Docetaxel and cisplatin as induction chemotherapy in patients with pathologically-proven stage IIIA N2 non-small cell lung cancer: a phase II study of the European organization for research and treatment of cancer (EORTC 08984)


Afdeling Longziekten, Jeroen Bosch Ziekenhuis, Nieuwstraat 34, 5211 NL ’s-Hertogenbosch, The Netherlands

Thoraxklinik Heidelberg, Germany (previously at Heidelberg University Medical Centre, Mannheim, Germany)

Rijnstate Ziekenhuis, Arnhem, The Netherlands

Leiden University Medical Centre, Leiden, The Netherlands

EORTC Data Centre, Brussels, Belgium

Universitair Ziekenhuis Gent, Belgium (previously at Erasmus University Medical Centre, Rotterdam, The Netherlands)

Vrije Universiteit Medical Centre, Amsterdam, The Netherlands

ARTICLE INFO

Article history:
Received 6 January 2006
Accepted 25 January 2006
Available online 8 June 2006

Keywords:
Stage IIIA non-small cell lung cancer
Induction chemotherapy
Docetaxel-cisplatin

ABSTRACT

The objective of this phase II study was to document activity and toxicity of docetaxel and cisplatin as induction chemotherapy in patients with stage IIIA N2 non-small cell lung cancer (NSCLC) before definitive local treatment. Forty-six chemotherapy-naïve patients (median age 60 years) were included. Treatment consisted of 3 cycles of docetaxel (85 mg/m² on day 1), followed by cisplatin (40 mg/m²/day on days 1 and 2) every 21 days. Grade 3–4 leukopenia and neutropenia occurred in 45.7% and 65.2% of the patients, respectively. Among 8 cases of febrile neutropenia (17.4%), one (2.2%) resulted in early death. Common grade 3–4 non-haematological toxicities were nausea (17.4%) and vomiting (13%). Eighty-five percent of the patients received three courses; six stopped prematurely due to toxicity, one due to protocol violation. Response rate was the primary endpoint of this study. Considering eligible patients (n = 40), 18 responses (1 complete and 17 partial responses) were observed (response rate 45%; 95% Confidence interval (CI): 29.3%–61.5%). In stage IIIA-N2 NSCLC patients, docetaxel-cisplatin could be administered and demonstrated manageable toxicity with modest efficacy.

1. Introduction

Patients with stage IIIA N2 non-small cell lung cancer (NSCLC) have a 5-year survival rate of less than 15% when treated with only surgery or radical radiotherapy. These poor results are mainly due to the occurrence of distant metastases which occur in many cases shortly after initial treatment.1 Interest in combined-modality treatment was generated when a 1995
meta-analysis demonstrated improved survival in stage III patients if radical radiotherapy was combined with chemotherapy. Results of several recent trials have supported the use of combination therapy in this subset of patients. In particular, the practice of chemotherapy administration prior to radical treatment has become a standard of care following the publication of two small phase III studies. This approach of neo-adjuvant chemotherapy is based on several considerations: chemotherapy may shrink the loco-regional macroscopic disease, making it more amenable to surgery, radiotherapy or both and at the same time chemotherapy may prevent development of distant metastases or eradicate micro-metastases. Both the combination of chemotherapy and radiotherapy may prevent development of distant metastases or eradicate macroscopic disease, making it more amenable to surgery, radiotherapy or both and at the same time chemotherapy may prevent development of distant metastases or eradicate micro-metastases. Both the combination of chemotherapy followed by surgery and the combination of chemotherapy followed by radiotherapy have demonstrated superior survival compared to surgery or radiotherapy alone. However, data from a more recent French phase III randomised study using neo-adjuvant chemotherapy in stage IB-IIIA patients did not demonstrate superior survival in the stage IIIA subset of patients, although a significant reduction in the development of distant metastases was observed in the chemotherapy group. This study provided evidence that newer, more effective drug combinations are required to further improve survival rates in this patient population.

