n of patients</th>
<th>Stage</th>
<th>Treatment</th>
<th>Survival</th>
<th>p-value</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paccagnella et al., 1996 [42]</td>
<td>&lt;70: 254</td>
<td>LD + ED</td>
<td>CAV/PE ± RT</td>
<td>3-year: 18%</td>
<td>n.s.</td>
<td>Compliance, response, and survival were similar in younger and elderly patients; thus, aggressive treatment seemed to be justified in selected elderly patients.</td>
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<td></td>
<td>≥70: 32</td>
<td></td>
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<td>3-year: 17.8%</td>
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<tr>
<td>Siu et al., 1996 [43]</td>
<td>&lt;70: 580</td>
<td>LD</td>
<td>CAV/PE + RT</td>
<td>5-year: 8%</td>
<td>n.s.</td>
<td>No difference in toxicity, except grade 3–4 cardiac toxicity was higher in the elderly patients; age was a negative prognostic factor only on univariate analysis.</td>
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<td></td>
<td>≥70: 100</td>
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<tr>
<td>Dajczman et al., 1996 [44]</td>
<td>≤70: 88</td>
<td>LD + ED</td>
<td>CAV or PE + RT</td>
<td>5-year: 11%</td>
<td>n.s.</td>
<td>Less high-grade toxicity and lower mean incidence of toxicity in elderly patients.</td>
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<td></td>
<td>&lt;60: 100</td>
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<td></td>
<td>60–69: 121</td>
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<tr>
<td></td>
<td>≥70: 100</td>
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<tr>
<td>Nou, 1996 [45]</td>
<td>&lt;70: 243</td>
<td>LD + ED</td>
<td>CT ± RT</td>
<td>5-year: 5%</td>
<td>n.s.</td>
<td>No differences between patients aged &lt;70 and ≥70 years.</td>
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<tr>
<td></td>
<td>≥70: 110</td>
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<tr>
<td>Jara et al., 1999 [46]</td>
<td>&lt;70: 20</td>
<td>LD</td>
<td>PE + RT</td>
<td>5-year: 1.3%</td>
<td>n.s.</td>
<td>No differences between patients aged &lt;70 and ≥70 years.</td>
</tr>
<tr>
<td></td>
<td>≥70: 12</td>
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<tr>
<td>Yuen et al., 2000 [47]</td>
<td>&lt;70: 271</td>
<td>LD</td>
<td>PE + either BID RT or QD RT</td>
<td>5-year: 19%</td>
<td>n.s.</td>
<td>Grade 3–4 hematologic toxicity higher in the elderly group.</td>
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<td></td>
<td>≥70: 50</td>
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<tr>
<td>Camps et al., 2001 [48]</td>
<td>&lt;70: 338</td>
<td>LD + ED</td>
<td>HDEP versus PE</td>
<td>5-year: 16%</td>
<td>.004</td>
<td>Treatment tolerance was noticeably worse in the elderly; however, statistical significance was not reached.</td>
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<tr>
<td></td>
<td>≥70: 64</td>
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<tr>
<td>Ludbrook et al., 2003 [49]</td>
<td>&lt;65: 55</td>
<td>LD</td>
<td>CT + RT</td>
<td>2-year: 37%</td>
<td>.003</td>
<td>Increasing age was associated with decreased PS and increased comorbidity, probably influencing OR and survival, which were lower with advanced age.</td>
</tr>
<tr>
<td></td>
<td>65–74: 76</td>
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<td></td>
<td>2-year: 22%</td>
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<tr>
<td></td>
<td>≥75: 43</td>
<td></td>
<td></td>
<td>2-year: 19%</td>
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<tr>
<td>Schild et al., 2004 [50]</td>
<td>&lt;70: 209</td>
<td>LD</td>
<td>PE + either BID RT or QD RT</td>
<td>5-year: 22%</td>
<td>.14</td>
<td>Despite having more weight loss, poorer PS, and increased toxicity, survival was not significantly worse in older individuals.</td>
</tr>
<tr>
<td></td>
<td>≥70: 54</td>
<td></td>
<td></td>
<td>5-year: 17%</td>
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</tbody>
</table>

Retrospective chart review.

