A Pilot Phase Ii Study Of Capecitabine With Carboplatin In Patients With Advanced Nonsmall Cell Lung Cancer

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Citation

B Sagar, F Estaphan, D Spell, F Klementich, D Jones Jr.. *A Pilot Phase Ii Study Of Capecitabine With Carboplatin In Patients With Advanced Nonsmall Cell Lung Cancer*. The Internet Journal of Oncology. 2008 Volume 6 Number 1.

Abstract

Carboplatin forms the backbone of many regimens for nonsmall cell lung cancer (NSCLC). 5-fluorouracil (5-FU) is modestly active in NSCLC and is synergistic with platinum analogs. This trial evaluated the activity and toxicity of capecitabine, an oral 5-FU prodrug, with carboplatin in patients with unresectable NSCLC. Eligibility criteria included untreated measurable stage III-B/IV NSCLC, ECOG performance status < 2, and adequate organ function. Carboplatin, AUC=5, was administered on day one, with capecitabine, 4000 mg days 1-14, every 28 days. Tumor assessments were obtained every other cycle. Fifteen patients (median age = 64; median performance status = 0) were enrolled and received 46 cycles of protocol therapy; 13 were evaluable for response, with 5 partial responses (38.5%). Five withdrew due to toxicity; four possibly related to study therapy. Median survival was 8 months. Capecitabine and carboplatin are active in NSCLC. Further investigation is not warranted, as this current regimen is too toxic.

INTRODUCTION

Lung cancer is the second most common form of cancer and the leading cause of cancer death in both men and women in the United States. Data from the American Cancer Society project nearly 215,000 new cases of lung cancer, with a slight male predominance in the year 2008. Approximately 35% to 40% of these patients have metastatic disease at the time of diagnosis. The incidence for men is beginning to decrease, and may have reached a plateau in women. While prostate and breast cancers are more common in men and women, respectively, lung cancer is still a far more lethal malignancy in both genders, with a five-year survival rate that is less than 15%. Indeed, lung cancer accounts for 33% of all cancer related deaths in men, and 5% of all cancer related deaths in women [1]. Chemotherapy for stage IV non-small cell lung cancer (NSCLC) is still suboptimal, and for all intents and purposes, metastatic lung cancer remains incurable. With treatment, advanced NSCLC has a median survival of 6 to 8 months in most series and a 1-year survival of 10-20% [2].

As recently as a decade ago, administration of chemotherapy to patients with NSCLC was regarded as an exercise in futility. The past ten years have seen a change in philosophy, with the approval of at least five agents that have demonstrated antineoplastic activity in NSCLC (gemcitabine, vinorelbine, irinotecan, docetaxel and paclitaxel). All these agents appear to have greater benefit when combined with platinum (either cisplatin or carboplatin). In May, 1997, the American Society of Clinical Oncology defined clinical practice guidelines for the treatment of patients with unresectable NSCLC [3]. These guidelines recommended platinum-based therapy, though a specific platinum regimen was not identified. The EORTC compared cisplatin to carboplatin, both in combination with etoposide, in patients with advanced NSCLC. This randomized trial demonstrated no differences in either response or survival rates between the two treatment arms [4]. However, there was a significant difference favoring carboplatin treatment with respect to toxicity, with less nausea and vomiting, ototoxicity, and nephrotoxicity. Unlike cisplatin, the primary toxicities of carboplatin are myelosuppression, especially thrombocytopenia, moderate nausea and vomiting, and less commonly ototoxicity and renal toxicity. However, no combination of a platinum with one of these “second generation” agents appears to be superior to any other, with overall survival benefits of approximately a few months.

Capecitabine is an oral 5-fluorouracil (5-FU) prodrug that has been approved for the therapy of advanced breast and colorectal cancers, though it is active in a variety of other malignancies. Chronic administration of capecitabine mimics prolonged infusional schedules of 5-FU, which may

be superior to bolus administration [5]. The fluoropyrimidines are synergistic with cisplatin and carboplatin, but there has been limited experience of a combination of these agents, and no reported data concerning the use of capecitabine, in NSCLC. As the ultimate outcome of systemic therapy in NSCLC is still poor, we investigated a combination of capecitabine with carboplatin in patients with advanced NSCLC.