The use of the so-called third generation chemotherapeutic drugs (gemcitabine, paclitaxel, vinorelbine, docetaxel) in combination with platinum drugs in stage IIIb/IV NSCLC has resulted in an (albeit small) increase in response rates (RR) and median survival (MS). Subsequently these two-drug combinations have become subject of investigation in combined modality treatment. This study provided evidence that newer, more effective drug combinations are required to further improve survival rates in this patient population.

As a single agent, docetaxel has demonstrated anti-tumour activity both in first-line and second-line treatment of NSCLC. Docetaxel has also demonstrated efficacy as a (neo)adjuvant drug in combination with surgery or chemoradiotherapy. Platinum-based combination chemotherapy is recommended as a standard of care in good performance status patients with advanced NSCLC. Docetaxel-cisplatin regimens have demonstrated to be amongst the most effective in this patient group, as demonstrated in several phase III trials. Furthermore, preliminary data from a Swiss study by Dr. Betticher and colleagues with docetaxel-cisplatin combination chemotherapy showed a promising response rate in patients with stage IIIA NSCLC.

As a consequence of these findings, the European Organization for the Research and Treatment of Cancer Lung Cancer Group (EORTC-LCG) initiated a phase II trial to define the activity and safety of the docetaxel-cisplatin combination as an induction regimen for patients with stage IIIA N2 NSCLC. This trial was the third and last of a series of phase II studies using new chemotherapy combinations within the setting of a recently finished randomised phase III trial in patients with stage IIIA N2 disease (EORTC 08941). Results of the two other phase II trials conducted by the LCG were published earlier. In the EORTC 08955 and 08958 studies, gemcitabine-cisplatin and carboplatin-paclitaxel were tested as induction regimens, respectively. In the EORTC 08941 trial, patients responding to chemotherapy were randomised between surgery and radical radiotherapy in order to define the optimal definitive local treatment.

2. Patients and methods

2.1. Objectives

The primary objective of this phase II trial was to assess the antitumour activity of docetaxel combined with cisplatin administered as an induction regimen to chemo-naive patients with stage IIIA N2 NSCLC. The secondary objective was to further establish the safety profile of docetaxel-cisplatin as an induction regimen in this patient group.

2.2. Patient selection

Main eligibility criteria for patients entering the study included the following: stage IIIA NSCLC with biopsy proven positive N2 nodes, age >18 years, World Health Organization (WHO) performance status ≤ 2, adequate baseline organ function defined as an absolute neutrophil count (ANC) ≥ 1.5 × 10^9/L, platelet count ≥ 100 × 10^9/L, renal and liver function within normal limits. Presence of at least one target lesion that could be accurately measured in at least one dimension as ≥20 mm with conventional techniques or as ≥ 10 mm with spiral CT-scan was requested. Patients had to be considered mentally and physically fit to receive docetaxel-cisplatin chemotherapy, and to undergo a lobectomy or pneumonectomy or radiotherapy following chemotherapy. Patients who had previous therapy for NSCLC, or presence of active infection were excluded, along with patients with pleural or pericardial effusion, superior vena cava syndrome and pre-existing motor or sensory neurotoxicity ≥ grade 2 National Cancer Institute of Canada Common Toxicity Criteria (NCIC-CTC).

The study was approved by the EORTC Protocol Review Committee (PRC) and by the ethics committees of the participating centres. All patients gave written informed consent prior to registration.

2.3. Treatment plan

Patients were scheduled to receive 3 courses of chemotherapy every 21 days unless progression of disease or unacceptable toxicity was recorded or patients refused further treatment. Based on the preliminary results of the study conducted by Dr. Betticher and colleagues, docetaxel 85 mg/m² was administered as a 1-hour intravenous (i.v.) infusion on day 1 and cisplatin 40 mg/m² was administered as a 30-minute i.v. infusion on days 1 (directly following docetaxel) and 2. Dexamethasone (or equivalent) at a dose of 8 mg bid was given orally the day prior to chemotherapy (day −1) and the day of chemotherapy (day 1). A SHTp antagonist was given on days 1–3; the dose and administration route was conducted in accordance with local policy. Adequate hydration was also given according to local practice.

