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

Caro C. Koning,[1] Sanne J. Wouterse,[1] Joost G. Daams,[2] Lon L. Uitterhoeve,[1] Michel M. van den Heuvel,[3] José S. Belderbos[4]

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.

Clinical Lung Cancer, Vol. 14, No. 5, 481-7
Keywords: Concurrent radiochemotherapy, Locally advanced non–small-cell lung cancer (NSCLC), Systematic review

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

[1]Department of Radiation Oncology, Academic Medical Center (AMC), University of Amsterdam, Amsterdam, The Netherlands
[2]Medical Library, Academic Medical Center (AMC), University of Amsterdam, Amsterdam, The Netherlands
[3]Department of Thoracic Oncology, Netherlands Cancer Institute-Antoni Van Leeuwenhoek Hospital, Amsterdam, The Netherlands
[4]Department of Radiation Oncology, Netherlands Cancer Institute-Antoni Van Leeuwenhoek Hospital, Amsterdam, The Netherlands

Received: Nov 16, 2012; Revised: Mar 12, 2013; Accepted: Mar 26, 2013; Epub: Jun 7, 2013

Address for correspondence: José S. Belderbos, MD, PhD, Department of Radiation Oncology, Netherlands Cancer Institute-Antoni van Leeuwenhoek Hospital 151, 1006 BE, Amsterdam, The Netherlands
E-mail contact: j.belderbos@nki.nl

1525-7304/$ - see frontmatter
http://dx.doi.org/10.1016/j.clc.2013.03.002

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

Table 2 Trial Design of Concurrent RCT Phase II and III Study-Arms for NSCLC Patients; Combinations With Carboplatin

Reference	Phase	No. of Patients	Chemotherapy	Radiotherapy Dose EQD2 (Gy)
Ball et al, 1999[12]	III	54	Carboplatin 70 mg/m^2/d days 1-5, days 29-33	60
Groen et al, 2004[13]	III	82	Carboplatin 20 mg/m^2/d days 1-42	60
Isaković-Vidović et al, 2002[14]	III	67	Carboplatin 20 mg/m^2/d before every radiation fraction	58.5 (split 14 d)
Lau et al, 1998[15]	II	60	Carboplatin 200 mg/m^2 days 1, 3, 29, 31 Etoposide 50 mg/m^2 days 1-4, days 29-32	60
Vokes et al, 2007[16]	III	182	Paclitaxel 50 mg/m^2, carboplatin AUC 2, weekly 7 wks	66

Abbreviation: AUC = area under the curve.

Table 3 Treatment Schedules of NSCLC Patients on Concurrent RCT Used in Phase II and Phase III Study Arms; Combinations With Cisplatin

Reference	Phase	No. of Patients	Chemotherapy	Radiotherapy Dose EQD2 (Gy)
Belderbos et al, 2007[6]	III	80	Cisplatin 6 mg/m^2, 1-2 h before every radiation fraction	70
Blanke et al, 1995[17]	III	104	Cisplatin 70 mg/m^2, every 3 wk, ×3	65
Cakir et al, 2004[18]	III	88	Cisplatin 20 mg/m^2, 1 h before radiation fraction d 1-5 of wk 2, wk 6	64
Furuse et al, 1999[9]	III	156	Cisplatin 80 mg/m^2 d 1, 29; vindesine 3 mg/m^2 d 1, 8, 29, 36, mitomycin 8 mg/m^2 d 1, 29	56 (split 10 d)
Furuse et al, 1995[19]	II	51	Cisplatin 100 mg/m^2 d 1, 29; vindesine 3 mg/m^2 d 1, 8, 29, 36; mitomycin 8 mg/m^2 d 1, 29	56 (split 10 d)
Ichinose et al, 2004[20]	II	70	Tegafur 400 mg/m^2 d 1-14, d 29-42; uracil 896 mg/m^2 d 1-14, d 29-42; cisplatin 80 mg/m^2 d 8,6	60
Kim et al, 2005[21]	II	135	Paclitaxel 40 mg/m^2; cisplatin 20 mg/m^2, 1×/wk, 8 wk	68.8
Pradier et al, 2005[22]	II	56	Cisplatin 6 mg/m^2 5 d in wk 1-2 and 5-6	60
Schaake-Koning et al, 1992[4] (d)	III	102	Cisplatin 6 mg/m^2 before every radiation fraction	58.5 (split 3-4 wk)
Schaake-Koning et al, 1992[4] (wk)	III	98	Cisplatin 30 mg/m^2 d 1 every radiotherapy week	58.5 (split 3-4 wk)
Schild et al, 2002[23]	III	117	Etoposide 100 mg/m^2; cisplatin 30 mg/m^2 d 1-3, d 28-30	60
Trovó et al, 1992[25]	II	94	Cisplatin 6 mg/m^2 1 h before every radiation fraction	48.6
Trovó et al, 1992[24]	III	85	Cisplatin 6 mg/m^2 1 h before every radiation fraction	48.6

