Phase I/II investigation of paclitaxel, ifosfamide and carboplatin for advanced non-small-cell lung cancer


Background: The aim of this study was to evaluate feasibility and tolerability of the three-drug combination of paclitaxel, ifosfamide and carboplatin (TIC) in patients with advanced non-small-cell lung cancer. The specific objectives of the study were: (i) to define the dose-limiting toxicities (DLTs) and the maximum-tolerated dose of ifosfamide administered as part of the combination; and (ii) to determine the overall response rate and overall survival of patients treated with this regimen.

Patients and methods: Patients with untreated, stage IIIB (pleural effusion) or stage IV non-small-cell lung cancer were enrolled in one of three cohorts. Patients received paclitaxel 200 mg/m² as a 1-h infusion on day 1 with carboplatin at an area under the concentration–time curve (AUC) of 6 mg·min/ml on day 2. For dose level I, ifosfamide was administered at a dose of 2 g/m² on days 1 and 2. For dose levels II and III, the dose of ifosfamide was decreased to 1.5 g/m² on days 1 and 2 and the dose of carboplatin was decreased to AUC 5 mg·ml/min. Therapy for dose levels I and III included filgrastim support (5 µg/kg/day), which was initiated on day 3 and continued until after day 11 or until an absolute neutrophil count >10000/µl. Treatment cycles were repeated every 21 days. Once the phase II dose was established, a full cohort of patients received therapy at this dose level to examine further the regimen’s activity and tolerability.

Results: Neutropenia was the DLT encountered for dose levels I and II. No DLT was encountered in the initial six patients treated at dose level III, and therefore this dose level was declared the recommended phase II dose. A total of 49 patients were treated at the recommended phase II dose. The predominant non-hematological toxicity encountered with this triplet regimen was cumulative peripheral neuropathy. Of the 65 eligible patients enrolled in this study, 17 (26%) responded. There were 15 patients with partial responses (23%), two with regression, and 26 with stabilization of disease (40%). Median progression-free and overall survival were 4.8 and 9.4 months, respectively.

Conclusions: The combination TIC is well-tolerated. This triplet regimen produced response and survival rates in advanced non-small-cell lung cancer similar to those of other current combination chemotherapy regimens.

Key words: carboplatin, ifosfamide, non-small-cell lung cancer, paclitaxel

Introduction

Non-small-cell lung cancer (NSCLC) remains a major public health problem worldwide. NSCLC is characterized by advanced stage at the time of diagnosis, and in this setting is managed with therapies to provide palliation [1]. Early randomized trials and meta-analyses showed that cisplatin-based chemotherapy improves the survival, enhances the quality of life, and alleviates the symptoms of patients with metastatic NSCLC [2]. During the 1990s, new drugs such as paclitaxel, docetaxel, vinorelbine, gemcitabine and irinotecan were combined with cisplatin or carboplatin [3]. Randomized trials comparing these two-drug regimens with single-agent cisplatin demonstrated that the newer two-drug regimens have superior efficacy [4, 5]. Another randomized trial comparing single-agent paclitaxel with the combination of paclitaxel and carboplatin showed the superiority in response rate and survival of single-agent versus doublet therapy [6]. In the phase III Eastern Cooperative Oncology Group (ECOG) trial, ECOG1594, comparing four novel doublets, paclitaxel–carboplatin, paclitaxel–cisplatin, docetaxel–cisplatin and vinorelbine–cisplatin, these regimens demonstrated equivalent efficacy, with response rates of 16–21% and median survival times of 8 months [7]. The ECOG1594 trial and other randomized trials have indicated that the newer doublet regimens result in 1- and 2-year survival rates of 30% and 15%, respectively [6–8].

Based on the results of the trials comparing doublet and single drug regimens, it may be hypothesized that triplet combinations may be more efficacious than doublet combinations. Therefore, one strategy to improve systemic therapy for advanced NSCLC is to combine three agents with known activity. Such three-drug combinations would ideally utilize drugs that have non-over-
lapping mechanisms of action and toxicity profiles. Although the triplet regimens studied in the 1980s appeared no more active than doublet combinations [9, 10], the availability of new agents with novel mechanisms of action provides a new opportunity to develop and evaluate new triplet combinations.

