Review

Toxicity of Concurrent Radiochemotherapy for Locally Advanced Non–Small-Cell Lung Cancer: A Systematic Review of the Literature

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Abstract

Concurrent radiochemotherapy (RCT) is the treatment of choice for patients with locally advanced non–small-cell lung cancer (NSCLC). Two meta-analyses were inconclusive in an attempt to define the optimal concurrent RCT scheme. Besides efficacy, treatment toxicity will influence the appointed treatment of choice. A systematic review of the literature was performed to record the early and late toxicities, as well as overall survival, of concurrent RCT regimens in patients with NSCLC. The databases of PubMed, Ovid, Medline, and the Cochrane Library were searched for articles on concurrent RCT published between January 1992 and December 2009. Publications of phase II and phase III trials with ≥ 50 patients per treatment arm were selected. Patient characteristics, chemotherapy regimen (mono- or polychemotherapy, high or low dose) and radiotherapy scheme, acute and late toxicity, and overall survival data were compared. Seventeen articles were selected: 12 studies with cisplatin-containing regimens and 5 studies using carboplatin. A total of 13 series with mono- or polychemotherapy schedules—as single dose or double or triple high-dose or daily cisplatin-containing (≤ 30 mg/m^2/wk) chemotherapy were found. Acute esophagitis ≥ grade 3 was observed in up to 18% of the patients. High-dose cisplatin regimens resulted in more frequent and severe hematologic toxicity, nausea, and vomiting than did other schemes. The toxicity profile was more favorable in low-dose chemotherapy schedules. From phase II and III trials published between 1992 and 2010, it can be concluded that concurrent RCT with monochemotherapy consisting of daily cisplatin results in favorable acute and late toxicity compared with concurrent RCT with single high-dose chemotherapy, doublets, or triplets.

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Introduction

In the past 2 decades, many trials of combined-modality treatment in patients with locally advanced (stage III) non–small cell lung cancer (NSCLC) have been published. Results of sequential and concurrent combinations of radiotherapy and chemotherapy were published as single reports as well as meta-analyses.

The first study reporting improved survival for patients with stage III NSCLC after treatment with sequential radiochemotherapy (RCT) was in 1990 by Dillman et al.[1] This approach became the standard treatment after the meta-analysis was published by the Non-Small Cell Lung Cancer Collaborative Group in 1995.[2] Induction chemotherapy added to radiotherapy yielded 4% 2-year and 2% 5-year survival benefit provided that the chemotherapy scheme contained cisplatin. This improvement was attributed to the cytotoxic effect on subclinical distant metastases. This effect was observed in a French trial[3] as well; however, patients with adenocarcinoma were not included in this study.

In the same period, a different schedule of combining radio- and chemotherapy was introduced: the concurrent RCT. The European Organisation for Research and Treatment of Cancer (EORTC) 08844 study indicated that concurrent chemotherapy works as a

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radiosensitizer: 6 mg/m^2 cisplatin daily preceding each fraction of radiotherapy improved local progression-free survival compared with radiotherapy alone: at 1 year 59% vs. 41% and at 2 years 31% vs. 19%.[4] Improved local control contributed to increased overall survival: 54% vs. 46%, 26% vs. 13% and 16% vs. 2% at 1, 2, and 3 years, respectively. Late toxicity was not increased. There was no difference in distant metastases rates. The same radiotherapy schedule concurrent with a weekly dose of 30 mg/m^2 cisplatin did not yield a statistically significant survival difference, but a trend in increased survival suggested that the way cisplatin is combined with the radiation might be crucial. A meta-analysis in 2006 of concurrent RCT vs. radiotherapy alone revealed a gain in overall 2- and 5-year survival rates similar to those of the sequential combination.[5] Prospective clinical trials randomizing between sequential and concurrent RCT were subsequently performed.[6-10] A meta-analysis of these trials published in 2010 showed that concurrent RCT is superior to sequential RCT, with improved 2-, 3- and 5-year overall survival rates of 35.6% vs. 30.3%, 23.8% vs. 18.1% and 15.1% vs. 10.6%, respectively ($P = .004$).[11] The most important reported acute toxicity of concurrent RCT was esophagitis ≥ grade 3 in up to 18% of the patients. Reported hematologic toxicities were dependent on the type of concurrent chemotherapy: polychemotherapy vs. daily or weekly monochemotherapy. Exact data on late toxicities other than esophagitis were missing in most trials.

