CONTINUOUSLY INFUSED CARBOPLATIN USED AS RADIOSENSITIZER IN LOCALLY UNRESECTABLE NON-SMALL-CELL LUNG CANCER: A MULTICENTER PHASE III STUDY


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Purpose: To determine the radiosensitizing effect of prolonged exposure of carboplatin in patients with locally unresectable non-small-cell lung cancer (NSCLC).

Patients and methods: Patients with histologically proven NSCLC, performance score <2, weight loss <10%, and normal organ functions were randomized between carboplatin 840 mg/m² administered continuously during 6 weeks of radiotherapy or thoracic radiotherapy alone (both 60 Gy). Toxicity was evaluated with National Cancer Institute Common Toxicity Criteria (NCI CTC) and the Radiation Therapy Oncology Group (RTOG) criteria. Quality of life was measured with European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30/LC13 questionnaires.

Results: One-hundred and sixty patients were included. Pathologically confirmed persistent tumor was present in 53% of patients in the combination arm versus 58% in the radiotherapy alone arm (P = 0.5). Median survival in the combination arm was 11.8 [95% confidence interval (CI) 9.3–14.2] months and in the radiotherapy alone arm 11.7 (95% CI 8.1–15.5) months; progression-free survival was not different between arms (6.8 and 7.5 months, respectively (P = 0.28)). Acute toxicity was mild, late toxicity was radiation-induced cardiomyopathy (three patients) and pulmonary fibrosis (five patients). Quality of life was not different between arms, but in all measured patients cough and dyspnea improved, pain became less, and slight paresthesia developed 3 months after treatment.

Conclusion: Addition of continuously administered carboplatin as radiosensitizer for locally unresectable NSCLC does not improve local tumor control or overall survival.

Key words: carboplatin, NSCLC, radiosensitization, radiotherapy, stage III

Introduction

Prognosis of locally unresectable non-small-cell lung cancer (NSCLC) patients is disappointing; their median survival time does not exceed 10–15 months [1]. A meta-analysis of randomized clinical trials comparing combined chemotherapy and radiation to radiation therapy alone has shown a survival benefit with platinum-based combination chemotherapy administered sequentially or concurrently with thoracic radiation therapy over radiation therapy alone [2, 3]. Concurrent use of radiation and weekly cisplatin does not improve local tumor control [4]. To circumvent toxicity of cisplatin, carboplatin in different schedules has been added to radiation to optimize their interactive effects [5, 6]. Good long-term results in terms of toxicity have been reported and this concurrent combination seems even feasible in poor-risk stage III NSCLC patients, giving similar results as in concurrent treatments with cisplatin [7, 8]. Phase III studies with weekly administered platinum salts including carboplatin and cisplatin added to parts of the radiation period did not improve overall survival [4, 5, 9], while daily administered cisplatin did improve local tumor control and overall survival. Moreover, low-dose carboplatin and etoposide added to hyperfractionated radiation in stage III NSCLC patients did improve local tumor control over hyperfractionated radiation alone [10]. Most of these studies also included induction chemotherapy which may obscure the effect of radiosensitization of concurrently administered drugs. Therefore, to evaluate whether mere radiosensitization with carboplatin is clinically beneficial we omitted induction chemotherapy. In vitro studies have shown that continuous and prolonged exposure of tumor cells to low levels of carboplatin together with radiation increased cell kill remarkably [11, 12]. We tested this...
hypothesis in locally unresectable NSCLC patients. First, we performed a phase I study at the Groningen University Hospital with continuously infused carboplatin administered via a venous access port by a portable pump over 6 weeks during radiotherapy [13]. Dose-limiting toxicity was leukopenia and thrombocytopenia which was observed at prolonged free plasma platinum levels of 200 μg/l. The maximum tolerable daily carboplatin dose was 25 mg/m² for 6 weeks. Carboplatin slowly binds to plasma proteins and tissue sites and is excreted by the renal route without causing significant nephrotoxicity. An additional advantage of the prolonged infusional carboplatin schedule was circumvention of cisplatin toxicity. Toxicity, especially nausea and vomiting, esophagitis and pneumonitis are important problems when cisplatin was incorporated into radiation schedules. The *in vitro* increased cell kill of prolonged carboplatin exposure and clinical advantages of carboplatin in conjunction with radiation in the phase I study led us to examine the efficacy of the radiosensitizing effect of carboplatin using a 6-week continuously administered schedule. The primary objective of this study was to determine whether this prolonged carboplatin schedule during radiation would improve survival.

