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WEEKLY PACLITAXEL AS A RADIATION SENSITIZER FOR LOCALLY ADVANCED GASTRIC AND PANCREATIC CANCERS:THE BROWN UNIVERSITY ONCOLOGY GROUP EXPERIENCE

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1. ABSTRACT

Many patients with cancer of the stomach or pancreas have locally advanced, unresectable disease at diagnosis or will develop an early local or regional recurrence despite potentially curative surgery. Effective local treatment could increase the proportion of patients able to undergo surgery and decrease locoregional recurrences, which should improve overall survival. External beam radiation (RT) by itself has little effect. Standard treatment, such as RT with concurrent administration of 5-fluorouracil-based chemotherapy as a radiation sensitizer, has, at best, a modest impact on locoregional recurrences and survival. The use of a more effective radiosensitizer might improve the efficacy of local treatment. Paclitaxel synchronizes cells at G2M, the phase of the cell cycle during which cells are most sensitive to the effects of ionizing radiation, and has been demonstrated to sensitize a variety of human cell lines to the effects of RT. In patients with locally advanced non-small cell lung cancer (NSCLC), the Brown University Oncology Group (BrUOG) has demonstrated a high response rate to low-dose weekly paclitaxel with concurrent RT. In addition, we demonstrated that the response to paclitaxel/RT was not affected by mutations in the p53 tumor suppressor gene. This suggested that paclitaxel/RT would be a rational treatment approach for other malignancies with a high frequency of p53 mutations, such as gastric and pancreatic cancers. We have completed a phase I study of weekly paclitaxel and concurrent radiation for locally advanced gastric and pancreatic cancers. The maximum tolerated dose of paclitaxel was 50mg/m2/week for six weeks with 50 Gray (Gy) abdominal radiation. The dose limiting toxicities were abdominal pain, nausea and anorexia. Preliminary response data from ongoing phase II studies suggest that preoperative paclitaxel/RT has substantial activity in patients with locally advanced gastric and pancreatic cancers, though whether this will translate into improved disease-free and overall survival in these patients is not known.

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2. INTRODUCTION

2.1 Background

Though the incidence of gastric cancer in the United States has fallen dramatically over the