Abbreviations: d = daily cisplatin; EQD2 = isoeffective dose display; wk = weekly cisplatin.

radiotherapy fractionation schemes were recalculated to a radiobiologically equivalent dose (isoeffective dose display [EQD2] α/β = 10) to compare the applied tumor doses. The total EQD2 tumor doses varied from 48.6 to 70 Gy.

As can be seen in Table 2, the chemotherapy consisted of carboplatin in 5 articles.[12-16] Carboplatin was administered continuously intravenously in the series reported by Groen et al.[13] Isaković-Vidović used the same dose as a bolus.[14] High-dose carboplatin was part of a polychemotherapy schedule in 2 articles and a monochemotherapy schedule in 3 articles. The concurrent carboplatin regimens selected revealed overall survival rates similar to those of radiotherapy-alone regimens.[12-14] In 12 articles containing 13 series, the

Table 4 Patient Characteristics of NSCLC Patients on Concurrent RCT Used in Phase II and Phase III Study Arms; Combinations With Cisplatin

Reference	Chemotherapy Scheme	No. of Patients	Median Age (y)	Performance Status	Median Follow-Up (mo)
Belderbos et al, 2007[6]	ML	80	62	WHO 0, 44%; WHO 1, 56%	39
Pradier et al, 2005[22]	ML	56	64	KPS 50-70, 23%; KPS 80-100, 77%	
Schaake-Koning et al, 1992[4] (d)	ML	102	61	WHO 0, 39%; WHO 1, 56%; WHO 2, 5%	> 22
Schaake-Koning et al, 1992[4] (wk)	ML	98	61	WHO 0, 31%; WHO 1, 62%; WHO 2, 7%	> 22
Trovó et al, 1992[25]	ML	94	62	KPS median 80% (60%-100%)	> 48
Trovó et al, 1992[24]	ML	85	62	KPS median 80% (60%-100%)	
Blanke et al, 1995[17]	MH	104	63	KPS 70%-100%	52
Cakir et al, 2004[18]	MH	88	60	ECOG 1, 65%; ECOG 2, 35%	
Furuse et al, 1999[9]	PH	156	64	WHO 0, 25%; WHO 1, 69%; WHO 2, 6%	60
Furuse et al, 1995[19]	PH	51	59	ECOG 0, 5%; ECOG 1, 74%; ECOG 2, 21%	33.5
Ichinose et al, 2004[20]	PH	70	61	WHO 0, 64%; WHO 1, 36%	33
Kim et al, 2005[21]	PH	135	60	ECOG 0, 7%; ECOG 1, 86%; ECOG 2, 7%	24
Schild et al, 2002[23]	PH	117	Unknown	ECOG 0, 49%; ECOG 1, 51%	43

Abbreviations: d = daily cisplatin; ECOG = Eastern Cooperative Oncology Group; H = high dose; L = daily low dose; KPS = Karnofsky score; M = monochemotherapy; P = polychemotherapy; WHO = World Health Organization; wk = weekly cisplatin.

chemotherapy regimen contained cisplatin.[4,6,9,17-25] Cisplatin was part of polychemotherapy courses in 5 trials; in all these schedules, high-dose cisplatin (> 30 mg/wk) was prescribed. In the cases in which single-agent cisplatin was used, it was prescribed in a high-dose regimen in 2 series and as a low-dose (≤ 30 mg/wk) daily regimen in 6 series (Tables 3 and 4).

