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CLINICAL TRIAL REPORT

A phase I study of gemcitabine plus palliative radiation therapy for advanced lung cancer

Brian Choi · H. Ian Robins · Joan Schiller · Minesh Mehta

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Abstract
Purpose To determine the maximum-tolerated dose (MTD) and antitumor activity of twice-weekly gemcitabine when combined with palliative-dose thoracic radiation therapy (RT) in patients with recurrent or progressive lung cancer.
Methods Patients were enrolled in a dose-escalating study of gemcitabine with a starting dose level of 40 mg/m^2 given as 30-minute infusions twice weekly concurrent with RT. The RT dose was 30 Gy in 10 fractions, 5 fractions per week.
Results A total of 18 patients were enrolled on three dose levels: 40, 50, and 65 mg/m^2. Four patients came off study early due to rapid progression of disease and therefore were not evaluated. The MTD of gemcitabine was found to be 50 mg/m^2. Dose-limiting toxicities were grade-4 esophagitis in one patient and grade-4 neutropenia in another patient. Overall response included 1 partial response (PR). Local response included six PR, four minor response (MR), three stable disease (SD), and one progressive disease (PD).
Conclusion The MTD of gemcitabine with concominant palliative thoracic radiation therapy is 50 mg/m^2 twice weekly. The DLTs observed were grade-4 esophagitis and grade-4 myelotoxicity at 65 mg/m^2.

B. Choi · H. I. Robins
Department of Medicine, University of Wisconsin, Madison, WI 53792, USA

H. I. Robins · M. Mehta (✉)
Department of Human Oncology, University of Wisconsin, K4/3, 600 Highland Ave., Madison, WI 53792, USA
e-mail: mehta@humonc.wisc.edu

J. Schiller
Department of Internal Medicine, UT Southwestern, Dallas, TX 75390, USA

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Introduction

It is estimated that lung cancer will lead to 213,380 new cases and 160,390 deaths in the United States in 2007. Five-year survival for all lung cancer patients is 15% and approaches 0% with overt metastatic disease [1]. For patients with metastatic disease or inability to tolerate the full dose of RT, treatment is given with palliation as the main goal, using an abbreviated course up to 30 Gy [2]. The addition of concurrent chemotherapy to curative-dose RT is known to improve outcome in stage III lung cancer [3–5], and a recent meta-analysis of the randomized clinical trials demonstrated that the bulk of this gain accrued from improved intrathoracic control, not a reduction in distant metastatic disease (for ref. see the ASTRO abstract book for 2007). This suggests that the synergistic (potentially through radiosensitization) or additive effects of chemotherapy to radiotherapy are critical. In the context of palliative thoracic RT, such an effect of radiosenstizing chemotherapy has not been systematically explored.

Several classes of drugs have demonstrated in vitro radiation enhancement activity; these include the platinum analogs, fluoropyrimidines, and gemcitabine [6]. Gemcitabine is a deoxycitidine analog with promising radiation enhancing properties in both preclinical and clinical studies [7]. The radiosenstizing effect of gemcitabine appears to be schedule-dependent, with weekly or twice-weekly regimen being superior (at least in terms of tolerance) to daily treatment [8]. The ultimate goal of the combination of gemcitabine and radiation should be a regimen for the entire course of RT that would maximize radiosensitization (i.e., as many radiation fractions as possible should be sensitized). Several

phase-I studies combining weekly gemcitabine and curative RT (50.4–60 Gy) have been performed for stage-3 NSCLC, with dose-limiting toxicities consisting of esophagitis and pneumonitis [9–12]. Twice-weekly gemcitabine has been evaluated in several studies for pancreatic cancer [7] but data are more limited in lung cancer. Furthermore, no study to date has explored the potential of using gemcitabine as a radiosensitizing agent to improve the efficacy of palliative RT. The objective of this study was to evaluate a twice-weekly gemcitabine schedule with palliative thoracic RT to determine the maximum tolerated dose (MTD), toxicity, and antitumor activity in advanced lung cancer.

Methods

This Phase-I clinical trial was approved by the Human Subjects Committee at the University of Wisconsin, which functions under a multiple project assurance issued by the United States Department of Health and Human Services.