**Patients and methods**

From February 1995 to October 1998 patients with the following criteria were included: locally advanced and unreseetable histologically documented NSCLC, age 18–76 years, weight loss <10% in previous 3 months before diagnosis, performance score [Eastern Cooperative Oncology Group (ECOG)] <2, normal renal, liver and bone marrow functions, and no prior chemo- or radiotherapy. Patients with evidence of central nervous metastases, concurrent malignancy except for basal skin malignancies, pregnancy and serious medical or psychiatric disease were excluded. Patients with contralateral supraclavicular lymph nodes were also excluded. Minimal staging procedures were chest X-ray, bronchoscopy, computerized tomography (CT) of the chest and upper abdomen, bone scan, cervical mediastinoscopy, except when supraclavicular lymph nodes on the side of the tumor were positive. The protocol was approved by all local medical ethics committees. All patients had to give informed consent.

**Study design**

Patients were stratified according to stage, performance status and hospital. Block randomization was used and treatment allocation was performed by telephone into either carboplatin and radiation, or radiation alone.

**Treatment schedules**

Radiotherapy was delivered on the primary tumor with a 2 cm margin around the tumor volume and ipsilateral hilum and to the mediastinum with a 2 cm margin around the involved mediastinum as estimated on CT scan. Treatment was performed by the two isocentric parallel opposed field technique (anterior–posterior and posterior–anterior) during the first 20 fractions up to 40 Gy, followed by a boost of 20 Gy with a CT-treatment plan for the last 2 weeks up to a total of 60 Gy, using 6–25 MV photons. The original tumor volume was treated with 2 Gy per day in five fractions per week. The planned dose of the first 40 Gy was calculated without correction for the lung inhomogeneity, the boost dose was 20 Gy in 10 fractions without correction for lung homogeneity or 22 Gy with correction for lung inhomogeneity. The dose specifications were in accordance with the ICRU-29 report. The dose to the spinal cord did not exceed 50 Gy in 25 fractions (α/β = 2).

Carboplatin was delivered in a dose of 20 mg/m²/day continuously during 6 weeks of radiotherapy. A 20 ml syringe with carboplatin in 5% glucose was supplied to each patient every 48 h, also during the weekends. The syringe was connected to a venous access port, which was implanted subcutaneously under local anaesthesia before treatment and connected to the subclavian vein. The needle and extension tube were renewed in the third treatment week.

**Assessments**

Pretreatment assessment included staging procedures, medical history and physical examination, complete blood count, platelets, electrolytes, renal and liver function tests, lung function tests and quality of life. During treatment, once every 2 weeks a complete blood count was performed and twice during the 6-week treatment renal and liver functions were tested. After treatment, tumor response was measured with CT-scan according to World Health Organization (WHO) criteria and by endobronchial evaluation. Bronchoscopical findings were defined as presence or absence of endobronchial tumor and a description of other mucosal abnormalities from which biopsies had been taken. In case biopsies were negative or not available, macroscopic mucosal evaluation prevailed in the bronchoscopical evaluation. Overall tumor response was assessed with both CT and bronchoscopical measurements.

Follow-up assessments were every 3 months in the first year, thereafter every 6 months for 2 years and then yearly with history, physical examination, blood tests, chest X-ray and appropriate imaging tests or biopsies in case of suspected metastases.

Toxicity was scored with the National Cancer Institute Common Toxicity Criteria (NCI CTC) and for acute and late radiation toxicity Radiation Therapy Oncology Group (RTOG) criteria were used. Pulmonary function was measured before and 3 months after treatment. Quality of life was assessed with European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30/LC13 questionnaires before, after and 3 months after treatment.

**Statistics**

In NSCLC the 2-year survival after thoracic radiation is 15% [4]. The study was designed to have 85% power to detect 15% difference in the 2-year survival. The accrual goal was 265 randomized patients. During the study the independent Data Monitoring Committee (DMC) periodically reviewed safety and efficacy data. Survival was calculated from the date of randomization to the date of death or last follow-up. Progression-free survival was defined as the time from randomization to the first date of progressive disease, relapse or death. Kaplan–Meier method with two-sided log-rank test was used for analyzing survival data. For patient characteristics, response rates and toxicity chi-square square tests were used. Quality of life data for both treatment groups were analyzed with ANOVA and changes of the last assessment from baseline was compared with paired t-test. P <0.05 was considered as statistically significant.

