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Phase II trial of preoperative pemetrexed plus carboplatin in patients with stage IB-III nonsquamous non-small cell lung cancer (NSCLC)

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ABSTRACT

Objectives: The combination of pemetrexed and carboplatin is a standard first-line treatment for patients with advanced NSCLC. In this pilot phase II trial, we evaluated the feasibility of using pemetrexed and carboplatin as neoadjuvant therapy, prior to definitive surgical resection, for patients with localized NSCLC.

Patients and methods: Patients with potentially resectable, previously untreated, clinical stage IB-III, non-squamous NSCLC were eligible for this trial. All patients received 4 cycles of pemetrexed (500 mg/m^2) and carboplatin (AUC 6.0) administered at 21 day intervals. Three to 6 weeks after completion of chemotherapy, definitive surgical resection was attempted. The primary endpoint of this trial was the 3-year survival rate.

Results: Forty-six patients began protocol treatment, and 40 completed 4 courses of pemetrexed/carboplatin. Surgical resection was performed in 27 patients (59%); all had pathologic partial responses. The estimated 3-year survival rate for the entire group was 46%. Toxicity of neoadjuvant therapy was consistent with toxicity previously reported with pemetrexed/carboplatin.

Conclusions: Administration of 4 courses of pemetrexed/carboplatin was feasible. The efficacy was similar to neoadjuvant regimens previously investigated. A significant number of patients 19 of 46 (41%) in this trial did not have surgical resection after neoadjuvant therapy. Further investigation of the role of neoadjuvant pemetrexed/carboplatin requires a larger, randomized clinical trial.

1. Introduction

Approximately one-third of patients with non-small-cell lung cancer (NSCLC) have potentially resectable cancer at the time of diagnosis. However, the recurrence rate following surgical resection is high for all patients except those with stage IA cancer [1]. Adjuvant chemotherapy with a cisplatin-containing regimen produces a modest improvement in disease-free survival [2,3], but further improvements are necessary.

Preoperative (neoadjuvant) therapy has also been evaluated in patients with potentially resectable stage IB, II, and IIIA NSCLC. Several randomized phase III trials have suggested modest benefit for preoperative combination chemotherapy when compared to surgery alone [4–6]. A variety of chemotherapy regimens were used in the various trials including mitomycin/ifosfamide/cisplatin [4], paclitaxel/carboplatin [5], and gemcitabine/cisplatin [6].

In recent years, pemetrexed has been incorporated into the first-line treatment of metastatic NSCLC [7–10]. Pemetrexed-containing regimens were the first chemotherapy regimens to show differential efficacy based on the histology of NSCLC [9,11]. In non-squamous NSCLC, first-line treatment with pemetrexed/cisplatin improved efficacy when compared to gemcitabine/cisplatin, while efficacy was inferior with the pemetrexed-containing regimen in squamous lung cancer [9]. Pemetrexed/platinum regimens have also been better tolerated in most studies than other platinum-containing doublets [9,10]. On the basis of these data, pemetrexed/platinum combinations are widely used as first-line treatment for non-squamous NSCLC. However, limited data is

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available regarding the use of pemetrexed-containing regimens in the adjuvant or neoadjuvant treatment of resectable NSCLC.

In this pilot phase II trial, we evaluated the feasibility of preoperative therapy with pemetrexed and carboplatin in patients with potentially resectable non-squamous NSCLC. The trial was designed to assess the toxicity of pemetrexed/carboplatin when used preoperatively, and to obtain a preliminary assessment of the efficacy of this treatment approach.

2. Materials and methods

This non-randomized multicenter phase II trial (NCT00906282) was initiated in 2009, and patients were enrolled at 10 participating sites (Appendix A). The study was approved by the institutional review boards at each site prior to patient enrollment.

2.1. Eligibility

Patients with histologically confirmed non-squamous NSCLC (adenocarcinoma, large cell carcinoma, or undifferentiated carcinoma) were eligible for this trial. All patients were required to have potentially resectable NSCLC and to be operative candidates. Specific clinical stages of NSCLC that were eligible for this trial included: 1) T2N0 with primary tumor ≥ 4 cm, 2) T1-2N1, 3) T3N0-1 (excluding superior sulcus tumors, 4) T1-2N2 (N2 disease limited to one nodal zone and nodes ≤ 2 cm in diameter), and 5) T4N0-1, excluding superior sulcus tumors and excluding tumors in which radiotherapy was planned as a part of treatment [12]. Additional eligibility criteria included: no evidence of extrathoracic metastatic disease, measurable disease (RECIST v1.0), ECOG performance status 0–1, adequate organ function (ANC ≥ 1500/μL, platelets ≥ 100,000/μL, liver function tests normal, calculated creatinine clearance ≥ 45 ml/minute), and ability to take concomitant medications required by protocol (folic acid, vitamin B12, dexamethasone). All patients were required to give written informed consent prior to study enrollment.