Abbreviations: BID = twice-daily; CAV = cyclophosphamide + doxorubicin + vincristine; CT = chemotherapy; ED = extensive disease; HDEP = high-dose epirubicin + cisplatin; LD = limited disease; MST = median survival time; n.s. = not significant; OR = objective response; PE = cisplatin + etoposide; PS = performance status; QD = once-daily; RT = radiotherapy; SCLC = small cell lung cancer.
these studies, summarized in Table 3, also confirms that using the same chemotherapy in the elderly that is used in younger patients induces good activity but with greater toxicity. The best approach is to specifically design clinical trials to develop active and well-tolerated regimens for elderly SCLC patients.

### Less Aggressive Treatment than Younger Patients, Including Empirical Drug Dose Reduction

Empirical drug dose reduction is an option that may be criticized. Furthermore, some drugs, such as anthracyclines and cisplatin, are absolutely contraindicated in patients with relevant cardiac or renal comorbidities.

This issue was addressed by several authors who retrospectively compared elderly patients treated with suboptimal therapy with those treated with optimal therapy [68–70]. Optimal treatment refers to treatment that could be considered standard (i.e., chemotherapy administered at the full doses used in younger patients). Suboptimal refers to the undertreatment of patients ranging from best supportive care alone to palliative RT alone and to low-dose chemotherapy. Table 4 summarizes the main retrospective chart reviews of suboptimal versus optimal treatment modalities in elderly SCLC patients. These retrospective analyses showed that optimal treatment was the best choice in terms of RR and MST (with results similar to those in their younger counterparts) but resulted in considerable toxicity [68–70].

A less aggressive treatment approach has been investigated, as shown in Table 5, in very few prospective studies of chemoradiotherapy treatment specifically designed for elderly patients with LD-SCLC [71, 72]. Murray et al. [71] designed an approach in the elderly consisting of one cycle of cyclophosphamide, doxorubicin (Adriamycin®; Bedford Laboratories, Bedford, OH, http://www.bedfordlabs.com), and vincristine (the CAV regimen) and one cycle of cisplatin plus etoposide (the PE regimen) and RT (20 Gy in five fractions or 30 Gy in 10 fractions). The RR was 89%, and complete responses occurred in 51% of patients. The MST was 12.6 months, the 2-year survival rate was 28%, and the actual 5-year survival rate was 18%. Indeed, toxicity was not pronounced, except for three treatment-related deaths. Jeremic et al. [72] administered two courses of carboplatin and oral etoposide along with accelerated hyperfractionated RT to a total dose of 45 Gy in 30 fractions in 15 treatment days. The RR was 75% and complete responses were observed in 57% of patients. The MST was 15 months and the 2- and 5-year survival rates were 32% and 13%, respectively. Acute grade 3 leukopenia, thrombocytopenia, and esophagitis were observed in 8.3%, 11%, and 2.8% of patients, respectively. Only one patient experienced grade 4 acute thrombocytopenia. Short treatment duration enhances QoL for patients both during and after treatment. Moreover, considering the superiority of combined chemoradiotherapy over chemotherapy alone in younger patients, a sequential combined approach specifically designed for the elderly with intermediate doses.

### Table 3. Phase II studies of carboplatin-based chemotherapy in elderly SCLC patients

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment</th>
<th>n of patients</th>
<th>RR (%)</th>
<th>MST (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Evans et al., 1995 [57]</td>
<td>cPE</td>
<td>11</td>
<td>68</td>
<td>12.2</td>
</tr>
<tr>
<td>Byrne and Carney, 1994 [58]</td>
<td>cPE</td>
<td>0</td>
<td>60</td>
<td>NA</td>
</tr>
<tr>
<td>Matsui et al., 1998 [59]</td>
<td>cPE</td>
<td>16</td>
<td>93</td>
<td>11.4</td>
</tr>
<tr>
<td>Santini et al., 1996 [60]</td>
<td>cPE</td>
<td>19</td>
<td>81</td>
<td>8</td>
</tr>
<tr>
<td>Berzinec et al., 1999 [61]</td>
<td>cPE</td>
<td>28</td>
<td>76</td>
<td>NA</td>
</tr>
<tr>
<td>Okamoto et al., 1999 [62]</td>
<td>cPE</td>
<td>16</td>
<td>63</td>
<td>11.6</td>
</tr>
<tr>
<td>Quoix et al., 2001 [63]</td>
<td>cPE</td>
<td>38</td>
<td>57.8</td>
<td>7.9</td>
</tr>
<tr>
<td>Larive et al., 2002 [64]</td>
<td>cPE</td>
<td>6</td>
<td>59</td>
<td>9.0</td>
</tr>
<tr>
<td>Kasahara et al., 2002 [65]</td>
<td>CEV</td>
<td>15</td>
<td>74</td>
<td>11.4</td>
</tr>
<tr>
<td>Goss et al., 1991 [66]</td>
<td>carboplatin + teniposide</td>
<td>17</td>
<td>72</td>
<td>NR</td>
</tr>
<tr>
<td>Michel et al., 1994 [67]</td>
<td>carboplatin + teniposidec</td>
<td>8</td>
<td>66</td>
<td>9</td>
</tr>
</tbody>
</table>

