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Carboplatin and paclitaxel (Taxol) as an induction regimen for patients with biopsy-proven stage IIIA N2 non-small cell lung cancer: an EORTC phase II study (EORTC 08958)☆

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Abstract

The aim of this study was to document the activity and toxicity of paclitaxel (Taxol)/carboplatin when used as induction chemotherapy in patients with stage IIIA N2 non-small cell lung cancer (NSCLC) prior to definitive local treatment within a large, ongoing comparative study (EORTC 08941). 52 eligible, consenting, chemotherapy-naïve patients with NSCLC, median age of 60 years, stage IIIA N2 disease and the ability to tolerate a pneumonectomy received paclitaxel 200 mg/m^2 as a 3-h infusion followed by carboplatin at an area under the concentration curve (AUC) of 6 every 3 weeks for three courses. Most patients received three courses. No grade 3/4 anaemia or thrombocytopenia was documented. Over all of the cycles, 6% (3 patients) experienced grade 3 leucopenia while 63% (32/51 patients) experienced grade 3-4 neutropenia. There was 1 patient (2%) with febrile neutropenia, no early or toxic deaths and no hypersensitivity reactions. Severe non-haematological toxicity was uncommon, with the exception of grade 3 alopecia in 39%, lethargy in 8% and myalgia in 6%. Of the eligible patients ($n=52$), there was one complete response (CR) and 32 partial responses (PR), resulting in a response rate of 64% (95% Confidence Interval (CI) 49%–76%). Of the 15 eligible patients randomised to surgery after induction chemotherapy, 3 patients did not receive surgery and 2 patients ($n=12$) had no tumour in the mediastinal nodes (17%). Resections were considered complete in 2 of the 12. Median survival for all eligible patients ($n=52$) was 20.5 months (95% CI 16.1–31.2), with an estimated 1-year survival rate of 68.5% (95% CI 55.2–81.7). In patients with N2 stage IIIA NSCLC, paclitaxel/carboplatin is an active and very well-tolerated induction regimen.

1. Introduction

Stage IIIA non-small cell lung cancer is in general treated with a combination of chemotherapy and radical radiotherapy. This management plan has evolved from the results of the meta-analysis on the use of initial radical radiotherapy followed by chemotherapy or no chemotherapy. In 3033 patients with stage IIIA disease, an improvement of 4% (95% Confidence Interval (CI) 1–7%) in overall survival was found in the combined arm [1]. A number of more recent trials have addressed this in another way, comparing chemotherapy followed by radical radiotherapy to radical radiotherapy alone and again the combined approach is superior with an

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11% improved survival at 5 years being observed with the combined approach [2].

Interesting results have been reported with the use of chemotherapy followed by surgery compared with surgery alone. Although these studies are aimed at patients with early-stage, operable disease, stage IIIA patients have been included. Two small phase III trials reported in 1994 sparked interest in this approach, as they both demonstrated a significant improvement in overall survival with the use of neoadjuvant chemotherapy [3,4]. In the trial in the USA, 60 patients were randomised to either three courses of pre-operative cyclophosphamide, etoposide and cisplatin followed by surgery and then a further three courses of chemotherapy ($n=28$), or to surgery alone ($n=32$). All patients with incompletely resected disease received additional radiotherapy. Overall response to pre-operative chemotherapy was 35%. There was a significant improvement in median survival with rates of 64 months and 11 months, respectively ($P<0.008$) and a 3-year overall survival (OS) rates of 56 and 15%, respectively. This increase in OS was maintained in a later analysis with a median follow-up of 82 months [5].

A group at Barcelona University published a similar trial, which again was ended prematurely because of significant results. 60 patients were randomised between three courses of pre-operative mitomycin-C, ifosfamide and cisplatin or surgical intervention alone. In this trial, all patients received postoperative radiotherapy. The median OS rates were 26 and 8 months ($P<0.001$) with a median disease-free survival (DFS) of 20 and 5 months, respectively ($P<0.001$). An update of the trial published in 1999 demonstrated that this survival difference was maintained, with a median OS of 22 and 10 months, respectively ($P=0.005$) [6].

