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Paclitaxel, Carboplatin and Gemcitabine Combination as Induction Chemotherapy for Stage IIIA N2 Bulky Non-Small Cell Lung Cancer

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Key Words

Lung cancer · Paclitaxel · Carboplatin, stage III · Chemotherapy

Abstract

Background: Induction chemotherapy followed by surgical resection or definitive radiotherapy for patients affected by stage IIIA N2 bulky non-small cell lung cancer (NSCLC) has been investigated in several trials. **Patients and Methods:** In this present study, 52 patients with stage IIIA N2 bulky NSCLC with cytologically or histologically confirmed mediastinal lymph node involvement received paclitaxel 175 mg/mq on day 1, carboplatin AUC 5 on day 1 and gemcitabine 1,000 mg/mq on day 1 and 8 every 3 weeks for three cycles as induction chemotherapy. **Results:** Objective response (4 complete remission and 36 partial remission) was achieved in 40/52 patients. No early or toxic deaths were observed. Twenty-two patients were surgically explored. Fifteen were excluded for resection for biopsy-proven residual tumour in mediastinal nodes. Complete surgical resection was performed in 15 patients with confirmed pathological downstaging. Pathological complete response

was achieved in 4 patients. No surgery-related mortality or significant morbidity was reported. Adjuvant radiotherapy was delivered in 15 patients, and 30 patients received definitive radiotherapy. **Conclusion:** In the present study, the combination of paclitaxel, carboplatin and gemcitabine has been a safe and active regimen in poor-prognosis stage IIIA N2 bulky NSCLC.

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Introduction

Lung cancer is the leading cause of death worldwide [1]. Non-small cell lung cancer (NSCLC) is locally advanced stage III in one third of patients at diagnosis. Single modality therapy, with either surgery or radiotherapy alone, is curative for only a small minority of patients who present stage III. After initial therapy, a majority of patients suffers disease recurrence. Relapses are local in one third and distant in two third of patients. Therefore, one important stage of the therapeutic strategy is the use of chemotherapy in addition to local treatment in the management of locally advanced NSCLC. A number of phase II–III trials have investigated the use of induction chemo-

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therapy followed by surgical resection in patients with N2 disease [2–9]. The data from these studies support the role of pre-operative chemotherapy in improving resectability and survival over surgery in stage IIIA N2.

The combination of paclitaxel and carboplatin is actually one of the common regimes used as induction chemotherapy for NSCLC. New triplet chemotherapy combinations are under investigation. The present study was designed to assess the efficacy and safety profile of paclitaxel, carboplatin and gemcitabine combination as induction chemotherapy for stage IIIA N2 bulky NSCLC. The primary endpoint of this study was objective radiological response. Secondary endpoints were survival, toxicity and safety of chemotherapy.

Patients and Methods

Patient Eligibility

Eligibility criteria were clinical stage IIIA NSCLC with pathologically documented N2 and locally unresectable disease. Mediastinal lymph nodes >2.0 cm in short-axis diameter at CT scan and measurable disease were required, as well as an age between 18 and 75 years and an Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2 . Preserved haematologic and renal functions were also required. No previous cancer, arrhythmias or cardiac insufficiency >2 (New York Heart Association Scale) were admitted.

Further exclusion criteria were pregnancy and inadequate contraceptive precautions. All patients were required to provide written informed consent prior to initiation of treatment.

