Editorial

Twice-daily chemoradiotherapy must still be the choice for patients with limited-stage small-cell lung cancer

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At the time of diagnosis, 30% of patients with small cell lung carcinoma (SCLC) present a limited stage of disease, which is now called I-IIIB (IASLC). However, the outcome of limited-stage SCLC remains poor, with a median survival of 16 to 24 months using current treatments, and only 15–25% of long-term survivors. The usual therapeutic strategy in SCLC with limited stage is the combination of chemotherapy and thoracic radiotherapy, with a combination of platinum (cisplatin or carboplatin) and etoposide compounds as the main scheme. Concomitant chemo-radiotherapy is superior to sequential treatment and early chest irradiation with the first or second cycle of chemotherapy has shown to be beneficial. Hyperfractionated accelerated radiation therapy has shown to be more effective than radiotherapy administered over a global period of prolonged treatment. Nevertheless, the availability and systematic use of hyperfractionated radiation therapy remains a matter of debate.

Since SCLC is a systemic disease, chemotherapy has been and continues to be the cornerstone of its treatment. However, adequate local treatment significantly improves long-term survival in combination with systemic treatment. It is noteworthy that the COCIS meta-analysis (1) of individual patients data showed that carboplatin regimens appear to be equally effective in first-line SCLC treatment, according to overall survival (OS), progression free survival (PFS) and overall response rate, than combinations with cisplatin, differing only in their toxicity profiles. Carboplatin regimens were associated with more cases of grade 3 or 4 haematological toxic effects, while cisplatin treatments were associated with more non-haematological toxic effects of any grade. There were no significant differences between cisplatin and carboplatin in OS according to sex, stage, functional status or age. Although only a small group of patients presented limited disease in the trials considered in the COCIS meta-analysis, and that definitive conclusions can probably not be drawn in this subgroup of patients with a poor prognosis, carboplatin is a widely accepted treatment option for advanced or limited SCLC as shown, for example, in the NCCN guidelines.

A meta-analysis of individual patient cases data showed that the addition of thoracic radiotherapy to chemotherapy improved survival (2), with an increase of 5.4% in absolute survival at 3 years in favor of groups that had received thoracic radiotherapy. Nevertheless, 5-year survival remained disappointedly low, at 10–15%. It was investigated in randomized trials the query of which chemotherapy should be combined with thoracic radiotherapy. Thus, cisplatin-etoposide (CE) was compared to a combination of cyclophosphamide, etoposide and vincristine (3). In patients presenting stages I–III, a significantly higher survival with CE was observed. In a small randomized study, replacement of cisplatin with carboplatin-both in combination with etoposide and chest radiation-resulted in the same survival (4). As in stage IV SCLC, different drugs have been added to CE and different regimens have been examined, including

irinotecan, with no improvement in therapeutic outcome (5-9).

Optimal dose and fractionation radiotherapy data come mostly from retrospective studies and prospective phase II studies. In non-randomized studies, patients treated with sequential chemo-radiotherapy or alternate regimens, achieved a significant improvement in local control of the disease with a dose increase of 35 to 40 Gy, and possibly a slight additional improvement with its enhancement to 50 Gy (10). However, it is not clear whether, also in the context of concomitant chemo and radiotherapy, it is beneficial to increase the dose of radiotherapy above 45–50 Gy.

It is important to define the target volumes of radiotherapy, given that the volume reduction of irradiated critical organs will also reduce side effects. Thus, in a prospective study of stage I–III SCLC, in which only positive mediastinal lymphadenopathies were included in the white volume, an 11% recurrence rate was observed, higher than predicted (11). In a Phase II study the exclusive irradiation of lymph nodes positive in PET with FDG was examined (12). Only 3% of isolated lymph node failures were observed and, what is striking, with only 13% grade 3 esophagitis, which contrasts favorably with the expected 30%. These results were later confirmed in a retrospective series published by the MD Anderson (13).