The most recent data on this approach have been from the French study which included 47% (167/355) of patients with stage IIIA disease [7]. They describe an increase in overall 3-year survival of 8.6% using a combination of mitomycin, ifosfamide and cisplatin before and after surgery compared with surgery alone. In a subgroup analysis, this was statistically significant in stages I and II only. There was an increased risk of postoperative infection, but not of pneumonitis, and overall, no statistical difference in toxicity between the two treatment arms.

Thoracic surgeons have also been making progress and now perform more radical mediastinal lymphadenectomies. In addition, the combination of improved surgical technique with better supportive pre- and postoperative care is gradually decreasing the operative mortality rate. The question of what the best local treatment for stage IIIA NSCLC is, is therefore still an open question between radical radiotherapy and surgery and is the prime aim of the European Organization for Research and Treatment of Cancer (EORTC) trial 08941.

The advent of new agents (gemcitabine, paclitaxel, vinorelbine and docetaxel) in the treatment of lung cancer has brought with it the hope of greater activity of drugs in this disease which will lead to a downstaging of bulky tumours to enable an improved chance of complete resection or smaller radiotherapy volumes, an independent truly adjuvant and neoadjuvant activity and a decrease in operative complications such as pneumonitis, fistulae and infection.

Paclitaxel is a novel cytotoxic agent whose major activity is to promote microtubule assembly and render microtubules resistant to depolymerisation. The main toxicities of paclitaxel are alopecia, neutropenia, arthralgia/myalgia and sensory peripheral neuropathy. Paclitaxel is usually given as a 3-h infusion or as a 24-h infusion with steroid and antihistamine premedication every 3 weeks.

The choice of dose of paclitaxel (200 mg/m^2/3 h) in combination with carboplatin (area under the concentration curve (AUC) 6) every 3 weeks was based on the results of seven phase I/II studies of this combination in NSCLC patients with stage IIIB and IV disease [8]. At the optimal dose level recommended by the authors for phase II studies of paclitaxel 175–200 mg/m^2 and a carboplatin dose targeted at an AUC of 6 or 7, response rates of 40–60% and a 1-year survival rate of 40% were observed in almost all of the studies in NSCLC, with a manageable toxicity profile.

The early suggestions of an increased efficacy for the paclitaxel/carboplatin combination prompted the EORTC Lung Cancer Group to initiate a phase II trial to better define the toxicity and activity of this combination as an induction regimen for patients with stage IIIA NSCLC. This trial was the second of a series of phase II studies using new chemotherapy combinations in patients with stage IIIA N2 disease prior to randomisation to surgery or radical radiotherapy (EORTC 08941).

2. Patients and methods

2.1. Study design and statistical considerations

The primary aim of this phase II study was to assess the antitumour activity and toxicity of carboplatin combined with paclitaxel as induction treatment for patients with stage IIIA N2 NSCLC. This study was designed according to the Simon's two-stage design (optimum) [9]. The objective was to select this induction treatment for further study if the response rate was 50% or more and to reject it if the response rate was 30% or less. The type 1 error was set to 0.2, while the power was set to 95%. The overall survival time was estimated using the Kaplan–Meier technique [10]. All results presented are based on eligible patients.

2.2. Patient selection

Eligibility criteria for study entry included the following: clinical stage IIIA NSCLC with pathology proof of positive N2 nodes judged as irresectable by the local thoracic surgeon and multidisciplinary team, presence of at least one bidimensionally measurable target lesion of the primary tumour of at least 2.0 cm in its largest diameter and/or mediastinal lymph nodes of at least 2.5 cm in their largest diameter and an adequate baseline organ function defined as an absolute neutrophil count (ANC) of at least 1.5×10^9/l, liver, cardiac and renal function within normal limits. Additionally, the multidisciplinary team had to evaluate the patient as being physically and mentally fit to receive all protocol treatment with spirometric values allowing pneumonectomy.

