Extensive small cell lung cancer: standard and experimental treatment approaches in elderly patients

N. Silvestris & V. Lorusso

1 Operative Unit of Medical Oncology, Hospital Santa Maria Goretti, Latina; 2 Operative Unit of Medical Oncology, Oncology Institute, Bari, Italy

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introduction
Small cell lung cancer (SCLC) represents 15–20% of all lung carcinomas, with a decreasing relative frequency over the last two decades [1]. According to the two-stage system of the Veterans Administration Lung Cancer Group, SCLC is defined as limited stage disease (LD), when tumor is confined to one hemitorax, comprising ipsilateral, mediastinal and supraclavicular lymph nodes, and as extensive stage disease (ED), when metastases are present in the contralateral chest or at distant sites [2]. Due to the early widespread of micrometastases, surgery is indicated only in few selected patients with very limited disease. In fact, the standard treatment for LD and ED-SCLC, is chemotherapy plus radiotherapy or chemotherapy alone, respectively. However, most patients present with clinically obvious ED, and their median overall survival (OS) is only 7–12 months long, with five-year survival less than 2% [3].

standard first line chemotherapy for extensive stage disease
Combination chemotherapy for SCLC demonstrated to be superior to single-agent treatment [4]. Anthracycline-based combination treatment with cyclophosphamide, doxorubicin and vincristine (CAV) became standard therapy during the 1970s [5]. Combination regimens with cisplatin and etoposide (PE) for first line treatment were introduced in the 1980s, with response rates (RRs) of around 40% [6]. Although alternating chemotherapy regimens were initially of interest, this approach did not achieve better results as compared to a single combination of platinum-based regimen in later trials [5]. Indeed, Sundstrom et al. randomised 436 patients with either LD/ED-SCLC to receive PE chemotherapy or CAV (cyclophosphamide, epirubicin, vincristine) [7]. With a minimum of 5 years’ follow-up, a significant benefit for PE chemotherapy was observed. Although this was primarily seen in the LD-SCLC cohort (median survival 14.5 months vs 9.7 months), a non significant trend was also observed in ED-SCLC patients (median survival 8.4 months vs 6.5 months). Today, the PE combination is considered as the reference first line regimen for SCLC patients.

The optimal number of chemotherapy cycle has been definitely assessed in randomised trials. In fact, in a large study 610 patients were randomly assigned to four versus eight cycles of chemotherapy with a second randomisation at relapse (treatment vs. no further therapy) [8]. Patients receiving four courses and treated symptomatically on relapse had the poorest median survival. On the other hand, the median survival in those patients initially receiving four chemotherapy cycles, followed by further chemotherapy on relapse, was not significantly different to those receiving longer chemotherapy on induction. Thus, six cycles of chemotherapy in the first line setting are actually considered the standard. Patients who achieve a complete remission may be considered for radiotherapy on the primary site [9].

In an attempt to prolong response duration, maintenance chemotherapy has been tested in several trials [10]. These trials did not show significant difference in survival in favour of patients submitted to maintenance chemotherapy. Therefore, prolonged therapies are not generally used, and early diagnosis of relapse with prompt administration of active drugs is the current treatment strategy [5].

Another approach has been the addition of one or more compounds to PE. With these regard, Loehrer et al. reported a longer survival with ifosfamide + PE as compared to PE alone [11]. Moreover, Pujol et al. randomized 226 ED-SCLC patients to PE versus PE + epirubicin and cyclophosphamide and observed a higher response rate (76% vs. 61%, P = 0.02) and improved survival (1-year survival: 40% vs. 29%, P = 0.06) in the four-drug combination arm [12]. Lastly, the ICE-V (ifosfamide, carboplatin, etoposide, vincristine) regimen was superior to standard platinum-based chemotherapy in terms of survival [13]. Nevertheless, these survival benefits were associated with a greater toxicity.

high-dose chemotherapy
Dose intensification is based on the hypothesis that higher doses of cytotoxic drugs may overcome drug resistance and eradicate
metastatic disease. Several randomised trials reported contrasting results with this treatment. Arrigada et al. demonstrated a survival advantage for a dose intense arm in LD-SCLC patients treated with doxorubicin, etoposide, cisplatin and cyclophosphamide [14]. On the contrary, no survival advantage with more toxicity were reported by Ihde et al. between high-dose PE (cisplatin 135 mg/m², etoposide 80 mg/m² days 1–5) and standard dose PE (cisplatin 80 mg/m², etoposide 80 mg/m² days 1–3) in ED-SCLC patients [15]. Only one randomised trial of high-dose chemotherapy with autologous bone marrow transplantation has been published in SCLC patients [16]. Although a significant relapse-free survival advantage was observed for patients in the high-dose arm (28 vs. 10 weeks, P = 0.002), this did not translate to an improved median OS.

