Treatment of limited disease small cell lung cancer

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Small cell lung cancer (SCLC) accounts for 10–15% of all lung cancers [1]. Approximately 20% of these patients present with so-called limited disease (LD) and are potentially amendable for treatment with curative intent.

A still widely used system divided SCLC into two disease subgroups: limited and extensive disease. At present, it is advocated to the TNM system as it reflects prognostic groups better than the LD and ED classification [2].

Chemotherapy

Because LD-SCLC is a systemic disease from the onset in the overwhelming majority of the patients, chemotherapy has become an essential part of the treatment.

Surgery, in most cases, is not possible because of the local extent of the tumour or lymph nodes, but it might be considered in rare, early stages. For the majority of patients, chest radiotherapy is the most important local therapy.

A meta-analysis [3] has shown an improvement of 5.4% in absolute survival at 3 years in patients who received chest irradiation in addition to chemotherapy versus those receiving chemotherapy alone.

In LD-SCLC, the chemotherapy schedule of first choice is the combination of cisplatin (P) and etoposide (E) [4].

To improve outcome, several drugs have been added and new regimens have been explored. However, none of them were superior to PE, which remains the recommended chemotherapy regimen to combine with thoracic radiotherapy in the treatment of limited-stage SCLC.

Thoracic radiotherapy

Local tumour failures still occur in over 30% of the patients, even with the best available concurrent chemo-radiation regimen [5].

It seems that the major improvement in local control is achieved when the dose is increased from 35 to 40 Gy, with a possible modest gain of 10% achievable with a further escalation to 50 Gy [6].

Many phase III studies have investigated the timing of chest radiation in LD-SCLC. In a systematic review, we found that when chest radiotherapy was given within 30 days after the initiation of PE, the 5-year survival rate of 20.2% for early versus 13.8% for late thoracic radiotherapy was at the expense of a 30% (versus 15% with a more protracted regimen) incidence of severe, though transient (3–6 weeks), oesophagitis [7]. Lung toxicity was not different according to the timing of radiotherapy.

Because a time-interaction between chest radiation and chemotherapy was suspected, we proposed an integrated approach [8]. Long-term survival was superior when the Start of *any* treatment to the End of Radiotherapy (SER) was kept below 30 days.

The irradiation of the post-chemotherapy volume of the primary tumour is probably safe [6]. At present, because concurrent chest radiotherapy delivered during the first cycle of PE chemotherapy is the treatment of choice, the primary tumour as well as the macroscopically involved nodal areas are well visualised.

The situation is different when it comes to the omission of the elective irradiation of mediastinal lymph nodes. By doing so, radiation volumes could be reduced and hence toxicity diminished. In contrast to CT-based selective nodal irradiation where high rates of isolated nodal recurrences were observed [9], when only the FDG-PET positive nodal zones were included in the radiotherapy field, only 3% of the patients had an isolated nodal recurrence [10]. Interestingly, the incidence of grade 3 oesophagitis was only half of what was expected. If confirmed, elective nodal irradiation could, as in NSCLC, be omitted in LD-SCLC on the basis of FDG-PET scans.

Prophylactic cranial irradiation (PCI)

Brain metastases (BM) are a frequent problem in LD-SCLC. Even after achievement of complete remission (CR), the cumulative rate of BM (symptomatic and

asymptomatic) at 2 years approaches more than 50% [11].

A meta-analysis showed a statistically significant absolute increase in the 3-year survival rate with PCI (15.3% versus 20.7%) [12]. Higher radiotherapy doses than the current EORTC standard of 25 Gy in 2.5 Gy daily fractions, administered within 6 weeks *after* the completion of chemotherapy, have not improved the outcome [13].

In patients who underwent formal neurocognitive testing before PCI, 47% had evidence of impaired cognitive function [14]. Despite transient declines in executive functions and language performance at early time points after PCI, persistent deterioration in cognitive function was not observed.

Large daily fraction sizes, as well as the use of concomitant chemotherapy, have to be considered as predisposing factors for neurological toxicity and should be avoided.

Conclusions

The current standard schedule for LD-SCLC on both sides of the Atlantic is early concurrent PE with thoracic radiotherapy, to a dose of 45 Gy delivered in 30 twice-daily fractions of 1.5 Gy, followed by prophylactic cranial irradiation in patients with no progression (Europe) or complete or near-complete remission (US).

However, because at least 50% of the patients are not eligible for this treatment strategy because of age and/or co-morbidity [15], more research is needed to optimise the treatment in this group. The same applies to the search for better ways to improve local tumour control, as well as the need to find active agents that are eagerly awaited by most patients who still develop refractory metastatic disease.

Conflict of interest statement

None declared.

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