PATIENTS AND METHODS

ELIGIBILITY

All patients were required to have a histologic diagnosis of NSCLC that was either locally advanced but not amenable to treatment with radiotherapy or surgery; or metastatic disease. Other eligibility criteria included an Eastern Cooperative Oncology Group (ECOG) Performance Status ≤ 2; have a life expectancy > 8 weeks; be >18 years old; be using effective contraception, have evidence of good end-organ function (absolute neutrophil count >1500/μL, platelet count >100,000/μL, serum creatinine ≤ 2.0 mg %, bilirubin ≤1.5x normal); and a total serum calcium ≤12 mg/dl. Patients were excluded if either pregnant or lactating; had a myocardial infarction or ischemia within six months, or had uncontrolled, clinically significant dysrhythmia; had a prior invasive malignancy within the prior five years (with the exception of non-melanoma carcinomas of the skin, and carcinoma in situ of the cervix); had prior chemotherapy; had prior radiotherapy to an indicator lesion unless there is objective evidence of tumor growth in that lesion; had evidence of uncontrolled metastatic disease of the central nervous system; had received either radiotherapy or surgery within two weeks; or had any co morbid condition that, in the view of the attending physician, might place the patient at an increased risk for treatment complications. All patients were required to provide signed informed consent form approved by the University of Texas Medical Branch Institutional Review Board.

TREATMENT PLAN

STUDY EVALUATIONS

Within three weeks of the initiation of therapy, all patients were required to undergo a baseline evaluation including a medical history and physical examination, complete blood count with leukocyte differential, serum chemistries, and computed tomography or magnetic resonance imaging scans for tumor measurement. Blood counts were repeated weekly during the first cycle, and along with the serum chemistries, prior to each cycle. Repeat radiographic evaluation was performed prior to every other cycle in order to document tumor response.

CHEMOTHERAPY GUIDELINES

Carboplatin at an Area Under the Curve (AUC, Calvert method, using the Cockroft and Gault method to estimate creatinine clearance) of 5, was administered intravenously over 30-60 minutes after adequate antiemetic premedication, including (but not limited to) a steroid (e.g. dexamethasone) and a serotonin receptor blocker (e.g. ondansetron, granisetron, or dolasetron) on day 1. Capecitabine at a fixed dose of 4000 mg, was administered orally each day in divided doses, days 1-14, followed by a fourteen day rest period, for a cycle duration of 28 days.

DEFINITION OF RESPONSE

All patients were eligible for evaluation of toxicity, even if they were unable to complete the first cycle. All participants were required to have at least one “measurable” lesion, defined at the outset of the trial as a bidimensionally measurable lesion with clearly defined margins by photograph or by X-ray/CT/MRI scan with at least one dimension > 0.5 cm, or a palpable lesion with both diameters > 2 cm.

A Complete Response (CR) was defined as the complete disappearance of all evidence of tumor for a period of at least one month, while a Partial Response (PR) was defined as at least a 50% decrease in the product of diameters of all measurable disease, also for a period of at least one month. Progressive Disease (PD) was defined as a 25% or greater increase in the product of diameters of any site of measurable disease, or any new sites of disease. Stable Disease (SD) was defined as either no change, or any change less than a 50% decrease or less than a 25% increase in the product of the diameters of any measurable disease, or any CR or PR that lasted less than one month.

STATISTICAL CONSIDERATIONS

The study was designed as a two-stage phase II protocol. A response rate of 20% or above to a combination of capecitabine with carboplatin was considered of interest in patients with NSCLC. Initially, 14 patients would be evaluated for response. If none of the 14 evaluable patients experienced a partial or complete response, then the study would be terminated. If the true response rate were 20%, the chance of rejection error would be less than 5%. However, in the event of one response among the first 14 patients, further accrual would continue to a total of 30 evaluable patients to

estimate the response rate more precisely with a standard error of no more than 9%.