Study Design

This study was designed according to Simon's two-stage design [10]. The primary aim was to assess the efficacy of paclitaxel, carboplatin and gemcitabine combination as induction treatment for patients with stage IIIA N2 bulky NSCLC. If the response rate was $\geq 50\%$, this induction chemotherapy was used in further patients. Baseline evaluation included complete history and physical examination, CT scan of brain, chest and upper abdomen, radionuclide bone scan, fibre-optic bronchoscopy with bronchoaspirate and/or brushing and/or bronchial biopsy, complete blood cell count and serum chemistry analysis. Transbronchial needle aspiration (TBNA) and/or mediastinoscopy was routinely performed. All pre-treatment imaging procedures were performed within 4 weeks from study entry. Tumour response was assessed with CT scan after three cycles according to WHO criteria. TBNA or mediastinoscopy was repeated in patients with no progressive disease, since chest CT scan is not accurate enough to predict pathological response in mediastinal lymph nodes. Patients without pathologically documented residual mediastinal disease were eligible for surgery. On the contrary, patients with pathologically (mediastinoscopy/TBNA/thoracotomy) documented disease in the mediastinal nodes received definitive radiotherapy. The combined modality therapy of this study (chemotherapy and surgery and/or radiotherapy) did not allow the formal 4-week confirmation of response to chemotherapy. Positron emission tomography was permitted, but not routinely

performed. All toxicities were coded according to the National Cancer Institute Bethesda Common Toxicity Criteria [11]. The overall survival was estimated using the Kaplan-Meier technique [12].

Treatment

Patients received paclitaxel 175 mg/mq on day 1, the carboplatin AUC 5 on day 1 and gemcitabine 1,000 mg/mq on day 1 and 8, every 3 weeks for three cycles. Paclitaxel infusion preceded carboplatin. Gemcitabine was infused after carboplatin infusion on day 1. All patients were pre-medicated with dexamethasone 8 mg given as an intravenous injection, chlorpheniramine 10 mg as intra-muscular injection and ranitidine 50 mg, intravenously. A combination of HT₃ antagonist and dexamethasone was administered to day 3 to prevent nausea and vomiting.

Treatment was repeated every 3 weeks if the neutrophil count was above 1,500/ml and platelets >100,000/ml. For patients who experienced drug toxicity, the dose for subsequent cycles was modified as outlined in table 1. After one episode of grade 4 neutropenia or febrile neutropenia, prophylaxis with recombinant human granulocyte colony-stimulating factors was administered. After grade 3–4 non-haematological toxicity, excluding hair loss, therapy was delayed until recovery. The use of recombinant erythropoietin was left to the individual decision of the physician. Within cycles, doses of gemcitabine on day 8 were modified as follows: no reduction for neutrophils >1,500/ml and platelets >100,000/ml; 25% dose reduction for neutrophils 1,000–1,500/ml and/or platelets 75,000–100,000/ml; no administration for neutrophils <1,000/ml and/or platelets <75,000/ml. Three cycles of chemotherapy were administered unless progressive disease or intolerable toxicity was registered.

Results

Efficacy

A total of 52 patients were enrolled from December 1999 to February 2004 (table 2). All patients were assessable for response and toxicity. The overall response rate was 70% in the interim analysis which was performed in May 2002 after the first 20 enrolled patients. Of the 52 evaluable patients, 40 responded, showing an overall response rate of 77% (95% CI 52–90%). Complete remission (CR) was achieved in 4 patients. Partial remission (PR) was observed in 36 patients. Stable disease (SD) was observed in 5 patients and progressive disease (PD) in 7. Repeated mediastinoscopy or TBNA was required in 15 patients.

Twenty-two patients were considered eligible for radical surgery after induction chemotherapy. At the present time, 17 patients were submitted to surgery with confirmed pathological downstaging. Five were excluded for biopsy-proven residual tumour in mediastinal nodes at thoracotomy. Lobectomy was performed in 15 cases, while pneumonectomy was only performed in 2 patients. Resections were considered complete in 15 patients. Four

Table 1. Dose modification protocol for treatment

Blood cells	Nadir	Dose (first episode, all three drugs), %	Dose (second episode, all three drugs), %
Haematological toxicity			
PMN	1,000–1,500/ml	100	100
PMN	500–1,000/ml	100	100
PMN	<500/ml	75 ^a	75 ^a
Platelets	75–100,000/ml	100	100
Platelets	50–75,000/ml	100	100
Platelets	25–50,000/ml	75	50
Platelets	<25,000/ml	50	Withdraw
Non-haematological toxicity ^b			
Grade 1–2		100	100
Grade 3		75	50
Grade 4		50	Withdraw

PMN = Polymorphonuclear neutrophil.

