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Weekly chemotherapy with carboplatin, docetaxel and irinotecan in advanced non-small-cell-lung cancer: a phase II study

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Abstract

The aim of this study was to evaluate the efficacy and tolerability of carboplatin, docetaxel plus irinotecan given weekly to patients with locally advanced or metastatic non-small cell lung cancer (NSCLC). 50 patients with previously untreated NSCLC (stage IIIB 10; stage IV 40; 44% squamous cell carcinoma; median Eastern Cooperative Oncology Group (ECOG) status 1) received intravenous (i.v.) carboplatin area under the curve (AUC) 2, docetaxel 20 mg/m^2 and irinotecan 60 mg/m^2 on days 1, 8 and 15, repeated every 5 weeks. Prophylactic granulocyte colony-stimulating factor (G-CSF) 150 ug/m^2 was given from days 3 to 6 and 10 to 13. Response was evaluated every two cycles. Four complete responses (8%) and 24 (48%) partial responses were observed, giving an overall intent-to-treat response rate of 56%. 8 patients (16%) achieved stable disease and 14 (28%) progressed. The median time to progression (TTP) was 9.6 months (range 2.5–21.8 months), median survival was 14.8 months (range 0.3–27+ months) and actuarial 1-year survival time was 55%. Grade 3/4 anaemia and thrombocytopenia occurred in 18 and 22% of patients, respectively; 13 patients (26%) developed grade 3/4 neutropenia and 7 (14%) had neutropenic fever that required hospitalisation, but was successfully treated with antibiotics and G-CSF support. One patient developed a severe allergy during docetaxel administration and was withdrawn. Other grade 3/4 adverse events included diarrhoea ($n=14$; 3 required hospitalisation), nausea/vomiting ($n=9$), neurotoxicity ($n=5$) and fatigue ($n=5$). 6 patients required a dose reduction. This combination of i.v. carboplatin AUC 2, docetaxel 20 mg/m^2 and irinotecan 60 mg/m^2 given weekly is highly effective in the treatment of chemotherapy-naïve advanced NSCLC. Toxicity was moderate, but manageable. © 2002 Published by Elsevier Science Ltd.

Keywords: Weekly chemotherapy; Carboplatin; Docetaxel; Irinotecan; Advanced NSCLC

1. Introduction

Approximately 40% of patients with non-small cell lung cancer (NSCLC) present with metastatic disease [1]. Compared with monotherapy, cisplatin-based combination chemotherapy has achieved improved response rates, with modest survival benefits, in patients with advanced NSCLC [2]. However, prior to 1995, the various cisplatin-based treatment combinations were broadly similar in terms of efficacy, with response rates of 20–30%, median survival time 6–8 months and 1-year survival 20–25% [3]. Despite existing combination chemotherapy, the long-term prognosis for patients presenting with advanced NSCLC remains poor, and there is a clear need for more effective treatment regimens that will improve survival.

Recently introduced anticancer agents, such as docetaxel and irinotecan, have demonstrated activity when used in the first-line treatment of NSCLC [4–9]. These agents have different mechanisms of action: docetaxel binds to tubulin and inhibits the formation of microtubule bundles, leading to cell death [10], whereas irinotecan inhibits the nuclear enzyme topoisomerase I, which is critical for DNA replication and transcription [11].

Although platinum compounds and docetaxel are not synergistic *in vivo*, they have an additive effect in the clinical setting [12]. One drawback of platinum-based

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combination therapy is the toxicity associated with cisplatin [13]. However, carboplatin is a cisplatin derivative which has shown comparable efficacy, but less toxicity, than the parent compound in the treatment of NSCLC [14]; one five-arm study of cisplatin combinations and analogues showed carboplatin to have the best 1-year survival rate and least toxicity [15]. There is therefore a strong rationale for combining docetaxel and carboplatin in the treatment of advanced NSCLC. Preliminary results of phase II trials of carboplatin at a dose corresponding to the area under the curve (AUC) 6 (5.2 in one study) plus docetaxel 60–80 mg/m^2 every 3 weeks reported response rates ranging from 35 to 55% [16–19].

In vitro studies have also demonstrated synergy between irinotecan and cisplatin [20], and recent phase II studies of irinotecan plus either cisplatin or carboplatin have reported response rates of 25–52% in patients with advanced or metastatic NSCLC [21–25]. In addition, promising results were reported in one phase I trial in which docetaxel was combined with irinotecan in the treatment of chemotherapy-naïve NSCLC [26].