Safety considerations also determined accrual. If 2 of the first 6 patients experienced grade 4 non-hematologic toxicity, the chemotherapy doses would be decreased by 20% in succeeding patients. If 2 of the next six patients continued to have grade 4 non-hematologic toxicity the protocol would be stopped.

All patients were followed for both progression-free and overall survival.

RESULTS

PATIENT DEMOGRAPHICS

A total of 15 patients were entered into this study, ten men and five women (for details, please see Table 1). The age range was typical for that which is seen with nonsmall cell lung cancer, from 52 to 79 years of age, with a median age of 64 years old. Ten patients were either asymptomatic or minimally symptomatic at the time of initiation of protocol therapy, with an ECOG PS of 0-1.

RESPONSES TO THERAPY

A total of 46 cycles of therapy were administered on this study (range = 1-6, median = 2). Two patients were removed from the study due to non-compliance with the oral medication, but were included in the response evaluation. Both patients received two cycles of carboplatin, and both patients experienced stable disease prior to removal from the study. Two patients were removed from the study due to toxicity after receiving only one cycle of therapy (see below), and were excluded from evaluation for response. Five of the 13 evaluable patients were observed to have an objective tumor response, for a response rate of 38.5%. Two additional patients had stable disease through six cycles of therapy as their best antitumor response, for an overall non-progression rate was 69.2%. The median duration of response was 4 months (range 1 - 7 months). The two noncompliant patients were offered alternative therapy: one patient progressed on a second regimen, while the other has had a partial response which has lasted 9+ months.

Four patients are still alive with persistent disease following additional therapy regimens. The median overall survival was 8 months (range 2 - 19+ months). As might be expected, the five patients with a marginal performance status (ECOG PS of 2) fared worse than those with a better performance status (ECOG PS of 0 - 1), with a median survival of 3 months (range 2 - 8 months) versus 13 months (range 2 - 19+ months), respectively.

TOXICITY

There were no episodes of febrile neutropenia or significant anemia or thrombocytopenia. However, several patients did not complete all of the protocol-specified laboratory assessments, making it difficult to determine if more severe myelosuppression may have been missed. Nevertheless, five patients were removed from the study due to significant non-hematologic toxicity, and four of these adverse events were directly related to the protocol therapy. Two patients developed severe (grade 4) diarrhea, one complicated by the development of Gram-negative sepsis and an ileus which resolved spontaneously after several days. The third patient developed grade 4 fatigue and weakness after cycle six of therapy. This patient experienced a partial response after four cycles, and as his disease was stable over the next two treatment cycles, he was removed from therapy. The fourth patient experienced grade 4 weakness and grade 3 nausea and vomiting despite aggressive antiemetics, and requested termination of antineoplastic therapy and hospice care referral. The final patient experienced bilateral internal jugular vein thrombosis and a right parietal lobe infarction and was removed from active therapy; this serious adverse event was deemed to not be related to the therapy, but to his underlying disease. Due to the pattern of toxicities seen over the first cohort of patients, it was determined by the investigators that the potential risks of this regimen were excessive for what was expected, and further accrual to this protocol was terminated.

DISCUSSION

Disseminated non-small cell lung cancer remains a frustrating disease to treat, with poor responses to treatment in the vast majority of patients. Although treatment with chemotherapy may offer some palliative benefit, the survival benefit of platinum-based chemotherapy, still considered the “gold standard”, is modest and measured in weeks. We need to identify and evaluate new agents and combinations that may offer improvements in response rate, and survival. Equally important is to identify regimens that may be equivalent in activity to the current standard regimens, but with less toxicity.

Over the past five years, several novel agents have demonstrated activity in NSCLC, expanding what has been, until recently, a very limited armamentarium. Second

generation agents, such as gemcitabine, the taxanes, and the camptothecin analogs are active and fairly well tolerated, though they all must be administered intravenously, often on a weekly or daily schedule that may prove prohibitively inconvenient for many of the patients that are seen. Thus far, none has proven superior to any other when combined with either cisplatin or carboplatin, as was demonstrated in the recent Eastern Cooperative Oncology Group randomized phase III trial [6].