^a + Recombinant human granulocyte colony-stimulating factor.

^b For hepatic toxicity grade 3: withdrawal of gemcitabine after the second episode.

Table 2. Patient demographics and baseline disease characteristics

Total patients	52
Age, years	
Median	64
Range	34–75
Sex	
Male	40
Female	12
ECOG performance status	
0	33
1	18
2	1
Histology	
Squamous cell	20
Adenocarcinoma	29
Large cell	3
Stage	
T2N2	20
T3N2	32

patients achieved pathological complete response (pCR). Patients who achieved a pCR were those having a major radiographic response. No surgery-related mortality was reported and no significant morbidity was observed during the 30 post-operative days. At a median follow-up of 26 months, the median duration of survival was 22 months (95% CI 16.9–32.1 months). Fifteen patients received adjuvant radiotherapy. Definitive radiotherapy (65 Gy) was given to 30 patients (23 with PR, 5 with SD

Table 3. High-grade toxicities (n = 52)

Toxicity	Grade 3	Grade 4
Neutropenia	26	11
Febrile neutropenia	2	0
Anemia	5	1
Thrombocytopenia	12	1
Neuropathy	2	0
Nausea/vomiting	5	0
Diarrhoea	1	0
Elevation of transaminases	3	1
Muscle pain	6	0
Asthenia	15	0

and 2 with locoregional PD) with persistent mediastinal disease after induction chemotherapy. For these patients, the overall response was 83% after sequential chemoradiotherapy and the median overall survival was 20 months (95% CI 15.9–31.1 months). Among the 15 completely resected patients, 3 had disease recurrence 9–12 months after surgery.

Toxicity

The highest toxicity was a haematological one, with neutropenia as the major side effect. Only 2 patients had febrile neutropenia. Other less frequent high-grade toxicities included nausea-emesis, neuropathy, muscle pain, asthenia, diarrhoea and liver toxicity (table 3). Grade 3

elevation of transaminases was observed in 3 patients, but it was reversible. There were no early or toxic deaths. All patients received all three cycles of induction chemotherapy. The median delivered relative dose intensity was 84% for paclitaxel (range 75–102), 84% for carboplatin (range 75–105) and 82% for gemcitabine (range 50–102.5)

Discussion

Combined modality therapy involving a combination of chemotherapy and local treatment has improved outcomes for patients with stage III NSCLC: a 5-year survival of 25 and 15% in stages IIIA and IIIB can be expected. Stage IIIA, including tumours with ipsilateral mediastinal node involvement (T1–3N2), represents the most controversial subset of lung cancer patients because of the heterogeneity in clinical presentation, treatment and prognosis.

Despite a negative pre-operative staging including CT scan, positron emission tomography and mediastinoscopy, mediastinal lymph node metastases after thoracotomy (incidental N2) were found in some patients. Nodal disease was found at the final pathological examination of surgical specimen or intra-operatively as an unexpected finding with frozen section pathologic examination of mediastinal nodes. However, a majority of patients with stage IIIA have enlarged (>1 cm in short-axis diameter) N2 nodes at CT scan. In this setting, mediastinoscopy was generally performed, since approximately 40% of moderately enlarged nodes are benign. To optimize the chance for cure, patients with pre-operatively documented N2 and potentially resectable disease should receive induction chemotherapy followed by surgery. Theoretical advantages of induction chemotherapy include decreasing tumour size to allow more ready resection and decreased micrometastases and surgical seeding. In stage IIIA, pre-operative phase II chemotherapy studies have shown improved outcome compared with historical controls. These studies showed a response rate of 64–77%, with 15–74% of complete resections and 0–18% treatment-related deaths. These results have been validated by three small randomized phase III studies [5–7] which, however, can be criticized on several points: no pathological staging of mediastinal nodes, inclusion of patients with inhomogeneous prognosis (T3 N0–1, bulky N2 or stage IIIB) and small samples. Furthermore, these results were not confirmed by other studies [13–16] and overall survival was not reported in two studies [13, 14]. No significant sur-

vival benefit for induction chemotherapy was achieved in two studies [15, 16]. At last, treatment-related mortality is high in some trials. However, for many patients with bulky N2 disease, the role of surgery is questionable.