Ifosfamide is a potential drug to combine with an active doublet. Phase II studies demonstrated that single-agent ifosfamide administered by various schedules produces response rates of 15–29%, with median survival times of 5–7 months [11, 12]. Ifosfamide has been used in various combination regimens to treat NSCLC, including carboplatin-based regimens. At the University of Chicago, we have investigated the administration of ifosfamide in combination with paclitaxel or vinorelbine in NSCLC [13, 14]. In a phase I study, we identified the maximum-tolerated dose (MTD) of ifosfamide to be 1.6 g/m²/day on days 1–3 when given in combination with paclitaxel 250 mg/m² over either 24 h or 3 h on day 2. The regimen included filgrastim support on days 4–11 or until neutrophil recovery. Neutropenia was the dose-limiting toxicity (DLT) and the regimen was well-tolerated. The response rate was 20%, with all responses noted at paclitaxel doses of 200 mg/m² or higher. The National Cancer Institute of Canada clinical trials group undertook a phase I dose escalation study to determine the maximum doses of paclitaxel and ifosfamide which could be administered without growth factor support [15]. The DLT of the regimen was neutropenia and recommended doses for phase II study were paclitaxel 225 mg/m² as a 3-h infusion and ifosfamide 4 g/m² as a 1-h infusion every 3 weeks. The Cancer and Leukemia Group B (CALGB) undertook a randomized phase II study to evaluate further the efficacy and toxicity of the University of Chicago ifosfamide–paclitaxel doublet in advanced NSCLC [16]. In this large phase II trial, the response rate was 36% and median survival time was 8.5 months. The incidence of neutropenia, the predominant toxicity encountered, was considered acceptable.

Based upon the known activity and the good tolerability of the doublets paclitaxel–carboplatin and paclitaxel–ifosfamide in NSCLC, we investigated the three drug combination of paclitaxel, carboplatin and ifosfamide (TIC). A phase I study was first undertaken to determine the maximum dose of ifosfamide that could be administered with carboplatin and paclitaxel. The regimen was designed to deliver paclitaxel and carboplatin at doses within the known range of single-agent activity with escalation of the ifosfamide dose [17]. When the maximum dose of ifosfamide was established for the combination, a separate phase II study was undertaken to evaluate the efficacy and tolerability of this triplet combination in NSCLC. This report describes the results of both studies.

### Patients and methods

#### Patient selection

Eligibility criteria included a histologically or cytologically confirmed diagnosis of stage IIB (with pleural effusion) or stage IV NSCLC. Measurable or evaluable disease was required. Prior treatment with a single chemotherapy regimen was allowed, if it included a single investigational agent. Prior radiation therapy to 40% or less of the bone marrow was also permitted. Patients with brain metastases were eligible following cranial irradiation if they were without neurological symptoms. A CALGB performance status of 0, 1 or 2 was necessary. Laboratory measures required at study entry included: white blood cell count (WBC) ≥3500/µl; absolute neutrophil count ≥1500/µl; hemoglobin ≥10 g/dl; platelet count ≥100 000/µl; creatinine ≤1.5 times the institutional upper limit of normal or creatinine clearance ≥50 ml/min [18]; bilirubin ≤1.5 mg/dl; and glutamic-oxaloacetic transaminase <2 times the institutional limit of normal. Patients with second- or third-degree heart block, bundle branch block, or supraventricular arrhythmia noted on electrocardiogram were excluded. All participating institutions were required to have the treatment protocol reviewed by their institutional review board. Written informed consent was obtained from all patients before commencing protocol treatment.

Before study entry, all patients underwent evaluation consisting of a complete history and physical examination; electrocardiogram; chest roentgenogram; chest and upper abdomen computed tomography (CT) scan; brain CT scan or magnetic resonance imaging; and bone scan.