Patient selection

Eligibility criteria included age ≥18 years; documented progressive or recurrent carcinoma of the lung requiring a course of palliative radiation therapy; Eastern Cooperative Oncology Group (ECOG) performance status ≤2; disease outside any previous radiotherapy port; adequate bone marrow function (hemoglobin ≥9.0 g/dl; WBC ≥3,500/mm^3; neutrophils ≥1,500/mm^3; platelets ≥100,000/mm^3); adequate renal function (creatinine ≤1.5 mg/dl); adequate hepatic function (serum bilirubin ≤2.0 mg/dl; SGOT/AST, SPGT/ALT, and alkaline phosphatase ≤2 times the upper limit of normal); and written informed consent. Exclusion criteria were concurrent brain irradiation (patients with clinically stable brain metastases were eligible if not receiving corticosteroids); significant, uncontrolled infection; active second malignancy; concurrent severe medical problems unrelated to the malignancy, which would significantly limit full compliance with the study or expose the patient to extreme risk of decreased life expectancy; active peptic ulcer disease, esophageal reflux, or hiatal hernia; concurrent chemotherapy with other agents, immunotherapy, or investigational therapy (RT to other sites was allowed unless the investigator deemed the mucosal toxicity to be intolerable, and prior chemotherapy was also allowed); pregnancy or lactation; patients should not have received more than 60 Gy external beam RT to the thorax at the end of protocol therapy.

Evaluation of toxicity and maximal tolerated dose

Adverse events were evaluated using the NCI common toxicity criteria, version 2.0. In a modified Fibonnaci phase-I design, three patients were entered per cohort, with additional patients entered at a given dose level if dose-limiting toxicity (DLT) was encountered. Dose-limiting toxicity was defined as grade-4 myelotoxicity, grade-3 constitutional symptoms, grade-4 esophagitis, or grade-4 pneumonitis. If two or more patients experienced DLT at one dose level, then the previous dose level was considered the maximum tolerated dose (MTD). If no patients experienced DLT at a dose level, then three patients were entered at the next dose level. At least six patients were evaluated at the MTD.

Chemotherapy

Gemcitabine was given intravenously, twice weekly, in escalating dose cohorts (as described above). Doses of gemcitabine were separated by at least one day. The dose cohorts studied were 40, 50, and 65 mg/m^2 (dose levels 1, 2, and 3, respectively). Modifications in the gemcitabine dose were permissible for treatment-related toxicities. Doses of gemcitabine were calculated weekly based on blood counts. One hundred percent of the gemcitabine dose was given if ANC > 1,000 and platelets > 75,000; 75% of the dose was given if ANC 500–999 or platelets 50,000–74,999; and the dose of gemcitabine was omitted if ANC < 500 or platelets < 50,000. For any grade-3 (except esophagitis and pneumonitis) or grade-4 treatment-related toxicities not mentioned above, the treatment was withheld until the toxicity resolved to grade-1 or less. The treatment was then resumed at 50% of the assigned dose (permanent dose reduction). Although standard phase I dose levels are often designed to increase by 33%, we elected to increase dose cohorts by 25% due to the mucosal toxicity of this combination that was previously reported [10,11,13].

Radiation therapy

Radiation therapy portals were designed with palliative intent to include all disease deemed necessary to be covered by the radiation oncologist. The dose of radiation was 30 Gy (3 Gy/day × 10 fractions, 5 fractions per week). On the days when gemcitabine was infused, RT was given after completion of drug infusion, without a mandated time interval. Treatment had to be given with photon energies in the 4–10 MV range; cobalt and electrons were not permitted; midline spine blocks were not permitted. Treatment breaks of a maximum of 2 days were allowed for holidays or travel issues only.

Overall response assessment

Assessment of all measurable disease on X-ray or computed tomography (CT) was performed at baseline,

4 weeks, and 8 weeks post-treatment. The following prespecified response criteria were used: complete response (CR) was defined as disappearance of all clinically detectable malignant disease for at least 4 weeks; partial response (PR) was defined as ≥50% decrease in the tumor area for at least 4 weeks; stable disease (SD) was defined as no significant change in measurable or evaluable disease for at least 4 weeks (i.e., 8 weeks after completion of therapy); and progressive disease (PD) was defined as ≥50% increase in the area of the index lesions smaller than 2 cm^2, ≥25% increase of index lesions larger than 2 cm^2, or deterioration in ECOG performance status by at least one level related to malignancy.

Local response assessment

Local response was measured separately. Disease encompassed within the radiation field was assessed on chest X-ray and CT performed at baseline and subsequent follow-up until death or tumor progression. The following response criteria were used: CR was defined as complete disappearance of disease; PR was defined as ≥50% reduction in the tumor area measured on chest X-ray or CT; minor response (MR) was defined as ≥25 to <50% decrease in the tumor area; SD was defined as any reduction in the tumor area <25%; and PD was defined as ≥25% increase in the tumor area between sequential CT or chest X-rays. Local response duration was defined as time from initial response to first objective evidence of progression or death for patients with CR, PR, MR, and SD.