Toxicity

Acute toxicity consisting of esophagitis ≥ grade 3 was mentioned in almost all reports on concurrent RCT. Its incidence varied from 1% up to 18% of patients. In 3 studies, the reported acute esophagitis ≥ grades 3 were similar: 16%, 17% and 18% (Table 5). Nausea and vomiting were encountered especially in the early trials. When high-dose cisplatin was given, nausea and vomiting was greater (at least 4 trials with ≥ 16%) than when applied in daily low-dose schedules. Hematologic toxicities, such as anemia, leukocytopenia, and thrombocytopenia, were more frequently observed in the high-dose chemotherapy schedules. In 7 studies, grade 5 complications (cardiomyopathy, massive hemoptysis, radiation pneumonitis, respiratory failure) were reported in up to 3% of the patients. Late toxicity was not reported systematically in most studies. The incidence of acute esophagitis ≥ grades 3 in chemotherapy regimens containing carboplatin varied from 9% up to 32%. Hematologic toxicity rates in carboplatin regimens were similar to those using high-dose cisplatin (Table 6). In the article by Ball et al., 3 of 54 patients experienced late grade 3 to 4 esophagitis.[12] In the low-dose cisplatin studies, late esophagitis ≥ grade 3 to 4 was reported in 5% of the patients. The overall survival in all studies (Table 7) ranged from 13% to 38.5% at 2 years and from 7% to 29.2% at 3 years. The median survival varied from 10 to 17 months.

Discussion

After analyzing the toxicity profiles of 17 selected articles on NSCLC patients treated with concurrent RCT, it was concluded that concurrent daily gifts of cisplatin monochemotherapy causes less severe toxicity compared to polychemotherapy or mono high-dose cisplatin. In 12 of the articles, cisplatin-containing chemotherapy was applied; in 8 studies, it was administered as a single agent and in 4 studies as part of a polychemotherapy regimen. In 7 series, high-dose cisplatin was administered and in 6 series, daily or weekly low-dose cisplatin was prescribed. Carboplatin-containing regimens

Table 5 Survival Results of NSCLC Patients on Concurrent RCT Used in Phase II and Phase III Study Arms; Combinations With Cisplatin

	Chemotherapy Scheme	Nausea/ Vomiting (%)	Esophagitis (%)	Leukopenia (%)	Anemia (%)	Thrombocytopenia (%)	Grade 5 Toxicity (%)
Belderbos et al, 2007[6]	ML	6	17	3	0	—	1
Pradier et al, 2005[22]	ML	—	—	5	—	—	0
Schaake-Koning et al, 1992[4] (d)	ML	24	4	3	—	0	0
Schaake-Koning et al, 1992[4] (wk)	ML	21	1	1	—	0	2
Trovó et al, 1992[25]	ML	5	2	—	0	—	1
Trovó et al, 1992[24]	ML	1	16	0	0	—	
Blanke et al, 1995[17]	MH	5	3	5	—	—	2
Cakir and Egehan,[a] 2004[18]	MH	24 (2)	10	15 (3)	8	—	—
Furuse et al, 1999[9]	PH	23	2.6	98.7	10.3	52.6	—
Furuse et al, 1995[19]	PH	16	6	95	28	45	2
Ichinose et al, 2004[20]	PH	4	3	16	6	1	0
Kim et al, 2005[21]	PH	—	4	[b]	[b]	[b]	0.7
Schild et al,[c] 2002[23]	PH	26	18 (2)	38 (40)	—	26 (3)	3

Abbreviations: d = daily cisplatin; H = high dose; L = daily low dose; M = monochemotherapy; P = polychemotherapy; wk = weekly cisplatin.
[a] Exact toxicity grade unknown, probably < grade 2 (grade 3).
[b] 19% hematologic toxicity not further specified.
[c] Numbers in parentheses represent grade 4 toxicity.