We conducted a phase I trial of carboplatin, docetaxel and irinotecan in chemotherapy-naïve patients with advanced NSCLC (unpublished data). Both carboplatin and docetaxel were fixed at an AUC 2 and 20 mg/m^2, given weekly, respectively. The starting dose of irinotecan was 30 mg/m^2, given weekly, and the dose was escalated by an increase of 10 mg/m^2 until the maximum tolerated dose (MTD) was reached. The MTD was 60 mg/m^2. Neutropenia and diarrhoea were the dose-limiting toxicities (DLT). Triplet chemotherapy of carboplatin AUC 2 plus docetaxel 20 mg/m^2 and irinotecan 60 mg/m^2 on days 1, 8 and 15 was recommended for phase II studies.

Given the different mechanisms of action of carboplatin, docetaxel and irinotecan, and on the basis of their single-agent and combined activity in NSCLC, we conducted a phase II study to evaluate the efficacy and tolerability of a combination of all three agents, administered on a weekly basis, to patients with previously untreated advanced or metastatic NSCLC.

2. Patients and methods

2.1. Patients

This phase II study enrolled adult (>18 years) patients with inoperable stage IIIB or IV NSCLC (according to the American Joint Committee on Cancer) [27], including patients with recurrent disease following surgery or radiotherapy. All patients were required to have histologically- or cytologically-proven NSCLC, an Eastern Cooperative Oncology Group (ECOG) performance status of 0–2, measurable disease outside prior radiotherapy ports (as assessed by physical examination, chest X-ray, computed tomography (CT) scan or other examinations as appropriate), and life expectancy of at least 12 weeks. Eligible patients were required to have adequate haematological white blood cells (WBC) $\geqslant 4\times10^9$ cells/l, neutrophils $\geqslant 2\times10^9$ cells/l, platelets $\geqslant 100\times10^9$/cells/l, haemoglobin $\geqslant 100$ g/l), renal (serum creatinine $\leqslant 132.6$ μmol/l, creatinine clearance $\geqslant 0.83$ ml/s) and hepatic (bilirubin <25.65 μmol/l and/or asparate aminotransferase (AST), alanine aminotransferase (ALT) and gamma-glutamyltransferase <3 times normal in patients with known liver metastases) function.

Patients were excluded if they had secondary malignancy (except carcinoma *in situ* of the cervix or adequately treated basal cell skin carcinoma), life-threatening metastases, history of atrial or ventricular arrhythmias, congestive heart failure (even if medically controlled), documented myocardial infarction or pre-existing motor or sensory neurotoxicity grade $\geqslant 2$ according to the World Health Organization (WHO) scale. Individuals with active infection or other serious underlying medical conditions that would impair their ability to receive the protocol treatment were also excluded. The protocol was approved by our hospital ethics committee and all patients provided informed consent.

2.2. Treatment

Treatment was administered on an outpatient basis. All patients received carboplatin at an AUC of 2 (according to the Calvert formula) [28] as a 1-hr intravenous (i.v.) infusion, followed by irinotecan 60 mg/m^2 as a 90-min infusion, then docetaxel 20 mg/m^2 as a 1-hr infusion on days 1, 8 and 15. Chemotherapy was repeated every 5 weeks. We chose these drug doses and this schedule based on our unpublished phase I data.

All patients also received oral dexamethasone 8 mg twice a day for 2 days, starting one day before chemotherapy. We chose this dose of dexamethasone which has been used in most weekly schedules for docetaxel. Recombinant human granulocyte-colony stimulating factor (G-CSF) was given prophylactically at a dose of 150 ug/m^2 subcutaneously (s.c.) from days 3 to 6 and days 10 to 13 to maintain the weekly administration of chemotherapy. Antiemetic prophylaxis (5-HT$_3$ antagonists) was also given before chemotherapy. Patients also received loperamide and/or somatostatin in cases of diarrhoea.

Subsequent doses of chemotherapy were adjusted at the start of each new cycle according to the WBC and platelet counts, creatinine clearance and liver function. Chemotherapy was continued at the same dose if the absolute granulocyte count was $\geqslant 2\times10^9$ cells/l and the

platelet count was $\geqslant 100\times10^9$ cells/l on the day of treatment. If the absolute granulocyte nadir was $<1\times10^9$ cells/l and/or platelet nadir $<75\times10^9$ cells/l, the dose was reduced for carboplatin to an AUC 1.75, for docetaxel to 17.5 mg/m^2 and for irinotecan to 50 mg/m^2 (level 1). If the absolute granulocyte nadir was $<0.5\times10^9$ cells/l and/or the platelet nadir $<50\times10^9$ cells/l, the doses were further reduced to an AUC of 1.5, 15 and 40 mg/m^2, respectively (level 2).