Results

Patient characteristics

A total of 18 patients, 9 males and 9 females, with a median age of 68.5 years (range 48–82), were enrolled. Four patients were not evaluable for toxicity or response. The first of these patients received one week of RT and gemcitabine, but rapidly declined due to disease progression and decided to pursue hospice care. The second patient developed severe abdominal pain on day 3 of the study and was found to have progressive disease requiring palliative RT to the abdomen. The third patient came off study on day 4 due to a new pathologic fracture of T1 spine requiring palliative RT. The last patient came off study after only 1 week of treatment due to general clinical decline secondary to progressive disease and patient's wish to pursue hospice care. Thus, there were 14 evaluable patients, the majority of whom had metastatic or unresectable NSCLC (one patient with pleural mesothelioma and one with carcinoid), requiring RT for palliation secondary to bulky tumor causing erosion, pain, obstruction, or compression. The demographic profile of the treated patients is presented in Table 1.

Treatment summary

Treatment course for the 14 evaluable patients is summarized in Table 2 according to dose level, including the major toxicities. Of the 14 evaluable patients, 12 received full doses of gemcitabine (at their assigned dose level) and RT. One patient at dose level 2 (50 mg/m^2) experienced Grade-2 thrombocytopenia after two doses of gemcitabine and subsequent doses were reduced by 25%, while another patient at dose level 3 (65 mg/m^2) dose level experienced Grade-4 esophagitis (DLT) after one dose of gemcitabine and received no further drug.

Table 1 Patient characteristics

Characteristic	No. of patients (n = 14)
Sex	
Male	8
Female	6
ECOG performance status	
0	4
1	8
2	2
Age (years)	
Median	68.5
Range	48–82
Tumor type	
Non-small cell lung cancer	12
Malignant mesothelioma	1
Carcinoid	1

Table 2 Treatment summary

Dose level (mg/m^2)	Number of patients	Dose modifications	Grade 3 or 4 toxicity[a]	Overall response
40	3	None	None	2 SD
				1 PD
50	6	1[c]	Dyspnea	1 PR
			Rash	3 SD
			Neutropenia, Fatigue[b]	2 PD
65	5	1[c]	Esophagitis[b]	1 SD
			Neutropenia[b], Nausea, Vomiting	4 PD

[a] One occurrence of each grade 3 or 4 toxicity was observed

[b] DLTs

[c] One patient at dose level 2 had a 25% dose reduction due to grade-2 thrombocytopenia. One patient at dose level 3 did not receive any further gemcitabine after one dose due to grade-4 esophagitis

Toxicity

Initially, there was no DLT at the first two dose levels of gemcitabine. At the next dose level, two patients developed DLT (grade-4 esophagitis and grade-4 neutropenia). Then three additional patients were enrolled at dose level 2 with only one patient developing DLT (grade-3 fatigue). Therefore, gemcitabine 50 mg/m^2 twice-weekly was declared the MTD. Other grade-3 adverse events related to treatment included dyspnea, skin rash, neutropenia, constipation, anorexia, nausea, and vomiting in one patient each. There was no other grade-4 toxicity. Two patients expired within 30 days of treatment, but these events were attributed to progressive disease.

Overall response to therapy in evaluable patients

Using ECOG solid tumor response criteria, PR was observed in one patient (at 50 mg/m^2), who remained without radiographic progression 16 weeks later. Stable disease was observed in six patients: two at 40; 3 at 50; and one at 65 mg/m^2. Eight patients experienced PD, four of whom progressed <8 weeks after completing treatment. Mean survival for patients with SD and PD was 22.6 and 23.4 weeks, respectively.

Local response to therapy

There were no complete local responses observed. However, there were six PR and four MR. Three patients had stable local disease after treatment. Two of these patients had SD until death, while the third had SD for 25 weeks before demonstrating local progression requiring a second course of RT to the lung. One patient demonstrated local progression at initial follow-up two weeks after completion of treatment. The median local response duration was 25 weeks (range 2–46 weeks). Three patients died within 2 months of achieving a local response. Local responses were observed at all three dose levels of gemcitabine evaluated.