One of the oldest antineoplastic agents available, 5-FU, has some activity against non-small cell carcinoma of the lung. The most recent studies have evaluated bolus infusions of 5-FU, usually in combination with other agents such as cisplatin and etoposide or a vinca alkaloid, or radiotherapy, often producing impressive response rates up to 71%.[7-11] Single agent 5-FU is modestly active in combination with leucovorin, with a 16% objective response rate noted in one study.[8] While 5-FU may be more active when administered continuously, prolonged infusion is cumbersome for most patients. Capecitabine is a new oral prodrug which is converted into 5-FU and its active metabolites. Thus, the equivalent of a protracted 5-FU infusion can be easily and conveniently achieved by oral administration, taking advantage of a continuous exposure of tumor cells to 5-FU. To date, there have only been three reports of an oral 5-FU prodrug (UFT; uridine and ftorafur) administered to patients with NSCLC. In two small series a, low response rate was observed, although low doses of UFT were used. In the third trial, UFT was administered as post-surgical adjuvant therapy, and was associated with a statistically significant increase in 5-year survival. [12-15]

Several of the observations from this limited study are parallel to those of the ECOG trial [6]. In the ECOG study, patients with a worse performance status (ECOG PS = 2) tolerated therapy poorly in general, necessitating an amendment to the trial that limited enrollment to patients with a better performance status. The median response rate across all arms was 19%, with a range of 16% - 21%, and few complete responses. Similar to this study, the median time to tumor progression was 3.7 months, and the median overall survival was 8 months. The one-year survival of 33% was similar to the 40% observed here, considering the small number of subjects enrolled on this study. Depending upon the treatment arm, between 15% and 27% were withdrawn from the ECOG study due to toxicity, as compared to 33% in this trial.

The combination of capecitabine and carboplatin appears to be active in NSCLC. This is similar to the findings of Japanese investigators, who have observed improved survival when a related oral fluoropyrimidine, UFT was administered as an adjuvant therapy for patients with completely resected early stage NSCLC [14,15]. It also appears that the capecitabine contributes activity in this regimen, as the platinums which are currently available in North America (cisplatin and carboplatin) actually have very limited activity as single agents in this disease. It is known that the fluoropyrimidines, the active product of capecitabine metabolism, are synergistic with the platinums, though it is unclear if this is the case in this setting. As such, this combination appeared to be a potential treatment regimen for this population of patients, but in combinaion with carboplatin was not well tolerated in our patient population.

One must be clear about the goals of therapy in patients with metastatic or locally advanced NSCLC. This is still a disease which cannot be cured by today's technology. Palliation is the predominant goal of therapy, requiring less toxic regimens than the one evaluated in this study. In common with other platinum-based regimens, this cannot be offered with impunity to patients with a poor performance status as they will not tolerate it. New palliative and treatment strategies must be devised for this population which accounts for a large number of the patients at the time of initial presentation presentation, and virtually all patients at the time of disease progression. The combination of a fluoropyrimidine and a platinum compound does appear to have significant activity in NSCLC. However, although the activity seems promising, this combination in the current dose and schedule is too toxic to be recommended for most patients with advanced NSCLC.

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References

1. American Cancer Society. Cancer Facts & Figures 2008. Atlanta: American Cancer Society; 2008.
2. Langer CJ. Chemotherapy inroads in treating stage IV non-small cell lung cancer. In: Langer C, Rosveld E., eds. Newer aspects in the diagnosis, treatment, and prevention of non-small cell lung cancer. Part II, Current Problems in Cancer. St. Louis: Mosby; 1996; Jul/Aug., Vol. XX:221.
3. American Society of Clinical Oncology. Clinical practice guidelines for the treatment of unresectable non-small cell lung cancer. Journal of Clinical Oncology. 1997;15:2996.
4. Klastersky J, Sculier JP, Lacroix H, Dabouis G, Bureau G,