Table 6 Toxicity Results ≥ Grade 3 of NSCLC Patients on Concurrent RCT Used in Phase II and Phase III Study Arms; Combinations With Carboplatin

Reference	Phase	No. of Patients	Nausea/Vomiting (%)	Esophagitis (%)	Leukopenia (%)	Anemia (%)	Thrombocytopenia (%)	Grade 5 Toxicity (%)
Ball et al, 1999[12]	III	54	—	21	—	0	6	0
Groen et al, 2004[13]	III	82	3%	9	11	3	11	—
Isaković-Vidović et al, 2002[14]	III	67	—	10	3	3	1.5	—
Lau et al, 1998[15]	II	60	3 (5)	16	50	5	23	0
Vokes et al, 2007[16]	III	182	—	32	62	5	36	—

added to radiotherapy did not result in improved progression-free and overall survival. This is in line with the findings of van de Vaart et al, indicating that the radiosensitizing effect of cisplatin derivatives is less compared with cisplatin itself.[26,27] Daily administration of cisplatin monochemotherapy did not yield inferior results in terms of overall and progression-free survival; however, selection criteria were different among the trials. In the meta-analysis of Aupérin et al,[11] there was no difference in the distant metastases rates between the concurrent and the sequential RCT arms. In addition, the daily administration of cisplatin, monochemotherapy caused less severe toxicity. Since polychemotherapy and high-dose chemotherapy regimens have not been randomized against single-agent daily cisplatin, it is currently impossible to select the optimal concurrent RCT combination.

Hematologic side effects were rarely observed in the low-dose cisplatin groups, avoiding risks of infections during a neutrocytopenic period. Nausea was high in the pioneer studies but decreased after the introduction of 5 hydroxytryptamine type 3 receptor antagonists in the early 1990s. With high-dose chemotherapy schedules, more toxicity was observed: hematologic toxicity and nausea and vomiting were reported in higher percentages (at least 4 trials with ≥ 16%). When the daily or weekly low-dose cisplatin schemes were used, the nausea and vomiting complaints were mild, and cisplatin administration was not frequently reduced. When high-dose cisplatin is concurrently administered with radiotherapy to patients with head and neck cancer, hearing loss is more frequently encountered when compared with the low-dose schedule.[28] To the best of our knowledge, this ototoxicity has never been studied in patients with locally advanced NSCLC, but arguments are lacking about why this side effect should be different from that found for patients with head and neck cancer. To avoid excessive severe (mucosal) toxicity, several clinicians recently started with low-dose chemotherapy in vulnerable patients

Table 7 Toxicity Results ≥ Grade 3 of NSCLC Patients on Concurrent RCT Used in Phase II and Phase III Study Arms; Combinations With Cisplatin

Reference	Phase	Chemotherapy Scheme	No. of Patients	Medium OS (mo)	2 Years OS (%)	3 Years OS (%)	5 Years OS (%)	PFS
Belderbos et al, 2007[6]	III	ML	80	16.5	38.5	29.2	—	36.6% at 1 y
Pradier et al, 2005[22]	II	ML	56	14	34	16	—	—
Schaake-Koning et al, 1992[4] (d)	III	ML	102	13	26	16	—	59% at 1 y, 31% at 2 y[a]
Schaake-Koning et al, 1992[4] (wk)	III	ML	98	12	19	13	—	42% at 1y, 30% at 2 y[a]
Trovó et al, 1992[25]	II	ML	94	12	24.4	10	—	—
Trovó et al, 1992[24]	III	ML	85	10	13	7	—	—
Blanke et al, 1995[17]	III	MH	104	10.8	18	9	5	—
Cakir et al, 2004[18]	III	MH	88	10	18	10	—	10% at 3 y
Furuse et al, 1999[9]	III	PH	156	16.5	34.6	22.3	15.8	—
Furuse et al, 1995[19]	II	PH	51	16	36.7	23.1	—	—
Ichinose et al, 2004[20]	II	PH	70	16.5	33	24	—	—
Kim et al, 2005[21]	II	PH	135	17	37	Unknown	—	36% at 1 y, 18% at 2 y
Schild et al, 2002[23]	III	PH	117	17	37	23	13	25% at 2 y, 23% at 2 y