*a* Oral etoposide.

*b* Includes unfit patients.

*c* Median age.

*d* Weekly administration.

**Abbreviations:** cPE = carboplatin + etoposide; ED = extensive disease; LD = limited disease; MST = median survival time; NA = not applicable; NR = not reported; RR = response rate; SCLC = small cell lung cancer.
(4.0–4.5 Gy) of RT and a moderately short chemotherapy regimen (i.e., four courses) is reasonable and should be investigated in large randomized trials.

Oral etoposide has been largely used as single-drug chemotherapy. Five phase II studies [73–77] showed RRs of 53%–84% with an MST ranging from 4.6–16 months. This treatment is generally well tolerated. Bork et al. [77] randomized elderly SCLC patients to receive one of two different schedules of oral etoposide (continuous treatment versus every 3 weeks) and reported no statistical differences in terms of RR and OS. However, the use of single-agent oral etoposide decreased dramatically after the release of the results from two randomized trials [78, 79].

Table 6 shows the results of those phase III trials comparing single-agent etoposide with combination chemotherapy in elderly or unfit SCLC patients.

A phase II randomized trial compared single-agent carboplatin with the CAV combination in poor-prognosis SCLC patients. The median age was 70 in both groups. CAV therapy produced a higher RR than carboplatin (37.9% versus 25.4%) with MSTs of 4.2 and 3.9 months, respectively. Grade 3–4 neutropenia was more common with the CAV regimen, while grade 3–4 thrombocytopenia was more frequent with carboplatin therapy [84].

Considering these retrospective and prospective data and the superiority of poly- versus monochemotherapy, single-agent chemotherapy should not be an a priori planned strategy in elderly SCLC patients.

New Regimens Specifically Designed for Elderly Patients

Several authors have performed phase II trials employing third-generation combination chemotherapy and designing specific regimens for the elderly [85–92]. A low-dose combination of cisplatin, doxorubicin, vincristine, and etoposide (the PAVE regimen) resulted in impressive RRs (92% in LD-SCLC and 87% in ED-SCLC, with MSTs of 16.2 and 10.8
months, respectively) [90]. Ardizzoni et al. [89], in a randomized phase II trial including 95 patients, compared two different doses (full versus low) of cisplatin plus etoposide, with G-CSF support in the full-dose arm. Those authors reported a 39.3% RR in patients treated with the low-dose chemotherapy, stopping the accrual because of low activity, and a 68.7% RR in the full-dose arm. The 1-year survival rates were 18% and 39%, respectively. The addition of G-CSF to standard combination chemotherapy was investigated by Gridelli et al. [85] in a phase II trial. The combination of carboplatin plus vinorelbine (Navelbine®; GlaxoSmithKline, Philadelphia, PA, http://www.gsk.com) plus G-CSF was administered to 38 elderly ED-SCLC patients. The RR was 39.3% with an MST of 7.9 months, but the treatment was poorly tolerated with remarkable toxicity. In fact, the treatment was found intolerable in 39.3% of patients [85]. The results of the main studies with combined chemotherapy are reported in Table 8.