**Results**

**Patients**

After randomizing 160 patients, the DMC decided that a survival improvement of 15% was not achievable with carboplatin as radiosensitizer. There was also no difference in local tumor control as estimated by CT-scan or bronchoscopy. Therefore the trial was closed. At that time 82 patients received prolonged carboplatin infusion and radiotherapy and 78 patients radiotherapy alone. Five patients were ineligible after data review because of pretreatment distant metastases: three in the carboplatin arm and two in the radiotherapy alone arm. This report is about these 160 patients. The pretreatment characteristics are listed in Table 1. Ninety-one
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per cent of patients in the combined treatment arm received the planned radiation dose and 92% of patients in the radiotherapy alone arm. The mean actual duration of radiation in the combined arm was 38.3 days and in the radiotherapy alone arm was 38.7 days, the radiated tumor area was 29.1 versus 26.5 cm², respectively. Both characteristics were not different from each other. The administered carboplatin dose was 98% of the planned dose.

Antitumor efficacy by CT-scan

Tumor response was re-evaluated with CT-scan by two independent observers in 154 of 160 patients. In two patients in the combination arm and four patients in the radiotherapy alone arm, tumor response measurements were not available for independent evaluation. In the carboplatin arm 52% (95% CI 44–60) of patients showed tumor response, in the radiotherapy arm 58% (95% CI 50–64). The complete response percentage in the carboplatin arm and radiotherapy alone arm was 1.6 and 2.9%, respectively; the partial response percentage was 35 and 43%, respectively. Stable disease occurred in 38 and 34% of patients, progressive disease in 25 and 21%, respectively.

Endobronchial antitumor efficacy

Bronchoscopic evaluation before treatment was performed in 150 patients. Ten patients had their diagnosis by other diagnostic routes. One-hundred and seventeen patients had centrally located and therefore bronchoscopically evaluable tumors and in 33 patients bronchoscopical findings were normal.

After treatment 117 patients had a repeat bronchoscopy. Normal endobronchial findings were observed in 32 patients and 85 patients had visible tumor and/or strongly inflammed mucosa at the site of the original tumor. There was no difference in pathologically confirmed endobronchial tumor response between both treatment arms: 32 of 60 (53%) bronchoscopically evaluable patients had endobronchial tumor in the combination arm and 33 of 57 (58%) in the radiotherapy alone arm (P = 0.5). In 31 of 117 patients endobronchial biopsies revealed no or inadequate tissue procurement and in these patients only endobronchial evaluation was taken for overall bronchoscopical response measurement.

Combining CT and bronchoscopy results revealed an overall tumor response of 40% (95% CI 31–49) in the combination arm and 45% (95% CI 36–54) in the radiotherapy arm (not significant; 117 patients).

Survival

The median survival in the combination arm was 11.8 (95% CI 9.3–14.2) months and in the radiotherapy alone arm 11.7 (95% CI 8.1–15.5) months (Figure 1). The 2-year overall survival was 20 and 28%, respectively. Progression-free survival was 6.8 (95% CI 5.7–8.0) and 7.5 (95% CI 3.6–11.3) months, respectively (P = 0.28). Local control in the combination arm and radiotherapy alone arm at 1 and 2 years was 60 and 72% and 35 and 38%, respectively. Second-line chemotherapy was administered to 14 patients in the combination arm and to 19 patients in the radiotherapy arm. Censoring for second-line chemotherapy did not change these results significantly. The median survival of overall tumor responders was 16.0 (95% CI 12.3–19.7) months; that of the non-responders was 10.0 (95% CI 8.4–11.7) months (P <0.001).

Toxicity

Hematological toxicity was mild and occurred more often in the combination arm (Table 2). Transient lymphocytopenia occurred in almost all patients during radiation. Non-hematological toxicity

Table 1. Patients characteristics at diagnosis of NSCLC

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<th>Carboplatin and radiotherapy</th>
<th>Radiotherapy</th>
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<tr>
<td>No. of patients</td>
<td>82</td>
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<td>Male/female</td>
<td>75/7</td>
<td>66/12</td>
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<td>Mean age (years)</td>
<td>59.6</td>
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<td>Mean weight loss (kg)</td>
<td>2.5</td>
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<td>0</td>
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ECOG, Eastern Cooperative Oncology Group; NSCLC, non-small-cell lung cancer.
was mainly radiation esophagitis and pneumonitis (Table 3). There were no differences between arms in grade 3 and 4 ototoxicity, renal and neurotoxicity. Two patients developed infections at the venous access port, resulting in septicaemia in one patient. All patients were successfully treated with antibiotics. No early deaths occurred. Late toxicity occurred in three patients with radiation-induced cardiomyopathy (all lower lobe tumors) and severe pulmonary radiation fibrosis in five patients.