Discussion

Gemcitabine has potent radiosensitizing properties in both pre-clinical and clinical studies. Several possible mechanisms have been suggested, including depletion of cellular deoxyadenosine triphosphate pools, cell-cycle redistribution, and reduction of the apoptotic threshold for radiation [7]. Preclinical studies have demonstrated that the maximum radiosensitizing effect of gemcitabine occurs if cells are irradiated immediately after being exposed to drug for 16–24 h [14]. However, this schedule is clinically impractical. Subsequent studies evaluated the cytotoxic efficacy of gemcitabine combined with RT using higher doses of drug, but with reduced exposure duration in attempts to develop clinically relevant schedules. These studies demonstrated that sensitization is apparent 4 h after treatment and is sustained for up to 2 days, with enhancement ratios of 1.8 at 24 h and 1.4 at 48 h [15]. We initiated this trial based on these preclinical data because a twice-weekly gemcitabine infusion schedule provides a good compromise between cytotoxic effect and clinical practicality.

Initial clinical studies evaluated the feasibility of combining weekly doses of gemcitabine with RT. A phase-II pilot study using full dose of gemcitabine with concurrent thoracic RT proved to be highly toxic, resulting in three treatment-related deaths and several others with severe esophagitis or pneumonitis [16]. Gemcitabine has also been evaluated in combination with cisplatin. A Phase II CALGB study evaluated two cycles of gemcitabine and cisplatin followed by two cycles of the same drugs with concomitant RT of 66 Gy. Although the gemcitabine-containing arm had a numerically higher (but statistically not significant) 3-year survival rate, it also had more pronounced rates of esophagitis and thrombocytopenia [17]. Thus, full-dose gemcitabine therapy in combination with RT is associated with high rates of mucosal toxicities. Given this limitation, and the preclinical demonstration that lower, repetitive dosing could provide radiosensitization, clinical trials were redesigned to explore this approach. A phase-I study to examine the maximum tolerated dose of twice-weekly gemcitabine combined with a 6-week course of RT for stage III NSCLC has been reported by Blackstock et al. The MTD of twice-weekly gemcitabine in this study was 35 mg/m^2, determined by two cases of grade-4 esophagitis that occurred at the 50 mg/m^2 dose level during the course of RT [13].

The objective of our study was to determine the MTD of twice-weekly gemcitabine when combined with a shorter course of RT in patients with progressive or recurrent lung cancer. Hypothetically, one would expect to identify a higher MTD than in the Blackstock study; the clinical value of this would be in providing a higher and more durable tumor control rate for better palliation, than standard thoracic palliative RT alone. The MTD of twice-weekly gemcitabine in this setting was indeed slightly higher at 50 mg/m^2. One possible reason for improved tolerability may be the lower radiation dose; both cases of Grade-4 esophagitis reported by Blackstock et al. occurred after 3 weeks of concurrent chemo-radiation (one occurred after 4 weeks of RT and the other during the 6th week). Another explanation may be treatment volume; Blackstock's patients had elective nodal irradiation to a dose of 39.6 Gy with a field reduction thereafter [13]. In our study only gross disease deemed necessary for palliation was covered

in the radiation volume. To further illustrate this point, gemcitabine given at 35 mg/m^2 twice-weekly led to unacceptable toxicity in a more recent CALGB study when the lung volume receiving >20 Gy exceeded 35% [18]. The DLTs in our trial, in keeping with other experiences, were also primarily mucosal and included grade-4 esophagitis and grade-4 neutropenia. In addition, one patient at 50 mg/m^2 of gemcitabine had to undergo a 25% dose reduction due to grade-2 thrombocytopenia following the administration of two doses of the drug. The observation of hematologic toxicities at these modest levels is an important finding and may reflect the effect of combination therapy, patient selection in terms of having received prior myelosuppressive therapy, or both. Because most NSCLC patients receiving palliative thoracic RT have previously received at least one, and often several, regimens of chemotherapy, the myelotoxicity from combination gemcitabine and thoracic RT would become an important limiting factor if this regimen were to be pursued further.

These two studies, taken collectively, underscore several key points. First, repetitive administration of gemcitabine with thoracic RT requires substantial gemcitabine dose reductions, to 50 mg/m^2 in our case and 35 mg/m^2 in Blackstock's study. Even when evaluated as a cumulative dose, this represents a very large dose reduction. Second, radiation dose and volume both appear to contribute to the effect of gemcitabine on normal tissue toxicity. The most commonly enhanced toxicity from the combination regimen is mucosal (esophagitis), but myelotoxicity cannot be ignored even at these low doses. This report in the context of the previous work (discussed above) sets the stage for prospective testing of palliative concurrent combined modality approaches, to determine if these produce more durable, and higher rates of palliation.

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