**treatment of elderly patients**

The median age of SCLC patients is generally ≥ 60 years, with more than 33% older than 70 years. Today, the optimal chemotherapy treatment for elderly SCLC patients is still debated. The choice of a medical treatment in this subset of patients should be based on the careful evaluation of the safety of the therapy proposed, and on accurate comprehensive geriatric assessment of the patient. In fact, in fit elderly patients, carboplatin replacing cisplatin in the PE combination, allowed the administration of effective chemotherapy (response rate 75%) with acceptable toxicity profile [17]. Indeed, the direct comparison of PE with carboplatin-etoposide, in a randomized study, showed comparable results with less toxicity for carboplatin treated patients [18]. By contrast, single agent chemotherapy (e.g., oral etoposide) has been proved inferior to standard combination chemotherapy [19]. The design of active and well-tolerated regimens specifically addressed for these patients is mandatory [20].

**second line chemotherapy**

The likelihood of response to second-line chemotherapy can be predicted on the basis of the time to progression (TTP) and the type of chemotherapy used in the first line. Patients whose disease fails to respond to first line chemotherapy, or relapses within 3 months after its completion, are defined ‘refractory’. In this subset, no drugs are active and survival is usually only of a few weeks. By contrast, SCLC patients whose TTP is longer than 3 months, are defined ‘sensitive’ and have a greater probability of response to second line chemotherapy [21]. For what concerns the type of the first line chemotherapy, Fukuoka et al. observed that about half of the patients previously treated with CAV regimen responded to platinum-based chemotherapy; on the contrary, only approximately 15% of patients obtained a benefit from second line chemotherapy with alkylating agents and anthracyclines [22]. There are no randomised trials demonstrating that combination chemotherapy is superior to single-agent chemotherapy. Moreover, the choice of second-line chemotherapy should take in account clinical patient characteristics, drug toxicity and cost of treatment.

**new cytotoxic drugs**

**topotecan**

A large multicenter study randomised 211 patients with a sensitive relapse to CAV or topotecan [23]. No differences were observed in terms of RR, TTP and OS, although more patients receiving topotecan reported symptom improvement. In an ECOG study, the administration of topotecan as maintenance therapy after four cycles of PE has improved TTP but not OS [24].

**irinotecan**

A phase III trial of the Japan Clinical Oncology Group comparing irinotecan/cisplatin (IP) to EP in patients with ED-SCLC showed a significant survival advantage for those receiving IP (median survival 12.8 months vs. 9.4 months, P = 0.002) [25]. Nevertheless, this treatment benefit was not seen in subsequent trials in the USA and Europe [26, 27].

**gemcitabine**

James et al. have reported a phase III trial of gemcitabine and carboplatin (GC) versus standard PE as first line therapy [28]. Antitumor activity and median survival were identical but GC was associated with more haematological toxicity.

**taxanes**

Both docetaxel and paclitaxel have been evaluated in SCLC. RRs with paclitaxel monotherapy seem to be better than with docetaxel. Two randomised trials comparing paclitaxel, etoposide and cisplatin or carboplatin with standard combination chemotherapy showed no survival benefit and produced excessive toxicity [29]. Overall, the use of taxanes at present should not be considered standard in any stage of the disease.

**targeted therapies**

Matrix metalloproteinase inhibitors have been tested in SCLC but the results have been largely negative [30]. A phase II trial tested the clinical efficacy of imatinib in SCLC without clinical response in any of the patients [31]. A trial of vaccination of BEC-2, an anti-idiotypic mAb that mimic the gangliside GD3, combined with adjuvant bacillus Calmette-Guérin (BCG), was performed in 15 patients who had a complete response post-chemotherapy [32]. Survival was improved in comparison to historical controls. Nevertheless, these results were not confirmed in an EORTC phase III trial of BEC-2/BCG as consolidation of complete response in LD-SCLC [33]. In a phase II study 26 SCLC patients received standard PE chemotherapy with concurrent and maintenance thalidomide [34]. In view of satisfactory tolerability and response rates, a phase III trial is warranted.

**conclusions**

Although SCLC is an exquisitely chemosensitive disease, it remains the most aggressive of lung-cancer subtypes. Currently, the use of platinum-based regimens represents the standard first
line chemotherapy. There are no unequivocal evidences for the use of modified dosing/cycling schedules or newer cytotoxic drugs outside clinical trials. Multiple therapeutic strategies that target molecular abnormalities in this malignancy are under investigation.

**References**