 Neither dose reduction or escalation for docetaxel was allowed. The protocol predefined that, if necessary, the next chemotherapy cycle should be postponed until ANC ≥ 1.5 × 10^9/L and platelet count ≥ 100 × 10^9/L, liver functions returned to normal as well as creatinine and creatinine clearance ≥ 50 ml/min. If febrile neutropenia (FNP) occurred during a cycle, prophylactic use of growth factors was allowed.
This study was designed according to the Simon one sample test. A complete history, physical examination, complete blood cell counts with differential, serum biochemistry, spirometry, bronchoscopy, chest X-ray, computer tomography (CT) of the chest and upper abdomen, bone scan and ECG were obtained at baseline. Patients were monitored throughout treatment by recording history, toxic events, and complete blood cell counts with differential (weekly). Serum chemistry determinations were repeated prior to start of each chemotherapy cycle. All toxicities were coded according to the NCIC-CTC.

Tumour response was evaluated by CT-scan after three cycles of treatment. CT examinations were reviewed by the principal investigator. Subsequently, CT-scans of all reported responders were reviewed by a panel of two independent radiologists. Response was evaluated according to RECIST criteria but confirmation of response after a minimum of 4 weeks was not available: the fact that responding patients were randomised for surgery or radiotherapy precluded a formal 4-week confirmation of response to chemotherapy according to RECIST criteria. The patients with responsive disease, if judged resectable by the local surgeon and multidisciplinary team, were proposed to undergo further randomisation to receive either surgery or radical radiotherapy as part of the EORTC 08941 trial. Repeated mediastinoscopy/thoracotomy was not required in the post-chemotherapy evaluation.

2.5. Statistical considerations

This study was designed according to the Simon one sample two-stage testing procedure. The primary endpoint was response rate and the objective of this study was to select this induction regimen for further study if the results were consistent with a true response rate of 75% or more and to reject it if results were consistent with a true response rate of 55% or less. The type I error was set to 20%, while the power was set to 95%. Under those hypotheses, the total sample size for this trial was 40 evaluable patients. The trial, however, would be discontinued after 24 patients according to the following rule: a first test was to be performed when the first 24 patients were evaluated for response: if \( \leq 10 \) responses were observed, the trial would be stopped with the conclusion that this regimen should not be further investigated. In all other cases accrual would continue until 40 patients were evaluable for response. A second test then would be performed amongst those 40 patients: if \( \leq 24 \) responses were observed, the conclusion would be that the drug combination should not be further investigated. If \( > 24 \) responses were observed, we would conclude that the drug combination warranted further investigation. Although not foreseen as a secondary endpoint by the protocol, overall survival was measured from the date of registration to the date of death or last follow-up examination and was estimated using the Kaplan-Meier method based on all patients who started protocol treatment.

3. Results

3.1. Patients characteristics

From January 2000 to August 2002, 46 patients were enrolled into the study. Six patients (13%) were subsequently found to be ineligible: three patients had pleural effusion at entry, one patient each had stage IIIB disease (T4 tumour), stage IV disease, and a serious concomitant disease. All patients enrolled were considered evaluable for toxicity; the six ineligible patients were excluded from the response analysis. Baseline characteristics of all patients are shown in Table 1. Median age was 60 years (range 27–74). Approximately two-thirds of patients (65.2%) had a WHO performance status of 1. Major histological tumour subtypes were squamous cell (43.5%) and adenocarcinoma (34.8%). All patients had N2-disease, pathologically proven either by mediastinoscopy or -thoracotomy (44 patients), video-assisted thoracoscopic surgery (VATS, 1 patient) or thoracotomy (1 patient).