Thus far it is not clear which chemotherapy regimen combined with radiotherapy is superior in terms of survival and toxicity profile. Besides the EORTC 08844 study, prospective randomized trials comparing different concurrent RCT regimens are lacking. We therefore performed a review of the literature to compare acute and late toxicities and to conclude which treatment should preferably be offered to patients with locally advanced nonmetastasized NSCLC.

Review Design

Search Strategy

A systematic search was performed in the databases of PubMed, Ovid, Embase, and the Cochrane Library for publications between 1992 and January 2010 reporting on studies of patients with NSCLC treated with concurrent RCT (Table 1). Articles had to be published in print in English. An exploratory search yielded 1 unique relevant record in PubMed that could not be retrieved by the final comprehensive search resulting from the fact that the aspect of concomitance was not captured in the metadata of this record by the search strategy. Adaptation of the search strategy to include this record retrieved only other irrelevant records and was therefore abandoned.

Selection Criteria

We selected those articles that studied concurrent RCT for patients treated in phase II and phase III studies and included at least 50 patients per treatment arm. Treatment arms that included surgery, consolidation and/or induction chemotherapy, or hyperfractionation schemes were excluded to rule out factors other than the concurrent chemotherapy regimen influencing toxicity and treatment results.

Radiotherapy had to be of radical or curative intent. Radical radiotherapy was defined as a minimum total dose of 48 Gy in daily 2-Gy fractions or its radiobiological equivalent. Selected data were number of patients treated, performance score (World Health Organization [WHO], Eastern Cooperative Oncology Group [ECOG], or Karnofsky), clinical TNM stage, histologic type, radiotherapy dose, chemotherapy type and dose, treatment schedule, acute and late side effects (WHO grade 3-5), local progression-free and overall survival, and year of publication.

Two of the authors (SW and CK) performed the literature search and independently reviewed and screened a total of 3016 articles; after reading the titles, 483 were selected for evaluation of the abstracts if available, leaving 135 that were studied in detail. The final result was 17 articles, including 1 from a screened reference list, representing 18 series, which were analyzed and are summarized here. The series that were selected are part of several different trial designs of RCT vs. radiotherapy alone, sequential vs. concurrent RCT, concurrent RCT vs. concurrent RCT after induction chemotherapy, and so on.

Table 1 Systematic Search Strategy

PubMed (the search in The Cochrane Library was adapted from the PubMed search)
December 2009
(Non-Small-Cell Lung Carcinomas OR Non-Small-Cell Lung Cancer OR nsclc[ttw]) AND ((adjuvant chemotherapy AND (radiation OR radiother* OR radiochem*)) OR concurrent radio chemotherap* OR concurrent radiochemotherap* OR concurrent chemoradiotherap* OR concomitant radio chemotherap* OR concomitant chemo radiotherap* OR concomitant radiochemotherap* OR concomitant chemoradiotherap* OR (("concurrent radiation therapy" OR "concomitant radiation therapy") AND (chemorad* OR chemotherap*)) OR ((radiotherapy AND chemotherapy) AND (concurrent or concomitant or "combined modality")))
Embase 1980 until Present, OVIDSP
December 2009
1. lung non small cell cancer.mp.
2. non small cell lung carcinoma?.ab,ti.
3. nsclc.ab,ti.
4. or/1-3
5. (concurrent radio adj1 chemotherap$).ab,ti.
6. concurrent radiochemotherap$.ab,ti.
7. concurrent chemoradiotherap$.ab,ti.
8. (concomitant radio adj1 chemotherap$).ab,ti.
9. concomitant radiochemotherap$.ab,ti.
10. concomitant chemoradiotherap$.ab,ti.
11. cancer radiotherapy/ and cancer chemotherapy/ and (concurrent or concomitant or "combined modaliy").mp.
12. (concomitant chemo adj1 radiotherap$).ab,ti.
13. (((concurrent or concomitant) adj2 radiation therapy) and chemo*).mp.
14. or/5-13
15. 4 and 14
16. limit 15 to Embase

Radiotherapy and Chemotherapy Regimens

Radiotherapy doses prescribed varied between 45 and 70.2 Gy, and the dose per fraction varied between 1.8 and 3.0 Gy. There were a total of 4 split-course series and 6 conventional series (Tables 2 and 3). The