On days 8 and 15, chemotherapy was continued if the absolute granulocyte nadir was $\geqslant 1.5\times10^9$/cells/l, the platelet count was $\geqslant 100\times10^9$ cells/l, and non-haematological toxicity was grade 2 or lower. If absolute granulocytes were 1–1.5×10^9 cells/l, or the platelet count was 75×10^9 cells/l, the doses were reduced to level 1. Treatment was withheld if the absolute granulocyte count was $<1\times10^9$ cells/l or platelet count was $<50\times10^9$ cells/l or any grade 4 non-haematological toxicity was present. Patients who required treatment to be withheld on either day 8 or day 15 because of toxicity had the doses reduced to level 2 for the subsequent cycles.

The carboplatin dose was also adjusted according to creatinine clearance. If creatinine clearance was <0.67 ml/s, treatment was delayed until recovery, but for no longer than 1 week, otherwise the patient was withdrawn from the study. For creatinine clearances between 0.67 and 0.82 ml/s, the carboplatin dose was reduced by 25%. In the event of grade 3 non-haematological toxicity, treatment was withheld until recovery to grade 1 or less. Grade 4 non-haematological toxicity resulted in treatment being delayed until recovery to grade 1 or less, and the doses of drugs were reduced as for myelosuppression.

2.3. Assessments

Before entering the study, all patients underwent a physical examination, complete blood count, blood chemistry, chest X-ray, bone scan, thoracic, abdominal and brain CT scans and other specific tests when indicated.

Responses were assessed every two cycles of treatment according to WHO criteria [29]. Treatment was administered for six cycles unless progressive disease or unacceptable toxicity occurred earlier, in which case treatment was discontinued. Patients who had achieved either complete or partial responses after six treatment cycles could continue treatment for two further cycles.

Patients were monitored weekly for WBC and serum creatinine levels. Toxicity was also evaluated weekly and graded using the WHO scale.

2.4. Statistical analysis

The primary endpoint of this study was to evaluate the response to chemotherapy and toxicity.

Sample size was based on the overall response rate. According to Simon's two-stage minimax design, assuming that the expected overall response rate would not be $\leqslant 40\%$ or would be $\geqslant 60\%$, a sample size of 16 patients is required in the first step. If a minimum of eight responses were observed, a total of 46 patients need to be accrued. Thus, if at least 24 responses occur the probability of accepting a treatment with a real response rate of less than 40% will be 5%. However, the risk of rejecting a treatment (at the second stage) with a response rate of more than 60% will be 20%.

Survival was calculated from the date of initiation of chemotherapy to the date of death using the Kaplan–Meier method [30]. Duration of response was calculated from the date response was documented until the date of first progression. Time to progression (TTP) was defined as the time that elapsed from the start of treatment to renewed disease progression.

3. Results

3.1. Study population

Between November 1997 and December 1999, 50 patients (44 male, 6 female) were enrolled and treated. Patient characteristics are listed in Table 1. Most patients had a performance status of 0 to 1 and stage IV disease. The most common histological types were squamous cell carcinoma and adenocarcinoma, which were almost equally distributed.

3.2. Treatment administration

The median number of cycles per patient was 5 (range 1–8). The total number of cycles administered was 272. The median relative dose-intensity (RDI) was 0.92 for carboplatin, 0.88 for docetaxel and 0.89 for irinotecan. The only toxicities that necessitated dose reduction were myelosuppression and diarrhoea.

3.3. Efficacy

47 patients were evaluable for response. One patient with liver metastases died soon after the first cycle of chemotherapy due to a rapid deterioration of his general condition. One patient with locally advanced disease (stage IIIB) withdrew from treatment after the first cycle of chemotherapy because of grade 4 nausea/vomiting and fatigue; he was treated with radiotherapy. The third patient (a woman with metastatic disease) developed a severe allergic reaction soon after commencing the first infusion of docetaxel infusion, and treatment was discontinued.