The two main research lines to explore in the future are the introduction of biological agents into the treatment schemes and the development of more tolerable combination therapy regimens. If new biological agents proved, in fact, to be effective in the treatment of SCLC, therapeutic strategies for the elderly could include a very useful tool. Considering their excellent toxicity profile, new biological agents would be very suitable for this particular patient population. Despite the fact that SCLC represents about 20% of all new lung cancers, this histology is under-represented in trials of targeted therapies. Furthermore, potential biological targets are as numerous and as well described in SCLC as in NSCLC [93]. Many new drugs that have already been tested in NSCLC could be worth studying in SCLC as well. Currently, a minority of these new agents offers the promise of improved outcomes, and negative results are reported more commonly than positive ones. However, this generation of clinical trials should be considered the first step for clinical research in this field. In Table 9, we

### Table 6. Phase III trials comparing single-agent with combination chemotherapy in elderly or unfit SCLC patients

<table>
<thead>
<tr>
<th>Study</th>
<th>Drug</th>
<th>n of patients</th>
<th>RR (%)</th>
<th>MST (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Girling, 1996</td>
<td>Oral etoposide versus EV or CAV</td>
<td>70/76 98/92</td>
<td>45</td>
<td>4.3</td>
</tr>
<tr>
<td>Souhami et al., 1997</td>
<td>Oral etoposide versus PE/CAV</td>
<td>7/4 66/72</td>
<td>32.9</td>
<td>4.8</td>
</tr>
</tbody>
</table>

*Median age.

**Abbreviations:** CAV = cyclophosphamide + doxorubicin + vincristine; ED = extensive disease; EV = etoposide + vincristine; LD = limited disease; MST = median survival time; PE = cisplatin + etoposide; RR = response rate; SCLC = small cell lung cancer.

### Table 7. Phase II studies of single-agent chemotherapy in elderly SCLC patients

<table>
<thead>
<tr>
<th>Study</th>
<th>Drug</th>
<th>n of patients</th>
<th>RR (%)</th>
<th>MST (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smit et al., 1989</td>
<td>Oral etoposide</td>
<td>13/28 22/22</td>
<td>84</td>
<td>16</td>
</tr>
<tr>
<td>Carney et al., 1990</td>
<td>Oral etoposide</td>
<td>24/16 29/16</td>
<td>79</td>
<td>9.5</td>
</tr>
<tr>
<td>Gatzmeier et al., 1991</td>
<td>Oral etoposide</td>
<td>33/13 22/11</td>
<td>56</td>
<td>7.5</td>
</tr>
<tr>
<td>Smit and Postmus, 1991</td>
<td>Oral etoposide</td>
<td>28/12 70/65</td>
<td>53</td>
<td>8</td>
</tr>
<tr>
<td>Bork et al., 1997</td>
<td>Oral etoposide</td>
<td>32/30 30/75</td>
<td>58</td>
<td>7</td>
</tr>
<tr>
<td>Quoix et al., 1992</td>
<td>Epirubicin</td>
<td>18/13 22/11</td>
<td>50</td>
<td>4.6</td>
</tr>
<tr>
<td>Cerny et al., 1988</td>
<td>Teniposide</td>
<td>16/11 16/11</td>
<td>37.5</td>
<td>7.5</td>
</tr>
<tr>
<td>Tummarello et al., 1992</td>
<td>Teniposide</td>
<td>13/10 11/65</td>
<td>61</td>
<td>9</td>
</tr>
<tr>
<td>Cascini et al., 1997</td>
<td>Teniposide</td>
<td>12/10 10/65</td>
<td>30</td>
<td>6</td>
</tr>
</tbody>
</table>

*Prolonged infusion.

**Abbreviations:** ED = extensive disease; LD = limited disease; MST = median survival time; NR = not reported; RR = response rate; SCLC = small cell lung cancer.
present some phase III studies for a few novel agents, the results of which, unfortunately, proved to be negative [94–96]. These failures stress the need for a better understanding of the molecular and biologic abnormalities of each tumor and the selection of appropriate therapies. Clearly, active oral and well-tolerated drugs are preferable, in order to combine new biological agents with other treatments more easily (i.e., chemotherapy and RT) and in view of the fact that the majority of lung cancers are diagnosed in elderly and unfit patients.

Although the number of elderly patients is increasing, few controlled clinical trials of SCLC chemotherapy in the elderly have been performed. We started a clinical study, Gemcitabine-based Small cell lung cancer Treatment in Elderly Patients (G-STEP), in ED-SCLC patients over the age of 70. This is a four-arm, randomized, phase II trial with gemcitabine (Gemzar®; Eli Lilly and Company, Indianapolis, IN, http://www.lilly.com) plus vinorelbine versus gemcitabine plus etoposide versus gemcitabine plus cisplatin versus gemcitabine plus carboplatin. The aim of our study is to select an active and well-tolerated combination to compare with a standard regimen (cisplatin or carboplatin plus etoposide) in a subsequent phase III trial.