Patients who had received previous chemotherapy, radiotherapy, or had an active infection were excluded from the study. Written informed consent had to be obtained from all patients and documented according to national regulatory requirements and to the local institution rules. In the course of the trial, we discovered that informed consent could not be documented for 18 patients (32%) who were included in the trial. Although we could not retrieve the documentation of informed consent, all of these patients were checked using other source data. For all of these patients, the responsible investigator has stated that he/she fully informed the patient orally on all aspects of the trial and certifies that each patient agreed to participate in the trial. The study was approved by the EORTC Protocol Review Committee (PRC) and by the ethics committees of the participating centres.

2.3. Treatment plan

Paclitaxel was given prior to carboplatin at a dose of 200 mg/m^2 as a 3-h infusion in 500 ml of normal saline or 5% dextrose/water solution. Premedication prior to paclitaxel treatment was given consisting of dexamethasone 20 mg orally (p.o.) (12 and 6 h prior to the start of the paclitaxel infusion), diphenhydramine 50 mg intravenously (30 min prior to the infusion) and cimetidine 300 mg i.v. (30 min prior to the infusion). Carboplatin was administered as a 30-min i.v. infusion in 500 ml of normal saline. The dose was calculated according to the Calvert formula [11] with an AUC of 6 using a calculated glomerular filtration rate from the Cockroft–Gault formula [12]. Both drugs were given on day 1 of a 21-day treatment cycle.

2.4. Dose delay and modifications

Each chemotherapy cycle could only start if the ANC and platelet counts on the day of treatment were $\geqslant1.5\times10^9$/l and $\geqslant100\times10^9$/l, respectively. Treatment was delayed until this level was achieved and if the delay was greater than 2 weeks the patient was taken off the treatment.

Chemotherapy was administered at 75% of the planned dose in the event of (a) ANC $<0.5\times10^9$/l and/or platelets $<50\times10^9$/l for two consecutive counts 1 week apart or (b) febrile neutropenia or (c) severe bleeding. In cases of recurrent toxicity after dose modification, patients were taken off the treatment.

Patients came off study for grade III or IV neurotoxicity or symptomatic arrhythmia or AV block and received a 75% dose of paclitaxel for grade II neurotoxicity. Three cycles of chemotherapy were administered unless progressive disease or intolerable toxicity was recorded.

2.5. Patient evaluation

A complete history, physical examination, complete blood cell count with differential, serum biochemistry, spirometry, bronchoscopy, computed tomography (CT) scan of the chest and upper abdomen, and electrocardiogram (ECG) were obtained at baseline. Patients were monitored throughout treatment by recording their history of toxic events, and complete blood cell counts with differential (weekly). Serum chemistry determinations were repeated just before the start of each chemotherapy cycle. All toxicities were coded according the National Cancer Institute of Canada-Common Toxicity Criteria (NCIC-CTC).

Tumour response was evaluated by CT scan after three cycles of treatment. CT examinations of responders were reviewed by a panel of two independent radiologists, the study chairman and the responsible physician. A complete response (CR) was defined as the complete disappearance of all abnormalities on the CT scan. A partial response (PR) was defined as a reduction of more than 50% in the sum of the products of two perpendicular diameters of the primary tumour and hilar and mediastinal nodes (if enlarged). Stable disease was defined as a less than 50% reduction or a less than 25% increase in the sum of the products of two perpendicular diameters per site. Patients with responsive disease were eligible for the second part of the trial if they agreed to be randomised to thoracic surgery or radical radiotherapy (ongoing trial EORTC 08941) and were judged resectable by the local surgeon and multidisciplinary team. Repeated mediastinoscopy/tomy was not required in the post-chemotherapy evaluation. The combined-modality approach of this study did not allow the formal 4-week confirmation of response to chemotherapy alone according to World Health Organization (WHO) criteria. 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 [10].