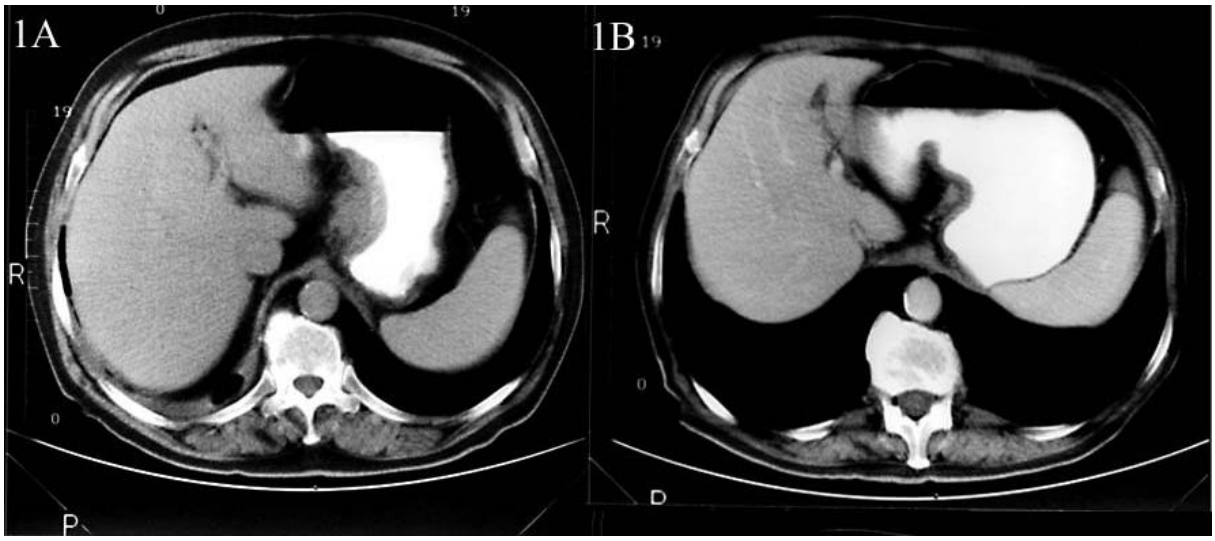

Figure 1A. Pre-treatment CT scan shows a large (7 cm) mass arising from the lesser curvature of the stomach. At laparoscopy the tumor was found to have invaded through to the serosa and enlarged retroperitoneal lymph nodes were seen.

Figure 1B. After completion of paclitaxel/RT, the CT shows marked regression of the gastric mass. The patient underwent complete resection. Pathology could identify only a 1.5 cm residual ulcerated tumor mass with negative lymph nodes.

past five decades, it remains the eighth leading cause of cancer deaths in the United States, and is the second leading cause of cancer deaths world-wide (1). Pancreatic cancer is the fifth leading cause of cancer deaths in the United States (1). Because of their location, and the often insidious and non-specific nature of the symptoms with which they present, cancers of the stomach and pancreas are often not diagnosed until they have spread to regional lymph nodes, adjacent organs, peritoneal surfaces, or distant sites. Of the approximately 70% of newly diagnosed patients with gastric cancer who are considered operative candidates, only 30-50% will have potentially curative resections (2,3). In these patients the locoregional failure rate is 38-67% (4,5). In a study from the University of Minnesota in which second look laparotomies were performed on patients with gastric cancer six months after they had undergone complete resections, locoregional recurrence was the only site of disease in 29% and a component of failure in 88% of patients with relapsed disease (5). For pancreatic cancer the situation is even more grim, with potentially resectable disease identified in less than 20% of patients at diagnosis, and locoregional recurrences developing in up to 80% of patients following a potentially curative resection (6). Although studies suggest a modest survival benefit for combined 5-fluorouracil (5-FU)-based chemotherapy and local radiation in patients with unresectable gastric or pancreatic cancers, in patients resected for cure post-operative adjuvant chemotherapy or combined chemoradiotherapy has not, thus far, been demonstrated to significantly reduce the incidence of locoregional recurrences or improve overall survival (7,8).

Pre-operative treatment to decrease the size and extent of these cancers could potentially increase the number of patients who are candidates for resection and/or decrease the post-operative locoregional recurrence rate. Unfortunately, conventional neoadjuvant treatments have been largely ineffective in either gastric or pancreatic cancer. Kelsen recently summarized phase II trials of neoadjuvant chemotherapy in patients with high risk, but potentially resectable gastric cancers (9). With the administration of an intensive