Libert P, Richez
5. A randomized study comparing cisplatin or carboplatin with etoposide in patients with advanced non-small cell lung cancer: European Organization for Research and Treatment of Cancer Protocol 07861. Journal of Clinical Oncology. 1990;8:1556.
6. Lokich JJ, Ahlgren JD, Gullo JJ, Philips JA, Fryer JG. A prospective randomized comparison of continuous infusion fluorouracil with a conventional bolus schedule in metastatic colorectal carcinoma: A Mid-Atlantic Oncology Program study. Journal of Clinical Oncology. 1989; 7:425.
7. Schiller JH, Harrington D, Belani CP, Langer C, Sandler A, Krook J, Zhu J, Johnson DH. Comparison of four chemotherapy regimens for advanced non-small-cell lung cancer. New England Journal of Medicine. 2002; 346:92.
8. Yang CT, Chang WC. Chen LH, Leung WM, Lee CH, Liaw CC. Concurrent 5-fluorouracil, leucovorin, etoposide, cisplatin and radiotherapy for locally advanced non-small cell lung cancer. Chang-Keng i Hsueh Tsa Chih. 1997; 20(3):187.
9. Ball D, Smith J, Bishop J, Olver I, Davis S, O'Brien P, Bernshaw D, Ryan G, Millward M. A phase III study of radiotherapy with and without continuous-infusion fluorouracil as palliation for non-small-cell lung cancer. British Journal of Cancer. 1997; 75(5):690.
10. Crawford J, O'Rourke M, Schiller JH, Spiridonidis CH, Yanovich S, Ozer H, Langleben A, Hutchins L, Koletsky A, Clamon G, Burman S, White R, Hohneker J, Spiridonidis CH. Randomized trial of vinorelbine compared with fluorouracil plus leucovorin in patients with stage IV non-small-cell lung cancer. Journal of Clinical Oncology. 1996; 14(10):2774.
11. Nakano T, Ikegami H, Nakamura S, Kawase T, Nishikawa H, Yokota S, Yoshida M, Tachibana T, Igarashi T, Komuta K, Higashino K. A phase II study of cisplatin, vindesine and continuously infused 5-fluorouracil in the treatment of advanced non-small-cell lung cancer. Osaka Lung Cancer Chemotherapy Study Group. British Journal of Cancer. 1996; 73(9):1096.
12. Tanaka F, Yanagihara K, Ohtake Y, Fukuse T, Hitomi S, Wada H. p53 status predicts the efficacy of postoperative oral administration of tegafur (FT) for completely resected non-small cell lung cancer (NSCLC) (Meeting abstract). Proceedings of the Annual Meeting of the American Society of Clinical Oncology. 1997; 16:A1746.
13. Xu G, Rong T, Lin P. Adjuvant chemotherapy following radical surgery for non-small-cell lung cancer: a randomized study on 70 patients. Chinese Medical Journal. 2000; 113(7):617.
14. Tanaka F, Miyahara R, Ohtake Y, Yanagihara K, Fukuse T, Hitomi S, Wada H. Advantage of post-operative oral administration of UFT (tegafur and uracil) for completely resected p-stage I-IIIa non-small cell lung cancer (NSCLC). European Journal of Cardio-Thoracic Surgery. 1998; 14(3):256.
15. Wada H, Hitomi S, Teramatsu T. Adjuvant chemotherapy after complete resection in non-small-cell lung cancer. West Japan Study Group for Lung Cancer Surgery. Journal of Clinical Oncology. 1996; 14(4):1048.
16. Wada H, Miyahara R, Tanaka F, Hitomi S. Postoperative adjuvant chemotherapy with PVM (Cisplatin + Vindesine + Mitomycin C) and UFT (Uracil + Tegafur) in resected stage I-II NSCLC (non-small cell lung cancer): a randomized clinical trial. West Japan Study Group for lung cancer surgery (WJSG). European Journal of Cardio-Thoracic Surgery. 1999; 15(4):438.

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