Abbreviations: d = daily cisplatin; H = high-dose; L = daily low-dose; M = monochemotherapy; OS = overall survival; P = polychemotherapy; PFS = progression-free survival; wk = weekly cisplatin.
[a] Survival without local recurrence.

with head and neck cancer.[29,30] Their preliminary reports are promising. A phase I study has been reported with low-dose paclitaxel administered as a radiosensitizer for patients with NSCLC.[31]

In this present overview, 1 study applied high-dose radiation of 70 Gy.[6] This 70-Gy regimen was tested in a phase II trial that had revealed the safety of this fractionation scheme in case a restriction for the length of the irradiated esophagus was met: < 18 cm up to 40 Gy and < 12 cm in the boost volume up to 66 Gy.[32] One might argue that patients with NSCLC with low tumor volumes were selected in this trial.

Most patients with lung cancer and a smoking history are at high risk for heart and vessel diseases as well as chronic pulmonary diseases such as emphysema and chronic obstructive bronchitis. In general, the highest incidence of NSCLC is observed in patients older than 65 years. As a consequence, a considerable percentage of patients with newly diagnosed NSCLC is frail and unfit for concurrent RCT treatments. More than half of patients with stage III lung cancer were theoretically not eligible for concurrent RCT in a population-based study.[33] Less toxic alternatives are needed for these patients. Uitterhoeve et al reported excellent tolerance of concurrent RCT with daily cisplatin for a group of elderly patients, with good survival data (1-, 2-, and 5-year overall survival of 60%, 34%, and 24%, respectively).[34]

A favorable toxicity profile makes low-dose concurrent RCT schedules suitable for combinations with targeted agents such as vascular epithelial growth factor antibodies, antifolates, and epidermal growth factor receptor antibodies. This is important because the addition of these new drugs to concurrent RCT with full-dose chemotherapy could increase toxicity.[35]

The feasibility of adding the epidermal growth factor receptor inhibitor cetuximab to concurrent chemoradiotherapy (CRT) with daily cisplatin has been reported for patients with NSCLC.[36] A study adding the antifolate pemetrexed to concurrent RCT is under way.[37] Gefinitib added to CRT did not yield improved survival in a phase II trial.[38]

Our review has some limitations because series of at least 50 patients treated in a phase II or III trial were selected. This selection was made to provide robust data on toxicity but leaves out numerous studies with smaller numbers of patients. Studies on induction and/or consolidation therapy added to concurrent RCT were not included to draw clear conclusions on the preferred concurrent treatment schedule. Moreover, until now these types of therapies did not yield further improved treatment outcome.[16,39] Recently, 2 articles were published on concurrent CRT with excellent treatment results at a cost of severe toxicity.[40,41] In the meta-analysis on sequential vs. concurrent RCT,[11] the staging examinations were less sensitive, so a significant number of patients (15% on estimation) probably had stage IV disease. In this patient group, however, an improved locoregional control in the concurrently treated patients did result in an increased overall survival. The patients with NSCLC selected today for RCT are more rigorously staged using fluorine-18 fluorodeoxyglucose positron emission tomography, magnetic resonance imaging of the cerebrum, endoesophageal ultrasonography, and/or endobronchial ultrasonography. It is to be expected that a current improved locoregional control rate result will have a more profound influence on overall survival. Compared with current radiotherapy techniques and fractionation schedules, the radiotherapy administered was suboptimal in many trials. There were 4 split-course radiotherapy schedules, and the radiotherapy dose was < 60 Gy (EQD2) in 6 trials. In addition, new radiotherapy techniques such as intensity-modulated radiotherapy have evolved, allowing higher radiation doses in the tumor-positive areas while avoiding high doses in the surrounding tissues. The frequently applied image-guided radiotherapy allows even more precise

dose delivery and is expected to further improve treatment outcome in patients with NSCLC. As long as subclinical distant metastases cannot yet be controlled efficiently, our main focus should be on improving survival by better locoregional tumor control.[42]