3. Results

3.1. Patient characteristics

From March 1997 to September 1998, 57 patients were enrolled onto the study. 5 patients were ineligible (9%): 2 patients had stage IIIB disease (T4 tumours) and 1 patient had <2.0 cm assessable disease on baseline scan. One patient had no baseline CT and 1 patient had metastatic disease at diagnosis and never received treatment. The characteristics of the 52 eligible patients are listed in Table 1 and included a median age of 60 years (range 37–75 years), WHO performance status of 0 in 37% of the patients, and squamous cell carcinoma as the predominant histological subtype (44%). All patients had N2 disease—2 cases had vocal cord paralysis, which was considered as clinical proof of N2 disease. Mediastinal lymph node involvement was confirmed by mediastinoscopy/thoracotomy (42 cases) or needle biopsy/aspiration cytology (8 cases).

3.2. Haematological toxicity

During treatment with paclitaxel/carboplatin, grade 3/4 neutropenia was observed in 63% of the patients. Only 1 patient (2%) had febrile neutropenia (grade 3). No grade 3/4 anaemias or thrombocytopenias were seen (Table 2). There were no early or toxic deaths.

Table 1
Patients' characteristics

	N (*N* = 52)	(%)
Eligibility		
Ineligible	5	(9)
Eligible	52	(91)
Gender		
Male	35	(67)
Female	17	(33)
Age (years)		
Median (range)	60	(37–75)
WHO Performance Status		
0	19	(37)
1	32	(62)
2	1	(2)
TNM staging		
T1N2M0	7	(14)
T2N2M0	35	(67)
T3N2M0	10	(19)
Histology		
Squamous	23	(44)
Adenocarcinoma	12	(23)
Large cell	16	(31)
Other	1	(2)

WHO, World Health Organization.

3.3. Non-haematological toxicity

Grade 3/4 toxicity was uncommon apart from alopecia (39%), lethargy (8%) and myalgia (6%). The following grade 3/4 non-haematological toxicities occurred only in 2–4% of the cases: arthralgia, anorexia, nausea, vomiting, motor neurotoxicity, sensory neurotoxicity, shortness of breath and a skin rash. There were no hypersensitivity reactions. Grade 1/2 sensory neuropathy occurred in 71% of patients (Table 3).

3.4. Dose intensity

94% of the eligible patients received all three cycles as planned by the protocol. The only reason to stop treatment early (6%) was progression of disease. The median delivered relative dose intensity was 99.6% (range 83.3–105.6%) for paclitaxel and 100% (range 80–130.5%) for carboplatin. Severe protocol violations in terms of dosage were recorded in 4 patients, all due to miscalculation of the carboplatin dosage (one overdosage to 130.5% and 3 patients received too low a dose).

Table 2
Haematological toxicity over all cycles (*N* = 52)

	NCIC CTC grade				
	0 (%)	1 (%)	2 (%)	3 (%)	4 (%)
Leucocytes	6 (12)	21 (40)	22 (42)	3 (6)	–
Neutrophils[a]	8 (15)	3 (6)	8 (15)	19 (37)	13 (25)
Thrombocytes	47 (90)	4 (8)	1 (2)	–	–
Haemoglobin	32 (62)	18 (35)	2 (4)	–	–

NCIC CTC, National Cancer Institute of Canada Common Toxicity Criteria.
[a] For 1 patient, no granulocyte count was done.

Table 3
Non-haematological grade III/IV toxicities over all cycles (*N* = 52)

	NCIC CTC grade				
	0 (%)	1 (%)	2 (%)	3 (%)	4 (%)
Arthralgia (joint pain)	33 (63)	9 (17)	8 (15)	2 (4)	–
Lethargy (fatigue, malaise)	14 (27)	21 (40)	13 (25)	4 (8)	–
Myalgia	25 (48)	16 (31)	8 (15)	3 (6)	–
Anorexia	36 (69)	14 (27)	1 (2)	1 (2)	–
Nausea	25 (48)	15 (29)	11 (21)	1 (2)	–
Vomiting	38 (73)	8 (15)	5 (10)	1 (2)	–
Febrile neutropenia	51 (98)	–	–	1 (2)	–
Motor neurotoxicity	50 (96)	1 (2)	–	1 (2)	–
Sensory neurotoxicity	13 (25)	29 (56)	8 (15)	2 (4)	–
Shortness of breath (wheezing)	35 (67)	11 (21)	5 (10)	1 (2)	–
Alopecia[a]	2 (4)	2 (4)	27 (53)	20 (39)	–
Other skin toxicity	42 (81)	8 (15)	1 (2)	1 (2)	–

[a] Data missing for 1 patient.