#### Treatment

Protocol treatment consisted of ifosfamide administered intravenously over 2 h on days 1 and 2. Intravenous mesna was given concomitantly with the ifosfamide and then again 4 and 8 h following ifosfamide on days 1 and 2. At the conclusion of the ifosfamide infusion on day 1, paclitaxel 200 mg/m² was administered intravenously as a 1-h infusion. Following the ifosfamide infusion on day 2, carboplatin at an area under the concentration–time curve (AUC) of 6 mg·min/ml [19] was administered intravenously over 1-h. Six and 12 h before each paclitaxel dose, the patient received dexamethasone 20 mg by mouth. All patients received diphenhydramine 50 mg and ranitidine 50 mg (or equivalent H₂-blocker) intravenously before each paclitaxel dose. Prophylactic antiemetic support with ondansetron 24 mg was recommended and other antiemetics were used at the discretion of the treating physician. Treatment cycles were administered every 21 days. For this study, the paclitaxel dose was fixed and the doses of ifosfamide and carboplatin were de-escalated as shown in Table 1. For dose levels I and III, prophylactic filgrastim support of 5 µg/kg/day was initiated on day 4 and continued until WBC >10 000/µl after day 11. Each patient was assigned treatment at a

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**Table 1. Dose escalation schema**

<table>
<thead>
<tr>
<th>Dose level</th>
<th>No. of patients</th>
<th>Paclitaxel day 1 (mg/m²)</th>
<th>Carboplatin, day 2 (AUC, mg·min/ml)</th>
<th>Ifosfamide, days 1 and 2 (g/m²)</th>
<th>Mesna, days 1 and 2 (mg/m²)</th>
<th>G-CSF support</th>
</tr>
</thead>
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<td>200</td>
<td>6</td>
<td>2.0</td>
<td>400</td>
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</tr>
<tr>
<td>II</td>
<td>8</td>
<td>200</td>
<td>5</td>
<td>1.5</td>
<td>300</td>
<td>No</td>
</tr>
<tr>
<td>III*</td>
<td>6</td>
<td>200</td>
<td>5</td>
<td>1.5</td>
<td>300</td>
<td>Yes</td>
</tr>
</tbody>
</table>

*Recommended phase II dose.

AUC, area under the concentration–time curve; G-CSF, granulocyte colony-stimulating factor.
particular dose level at the time of registration and no within-patient dose escalation was permitted.

**Phase I study dose escalation and definition of MTD and DLT**

The objective of the phase I study was to identify the DLTs and MTD of ifosfamide when administered in combination with paclitaxel and carboplatin. Dose escalation was based on toxicities encountered during cycle 1 of therapy only. Cohorts of at least three patients were treated at each dose level. If none of the first three patients experienced DLT, escalation was to proceed to the next dose level. If one of three patients experienced DLT, additional patients were to be enrolled at the same dose level to a total of at least six patients. The MTD was defined as the dose level at which fewer than 33% of patients experienced DLT, with the next higher dose level having a frequency of DLT of ≥33%. Although this trial was not originally designed to include dose de-escalation, the protocol was amended to stipulate dose de-escalation if >33% of patients treated at the initial dose level studied experienced a DLT. If dose de-escalation was required, the MTD would be defined as the highest dose level at which <33% of patients experienced DLT.

For dose levels I and III, which included prophylactic granulocyte colony-stimulating factor, hematological DLT was defined as: grade 4 thrombocytopenia or neutropenia of >5 day duration, neutropenic fever [as defined by absolute neutrophil count (ANC) ≤500 cells/µl and fever of ≥38.2°C], or the need for platelet transfusion, or failure to achieve recovery to grade ≤1 toxicity by day 21. For dose level II, DLT was defined as grade 4 thrombocytopenia of ≥5 days duration or need for platelet transfusion; or neutropenic fever; or grade 4 neutropenia of any duration. Any non-hematological toxicity of grade ≥3 was considered dose-limiting if of ≥7 days duration.

**Dose modifications**

Dose modification of the paclitaxel, ifosfamide and carboplatin doses was specified for myelosuppression, nephrotoxicity, neurotoxicity and hepatic dysfunction. Therapy was delayed 1 week for inadequate hematological recovery (ANC <1800/µl or platelet count <100,000/µl) by day 22. In these instances, if recovery occurred before day 42, no dose reduction was utilized for the subsequent cycle of chemotherapy. If recovery was delayed beyond 42 days, protocol therapy was discontinued. Dose reduction was required for neutropenic fever requiring hospitalization, nadir thrombocytopenia with platelet count ≤25,000/µl, or neutropenia with ANC <500/µl lasting >4 days. If grade 2 or 3 neurotoxicity developed, therapy was held until resolution to grade ≤1 then resumed, if medically appropriate, with a dose reduction of all three drugs by 25%. Patients who developed grade 4 neurotoxicity discontinued protocol therapy.