These patients may be suitable for combined modality treatment with chemotherapy and radiotherapy, as several trials of induction chemotherapy followed by radiotherapy and of chemotherapy delivered concomitantly with radiotherapy have shown improved survival over definitive radiotherapy alone. Furthermore, three meta-analyses of trials comparing radiotherapy alone with cisplatin-based chemoradiation for locoregional disease have confirmed the survival benefit of combined modality therapy [17–19]. There have been trials of cisplatin-based sequential chemoradiation which have shown an advantage over combined modality therapy in patients with unresectable locoregional disease. In the first trial of Dillman et al. [20] addressing this issue, the objective tumour response rate was improved with chemoradiation as compared with radiotherapy alone (56 vs. 43%). Additionally, a survival advantage over combination therapy was detected (5-year overall survival 13 vs. 6%). A trial by the Radiation Therapy Oncology Group [21] and a trial from France [22] also showed a survival benefit of the use of sequential chemoradiotherapy.

These patients may be suitable for sequential radiotherapy as the disease is considered unresectable. Therapeutic strategy is complicated by the lack of a clear definition of what constitutes ‘bulky N2’ and/or ‘unresectable’ disease. The definition of ‘resectable’, ‘marginally resectable’ or ‘unresectable’ is not clear as it is subjective and highly dependent on the experience and expertise of the thoracic surgeon, as is the definition of bulky N2 disease. In this present study, bulky N2 disease is defined as involving mediastinal nodes >2 cm in short-axis diameter in CT scan.

Furthermore, since clinical restaging after induction chemotherapy with chest CT scans and/or positron emission tomography is not accurate to predict pathological response in mediastinal lymph nodes, repeated mediastinoscopy or TBNA was required in some patients. Patients with pathologically documented residual mediastinal disease were excluded from surgery and received definitive radiotherapy. Patients without mediastinal disease were submitted to surgery. In this present phase II study, the combination of paclitaxel, carboplatin and gemcitabine showed promising anti-tumoral activity and was well tolerated in combined modality therapy of stage IIIA N2 bulky NSCLC, with cytological or histological confirmation of lymph node involvement. Objective response was

achieved in 40/52 patients. Mediastinoscopy or TBNA was repeated after induction chemotherapy in some patients. After induction chemotherapy, 22 patients were considered eligible for radical surgery. Patients with pathologically documented residual mediastinal tumour were excluded for surgery. Seventeen patients were subjected to radical surgery with confirmed pathological downstaging. Resections were considered complete in 15 patients. pCR was observed in 4 patients. No surgery-related mortality or significant morbidity was observed. The use of induction chemotherapy appeared safe and did not increase surgical complications. At a median follow-up of 26 months, the median overall survival was 22 months. Thirty patients with persistent mediastinal disease after induction chemotherapy received definitive radiotherapy. For these patients (23 with RP, 5 with SD and 2 with locoregional PD after induction chemotherapy), the overall response rate was 83% after sequential chemoradiotherapy and the median overall survival was 20 months. These results are encouraging if compared with a number of trials using different platinum-based chemotherapy regimens followed by resection in stage IIIA.