Many phase III trials have investigated the optimal time of thoracic radiotherapy (14). At 5 years, survival was significantly higher with early thoracic radiation therapy, that is, administered within 30 days after the start of platinum-based chemotherapy, equivalent to a 20% survival rate at 5 years with early thoracic radiotherapy, compared with 14% with late radiotherapy. In a pivotal phase III trial (15), the decrease in overall treatment time of thoracic radiotherapy was from 5 weeks (2 Gy once a day) to 3 weeks (1.5 Gy twice a day), maintaining the total dose at 45 Gy, which increased survival at 5 years from 16% to 26%. In both study groups, thoracic radiotherapy was administered concomitantly with cisplatin and etoposide. Early concomitant chemotherapy with accelerated radiation therapy resulted in approximately 30% grade 3 acute esophagitis, compared to approximately 15% with early concomitant non-accelerated radiation therapy, and approximately 5% with sequential regimens. In this trial, elective mediastinal radiation therapy was used. It should be noted that pulmonary toxicity did not differ depending on the timing of radiotherapy. When the existence of a time interaction between thoracic radiotherapy and chemotherapy was suspected, it was suggested that the first dose of any effective cytotoxic agent triggered an accelerated repopulation and that, in order to achieve local tumor control, at the end of radiotherapy the last tumor clonogen should be destroyed. From these two assumptions, it follows that long-term survival should decrease as time increases "from the Start of any treatment to the End of Radiotherapy" (SER). A meta-analysis of published data, which was subsequently updated, showed better long-term survival when the SER was maintained for less than 30 days (16,17). These results correlate with the hypothesis that radiotherapy and/or chemotherapy trigger an accelerated proliferation of tumor clonogens.

On the CONVERT trial 547 patients were randomly assigned (1:1) to receive either concurrent twice-daily RT (45 Gy in 30 twice-daily fractions) or concurrent once-daily RT (66 Gy in 33 once-daily fractions) both starting on the 22nd day of the first cycle of CE (18). The primary outcome of the study was OS and the secondary outcomes included compliance with chemotherapy and radiotherapy, acute and late toxicity and PFS. The median OS was 30 months in the twice-daily group versus 25 months in the once-daily group. The 2-year OS was 56% *vs.* 51% respectively with an absolute difference of 5.3%. And finally the 5-year OS was 34% *vs.* 31%. The median PFS was 15.4 months in the twice-daily group and 14.3 months in the once-daily group. There was not any statistically significant difference between the two groups. The most common adverse event (grade 3–4) was neutropenia, affecting 74% of the patients in the twice-daily group *vs.* 65% in the once-daily group. The frequencies of the most adverse recorded events were similar in both groups. There were more grade 4 neutropenia cases recorded in the twice-daily group. However, the acute RT toxicity grade 3–4 (esophagitis and pneumonitis) was similar in both groups. The results of this trial show that the once-daily RT did not improve the OS in patients with a limited-stage SCLC, compared with the twice-daily RT, when given concurrently with chemotherapy. The acute and late radiation toxicities were lower than expected, compared with the Intergroup 0096 study, and probably the use of modern radiotherapy techniques can explain these differences (19).

The results of CONVERT trial allow us to conclude that twice-daily RT should continue to be considered as the standard of treatment in patients with limited-stage SCLC. However, it is important to remember that only 15% of the patients, included in this study, were older than 70 years and this is a big limitation of this study. Nowadays, we cannot still explain the reasons why a small improvement of the OS in the twice-daily RT group exists. It is possible that doses bigger than 60 Gy have not an impact on the disease control

or that the twice-daily RT is more active biologically and manages to destroy the last tumor clonogen. Biologically many questions remain unanswered but in the clinical practice these results allow us to recommend the use of the twice-daily RT in patients with a limited-stage SCLC.

Currently, the Spanish Lung Cancer Group-ETOP (European Thoracic Oncology Platform) have on going the phase II STIMULI trial (Small cell lung carcinoma trial with nivolumab and ipilimumab in limited disease) which evaluates the role of adjuvant immunotherapy in patients with a limited disease after the concurrent chemoradiotherapy with platin-etoposide and a twice-daily radiotherapy scheme, in order to try improve the outcome of the standard treatment.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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