**Assessment of response and toxicity**

Toxicities were assessed at least once during each treatment cycle and graded according to the CALGB toxicity criteria. Complete blood counts were performed at least twice weekly. Serum chemistry and liver function tests were obtained before each cycle of chemotherapy. Patients were monitored weekly throughout treatment by physical examination and recording of toxic effects.

Assessment of response to protocol therapy was performed after every two cycles of therapy. A complete response (CR) was defined as the complete clinical and radiological disappearance of tumor without the appearance of new lesions. A partial response (PR) was characterized as a reduction by at least 50% of the products of the longest perpendicular diameters of all measurable lesions. A PR also required that there was no growth of other lesions or the appearance of new lesions over at least 28 consecutive days. Stable disease (SD) was defined as a decrease in the sum of the products of two perpendicular diameters of all measured lesions by <50% or an increase by <25% after a minimum of two cycles of therapy. Progressive disease was characterized as an increase in the product of the longest diameters of measured lesion by ≥25%, or the appearance of new lesions. Regression of evaluable lesions was defined as a definite decrease in tumor size agreed upon by two independent investigators [including one radiologist (T. C.)] and no new lesions for >8 weeks.

Those patients who achieved SD or response after two cycles of therapy continued to receive protocol-specified therapy until disease progression, unacceptable toxicity, or the patient’s desire to discontinue therapy.

**Phase II study statistical planning and analysis**

The primary objective of the phase II portion of the study was to test the null hypothesis that the overall response rate—among patients evaluable for response (see definition above)—is less than 0.15 versus the alternative that it is at least 0.35. The study was performed in two stages, with 19 evaluable patients being enrolled during the first stage. If more than three of the first 19 patients responded, then an additional 25 evaluable patients were to be enrolled, for a total of 44. Only if 11 or more responses were observed were we to reject the null hypothesis. This design limited the probabilities of type I (α) and type II (β) error to 0.05 and 0.10, respectively, and minimized the expected sample size if the true response rate is 0.15 [20].

In addition to the hypothesis test described above, the overall response rate (combining CR, PR and disease regression among patients without measurable disease) was computed using all enrolled patients, and a 95% confidence interval (CI) was constructed based on the binomial distribution but ignoring the multi-stage nature of the design. Progression-free survival (defined as the time from registration until progression or death from any cause) and survival (also from date of registration) curves were estimated for all enrolled patients using the Kaplan–Meier method, and approximate 95% CIs were computed using the method described by Kalbfleisch and Prentice [21]. CIs for the median survival times were obtained as described in Bookmeyer and Crowley [22].

**Results**

**Patient characteristics**

The patients who enrolled in this trial received therapy at one of several institutions within the University of Chicago Phase II Network. Between February 1997 and September 1998, a total of 65 patients enrolled in the study. One additional patient signed consent but was not eligible due to heart block evident on an electrocardiogram and did not receive protocol therapy. Sixty-five patients were evaluable for toxicity. The patients’ characteristics are presented in Table 1. There were 41 men and 24 women with a median age of 62 years (range 44–78). Sixty-one patients (94%) had a performance status of 0 or 1. The majority of patients had stage IV disease and adenocarcinoma histology. Eight patients had received prior radiation therapy. Five patients had received prior therapy with an investigational drug, 9-aminocamptothecin [23].

**Phase I dose escalation and determination of MTD**

A total of 16 patients were treated during the phase I study. Table 1 lists the dose de-escalation schema and the number of patients treated at each dose level, while Table 2 summarizes the hematological toxicity encountered during cycle 1. Out of the eight patients who received treatment at dose level I, three experienced grade 4 neutropenia during cycle 1, although by duration it was not dose-limiting. When cumulative thrombocytopenia was noted...
in three patients treated at this dose level, dosing delays and dose reductions were necessary. Because of this severe cumulative thrombocytopenia, this dose level was not considered feasible and a dose de-escalation was undertaken. For subsequent dose levels the ifosfamide and carboplatin doses were decreased in an attempt to cumulative thrombocytopenia. The paclitaxel dose was maintained in subsequent dose levels to ensure delivery of this agent at a known level of single-agent activity. Delivery of the regimen was attempted without prophylactic growth factor support in dose level II.