Conclusion

A systematic review of the literature was performed to compare acute and late toxicity in patients with NSCLC treated with concurrent CRT. It can be concluded that concurrent RCT regimens with low-dose daily cisplatin yield a favorable toxicity profile compared with high-dose mono- or polychemotherapy. Concurrent RCT with low-dose cisplatin and high-dose radiotherapy can be considered the preferred treatment.

Disclosure

The authors have stated that they have no conflicts of interest.

References

1. Dillman RO, Seagren SL, Propert KJ, et al. A randomized trial of induction chemotherapy plus high-dose radiation versus radiation alone in stage III non-small-cell lung cancer. *N Engl J Med* 1990; 323:940-5.
2. Non-Small Cell Lung Cancer Collaborative Group. Chemotherapy in non-small cell lung cancer: a meta-analysis using updated data on individual patients from 52 randomised clinical trials. *BMJ* 1995; 311:899-909.
3. Le Chevalier T, Arriagada R, Quoix E, et al. Radiotherapy alone versus combined chemotherapy and radiotherapy in nonresectable non-small-cell lung cancer: first analysis of a randomized trial in 353 patients. *J Natl Cancer Inst* 1991; 83:417-23.
4. Schaake-Koning C, van den Bogaert W, Dalesio O, et al. Effects of concomitant cisplatin and radiotherapy on inoperable non-small-cell lung cancer. *N Engl J Med* 1992; 326:524-30.
5. Aupérin A, Le Péchoux C, Pignon JP, et al. Concomitant radio-chemotherapy based on platin compounds in patients with locally advanced non-small cell lung cancer (NSCLC): a meta-analysis of individual data from 1764 patients. *Ann Oncol* 2006; 17:473-83.
6. Belderbos J, Uitterhoeve L, van Zandwijk N, et al. Randomised trial of sequential versus concurrent chemo-radiotherapy in patients with inoperable non-small cell lung cancer (EORTC 08972-22973). *Eur J Cancer* 2007; 43:114-21.
7. Curran WJ, Scott CB, Langer CJ, et al. Long-term benefit is observed in a phase III comparison of sequential vs concurrent chemoradiation for patients with unresected stage III nsclc: RTOG 9410. *Proc Am Soc Clin Oncol* 2003; 22:abstract 621.
8. Fournel P, Robinet G, Thomas P, et al. Randomized phase III trial of sequential chemoradiotherapy compared with concurrent chemoradiotherapy in locally advanced non-small-cell lung cancer: Groupe Lyon-Saint-Etienne d'Oncologie Thoracique-Groupe Français de Pneumo-Cancérologie NPC 95-01 Study. *J Clin Oncol* 2005; 23:5910-7.
9. Furuse K, Fukuoka M, Kawahara M, et al. Phase III study of concurrent versus sequential thoracic radiotherapy in combination with mitomycin, vindesine, and cisplatin in unresectable stage III non-small-cell lung cancer. *J Clin Oncol* 1999; 17:2692-9.
10. Zatloukal P, Petruzelka L, Zemanova M, et al. Concurrent versus sequential chemoradiotherapy with cisplatin and vinorelbine in locally advanced non-small cell lung cancer: a randomized study. *Lung Cancer* 2004; 46:87-98.
11. Aupérin A, Le Péchoux C, Rolland E, et al. Meta-analysis of concomitant versus sequential radiochemotherapy in locally advanced non-small-cell lung cancer. *J Clin Oncol* 2010; 28:2181-90.
12. Ball D, Bishop J, Smith J, et al. A randomised phase III study of accelerated or standard fraction radiotherapy with or without concurrent carboplatin in inoperable non-small cell lung cancer: final report of an Australian multi-centre trial. *Radiother Oncol* 1999; 52:129-36.