4 of the 50 patients achieved complete responses (Table 2) and partial responses were observed in 24

patients, giving an overall intent-to-treat response rate of 56%. Most responses were noted in the lung, lymph nodes, subcutaneous nodules and pleura. Of the 10 patients with liver metastases, 1 patient obtained a complete response and 4 others obtained partial responses. Partial response was also observed in one patient with large adrenal metastases.

The median duration of response was 9.2 months (range, 2.8–23 months), the median TTP was 9.6 months (range 2.5–21.8 months), the overall median survival was 14.8 months (range 0.3–27+ months) and the 1-year survival rate was 55%. The median survival time for responders was 16.8 months (range 5.5–27+ months), compared with 8.6 months (range 0.3–13.2 months) for non-responders.

Table 1
Patient characteristics

Characteristics	Patients *n* (%)
Total enrolled	50
Sex	
Male	44 (88)
Female	6 (12)
Age (years)	
Median (range)	57 (33–75)
ECOG performance status	
0	16 (32)
1	24 (48)
2	10 (20)
Histological type	
Squamous	22 (44)
Adenocarcinoma	20 (40)
Mixed	2 (4)
Unspecified	6 (12)
Differentiation grade	
Well	6 (12)
Moderate	12 (24)
Poor	20 (40)
Unspecified	12 (24)
Stage	
III B	10 (20)
IV	40 (80)
Prior surgery	7 (14)
Prior radiotherapy	
Primary	6 (12)
Metastatic	9 (18)
Weight loss >10%	8 (16)

ECOG, Eastern Cooperative Oncology Group.

Table 2
Response rates ($n=50$)

	n	Patients (%)	Confidence Interval (%)
Complete response	4	8	2.2–19.2
Partial response	24	48	32.2–60.5
Intent-to-treat response rate	28	56	39.5–67.8
Stable disease	8	16	
Progressive disease	14[a]	28	

[a] Includes 3 patients who discontinued treatment.

3.4. Safety

All patients were assessable for safety, and toxicities are listed in Table 3. Grade 3/4 neutropenia occurred in 13 patients (26%), grade 3/4 thrombocytopenia in 11 patients (22%) and grade 3/4 anaemia in 9 patients (18%). No cumulative thrombocytopenia was seen. There were seven episodes (14%) of febrile neutropenia that required hospitalisation, all of which were resolved with broad-spectrum antibiotics and G-CSF support. Despite the prophylactic use of haematopoietic growth factors, 6 patients (12%) required a dose reduction, 3 of whom (6%) required two dose reductions. Most of those dose modifications were seen on day 15. However, neutropenia was generally of short duration and there were few treatment delays due to myelosupression. No patient required hospitalisation for platelet transfusions.

More than one-quarter of patients (28%) experienced grade 3/4 diarrhoea, which resulted in a dose reduction in 7 patients (14%) and treatment delay in 6 patients (12%). 3 patients with grade 4 diarrhoea required hospitalisation for fluid rehydration, electrolyte supplementation and treatment with loperamide and 1 required treatment with somatostatin. In only these 3 patients, the day 15 treatment was omitted. Grade 3/4 nausea/vomiting occurred in 9 patients (18%) and grade 3 nephrotoxicity in 2 patients (4%). 2 patients (4%) developed grade 3 mucositis and 2 patients (4%) grade 3 fluid retention, which was easily managed by oral

Table 3
Incidence of toxicity: number of patients and percent

Toxicity	WHO grading of toxicity	
	3	4
	n (%)	*n* (%)
Haematological		
Neutropenia	7 (14)	6 (12)
Anaemia	6 (12)	3 (6)
Thrombocytopenia	6 (12)	5 (10)
Non-haematological		
Alopecia	24 (48)	12 (24)
Nephrotoxicity	2 (4)	0 (0)
Nausea/vomiting	5 (10)	4 (8)
Neurosensory	4 (8)	1 (2)
Fluid retention	2 (4)	0 (0)
Mucositis	2 (4)	0 (0)
Diarrhoea	7 (14)	7 (14)
Allergy	1 (2)	1 (2)
Cutaneous	0 (0)	0 (0)
Cardiac	0 (0)	0 (0)
Fatigue	4 (8)	1 (2)

WHO, World Health Organization.

diuretics. One patient experienced cardiac arrhythmia that resolved on discontinuation of the docetaxel infusion. Grade 2–4 paresthesia, loss of vibration sensation and loss of deep tendon reflexes occurred in 10 patients (20%). Allergy occurred in 5 patients (10%), but resolved in 5–10 min, except for one patient who developed severe allergic reaction that required treatment with adrenaline, corticosteroids and antihistamines; this patient was withdrawn from the study. 13 patients (26%) reported grade 2–4 fatigue that negatively impacted on their quality of life. Alopecia was universal and reversible.