Out of the eight patients treated at dose level II, three developed dose-limiting grade 4 neutropenia. One patient developed neutropenic fever without documented infection. There were no other DLTs noted at dose level II. This dose level was not considered feasible due to neutropenia and the regimen was modified to include prophylactic growth factor support in dose level III. Six patients were treated at dose level III and none experienced DLT during the first cycle of therapy. Therefore, this dose level was declared the recommended phase II dose and accrual was continued to further study the regimen’s activity and tolerability.

**Phase II study of the TIC regimen**

A total of 49 patients received protocol therapy at the recommended phase II dose. The total number of cycles administered was 201 with the median number of cycles delivered per patient was four (range one to eight). Only 9% of all cycles were delayed to allow hematological toxicity to recover.

**Overall toxicity**

The total number of treatment cycles administered to patients enrolled in the phase I and II portions of the trial was 278. Table 3 summarizes the hematological toxicity encountered during cycle 1 for patients enrolled in the phase I portion of the study. The maximum hematological toxicity experienced for all patient during all courses of therapy is listed by dose level in Table 4. Overall the

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No. of patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients enrolled</td>
<td>65</td>
</tr>
<tr>
<td>Age, median (range)</td>
<td>62 (44–78)</td>
</tr>
<tr>
<td>Gender</td>
<td>Male 42 (65)  Female 23 (35)</td>
</tr>
<tr>
<td>Initial performance status (CALGB)</td>
<td>0 28 (43) 1 33 (51) 2 4 (6)</td>
</tr>
<tr>
<td>Stage</td>
<td>IIIIB 14 (22)  IV 51 (78)</td>
</tr>
<tr>
<td>Histology</td>
<td>Adenocarcinoma 31 (48)  Squamous cell carcinoma 12 (18)  Large cell carcinoma 5 (8)  Undifferentiated carcinoma 17 (26)</td>
</tr>
<tr>
<td>Prior therapy</td>
<td>Radiotherapy 14 (22)  Investigational chemotherapy regimen 11 (17)</td>
</tr>
</tbody>
</table>

**Table 2.** Patient characteristics

<table>
<thead>
<tr>
<th>Dose level</th>
<th>No. of evaluable patients</th>
<th>WBC Grade 3</th>
<th>WBC Grade 4</th>
<th>ANC Grade 3</th>
<th>ANC Grade 4</th>
<th>Neutropenic fever Grade 3</th>
<th>Neutropenic fever Grade 4</th>
<th>Platelets Grade 3</th>
<th>Platelets Grade 4</th>
<th>DLT</th>
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<tbody>
<tr>
<td>I</td>
<td>8</td>
<td>3</td>
<td>0</td>
<td>1</td>
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<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>8</td>
<td>2</td>
<td>0</td>
<td>3</td>
<td>3</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>3’</td>
</tr>
<tr>
<td>III</td>
<td>6</td>
<td>3</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
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</tr>
</tbody>
</table>

*Did not meet criteria for DLT as duration <5 days.

ANC, absolute neutrophil count; DLT, dose-limiting toxicity; WBC, white blood cell count.

**Table 3.** Phase I investigation: hematological toxicity for cycle 1

<table>
<thead>
<tr>
<th>Dose level</th>
<th>No. of evaluable patients</th>
<th>WBC Grade 3</th>
<th>WBC Grade 4</th>
<th>ANC Grade 3</th>
<th>ANC Grade 4</th>
<th>Neutropenic fever Grade 3</th>
<th>Neutropenic fever Grade 4</th>
<th>Platelets Grade 3</th>
<th>Platelets Grade 4</th>
<th>DLT</th>
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<tbody>
<tr>
<td>I</td>
<td>8</td>
<td>34</td>
<td>4</td>
<td>0</td>
<td>1</td>
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<td>0</td>
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<td>5</td>
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<tr>
<td>II</td>
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<tr>
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<td>3</td>
<td>9</td>
<td>7</td>
<td>1</td>
<td>9</td>
<td>6</td>
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<tr>
<td>Total</td>
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<td>273</td>
<td>14</td>
<td>3</td>
<td>11</td>
<td>16</td>
<td>2</td>
<td>12</td>
<td>11</td>
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</tbody>
</table>

ANC, absolute neutrophil count; WBC, white blood cell count.
hematological toxicity encountered in patients treated at the recommended phase II dose was mild with only 14% experiencing grade 4 neutropenia of any duration and only one patient developing neutropenic fever. Cumulative thrombocytopenia was noted with this regimen with typical onset after four cycles of therapy.