Patients with squamous carcinoma (or with mixed histology containing squamous elements), small-cell carcinoma, or pulmonary carcinoid tumors were excluded. Additional exclusion criteria included: significant cardiovascular disease, pregnancy or lactation, use of erythropoietin as a hematopoietic growth factor, presence of third space fluid not controlled by drainage, any concurrent severe medical or psychiatric illness that could affect the ability to participate in the trial, and history of hypersensitivity to any components of the treatment.

2.2. Pretreatment evaluation

Before the initiation of study treatment, all patients underwent a complete medical history, physical examination, complete blood counts, chemistry profile, and assessments of ECOG performance status and concomitant medications. A serum pregnancy test was required for all women of childbearing potential. Tumor staging evaluation included computerized tomography of the chest and abdomen, PET scan or bone scan, and CT or MRI scan of the brain. Patients with apparent N2 adenopathy on scans required confirmation by biopsy.

2.3. Study design

The treatment plan is summarized in Fig. 1. All patients received 4 cycles of pemetrexed (500 mg/m^2 IV infused over 10 min) and carboplatin (AUC 6.0 IV infused over 30–60 min), administered at 21 day intervals. The carboplatin dose was calculated using the Calvert formula [13]. Doses of both drugs were recalculated if the body weight changed by ≥ 10% during study treatment. All patients received folic acid (350–1000 μg orally daily), vitamin B12 (1000 μg IM 1–2 weeks prior to the first dose of pemetrexed, after the third cycle, and 3 weeks after the last dose), and dexamethasone (10 mg IV concurrently with each pemetrexed dose). Prophylactic antiemetics were administered per institutional guidelines.

Patients were re-evaluated after completing 2 cycles of chemotherapy; patients with progressive disease were removed from study. After completion of 4 cycles of chemotherapy, patients were restaged with CT scans of the chest and abdomen; repeat PET scan was recommended, but not required. All patients who remained surgical candidates had resection, preferably within 3–6 weeks of completion of chemotherapy. Surgical resection followed standard guidelines (1) for the resection of NSCLC, and could include lobectomy or pneumonectomy, as well as resection of adjacent chest wall or mediastinal structures if necessary. The surgical procedure included either ipsilateral mediastinal node dissection or node sampling.

Following surgical resection, patients received no further planned protocol treatment. For patients who had complete (R0) resection, follow-up without further treatment was recommended. Patients who had residual cancer after surgical resection had further treatment off-study at the discretion of their physician. Patients were seen in follow-up every 3 months during the first 2 years, and every 6 months subsequently; CT scans were performed at 6 month intervals until relapse or progression was documented.

2.4. Dose modifications

Dose modifications for hematologic and non-hematologic toxicity were specified in the protocol. Two dose level reductions were allowed for pemetrexed (dose level −1, 400 mg/m^2; dose level −2, 300 mg/m^2) and carboplatin (dose level −1, AUC = 5; dose level −2, AUC = 4). If patients required more than a 3 week treatment delay due to toxicity, they were required to discontinue study treatment.

Complete blood counts were assessed on the first day of each treatment cycle. If the ANC was ≥ 500/μL and the platelet count was ≥ 50,000/μL, full doses of both agents were administered. If either count was below these minimum values, treatment was delayed for 1 week, and resumed with 1 dose level reductions of both drugs when the counts had risen to minimum required levels. Dose reductions were also required following episodes of neutropenic fever. Granulocyte colony stimulating factors were not used with the first treatment cycle, but subsequent addition of these agents was permitted at the discretion of the treating physician.

For grade 3 or 4 non-hematologic toxicity, treatment was delayed until the toxicities had resolved to ≤ grade 1, and then resumed with a 1 dose level reduction of the offending agent or agents. For grade 4 toxicity associated with pemetrexed (mucositis, myelosuppression), leucovorin (100 mg/m^2 IV followed by oral leucovorin 50 mg/m^2 every 6 h until resolution of toxicity) was recommended.

2.5. Statistical analysis

The primary objective of this study was to determine the 3-year overall survival (OS) rate following this neoadjuvant treatment. The expected 3-year OS following resection alone (assuming enrollment of < 20% Stage IB patients, based on our patient population in previous trial) was estimated to be 33% [14]. A 3-year OS of ≥ 50% was considered a treatment result of interest. The sample size of 50 patients in this phase II trial was selected in order to yield a 3-year OS with 95% confidence intervals of ± 12%.

Secondary endpoints in this trial included: objective response rate, pathologic response rate, complete resection rate, and treatment-related toxicity.

Actuarial survival curves were constructed using the method of Kaplan and Meier [15]. Overall survival was defined as the interval from first study treatment until the date of death. All patients who received at least 1 dose of study treatment were included in the toxicity analysis. Toxicity was measured using the National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0.