In the largest published phase II trial, 136 patients with stage IIIA, with bulky or multilevel clinical N2, received two to three cycles of cisplatin-mitomycin and vinblastin or vindesine combination chemotherapy before exploratory surgery [2]. Seventy-seven of these patients responded to neo-adjuvant chemotherapy, 72% were surgically explored and 84% of them underwent complete resection of tumour tissue. pCR was achieved in 19% of the patients. The median survival of all patients was 19 months. In completely resected patients, median survival was 27 months. Survival was impressive (>50% at 5 years) in patients who achieved complete response to the induction chemotherapy. This highlights the importance of a pCR for long-term survival. However, in trials employing the combination of cisplatin, vinca-alkaloid and mitomycin, a mortality of 18% was reported [3]. Indeed, triple combination with 'older drugs' as induction chemotherapy may be associated with high treatment-related mortality. Newer generation chemotherapeutic agents are being incorporated into combined modality therapy for locally advanced NSCLC. The EORTC 09858 phase II study reported that carboplatin and taxol are an active induction regimen in biopsy-proven stage IIIA N2 bulky NSCLC [23]. Of the 52 eligible patients, 33 responded (1 CR and 32 PR) at an overall response rate of 64%. Median overall survival was 20.5 months. Grade 3–4 neutropenia was reported in 63% of patients. A total of 35

patients was randomized to additional surgery or radiotherapy according to the protocol. From the 15 patients randomized in the surgery arm, 12 received surgery. Resection was considered complete in 2 of them. One patient died 5 days after surgery with pulmonary hypertension. Furthermore, a phase II trial of combined modality therapy, with carboplatin and paclitaxel concurrent with radiotherapy, yielded an overall response rate of 55% in 38 valuable patients [24]. Triple combination with carboplatin and new drugs gemcitabine and paclitaxel may be superior to paclitaxel and carboplatin alone as induction chemotherapy. Data from several studies [25–27] have evaluated the addition of gemcitabine to paclitaxel plus carboplatin in advanced NSCLC. The response rates ranged from 21 to 61%. Only a mild increase in thrombocytopenia was observed as compared with paclitaxel and carboplatin alone. Preliminary results of randomized trials in advanced NSCLC indicated an advantage for drug combination paclitaxel, carboplatin and gemcitabine as compared with paclitaxel and carboplatin alone [23, 28, 29]. In the present study, the combination of paclitaxel, carboplatin and gemcitabine is an active regimen in bulky N2 disease. Forty of the 52 eligible patients responded. Seventeen patients were submitted to surgery. Resection was considered complete in 15 of them. Additionally, 4 patients achieved pCR. The studies conducted in N2 disease have pointed towards improved survival for those patients able to undergo a complete resection and for patients who achieved pCR after induction chemotherapy. In conclusion, this regimen is safe, and no treatment-related mortality or significant morbidity was reported. These results are encouraging. Phase III studies are currently underway to verify the role of induction chemotherapy and to assess the best chemotherapy to be used.