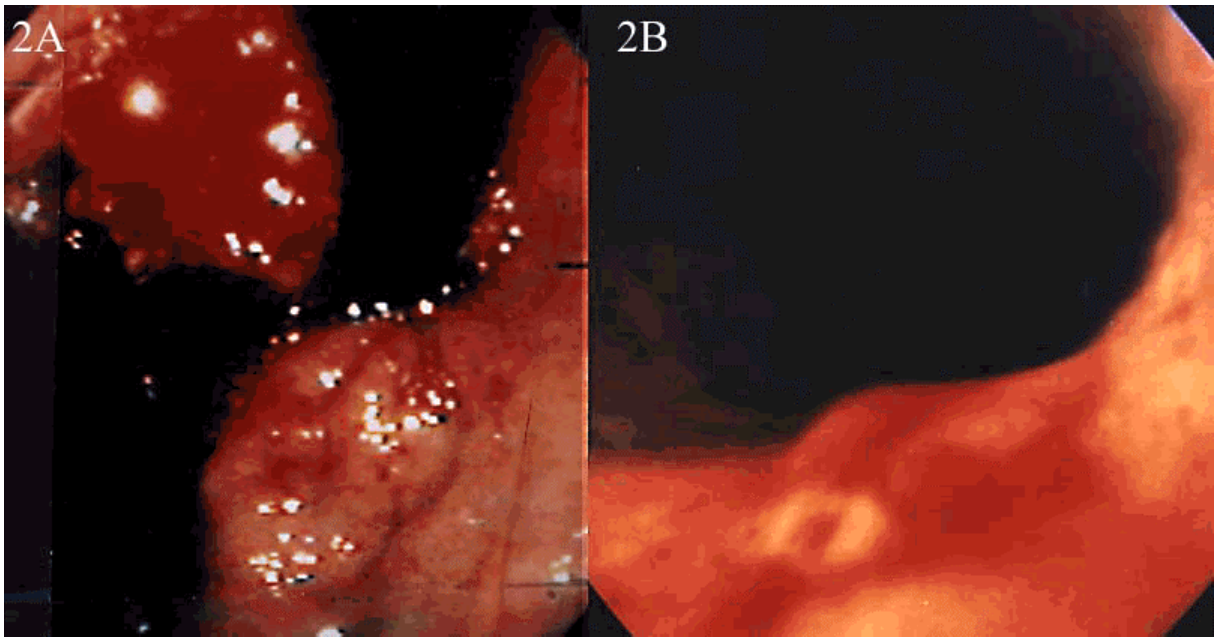

Figure 2A. Pretreatment endoscopy shows a large hemorrhagic proximal gastric cancer extending to the GE junction in this 88 year old man. He could not tolerate esophagogastrectomy due to severe aortic stenosis and coronary artery disease. He was treated with paclitaxel/RT without significant side effects.

Figure 2B. Follow-up endoscopy shows signs of inflammation but resolution of the gastric mass. Biopsies showed no evidence of residual disease. The patient remains alive without evidence of disease a year later.

Chemotherapy regimen such as etoposide, doxorubicin, and cisplatin (EAP), while most patients were able to undergo a potentially curative resection, the median survival is still only 15-18 months due to local and distant recurrences. In 53 patients with potentially resectable pancreatic adenocarcinomas treated on an Eastern Cooperative Oncology Group trial, there was only one partial response to preoperative 5-FU, mitomycin and radiation (10). More effective, less toxic, preoperative therapy is clearly needed for both diseases.

2.2 Paclitaxel

Paclitaxel is a chemotherapeutic agent extracted from the bark of the Pacific yew (Taxus brevifolia) (11). Paclitaxel interferes with the function of the mitotic spindle by enhancing the rate of microtubule assembly and preventing microtubule depolymerization (12). As a single agent, paclitaxel has substantial activity against a range of tumor types, including ovarian, breast, and lung carcinomas, but has demonstrated minimal activity in advanced gastric and pancreatic cancers (13-17).

2.3 Paclitaxel, radiation and the cell cycle

In actively growing cells, the cell cycle is divided into four phases. In S phase the chromosomal DNA is replicated and in M phase chromosomes are segregated to daughter cells by the mitotic spindle. Each of these active phases is preceded by "rest" phases (G1 and G2, respectively) during which a number of factors influence the rate of progression of the cell through the cell cycle. The differential radiation sensitivity of cells in various phases of the cell cycle is well documented. Cells in G2/M are up to four-fold more sensitive to radiation than cells in early G1 and S phase (18). Paclitaxel's unique mechanism of action synchronizes cells in G2/M, by blocking their progression through M phase. This likely accounts for much of its demonstrated radiosensitizing ability (12,19).

