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Guidelines

Guideline for the Initial Management of Small Cell Lung Cancer (Limited and Extensive Stage) and the Role of Thoracic Radiotherapy and First-line Chemotherapy

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Abstract

Aims: We investigated the efficacy of adding radiotherapy to chemotherapy in patients with extensive stage small cell lung cancer (ES-SCLC) and the appropriate timing, dose and schedule of treatment for patients with ES-SCLC or limited stage SCLC (LS-SCLC).
Materials and methods: The guideline was developed by Cancer Care Ontario's Program in Evidence-Based Care and by the Lung Cancer Disease Site Group through a systematic review of randomised controlled trials.
Key recommendations: In patients with LS-SCLC (stage I, II and III), the addition of thoracic radiotherapy to standard chemotherapy is recommended. However, there is no clear evidence to inform definitive recommendations for optimal timing, sequential versus concurrent therapies and optimal dose or regimen. In patients with LS-SCLC, etoposide–cisplatin is the preferred regimen for adults who are being treated with combined modality therapy with curative intent. In patients with ES-SCLC (stage IV), there is insufficient evidence to recommend the addition of thoracic radiotherapy to standard chemotherapy as a standard practice for survival benefit; however, it could be considered on a case-by-case basis to reduce local recurrence. In patients with ES-SCLC, a platinum agent plus etoposide is the preferred regimen for adult patients who are being treated with combined modality therapy. Cisplatin and irinotecan represents an alternative treatment option to this, but is associated with increased rates of adverse events such as diarrhoea.

Keywords: Chemotherapy; evidence-based clinical practice guideline; irinotecan; platinum–etoposide; radiation; small cell lung cancer

Introduction

Due to its aggressive nature and early metastatic spread, chemotherapy is the most common treatment for small cell lung cancer (SCLC). There are two main stages of SCLC: limited stage (LS-SCLC; stages I, II and III), which is local or regional, followed by extensive stage (ES-SCLC; stage IV), where the cancer has spread more widely. For both stages of SCLC, platinum-based chemotherapy, such as commonly used cisplatin or carboplatin, is the standard of care. This is often combined with the non-platinum agent, etoposide. For patients with LS-SCLC, the addition of thoracic radiation therapy to standard combination chemotherapy improves both local control and overall survival and is considered the standard of care [1,2]. Cancer Care Ontario's (CCO's) Lung Cancer Disease Site Group (DSG) developed this guideline to

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create recommendations for the optimal dose, schedule and timing of thoracic radiotherapy and first-line chemotherapy in the treatment of non-resected patients with SCLC.

Methods

This guideline, developed by the CCO's Program in Evidence-Based Care (PEBC) and the Lung Cancer DSG, used the methods of the Practice Guidelines Development Cycle [3,4]. The process included a systematic review, with interpretation of the evidence by the authors, who then drafted recommendations based on the evidence, and expert consensus, internal review by content and methodology experts, and external review by Ontario clinicians and other stakeholders. The authors had expertise in radiation oncology, medical oncology, surgery and health research methodology.

Further details of the methods and findings of the systematic review that informed these recommendations have been published elsewhere [5]. Briefly, this systematic review updated the search from two previous guidelines [1,6]. Studies included in the most recent systematic review [5] have been referenced below, unless a meta-analysis was carried out or new evidence changed the recommendations from the previous guidelines. For the most recent systematic review [5], MEDLINE and EMBASE were searched for randomised controlled trials (RCTs) comparing treatment with radiotherapy plus chemotherapy against treatment with chemotherapy alone in patients with ES-SCLC. RCTs were also included if they compared different timing, doses and schedules of treatment for patients with ES-SCLC or LS-SCLC. Pre-planned study selection criteria were used to screen the literature. Studies were assessed for quality using the Cochrane Risk of Bias tool. The GRADE method for assessing the quality of aggregate evidence was used for each comparison [7].

Practice Guideline

The recommendations (see Table 1) were developed by integrating evidence from RCTs found in the systematic review [5] with feedback obtained through the external review process, and had obtained final approval from the Lung Cancer DSG and the Report Approval Panel of the PEBC. In keeping with recommendations from the International Association for the Study of Lung Cancer and CCO, we have transitioned to the use of TNM staging rather than the Veterans Affairs staging of LS versus ES. The target population for this guideline are adult patients with non-resected LS-SCLC (stage I, II and III) and ES-SCLC (stage IV) who can safely receive definitive radiation. The intended users of the guideline are clinicians involved in the treatment of non-resected adult patients with LS-SCLC (stage I, II and III) and ES-SCLC (stage IV).

The authors believed that overall survival was a critical outcome and toxicity and quality of life were important outcomes for recommendation development. The authors were unanimous in their opinion that patients would value increased survival benefit in addition to acceptable adverse events, although patient input was not sought.

Recommendations, Key Evidence and Interpretation of Evidence

Recommendations for Patients with LS-SCLC (Stage I, II and III)

Thoracic Radiotherapy

In patients with LS-SCLC (stage I, II and III), the addition of thoracic radiotherapy to standard chemotherapy is recommended. However, there is no clear evidence to inform definitive recommendations for optimal timing, sequential versus concurrent therapies and optimal dose or regimen.

Optimal Timing. Qualifying statement: It was the consensus of the authors that consultation of radiation oncology should happen as early as possible to facilitate timely therapy with radiation.

Key evidence: Two RCTs of aggregate moderate quality reported on overall survival. Overall survival was comparable in both early and late thoracic radiation therapy arms [8,9]. Two RCTs of aggregate moderate quality reported on toxicities. A greater percentage of patients in the early thoracic radiation therapy arms experienced non-haematological toxicities (39% versus 23%, $P = 0.001$) [8] and greater febrile neutropenia and neutropenia [9] than patients in the late thoracic radiation therapy arms. None of the trials reported on quality of life outcomes.

Interpretation of evidence: The quality of evidence was considered to be moderate. There was no difference in desirable effects (i.e. with no statistically significant difference in overall survival) and the undesirable effects were moderate (i.e. there was clinically meaningful difference in toxicity). Patients receiving thoracic radiotherapy with the first cycle of chemotherapy showed significantly greater non-haematological toxicities in one study and grade 3/4 febrile neutropenia and neutropenia in another study. Despite the result of the two trials that showed higher toxicity in the early group, it was the consensus of the authors that the current standard of care was to incorporate thoracic radiation early in the treatment of care. This is reflected in the design of clinical trials in LS-SCLC that use radiation upfront with chemotherapy [10–12].

Sequential or Concurrent. Qualifying statement: It was the consensus of the authors that concurrent chemotherapy and radiation would generally be considered the standard of care.

Key evidence: A meta-analysis by Pignon *et al.* [13] examined the question of the timing of thoracic radiotherapy (sequential, alternating and concurrent) and found no significant differences among the treatment schedules. Pignon *et al.* [13] were unable to examine toxicity due to heterogeneity. In a RCT by Takada *et al.* [14], patients were randomised to sequential or concurrent thoracic

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