The maximum non-hematological toxicities noted for all patients treated are listed in Table 5. The predominant non-hematological toxicity observed with this triplet combination was peripheral neuropathy. Six patients (9%) developed grade 3 peripheral neuropathy and two patients (3%) developed grade 4 neuropathy. Three patients developed grade 4 cardiac arrhythmia, including atrial arrhythmia in two patients and bradycardia in one patient. Grade 4 infection was noted in one patient (2%). One patient developed grade 3 neurocortical toxicity that was presumed related to ifosfamide and received no further ifosfamide in subsequent cycles. Other grade 3 or 4 non-hematological toxicities included vomiting, anorexia, fatigue and infection.

Two patients died while on study from causes of death other than disease progression. One patient died of myocardial infarction on day 3 of cycle 1. Another patient died of unknown causes during cycle 1 on day 18. One patient withdrew from the study after one cycle of therapy. The patient who experienced the septic episode did not receive further therapy after cycle 1. One of the patients who developed atrial arrhythmia discontinued therapy after cycle 1.

Response and survival
Among the first 19 patients treated in the phase II study who were evaluable for response, six had PRs and thus an additional 25 evaluable patients were enrolled. However, out of these 44 total patients only 10 responses (all partial) were observed, and thus we cannot reject the null hypothesis that the true response rate is less than 0.15. Four additional patients with non-measurable disease and one additional patient with measurable disease were treated during the phase II study for a total of 49. The responses for all 65 patients treated are shown in Table 6, separately by dose level. The overall response rate (including two responses by patients without measurable disease) for all 65 patients was 0.26 (95% CI 0.16–0.39). Twenty-six patients (40%) had SD.

Among all 65 patients, the median progression-free survival was 4.8 months (95% CI 2.8–6.7), with a 1-year progression-free survival rate of 0.18 (95% CI 0.10–0.29). One patient remained progression-free at 44 months. The median survival for all patients (Figure 1) was 9.4 months (95% CI 7.4–13.4), with 1- and 2-year survival rates of 0.42 (95% CI 0.30–0.53) and 0.09 (95% CI 0.04–0.18). At 1 June 2001, four patients remained alive with survival times of 33, 35, 36 and 44 months.

Discussion
Combination chemotherapy containing a platinum regimen is the cornerstone of therapy for patients with advanced NSCLC. However, the survival gains achieved with combination chemotherapy have been modest, with a 10% improvement in 1-year survival and a 2-month improvement in median survival. Doublet regimens employing newer chemotherapy agents confer additional benefit, although the magnitude of benefit is small. Clearly, new treatment approaches are necessary to improve the outcomes associated with this disease. One strategy is to combine three drugs with different mechanism of action and known activity in NSCLC.

This phase I/II trial demonstrates the feasibility of administering the TIC triplet regimen to patients with advanced NSCLC. In this phase I/II study, neutropenia was the DLT and prophylactic filgrastim support was necessary in order to maintain dose intensity. The recommended phase II dose of ifosfamide is 1.5 g/m² administered on days 1 and 2 with paclitaxel 200 mg/m² (1-h infusion) on day 1 and carboplatin AUC 5 mg·min/ml on day 2. The regimen also included mesna given concomitantly with the ifosfamide then again 4 and 8 h following ifosfamide. In a phase I study of this triplet combination in patients with resistant small-cell lung cancer reported by van Putten et al. [24], MTD of ifosfamide was 2000 mg/m² given in combination with paclitaxel 175 mg/m² and carboplatin AUC 6 mg·min/ml on day 1 of a

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
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<tr>
<td>Fatigue</td>
<td>24</td>
<td>21</td>
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<td>Vomiting</td>
<td>13</td>
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<td>Anorexia</td>
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<td>Diarrhea</td>
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<td>Infection</td>
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<tr>
<td>Creatinine elevation</td>
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</table>