3.5. Response to induction therapy and additional treatment

It was foreseen in the protocol that the CT scans of all responders would be reviewed retrospectively by an independent panel of radiologists. Out of the 33 eligible patients reported as having a clinical response, 28 patients were reviewed and the response was confirmed. For the 5 remaining patients, logistical problems occurred which meant not all of the CT scans were available for the review. These responses were nevertheless accepted and included as having a clinical response. Of the 52 eligible patients, 33 patients responded (one CR and 32 PRs), for an overall response rate of 64% (95% CI 49%–76%). In addition, there were 10 patients with no change (NC) (19%) and 9 with progressive disease (PD) (17%) (Table 4). Among the total group (eligible and ineligible), the response rate was 58%, with 21% NC and 16% with PD ($n=57$).

Of the 52 eligible patients, a total of 35 patients were randomised according to the protocol (EORTC 08941) to additional surgery ($n=15$) or radiotherapy ($n=20$). The main reason for not randomising was insufficient response (SD or PD). From the 15 patients randomised in the surgery arm, 3 did not undergo surgery. Of the remaining 12 patients, 2 patients (17%) had no mediastinal node involvement—this data will be included in a later report on the results of the EORTC 08941 trial.

3.6. Survival

At the time of this analysis, after a median follow-up period of 25.8 months, 28 of the 52 patients have died (54%). In 23 cases (82%), the deaths were related to a malignant diagnosis. 2 patients died due to infection during second-line treatment. One patient died from a cardiovascular cause. In another case, pulmonary hypertension occurred 5 days postsurgery and the patient died, and in the last case the cause was unknown. The median duration of survival was 20.5 months (95% CI 16.1–31.2 months), and the estimated 1-year survival rate was 68.5% (95% CI 55.2%–81.7%).

Table 4
Best response to treatment in eligible patient population ($N=52$)

	Total ($N=52$) N (%)
CR	1 (2)
PR	32 (62)
NC	10 (19)
PD	9 (17)
Number of responders	33
% (95% CI)	64 (49–76)

CR, Complete Response; PR, Partial Response; NC, No Change; PD, Progressive Disease; CI, Confidence Interval.

4. Discussion

The combination of carboplatin and paclitaxel has become one of the standard palliative chemotherapy treatments for NSCLC because of the convenience of the administration (i.e. on an outpatient basis, every 3 weeks) and the acceptable toxicity profile. Paclitaxel in combination with cisplatin has been tested in a number of phase III trials. The Eastern Cooperative Oncology Group (ECOG) study compared two doses paclitaxel (250 and 135 mg/m^2) with cisplatin with etoposide/cisplatin [13]. Both paclitaxel/cisplatin doses resulted in similar response rates, which were higher than those in the etoposide/cisplatin arm (32% versus 27% versus 12%). Hence, the two paclitaxel/cisplatin arms were combined for the survival analysis. The median survival was extended by approximately 2 months (10 and 9.6 versus 7.7 months, $P=0.048$) in the paclitaxel/cisplatin arms with an improvement in the 1-year survival rates (39 and 37% versus 32%). The EORTC performed a two arm study comparing cisplatin/paclitaxel to cisplatin/tenoposide and although the overall response rate was higher (36% v 25%, $P=0.03$) with the paclitaxel treatment, there was no survival difference between the two treatments. Quality of life (QoL) was superior in the paclitaxel arm at 6 weeks, but not at 12 weeks [14].