4. Discussion

This is the first phase II study of a combination of carboplatin, docetaxel and irinotecan administered weekly to chemotherapy-naïve patients with locally advanced or metastatic NSCLC. The study rationale was that these drugs represent three of the most active single agents against advanced NSCLC, and the use of triple combination chemotherapy involving drugs with complementary mechanisms of action may enhance response rates and survival [31].

Platinum compounds and docetaxel appear to be non-cross-resistant clinically, with an additive effect and predominantly non-overlapping toxicity profiles [32]. *In vitro* studies have demonstrated a synergy between irinotecan and platinum compounds in NSCLC cell lines both when cisplatin was administered before the active metabolite of irinotecan and *vice versa* [20]. However, *in vitro* studies combining taxanes with topoisomerase I inhibitors have yielded conflicting results: Chou and colleagues [33] demonstrated synergistic activity with a combination of topotecan and paclitaxel in a cultured human teratocarcinoma cell line, but Kaufmann and colleagues [34] found this combination to be antagonistic in a human NSCLC cell line. The results may depend on the cell type studied and the sequence of drug administration.

Phase I clinical studies have attempted to determine whether these *in vitro* studies have any predictive value, and the importance of the administration schedule. A recent phase I study at the Mayo Clinic showed partial responses in 3 of 5 patients with solid tumours who received irinotecan followed by docetaxel [35]. Another phase I study, conducted at Yale Cancer Center, in which escalating doses of docetaxel (25–40 mg/m^2) were given weekly before irinotecan 50 mg/m^2 for 4 weeks, followed by a 2-week rest, reported one partial response among 5 patients with chemotherapy-naïve NSCLC [36]. A Japanese dose-finding phase I study, which evaluated irinotecan 50 mg/m^2 on days 1, 8 and 15 followed by docetaxel 50mg/m^2 on day 2 in patients with previously untreated advanced NSCLC, reported an objective response rate of 34%, median survival of 39.3 weeks and a 1-year survival rate of 38% [26].

Building on these promising phase I results, we incorporated a platinum compound into our treatment regimen. However, as cisplatin-based chemotherapy is associated with gastrointestinal toxicity and nephro-, oto- and neurotoxicity [13], cisplatin was substituted with carboplatin, which has a similar antitumour activity and less toxicity. In addition, weekly administration was investigated, as these agents may be better tolerated weekly than when given every 3–4 weeks [23,36,37).

Our triple combination of carboplatin, docetaxel and irinotecan demonstrated impressive efficacy in the treatment of patients with chemotherapy-naïve NSCLC, with an objective response rate of 56%, median survival of 14.8 months and 1-year survival of 55%. These results are among the highest reported and are superior to either irinotecan or docetaxel alone: first-line docetaxel in advanced NSCLC has achieved an overall response rate of 30% (range 21–38%), a median survival of 9 months (range 6–12 months) and a 1-year survival rate of 38% [37,38], and irinotecan has attained response rates of 16–34% and median survival ranging from 6.2 to 10.5 months [9,39].

Our results also compare favourably with those obtained with combinations of either docetaxel plus carboplatin or irinotecan plus cisplatin. Four phase II studies of carboplatin AUC 6 combined with doses of docetaxel ranging from 60 to 80 mg/m^2 in advanced NSCLC reported response rates ranging from 35 to 55% [16–19]. Four mature phase II studies that evaluated the combination of cisplatin and irinotecan reported response rates from 29 to 52% in patients with stage III or IV NSCLC [21–24], and one study that combined carboplatin with irinotecan achieved a response rate of 25% in locally advanced and metastatic NSCLC, and a median survival of 10.8 months [25].

Preliminary results from a phase III randomised trial in Japan, which compared the combination of cisplatin plus irinotecan versus cisplatin plus vindesine versus irinotecan alone, reported the highest response rate with cisplatin plus irinotecan (43% versus 31% versus 21%) [40]. The incidence of grade 4 neutropenia with cisplatin/vindesine (53%) or cisplatin/irinotecan (36%) was higher than that reported with irinotecan alone (8%). Severe diarrhoea was more common in the irinotecan-containing regimens (13–15% versus 4% for cisplatin/vindesine).