2.4 Paclitaxel as a radiation sensitizer in NSCLC

The BrUOG initially investigated paclitaxel as a radiation sensitizer in patients with unresectable stage IIIA and IIIB NSCLC. Our phase I study of weekly paclitaxel and thoracic radiation in NSCLC demonstrated a maximum tolerated dose (MTD) of 60 mg/m2/week for six

Table 1. Patient Characteristics, Phase II Studies

	Pancreatic Study (N=13)	Gastric Study (N=11)
Age		
Median (range)	69 (48-79)	70 (47-88)
Performance Status		
0	1	2
1	10	7
2	2	2
Disease Extent		
Unresectable by CT	6	1
Borderline resectable by CT	0	4
Resectable by CT	0	1
Unresectable at surgery	6	3
Medically inoperable	1	2

Table 2. Response to Treatment, Phase II Studies

	Pancreatic Study (N=10)	Gastric Study (N=10)
Complete response	0	1 (10%)
Partial response	4 (40%)	7 (70%)
Stable disease	5 (50%)	0
Progressive disease	1 (10%)	2 (20%)

weeks when given concurrent with 60 Gy chest irradiation (20). Thedose limiting toxicity (DLT) was esophagitis. We subsequently performed a phase II study at this dose in 33 patients with unresectable stage IIIA and IIIB NSCLC, which demonstrated an 86% overall response rate with one and two year overall survivals of 61% and 35% (21).

2.5 Paclitaxel/RT is unaffected by p53 mutations in NSCLC

Mutations in the tumor suppressor gene p53 are among the most common genetic alterations found in human tumors (22). Such mutations are found in approximately half of lung, gastric, and pancreatic cancers. In vitro data from a variety of cell lines indicate that wild-type p53 function is required for the efficient activation of apoptosis in response to ionizing radiation, 5-FU, cisplatin and most other chemotherapeutic drugs (23,24). Fisher et al. and Wahl et al demonstrated that paclitaxel could induce apoptosis and kill tumor cells independent of their p53 status (25,26). We sought to test this observation in vivo by determining whether p53 mutations affected responses to paclitaxel/RT in patients with NSCLC. The response rates to paclitaxel/RT in patients with stage III NSCLC with and without p53 mutations were nearly identical, with a 75% response rate observed in tumors with p53 mutations and an 83% response rate in tumors without a demonstrable p53 mutation (27). These findings suggest that paclitaxel/RT can induce apoptosis or cause cell death by some mechanism independent of normal p53 function, and that paclitaxel/RT should be investigated in other malignancies in which p53 mutations are frequent, such as gastric and pancreatic cancers.

3. PHASE I STUDY OF PACLITAXEL/RT FOR GASTRIC AND PANCREATIC CANCERS

Because the of the promising results with paclitaxel/RT in locally advanced NSCLC and the activity of paclitaxel/RT even in the setting of a p53 mutation, we sought to apply the paclitaxel/RT regimen to gastric and pancreatic cancers. Therefore, we initiated a phase I study to determine the MTD of weekly paclitaxel with standard dose

Table 3. Toxicity Phase II Studies (N=20)

	Grade 2	Grade 3	Grade 4
Nausea/Anorexia	1	2	3
Abdominal pain	2	1	1
Weight loss	3	1	0
Anemia	2	0	0
Neutropenia	1	1	0

Table 4. Responses According to p53 Status

Gastric cancer (N=6)		
	p53 wild type:	3/3 responded
	p53 mutations:	2/3 responded
Pancreatic cancer (N=7)		
	p53 wild type:	1/4 responded
	p53 mutations:	2/3 responded