Pulmonary function tests were measured before and 3 months after treatment and were complete in 120 patients (Table 4). A slight but significant mean decrease in vital capacity (140 ml) and the forced expiratory volume in the first second (100 ml) occurred after treatment. Decrease in total lung capacity (210 ml) and diffusion capacity (2.3% predicted) was not significant. Changes in pulmonary function were not different between treatment groups.

### Quality of life

EORTC questionnaires were filled in by 148 (92%) patients before treatment, by 127 (79%) patients shortly after treatment and by 116 (72%) patients 3 months after treatment. No significant differences in the main quality of life domains or symptoms between treatment groups were observed. Taking both treatment groups together for symptoms, cough \((P <0.02)\) and dyspnea \((P = 0.01)\) improved and pain became less \((P <0.002)\) directly after treatment. Slight paresthesia in hands and feet developed 3 months after treatment \((P <0.001)\).

### Discussion

At the time the study was designed high-dose radiotherapy was standard treatment for stage III unresectable NSCLC. Therefore, we chose this arm as our control arm. Nowadays induction
chemotherapy followed by radiotherapy or concurrent chemoradiotherapy is the treatment of choice. This study shows that the 2-year survival of locally advanced NSCLC patients is favorable as compared with the Schaake–Koning study, that showed a radio-sensitizing effect of daily cisplatin administration. Addition of continuously administered carboplatin over 6 weeks to radiation does not improve local tumor control. Interactions between cytotoxic drugs and radiation are usually small and may be more difficult to demonstrate in patients with improved survival. Potential other explanations are the fact that not enough platinum reaches the tumor for radiosensitization and that perhaps the vascular access for carboplatin diminishes with radiation time, slowing down the platinum deposition into the tumor. In animal studies the formation of cytotoxic platinum–DNA adducts is slower with carboplatin than with cisplatin [14]. With prolonged exposure to carboplatin the amount of DNA platination was not different compared to cisplatin [15]. Differences in carboplatin-associated toxicities were small as were the range of creatinine clearances according to Cockcroft. Therefore the variability in platinum exposure to the tumor must have been small although carboplatin was not dosed according to renal function.

The principal disadvantage of concomitant therapy remains the enhancement of normal tissue toxicity, both hematological and esophageal, resulting in unnecessary patient morbidity and attenuation of radiotherapy and/or chemotherapy delivery. The present study shows that low-dose carboplatin gives little hematological toxicity and adds mild non-hematological toxicity to radiation toxicity. At 3 months after treatment slight paresthesia of hand and feet was reported by patients in this study but even after longer follow-up no symptoms of radiation myelitis were observed. Radiation myelitis was also not observed in 158 patients who received 50.4 Gy on their spine and who lived more than 1 year [16].

Many studies have looked into the problem of carboplatin scheduling in relation to radiation [17]. Different scheduling of carboplatin either weekly or every other week together with hyperfractionated radiotherapy did not change the toxicity profile or local antitumor effect [18]. However, one study showed that median time to local recurrence with 5 months difference was significantly longer in patients treated with concurrent hyperfractionated radiotherapy and low-dose carboplatin and etoposide, but the distant metastasis-free survival rate did not differ as compared with hyperfractionated radiotherapy alone [10]. A Japanese phase II study performed in elderly NSCLC patients with stage III showed that daily low-dose carboplatin using 30 mg/m2/day during 4 weeks added to 50–60 Gy radiotherapy gave a response rate of 50% and 2-year actuarial survival rate of 20% [19]. In the present study the median survival was slightly lower than in the study of Clamon et al., where patients also received induction chemotherapy [5]. The radiosensitizing effect of low-dose continuous carboplatin schedule used in this study is clinically not relevant. Low-dose continuous chemotherapy may have effects on endothelial cells, preventing their recovery and effectively starving tumors of their blood supply [20]. However, 6 weeks is clearly too short a period to show an interaction of radiation and carboplatin on endothelial level in terms of survival. Longer periods of continuous low-dose chemotherapy may be necessary [21]. We conclude that addition of continuous carboplatin to thoracic radiotherapy is not beneficial for patients with locally unresectable NSCLC and that in more than half of the NSCLC patients histologically confirmed endobronchial tumor remained present after treatment.

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References
13. Groen HJM, Van der Leest AHD, De Vries EGE et al. Continuous carboplatin infusion during 6 weeks radiotherapy in locally inoperable non-