The results of trials using paclitaxel and carboplatin are only just starting to appear in the literature. In the most recent study by the South Western Oncology Group (SWOG) (9509), vinorelbine with cisplatin and paclitaxel (225 mg/m^2) combined with carboplatin (AUC 6) were compared in a randomised phase III trial. The objective response rate and median survival time were the same in both arms (27% and 8 months): and the 1-year survival rates were also similar (36% compared with 38% (non-significant (NS))). QoL was similar, with approximately 60% of patients having improved or stable QoL scores in both arms of the study. However, the cost of treatment with paclitaxel/carboplatin is several-fold higher than that of vinorelbine/cisplatin [15,16].

A four-arm study including 1207 patients has compared four of the most frequently used platinum doublets in the treatment of NSCLC [17]. The primary endpoint was survival. There were no formal QoL assessments or cost comparisons. Initially patients with PS 0, 1 and 2 were included. However, the poor outcome and toxicity in the PS 2 group resulted in this group being excluded from the trial. The four treatments compared were cisplatin/paclitaxel, cisplatin/gemcitabine, carboplatin/paclitaxel and cisplatin/docetaxel. The response rates were of the order of 20% and median survivals were the same at around 8 months and the percentage alive at 1 year was 31–36%. Although the response rate (15.3%) and time to progression (3.3 months) were lowest for carboplatin/paclitaxel, this was

not statistically significant and median and 1-year survival rates were as good as with the other three regimens. Of the patients treated with carboplatin and paclitaxel, 53% were withdrawn because of disease progression compared with 44% of the patients who received cisplatin and paclitaxel ($P < 0.001$). The carboplatin and paclitaxel doublet was less emetogenic and associated with a low incidence of febrile neutropenia (4%).

The combination of carboplatin/paclitaxel is the regimen of choice for the large United States (US) neoadjuvant trial in NSCLC (SWOG 9900). This follows on from the phase II study using the same regimen carried out by the Bimodality Lung Oncology Team (BLOT). In this study, two cohorts of patients were described; the first ($n = 94$) group of patients were treated with two courses of carboplatin/paclitaxel before surgery and 3 courses after surgery and in the second cohort ($n = 40$) patients received three courses of chemotherapy before and two after surgery. The patients all had operable lung cancer stage IB-IIIA and all had a negative mediastinoscopy. The response rate was 56% in cohort I and 38% in cohort II, with no difference in overall survival between the two groups and with 63% alive at 3 years [18]. This series of patients and others at the same centre ($n = 380$), treated with the same chemotherapy regimen, have been extensively studied and compared with other patients treated with surgery alone, focusing particularly on operative morbidity. The conclusion was that this treatment did not result in increased toxicity [19]. A different centre has described a different experience with this regimen in the preoperative setting. Roberts and colleagues described 34 patients who underwent chemotherapy with carboplatin/paclitaxel prior to surgery and compared them with 67 matched patients who underwent surgery alone. Life-threatening complications occurred in 26.5% of those treated with chemotherapy compared with 6% of those patients who had surgery alone [20].

There are other neoadjuvant studies being carried out, none of which include stage IIIA patients with positive mediastinoscopy, and all will be completed over the next 2–3 years. The current Spanish neoadjuvant trial is a three arm trial which also uses carboplatin/paclitaxel as the chemotherapy treatment. This study compares surgery alone to neoadjuvant chemotherapy followed by surgery or to surgery followed by adjuvant carboplatin/paclitaxel. A number of biological parameters have been included in the design of this study. The use of neoadjuvant chemotherapy followed by surgery allows us to obtain more tissue from lung cancers than has been previously possible and with this, the possibility of studying factors that may become prognostic factors or are related to the natural history and response of this disease to a number of treatment modalities.

Gemcitabine/cisplatin was selected as the first combination to be tested and reported by the EORTC in the context of the 08955 trial [21]. The results of this study, in which almost 60% of patients had grade 3/4 thrombocytopenia, are in line with previous studies reporting on gemcitabine. The thrombocytopenia was not associated with an increase in bleeding events. The response rate, median and 1-year survival produced by three courses of gemcitabine/cisplatin appears similar to that with paclitaxel/carboplatin.

We therefore feel the combination of carboplatin and paclitaxel is an active and well tolerated regimen and deserves more study in the neoadjuvant setting.

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