Our triple combination was also superior to the combination of docetaxel plus irinotecan as first-line treatment for advanced NSCLC. One phase I/II study combined irinotecan on days 1, 8 and 15 plus docetaxel on day 2 in 32 chemotherapy-naïve patients with advanced NSCLC [26]. The maximum tolerated doses were docetaxel 50 mg/m^2 with irinotecan 60 mg/m^2 or docetaxel 60 mg/m^2 with irinotecan 50 mg/m^2. The

recommended dose was 50 mg/m^2 for both agents; at these doses, toxicity was moderate to severe—2/6 patients developed grade $\geqslant$2 diarrhoea and 6/6 had grade $\geqslant$2 neutropenia. This combination produced an objective response rate of 37%, with median survival 48 weeks and 45% 1-year survival.

The main toxicity reported in all of these studies was myelosuppression, the incidences of grade $\geqslant$3 neutropenia and thrombocytopenia reaching 76–80% [21,25] and 43–47% [24,25], respectively. In our study, the toxicity of weekly carboplatin, docetaxel and irinotecan was moderate, with neutropenia, diarrhoea and alopecia being the most common toxicities. Grade 3/4 neutropenia and thrombocytopenia occurred in only 26 and 22% of patients, respectively; 7 (14%) patients experienced febrile episodes requiring hospitalisation. All episodes were successfully treated with broad-spectrum antibiotics.

Despite the prophylactic use of G-CSF, dose reduction was required with our triple regimen in six patients, three of whom required two dose reductions. Grade 3/4 diarrhoea occurred in 28% of patients, who required dose reduction and treatment delay. 3 patients with grade 4 diarrhoea required hospitalisation for fluid and electrolyte rehydration and treatment with loperamide, and 1 required treatment with somatostatin. Diarrhoea could be attributed to irinotecan. Although grade 3/4 diarrhoea is uncommon with docetaxel monotherapy [41], an increased incidence was reported in combination with CDDP [42] and/or irinotecan [26,43,44], in which grade 3/4 diarrhoea occurred in more than 20% of treated patients. High-dose loperamide has been proved efficacious for this side-effect [45]. 5 patients experienced mild to moderate allergic reactions evidenced by chest tightness, dyspnoea, cough and flushing, all of which resolved after a few minutes. However, 1 patient developed severe allergy during docetaxel administration that required treatment with adrenaline, dexamethasone and antihistamines; this patient discontinued treatment. 5 patients experienced grade 3/4 asthenia, but despite this severe fatigue, all patients except 1 adhered to the treatment protocol. Oedema caused by fluid retention was easily managed with oral diuretics. Nausea and vomiting were mild to moderate in most patients, but manageable. Alopecia was almost universal, but reversible.

Several investigators are currently exploring triple chemotherapy in advanced NSCLC. The efficacy and toxicity of the regimen described here compare well with results published to date. In a phase I study of carboplatin at a dose of AUC 5, docetaxel 60 mg/m^2 plus irinotecan 40 mg/m^2 (increasing in increments of 10 mg/m^2), with G-CSF support, every 3 weeks, a response rate of 38% was reported, with a median survival of 9.9 months [43]. The recommended dose of irinotecan in this regimen was 50 mg/m^2; at this dose, grade $\geqslant$3 neutropenia was seen in 32% of patients and diarrhoea (the overall dose-limiting toxicity) in 9% of patients. Another study of carboplatin AUC 5 plus irinotecan 100 mg/m^2 plus paclitaxel 175 mg/m^2 on day 1 every 3 weeks reported a response rate of 39%, median survival 11 months (range 1.3 to 34.9 months) and a 1-year survival probability of 0.46 (95% CI: 0.29 to 0.64) [46]. Grade 3/4 neutropenia occurred in 16/32 (50%) patients.

In conclusion, this combination of carboplatin, docetaxel and irinotecan administered on a weekly schedule to patients with previously untreated advanced and metastatic NSCLC was a highly effective and well-tolerated regimen, with moderate toxicity. This triple combination achieved one of the highest response rates and 1-year survival reported to date. Another advantage is that the chemotherapy can be administered in the outpatient setting. Improvement in outcome of treatment for advanced NSCLC has been few and minor and this study adds significantly to our knowledge. In order to determine the optimal treatment for patients with advanced NSCLC, prospective randomised trials comparing this triple combination with other cisplatin- or carboplatin-based chemotherapy are required.

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