References

- 1 Parker SL, Tong T, Bolden S, Wingo PA: Cancer statistics, 1997. *CA Cancer J Clin* 1997;47:5–27.
- 2 Martini N, Kris MG, Flehinger BJ, Gralla RJ, Bains MS, Burt ME, Heelan R, McCormack PM, Pisters KM, Rigas JR: Preoperative chemotherapy for stage IIIA (N2) lung cancer: the Sloan-Kettering experience with 136 patients. *Ann Thorac Surg* 1993;55:1365–1374.
- 3 Burkes RL, Ginsberg RJ, Shepherd FA, Blackstein ME, Goldberg ME, Waters PF, Patterson GA, Todd T, Pearson FG, Cooper JD: Induction chemotherapy with mitomycin, vindesine and cisplatin for stage III unresectable non-small cell lung cancer: results of the Toronto phase II trial. *J Clin Oncol* 1992;10:580–586.
- 4 Elias AD, Skarin AT, Leong T, Mentzer S, Strauss G, Lynch T, Shulman L, Jacobs C, Abner A, Baldini EH, Frei E 3rd, Sugarbaker DJ: Neoadjuvant therapy for surgically staged IIIA N2 non-small cell lung cancer. *Lung Cancer* 1997;17:147–161.
- 5 Pass HI, Pogrebniak HW, Steinberg SM, Mulshine J, Minna J: Randomized trial of neoadjuvant therapy for lung cancer: interim analysis. *Ann Thorac Surg* 1992;53:992–998.
- 6 Roth JA, Fossella F, Komaki R, Ryan MB, Putnam JB Jr, Lee JS, Dhingra H, De Caro L, Chasen M, McGavran M: A randomized trial comparing perioperative chemotherapy and surgery with surgery alone in resectable stage IIIA non-small cell lung cancer. *J Natl Cancer Inst* 1994;86:673–680.
- 7 Rosell R, Gomez-Codina J, Camps C, Maestre J, Padille J, Canto A, Mate JL, Li S, Roig J, Olazabal A: A randomised trial comparing preoperative chemotherapy plus surgery with surgery alone in patients with non-small cell lung cancer. *N Engl J Med* 1994;330:153–158.
- 8 Rosell R, Gomez-Codina J, Camps C, Javier Sanchez J, Maestre J, Padilla J, Canto A, Abad A, Roig J: Preresectional chemotherapy in stage IIIA non-small cell lung cancer: a 7-year assessment of a randomised trial. *Lung Cancer* 1999;47:7–14.
- 9 Roth JA, Atkinson EN, Fossella F, Komaki R, Bernadette Ryan M, Putnam JB Jr, Lee JS, Dhingra H, De Caro L, Chasen M, Hong WK: Long-term follow-up of patients enrolled in a randomized trial comparing perioperative chemotherapy and surgery with surgery alone in resectable stage IIA non-small-cell lung cancer. *Lung Cancer* 1998;21:1–6.
- 10 Simon R: Optimal two-stage design for phase II clinical trials. *Control Clin Trials* 1989;10:1–10.
- 11 Cancer Therapy Evaluation Program, Common Toxicity Criteria, Version 2.0. <https://webapss.ctep.nci.nih.gov/ctcv2/1999>.
- 12 Kaplan EI, Meier P: Non-parametric estimation from incomplete observations. *J Am Stat Assoc* 1958;53:457–481.
- 13 Elias A, Herdan J, Kumar P, et al: A phase III comparison of 'best local-regional therapy' with or without chemotherapy for stage IIIA T1–3N2 non-small cell lung cancer (NSCLC). Preliminary results (abstract A1 622). *Proc Am Soc Clin Oncol* 1997.
- 14 Fleck J, Camargo K, Godoy D, et al: Chemoradiation therapy versus chemotherapy alone as a neo-adjuvant treatment for stage III non-small cell lung cancer. Preliminary report of a phase III prospective randomised trial (abstract A1 105). *Proc Am Soc Clin Oncol* 1997.
- 15 Nagai K, Tsuchiya R, Mori T, Tada H, Ichinose Y, Koike T, Kato H; Lung Cancer Surgical Study Group of the Japan Clinical Oncology Group: A randomized trial comparing induction chemotherapy followed by surgery with surgery alone for patients with stage IIIA N2 non-small cell lung cancer (JCOG9209). *J Thorac Cardiovasc Surg* 2003;125:254–260.