CONCLUSION
SCLC is a highly aggressive and chemoresponsive disease in which the best predictor of outcome appears to be stage at diagnosis. In the elderly, the mainstay of treatment remains combination chemotherapy.

For LD-SCLC, the addition of RT (thoracic RT and PCI) seems to provide a slight survival benefit with the potential for considerable toxicity. However, in this setting, the potential for achieving long-term survival justifies this more aggressive approach in good PS patients.

The optimal chemotherapy treatment for elderly SCLC patients is still unknown. Clinical trials specifically addressed to the elderly to develop active and well tolerated regimens in this patient population should be performed while considering that, particularly in ED-SCLC patients who have a poor prognosis (7–10 months median survival), QoL should be the primary end point.

Table 8. Phase II studies of combination chemotherapy in elderly SCLC patients

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment</th>
<th>n of patients</th>
<th>RR (%)</th>
<th>MST (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gridelli et al., 2002</td>
<td>carboplatin + vinorelbinea</td>
<td>0 38 ≥65</td>
<td>NA 39.3</td>
<td>NA 7.9</td>
</tr>
<tr>
<td>Okamoto et al., 2004</td>
<td>carboplatin + irinotecan</td>
<td>8 10 ≥70</td>
<td>89</td>
<td>12</td>
</tr>
<tr>
<td>Fernandez et al., 2000</td>
<td>PE</td>
<td>26 23 ≥65</td>
<td>75</td>
<td>10.7</td>
</tr>
<tr>
<td>Ardizzoni et al., 2005</td>
<td>PE versus PE</td>
<td>16 12 &gt;70</td>
<td>39.3</td>
<td>7.7</td>
</tr>
<tr>
<td>Westeel et al., 1998</td>
<td>PAVE</td>
<td>25 41 ≥65</td>
<td>68.7</td>
<td>10.2</td>
</tr>
</tbody>
</table>

*Plus G-CSF.
*Phase II randomized trial.

Abbreviations: ED = extensive disease; LD = limited disease; MST = median survival time; NA = not applicable; PAVE = cisplatin + doxorubicin + vincristine + etoposide; PE = cisplatin + etoposide; RR = response rate; SCLC = small cell lung cancer.

Table 9. Completed randomized trials of targeted therapies in SCLC

<table>
<thead>
<tr>
<th>Study</th>
<th>Study population</th>
<th>Treatment</th>
<th>n of patients</th>
<th>OS (months)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shepherd et al.,</td>
<td>Limited and extensive</td>
<td>Marimastat versus</td>
<td>266</td>
<td>9.3</td>
<td>Negative; 32% of patients stopped marimastat because of musculoskeletal</td>
</tr>
<tr>
<td>2002 [94]</td>
<td>disease in CR and PR</td>
<td>control</td>
<td>266</td>
<td>9.7</td>
<td>toxicity</td>
</tr>
<tr>
<td>Rigas et al.,</td>
<td>Limited and extensive</td>
<td>BAY 12-9566 versus</td>
<td>327</td>
<td>3.2</td>
<td>Negative; adverse events higher in BAY 12-9566 arm</td>
</tr>
<tr>
<td>2003 [95]</td>
<td>disease in CR and PR</td>
<td>control</td>
<td>327</td>
<td>5.3</td>
<td></td>
</tr>
<tr>
<td>Giaccone et al.,</td>
<td>Limited disease in CR</td>
<td>BEC2 vaccine versus</td>
<td>257</td>
<td>14.3</td>
<td>Negative. The main adverse events were grade 3 local reaction and lethargy</td>
</tr>
<tr>
<td>2004 [96]</td>
<td></td>
<td>control</td>
<td>258</td>
<td>16.3</td>
<td>35% and 3%, respectively.</td>
</tr>
</tbody>
</table>

Abbreviations: CR = complete response; OS = overall survival; PR = partial response; SCLC = small cell lung cancer.
In conclusion, to plan medical treatment for elderly SCLC patients and to further individualize treatment choice, it is mandatory to include QoL evaluation among the primary end points and to use a CGA.

DISCLOSURE OF POTENTIAL CONFLICTS OF INTEREST

Dr. Gridelli has acted as a consultant for Eli Lilly, Roche, AstraZeneca, and Aventis and has received a research grant from AstraZeneca.

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