3.2. Treatment information

All 46 enrolled patients started chemotherapeutic treatment. The majority of patients (84.8%) received the planned three chemotherapy cycles. One patient (2.2%) received two cycles, while 6 (13.0%) received only one cycle. Median number of administered cycles was three (range 1–3). A total of 125 cycles of docetaxel-cisplatin was administered. Dose modifications and schedule modifications occurred in 4/125 and 13/125 cycles, respectively. Three patients (6.5%) were reported with at least one dose modification but no schedule modifications (cisplatin reduction in 1 patient, cisplatin escalation in 1 patient, docetaxel and cisplatin reduction in 1 patient), 10 patients (21.7%) were reported with at least one schedule modification but no dose modifications and only one patient (2.2%) was reported with at least one dose modification and one schedule modification (treatment interrupted and not restarted) for the cycles received. The median relative dose intensity (ratio of the observed dose intensity to the dose intensity planned by the protocol) was 100.5% (range 0.6%–106.4%) for docetaxel and 101.2% (range 0%–124.2%) for cisplatin. Five patients (10.9%) were identified with severe protocol violations: undertreatment in three patients, overtreatment in one and other violations (chronic idiopathic intestinal pseudo-obstructive syndrome as pre-existing disease) also in one patient. Three of these 5 patients were also identified as ineligible for the study. A summary of treatment is presented in Fig. 1. Of the 40 eligible patients, 17 were subsequently randomized to additional treatment with surgery (9 patients) or radiotherapy (8 patients) according to EORTC protocol 08941. At the request of one participating centre, the 11 patients it included were not randomized.
3.3. Haematologic and non-haematologic toxicity

Grade 3/4 neutropenia was observed in 65.2% of the patients (Table 2). A total of 8 patients (17.4%) experienced febrile neutropenia. No grade 3/4 anaemia or thrombocytopenia was encountered.

Treatment related non-haematologic toxicity grade 3/4 (Table 3) was observed in only a minority of patients and consisted mainly of nausea (17.4% of patients), vomiting (13.0%), fatigue (8.7%), anorexia (6.5%). Grade 3/4 sensory neuropathy and other neurotoxicity occurred in 2.2% of the patients. One patient experienced a grade 4 hypersensitivity reaction during first cycle docetaxel infusion, and further treatment was stopped. In addition, one patient stopped treatment after experiencing a grade 4 rash and another due to grade 4 vomiting.

There were 2 toxic deaths: one patient died of pneumonia complicated by grade 4 neutropenia and sepsis after cycle 1. The second patient completed 2 cycles of chemotherapy but refused further chemotherapeutic treatment due to toxicity. He received additional radiotherapy and died due to radiation pneumonitis. Seven patients died of other not tumour-related reasons: cardiovascular disease (1), infection not due to protocol treatment (1), pulmonary embolism (2), acute cardiac failure (1), cachexia (1), and sepsis (1).

3.4. Response to induction chemotherapy and additional treatment

In total, CT-scans of 24 patients were reviewed, including 4 patients reported by the principal investigators to have no response and one reported not evaluable for response. Among the 40 eligible patients, six were not evaluable for response because of early treatment discontinuation due to toxicity (5 patients) or missing baseline measurements (1 patient). Overall response rate for the 40 eligible patients who started protocol treatment was 45.0% (95% CI: 29.3–61.5%). Of 18 responding patients, one reached a complete response (CR), while 17 patients demonstrated a partial response. In addition 14 patients (35.0%) had stable disease. Progressive disease was observed in one patient and early death due to toxicity for another one. Of the 35 eligible patients who received at least 2 cycles of chemotherapy, the response rate was 51.4% (95% CI, 34.0–68.6).

3.5. Survival

At the time of this analysis, after a median follow-up period of 27 months, 36 patients (78.3%) had died. In 27 cases (75.0%)
death was related to malignant disease. The median duration of overall survival was 15.8 months (95% CI: 12.2–20.8 months). The estimated 1-year survival rate was 64.5% (95% CI: 50.6–78.5%). The survival curve is depicted in Fig. 2.

4. Discussion

This study reports the activity of a docetaxel-cisplatin induction chemotherapy combination in a multicentre homogeneous population of proven stage IIIA-N2 NSCLC. This trial was the third and last of a series of phase II studies using new chemotherapy combinations within the setting of a recently finished randomised phase III trial in patients with stage IIIA N2 disease (EORTC 08941). Our goal was to select a docetaxel-cisplatin combination for further studies if a true response rate of 75% or more was achieved and to reject the combination for further investigation in this patient group if a true response rate of 55% or less was observed. We observed a response rate of 45% among eligible patients with a medium survival of 15.8 months if all included patients were considered. Similar phase II studies in a similar population were conducted by the EORTC Lung Cancer Group with gemcitabine-cisplatin and paclitaxel-carboplatin (Table 4). Based on similar entry criteria, the EORTC study 08955 study, using gemcitabine (1000 mg/m² days 1, 8 and 15) and cisplatin (100 mg/m² day 2) every 4 weeks, showed a response rate of 70.2% (95% CI 55.1%–82.7%), while the paclitaxel (200 mg/m² day 1) and carboplatin (area under the concentration curve of 6) regimen administered every 3 weeks (EORTC 08958) resulted in a response rate of 64% (95% CI 49%–76%).