- 16 Depierre A, Milleron B, Moro-Sibilot D, Chevret S, Quoix E, Lebeau B, Braun D, Breton JL, Lemarie E, Gouva S, Paillot N, Brechot JM, Janicot H, Lebas FX, Terrioux P, Clavier J, Foucher P, Monchatre M, Coetmeur D, Level MC, Leclerc P, Blanchon F, Rodier JM, Thiberville L, Villeneuve A, Westeel V, Chastang C; French Thoracic Cooperative Group: Preoperative chemotherapy followed by surgery compared with primary surgery in resectable stage I (except T1N0), II, and IIIA non-small cell lung cancer. *J Clin Oncol* 2002;20:247–253.
- 17 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 randomized clinical trials. *BMJ* 1995;311:899–909.
- 18 Pritchard RS, Anthony SP: Chemotherapy plus radiotherapy compared with radiotherapy alone in the treatment of locally advanced, unresectable, non-small cell lung cancer. A meta-analysis. *Ann Intern Med* 1996;125:723–729.
- 19 Mariano P, Preatoni A, Cantoni A: Randomized trials of radiotherapy alone versus combined chemotherapy and radiotherapy in stages IIIA and IIIB non-small cell lung cancer. *Cancer* 1995;76:593–601.
- 20 Dillman RO, Herndon J, Seagren SL, Eaton WL Jr, Green MR: Improved survival in stage III non-small-cell lung cancer: seven-year follow-up cancer and leukemia group B (CALGB) 8433 trial. *J Natl Cancer Inst* 1996;88:1210–1215.
- 21 Sause WT, Scott C, Taylor S, Johnson D, Livingston R, Komaki R, Emami B, Curran WJ, Byhardt RW, Turrisi AT, et al: Radiation Therapy Oncology Group (RTOG) 88-08 and Eastern Cooperative Oncology Group (ECOG) 4588: preliminary results of a phase III trial in regionally advanced, unresectable non-small-cell lung cancer. *J Natl Cancer Inst* 1995;87:198–205.
- 22 Le Chevalier T, Arriagada R, Quoix E, Ruffie P, Martin M, Tarayre M, Lacombe-Terrier MJ, Douillard JY, Laplanche A: 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;83:417–423.
- 23 O'Brien ME, Splinter T, Smit EF, Biesma B, Krzakowski M, Tjan-Heijnen VC, Van Bochove A, Stigt J, Smid-Geirnaerd MJ, Debruyne C, Legrand C, Giaccone G; EORTC Lung Cancer Group: Carboplatin and paclitaxel (Taxol) as an induction regimen patients with biopsy-proven stage IIIA N2 non-small cell lung cancer: an EORTC phase II study (EORTC 08958). *Eur J Cancer* 2003;39:1416–1422.
- 24 Langer C: Concurrent chemoradiation using paclitaxel and carboplatin in locally advanced non-small cell lung cancer. *Semin Radiat Oncol* 1999;9:105–116.
- 25 Hainsworth JD, Burrell HA 3rd, Erland JB, Morrissey LH, Meluch AA, Kalman LA, Hon JK, Scullin DC Jr, Smith SW, Greco FA: Phase I/II trial of paclitaxel, by 1-hour infusion, carboplatin, and gemcitabine in the treatment of patients with advanced non-small cell lung carcinoma. *Cancer* 1999;85:1269–1276.
- 26 Kelly K, Mikhael-Kamel N, Pan Z, Murphy J, Prindiville S, Bunn PA Jr: A phase I/II trial of paclitaxel, carboplatin, and gemcitabine in untreated patients with advanced non-small cell lung cancer. *Clin Cancer Res* 2000;6:3474–3479.
- 27 Favaretto A, Ceresoli GL, Paccagnella A, Barbieri F, Bearz A, Ghiotto C, Oniga F, Schiavon S, Frustaci S, Villa E: Paclitaxel and carboplatin in combination with gemcitabine: a phase I-II trial in patients with advanced non-small-cell lung cancer. Gruppo Studio Tumori Polmonari Veneto (GSTPV). *Ann Oncol* 2000;11:1421–1426.
- 28 Hussein A, Birch R, Walzer J, et al: Preliminary results of a randomized study comparing paclitaxel and carboplatin (PC) with or without gemcitabine (G) in newly diagnosed non-small cell lung cancer (NSCLC). *Proc Am Soc Clin Oncol* 2000 (abstr 1973).
- 29 Paccagnella A, Favaretto A, Oniga F, et al: Paclitaxel/carboplatin (PC) versus paclitaxel/carboplatin/gemcitabine (PCG) in advanced NSCLC: preliminary results of a phase II–III study (abstract 488PD). *Ann Oncol* 2002.

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