Table 6. Treatment response by dose level

<table>
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<tr>
<th>Dose level</th>
<th>No. of patients</th>
<th>Partial response</th>
<th>Disease regression</th>
<th>Stable disease</th>
<th>Progressive disease</th>
<th>Not evaluated</th>
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<tbody>
<tr>
<td>I</td>
<td>8</td>
<td>3</td>
<td>1*</td>
<td>2</td>
<td>2</td>
<td>0</td>
</tr>
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<td>II</td>
<td>8</td>
<td>2</td>
<td>1*</td>
<td>3</td>
<td>1</td>
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<td>4</td>
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<tr>
<td>All</td>
<td>65</td>
<td>15 (23%)</td>
<td>2 (3%)</td>
<td>26 (40%)</td>
<td>17 (26%)</td>
<td>5</td>
</tr>
</tbody>
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*Includes patients enrolled at phase I dose levels who did not have measurable disease.
21-day cycle. The DLT reported in the van Putten trial was thrombocytopenia.

Our large phase II experience confirms the feasibility of delivering TIC at doses that are active, with an acceptable level of toxicity.Cumulative myelosuppression of leukopenia and thrombocytopenia was encountered at all dose levels studied. The predominant non-hematological toxicity of the regimen, peripheral neuropathy, was moderate-to-severe in 25% of patients. This triplet regimen was active in advanced NSCLC and produced an overall response rate of 26% and a median survival time of 9.4 months. The efficacy of this regimen compares favorably with results reported from randomized trials evaluating the newer doublet chemotherapy regimens [6–8], and is similar to those reported for other recent trials at our institution [13, 14, 25]. However, this regimen with this level of activity is not considered sufficient for further investigation. In addition, the need for prophylactic growth factor which is not cost-effective and beneficial in NSCLC limited its further utility.

Other trials investigating other triplet regimens in NSCLC have been completed. The combination of paclitaxel, gemcitabine and carboplatin has been studied in several phase II trials. Studies from the University of Colorado Cancer Center and the Sarah Cannon Cancer center indicated that full doses of these agents could be delivered [26, 27]. Kelly et al. [26] reported a response rate of 26% and a 1-year survival rate of 33%. Results of the Sarah Cannon trial [27] were more favorable, with a response rate of 48% with a reported 1-year survival of 47%. Hainsworth et al. [28] have evaluated the combination of paclitaxel, carboplatin and vinorelbine in a phase II trial where the regimen produced an overall response rate of 35% and 1-year survival rates of 43%. Comella et al. [29, 30] have conducted a trial evaluating the triplet regimen of gemcitabine, vinorelbine and cisplatin. They reported interim analysis results of a randomized phase III trial investigating this triplet combination and noted a median survival time of 48 weeks. Preliminary results of a randomized trial undertaken by the Spanish Lung Cancer Group [31] comparing a cisplatin-based three-drug regimen with a cisplatin doublet combination showed more favorable median survival times for the triplet regimen, 40.8 versus 44.8 weeks. A second trial comparing paclitaxel–carboplatin–gemcitabine with paclitaxel-cisplatin also favored longer survival with the three-drug regimen, 7.8 versus 10.5 months, although the difference was not statistically significant [32]. Preliminary analysis of a randomized phase II trial completed by Thompson and colleagues [33] has shown comparable survival between the two- and three-drug regimens, although results of the phase III analysis are awaited. Although the results of our phase I/II experience and other phase II trials suggest that triplet therapy might be more efficacious than doublet therapy, randomized trials are necessary to confirm superiority.

Another potential strategy for developing more active therapies is to add molecularly targeted agents to standard doublet chemotherapy approaches. Recent advances in the understanding of the biology of lung cancer and other tumors have led to the development of various novel therapies directed at tumor-specific targets. The potential combination of standard chemotherapy and these new drugs is attractive given their different mechanisms of action and toxicity profiles. Several phase I, II and III trials in patients with NSCLC are in progress to examine the feasibility and efficacy of regimens that combine targeted therapies with cytotoxic chemotherapy. A recently reported randomized phase II trial evaluated the triplet combination of anti-vascular endothelial growth factor antibody with carboplatin and paclitaxel in patients with advanced NSCLC [34]. Several other trials are underway to combine novel cellular therapies, which target receptor tyrosine kinase growth factor receptors with cytotoxic chemotherapy. It is hoped that the combination of standard chemotherapy and targeted therapies will result in improved outcomes for patients with NSCLC. These approaches appear more promising for advanced NSCLC and therefore we are no longer pursuing classic cytotoxic triplet combinations.

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References