13. Groen HJ, van der Leest AH, Fokkema E, et al. Continuously infused carboplatin used as radiosensitizer in locally unresectable non-small-cell lung cancer: a multicenter phase III study. *Ann Oncol* 2004; 15:427-32.
14. Isaković-Vidović S, Radosević-Jelić L, Borojević N. Combined chemoradiotherapy in the treatment of locally advanced non-small cell lung cancer. *J BUON* 2002; 7:47-51.
15. Lau DH, Crowley JJ, Gandara DR, et al. Southwest Oncology Group phase II trial of concurrent carboplatin, etoposide, and radiation for poor-risk stage III non-small-cell lung cancer. *J Clin Oncol* 1998; 16:3078-81.
16. Vokes EE, Herndon JE, Kelley MJ, et al. Induction chemotherapy followed by chemoradiotherapy compared with chemoradiotherapy alone for regionally advanced unresectable stage III non-small-cell lung cancer: cancer and Leukemia Group B. *J Clin Oncol* 2007; 25:1698-704.
17. Blanke C, Ansari R, Mantravadi R, et al. Phase III trial of thoracic irradiation with or without cisplatin for locally advanced unresectable non-small-cell lung cancer: a Hoosier Oncology Group protocol. *J Clin Oncol* 1995; 13:1425-9.
18. Cakir S, Egehan I. A randomised clinical trial of radiotherapy plus cisplatin versus radiotherapy alone in stage III non-small cell lung cancer. *Lung Cancer* 2004; 43: 309-16.
19. Furuse K, Kubota K, Kawahara M, et al. Phase II study of concurrent radiotherapy and chemotherapy for unresectable stage III non-small-cell lung cancer. Southern Osaka Lung Cancer Study Group. *J Clin Oncol* 1995;13:869-75.
20. Ichinose Y, Nakai Y, Kudoh S, et al. Uracil/tegafur plus cisplatin with concurrent radiotherapy for locally advanced non-small-cell lung cancer: a multi-institutional phase II trial. *Clin Cancer Res* 2004; 10:4369-73.
21. Kim YS, Yoon SM, Choi EK, et al. Phase II study of radiotherapy with three-dimensional conformal boost concurrent with paclitaxel and cisplatin for stage IIIB non-small-cell lung cancer. *Int J Radiat Oncol Biol Phys* 2005; 62:76-81.
22. Pradier O, Lederer K, Hille A, et al. Concurrent low-dose cisplatin and thoracic radiotherapy in patients with inoperable stage III non-small cell lung cancer: a phase II trial with special reference to the hemoglobin level as prognostic parameter. *J Cancer Res Clin Oncol* 2005; 131:261-9.
23. Schild SE, Stella PJ, Geyer SM, et al. Phase III trial comparing chemotherapy plus once-daily or twice-daily radiotherapy in stage III non-small-cell lung cancer. *Int J Radiat Oncol Biol Phys* 2002; 54:370-8.
24. Trovó MG, Minatel E, Franchin G, et al. Radiotherapy versus radiotherapy enhanced by cisplatin in stage III non-small cell lung cancer. *Int J Radiat Oncol Biol Phys* 1992; 24:11-5.
25. Trovò MG, Minatel E, Franchin G, et al. Radiotherapy enhanced by cis-platinum in stage III non-small cell lung cancer: a phase II study. *Radiother Oncol* 1992; 23:241-4.
26. Saris CP, van de Vaart PJ, Rietbroek RC, et al. In vitro formation of DNA adducts by cisplatin, lobaplatin and oxaliplatin in calf thymus DNA in solution and in cultured human cells. *Carcinogenesis* 1996; 17:2763-9.
27. van de Vaart PJ, Belderbos J, de Jong D, et al. DNA-adduct levels as a predictor of outcome for NSCLC patients receiving daily cisplatin and radiotherapy. *Int J Cancer* 2000; 89:160-6.
28. Zuur CL, Simis YJ, Verkaik RS, et al. Hearing loss due to concurrent daily low-dose cisplatin chemoradiation for locally advanced head and neck cancer. *Radiother Oncol* 2008; 89:38-43.