Table 2 – Haematologic toxicity

<table>
<thead>
<tr>
<th>Haematologic Toxicity – Worst grade over all cycles</th>
<th>Nadir (NCI-CTC)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Grade 0</td>
</tr>
<tr>
<td></td>
<td>No. of Patients</td>
</tr>
<tr>
<td>Leukocytes*</td>
<td>7</td>
</tr>
<tr>
<td>Neutrophils*</td>
<td>7</td>
</tr>
<tr>
<td>Thrombocytes*</td>
<td>40</td>
</tr>
<tr>
<td>Hemoglobin*</td>
<td>23</td>
</tr>
</tbody>
</table>

All registered patients (N = 46).
* No lab values available in 1 patient.

Table 3 – Non-haematologic toxicity (main related adverse events)

<table>
<thead>
<tr>
<th>Number of patients with non-haematologic toxicities* – Worst grade over all cycles</th>
<th>NCI-CTC Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
</tr>
<tr>
<td>Nausea</td>
<td>7</td>
</tr>
<tr>
<td>Vomiting</td>
<td>18</td>
</tr>
<tr>
<td>Headache</td>
<td>45</td>
</tr>
<tr>
<td>Sensory neuropathy</td>
<td>34</td>
</tr>
<tr>
<td>Other neurotoxicity*</td>
<td>40</td>
</tr>
<tr>
<td>Alopecia</td>
<td>15</td>
</tr>
<tr>
<td>Fatigue</td>
<td>19</td>
</tr>
<tr>
<td>Anorexia</td>
<td>24</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>38</td>
</tr>
<tr>
<td>Fever without neutropenia</td>
<td>42</td>
</tr>
<tr>
<td>Infection</td>
<td>43</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>27</td>
</tr>
<tr>
<td>Constipation</td>
<td>41</td>
</tr>
<tr>
<td>Hemorrhage (without G3-4 thrombopenia)</td>
<td>44</td>
</tr>
<tr>
<td>Edema</td>
<td>38</td>
</tr>
<tr>
<td>Hypotension</td>
<td>43</td>
</tr>
<tr>
<td>Trombosis/embolism</td>
<td>45</td>
</tr>
<tr>
<td>Shortness of breath</td>
<td>46</td>
</tr>
<tr>
<td>Stomatitis/Pharyngitis</td>
<td>30</td>
</tr>
<tr>
<td>Skin (rash/desquamation)</td>
<td>36</td>
</tr>
</tbody>
</table>

All registered patients (N = 46).
Toxic deaths (2): febrile neutropenia (1), pneumonia (1).
* Main related adverse events.
** Other neurotoxicity excludes constipation, headache, and sensory neurotoxicity.
comparison to those results, the activity observed in this trial (45%; 95% CI, 29.3–61.5) appears moderate. Examination of patients’ characteristics of the three studies shows that, in the EORTC 08955 study, more patients with PS 0 (60%) and slightly less patients with T3N2 tumours (9%) were included compared to the present study. No difference was apparent between the patient characteristics in the EORTC 08958 study and this study. The median survival of this study (15.8 months) was also lower than in the EORTC 08955 study (18.9 months) and the EORTC 08958 study (20.5 months). In our study, 6 (13%) ineligible patients were entered, while in the EORTC 08955 and 08955 study 9% and 11% of the patients were ineligible, respectively. In the Swiss study, one patient (1%) was ineligible. As ineligible patients were included in the survival analysis, this may have affected the outcome. However, both survival results and a comparison of these survival data should be interpreted carefully as they are based on three single-arm phase II studies, each comprised of a limited number of patients.