29. Barkati M, Fortin B, Soulières D, et al. Concurrent chemoradiation with carboplatin-5-fluorouracil versus cisplatin in locally advanced oropharyngeal cancers: is more always better? *Int J Radiat Oncol Biol Phys* 2010; 76:410-6.
30. Wolff HA, Overbeck T, Roedel RM, et al. Toxicity of daily low dose cisplatin in radiochemotherapy for locally advanced head and neck cancer. *J Cancer Res Clin Oncol* 2009; 135:961-7.
31. Chen Y, Pandya KJ, Feins R, et al. Toxicity profile and pharmacokinetic study of a phase I low-dose schedule-dependent radiosensitizing paclitaxel chemoradiation regimen for inoperable non-small-cell lung cancer. *Int J Radiat Oncol Biol Phys* 2008; 71:407-13.
32. Uitterhoeve AL, Belderbos JS, Koolen MG, et al. Toxicity of high-dose radiotherapy combined with daily cisplatin in non-small cell lung cancer: results of the EORTC 08912 phase I/II study. European Organization for Research and Treatment of Cancer. *Eur J Cancer* 2000; 36:592-600.
33. De Ruysscher D, Botterweck A, Dirx M, et al. Eligibility for concurrent chemotherapy and radiotherapy of locally advanced lung cancer patients: a prospective, population-based study. *Ann Oncol* 2009; 20:98-102.
34. Uitterhoeve AL, Koolen MG, van Os RM, et al. Accelerated high-dose radiotherapy alone or combined with either concomitant or sequential chemotherapy; treatments of choice in patients with non-small cell lung cancer. *Radiat Oncol* 2007; 2:27.
35. Spigel DR, Hainsworth JD, Yardley DA, et al. Tracheoesophageal fistula formation in patients with lung cancer treated with chemoradiation and bevacizumab. *J Clin Oncol* 2010; 28:43-8.
36. Schaake EE, Aukema TS, Belderbos J, et al. Cetuximab in combination with single agent daily cisplatin chemotherapy concurrent with radiotherapy in locally advanced nonsmall cell lung carcinoma: a feasibility study. *Eur J Clin Med Oncol* 2010; 2:65-71.
37. Brade A, Bezjak A, MacRae R, et al. Phase I trial of radiation with concurrent and consolidation pemetrexed and cisplatin in patients with unresectable stage IIIA/B non-small-cell lung cancer. *Int J Radiat Oncol Biol Phys* 2011; 79:1395-401.
38. Ready N, Jänne PA, Bogart J, et al. Chemoradiotherapy and gefitinib in stage III non-small cell lung cancer with epidermal growth factor receptor and KRAS mutation analysis: cancer and leukemia group B (CALEB) 30106, a CALGB-stratified phase II trial. *J Thorac Oncol* 2010; 5:1382-90.
39. Guida C, Maione P, Rossi A, et al. Combined chemo-radiotherapy for locally advanced non-small cell lung cancer: current status and future development. *Crit Rev Oncol Hematol* 2008; 68:222-32.
40. Phernambucq EC, Spoelstra FO, Verbakel WF, et al. Outcomes of concurrent chemoradiotherapy in patients with stage III non-small-cell lung cancer and significant comorbidity. *Ann Oncol* 2011; 22:132-8.
41. Yamamoto N, Nakagawa K, Nishimura Y, et al. Phase III study comparing second- and third-generation regimens with concurrent thoracic radiotherapy in patients with unresectable stage III non-small-cell lung cancer: West Japan Thoracic Oncology Group WJTOG0105. *J Clin Oncol* 2010; 28:3739-45.
42. Jeremic B, Milicic B, Acimovic L, et al. Concurrent hyperfractionated radiotherapy and low-dose daily carboplatin and paclitaxel in patients with stage III non-small-cell lung cancer: long-term results of a phase II study. *J Clin Oncol* 2005; 23:1144-51.