The combination also appears less active than a recently published schedule examined by Dr Betticher which demonstrated a response rate for docetaxel (85 mg/m² day 1) and cisplatin (40 mg/m² days 1 and 2) of 66% (95% CI 55%–75%) if administered every 3 weeks for a total of 3 cycles.25 With 15.8 months, the median survival in the present study appears inferior to the one observed in the Swiss study (27.6 months). In the Swiss study, the cisplatin dose was increased to 50 mg/m² days 1 and 2, as Betticher and colleagues observed a high response rate and low toxicity in the first 36 patients. The difference in achieved response rates can not be attributed to the higher cisplatin dose used after the first 36 patients, as the response rate in the first 36 patients in the Swiss trial was also 66%.20 However, several possible explanations apply for the observed discrepancy in activity. Patient characteristics at study entry, among which some of prognostic significance, were different in both studies and can help to explain the different study outcome. In the present series, 35% of the patients had PS 0, compared to 59% in the Swiss study. In contrast, a higher percentage T3 tumours was included in the Swiss study. Recently, several authors have advocated a sub-classification of N2-disease based on preoperative staging and/or the number of involved mediastinal lymph nodes.26–28 Based on the available information one can only speculate that this may explain the observed difference in response rate. Of note, disease control (complete response [CR], partial response [PR] and stable disease [SD]) appeared similar in our study and the studies discussed.10,11,25 Regarding overall survival, results might also have been influenced by the different prognosis of the patients registered.

The observed toxicities are comparable in both series and compare favourably with the toxicities observed in the studies where docetaxel and cisplatin were given on the same day.29,30 In the Swiss study, increasing the cisplatin dose, did not affect cisplatin-related toxicity. Haematological toxicity mainly consisted of grade 3/4 neutropenia, with 8 patients experiencing febrile neutropenic event and one toxic death. The frequency of grade 3/4 neutropenia was similar to that in the Swiss study. Dr Betticher and colleagues, however, reported no febrile neutropenic events.
In conclusion, the present study shows that in stage IIIA-N2 NSCLC patients, docetaxel-cisplatin can be administered, to demonstrate manageable toxicity and modest efficacy. Efficacy was modest compared to other regimens investigated by the EORTC LCG and the same regimen investigated by others in this patient group and, furthermore, did not meet the criteria set up by our statistical design. In comparison with the other EORTC trials and the study published by Dr Betticher and colleagues, this study demonstrated no differences with regard to the patient characteristics. The outcome of this study, we feel can be considered intrinsic to the chemotherapy combination used, and is not likely to be due to patient selection.

Conflict of interest statement

B. Biesma, C. Manegold, H.J.M. Smit, L. Willems, C. Legrand, A. Passioukov, J.P. van Meerbeeck and G. Giaccone, hereby declare not to be engaged in any financial or personal relationships with other people or organisations that could inappropriately influence their work.

Acknowledgement

This publication was supported by grant(s) number SU10CA11488-29 through SU10CA11488-35 from the National Cancer Institute (Bethesda, Maryland, USA). Its contents are solely the responsibility of the authors and do not necessarily represent the official views of the National Cancer Institute.

We are grateful to Aventis Pharmaceuticals, part of the sanofi-aventis group, for the financial support they provided to this study.

The authors would like to acknowledge the contribution to patient accrual of the following investigators: Dr. Stigl (Isala Klinieken, Zwolle - NL); Dr O’Byrne (Royal Infirmary, Leicester - UK; now at St James’s Hospital, Dublin - IE); Dr Ardizzoni (Istituto Nazionale per la Ricerca sul Cancro, Genova - IT; now at Azienda Ospedaliera Di Parma, Parma - IT); Dr. van Zandwijk (A. van Leeuwenhoek Ziekenhuis, Amsterdam - NL).

The authors would also like to thank Sonia Dussenne of the EORTC Data Centre for data management. This work was presented in part at the 40th Annual Meeting of the American Society of Clinical Oncology, New Orleans, Louisiana, USA, June 2004.

REFERENCES