(50 Gy) upper abdominal radiation in patients with locally advanced gastric and pancreatic cancers (28). Of the 34 patients treated on the study, 18 had pancreatic cancer, of which 15 were considered unresectable and 3 had undergone surgery but were found to have positive surgical margins or involved regional lymph nodes. Of 16 patients with gastric cancer 10 were considered unresectable or borderline resectable, including 3 with retroperitoneal adenopathy, 2 with linitus plastica, and 5 with extensive cancers of the body of the stomach that extended proximally to involve the lower half of the esophagus, and 6 had undergone gastrectomy, but had residual adenopathy (4) or involved margins (2). No patient had known disease outside the planned radiation field. Paclitaxel was administered by 3-hour intravenous (IV) infusion repeated weekly for 6 weeks. Radiation therapy was delivered in 28 fractions of 1.8 Gy per fraction to the tumor and draining lymph nodes. The starting dose of paclitaxel was 30 mg/m2/week, and the paclitaxel dose was increased in cohorts of patients by 10 mg/m2/week until dose-limiting toxicities were observed. There were separate dose escalations for patients with pancreatic and gastric cancers. The 34 patients were treated at four dose levels from 30-60 mg/m2/week. Treatment was well tolerated until the 60 mg/m2/week dose level was reached, at which four of six patients developed dose-limiting abdominal pain, nausea, and/or anorexia. On endoscopy two of these patients were found to have severe gastritis with linear ulcerations at the gastroesophageal junction. The other two had edema of the stomach and small bowel by CT scan. Other toxicities included weight loss and diarrhea, which were more pronounced at the higher dose levels. Four patients required supplemental parenteral nutrition and another two had supplemental enteral nutrition via a jejunostomy tube. In general, gastrointestinal toxicities developed during the fifth and sixth weeks of treatment and resolved within 2-4 weeks of completing therapy. Myelosuppression was uncommon and generally mild with only two incidences of grade 3 neutropenia. There were no differences in toxicities between patients with gastric and pancreatic cancers, and patients who received treatment after surgery tolerated it as well as those who had been deemed unresectable. The best predictor for toxicity was pretreatment performance status.

Of 31 evaluable patients, 23 had radiographically assessable disease. In 10 patients with gastric cancer there were 7 partial responses and 3 patients with progressive disease. Within 1-2 weeks of initiating treatment, responding patients had subjective improvement in dysphagia and pain. Objective responses were typically seen on a CT scan done within 3 weeks of completion of treatment. In 13 patients with pancreatic cancer there were 4 partial responses, including 3 in

patients with large (>5 cm) tumors, 4 patients with stable disease and 5 with disease progression.

4. PHASE II STUDIES OF NEOADJUVANT PACLITAXEL/RT IN LOCALLY ADVANCED GASTRIC AND PANCREATIC CANCERS:

4.1. Preliminary results

Based on the results of this phase I study, the BrUOG and its affiliates have initiated phase II studies to determine the response to and toxicity of neoadjuvant paclitaxel/RT in patients with locally advanced gastric and pancreatic cancers. Patients with deeply invasive adenocarcinomas of the stomach without distant metastases (T3-T4 N0-N3 M0) are eligible for the gastric trial. All patients receive paclitaxel 50 mg/m2/week for 5 weeks with 45 Gy concurrent radiation. Resectable patients undergo surgery 4-6 weeks after completion of treatment. Patients who are medically inoperable receive a sixth paclitaxel treatment and three more radiation treatments to bring their total radiation dose to 50 Gy. Patients with pancreatic cancers limited to the gland and adjacent nodes (T1-3 N0-1 M0) receive paclitaxel 50 mg/m2/week for six weeks with 50 Gy concurrent radiation, and proceed to surgery 4-6 weeks later. All patients are required to sign a BrUOG-approved institutional consent form. Characteristics of patients entered on these trials to date are listed in Table 1. Of the eleven patients entered thus far on the gastric study, ten have completed paclitaxel/RT and are assessable for response and toxicity. Eight of the first ten patients have responded (1 CR, 7 PR). Several of the responses have been dramatic, as illustrated in Figures 1A and 1B and 2A and 2B. Abdominal pain, nausea and anorexia have been the most common toxicities, with 4 of the first 10 patients developing NCI grade 3-4 toxicities. Two patients progressed with the development of malignant ascites during treatment. Of thirteen patients entered to date on the pancreatic study, ten have completed paclitaxel/RT and are assessable for response and toxicity. Four of the first 10 patients have had an objective partial response. One patient who presented with tumor encasing the superior mesenteric artery was rendered completely resected. A second patient with a 10 cm tumor seen at pretreatment laparotomy had no residual identifiable tumor at second look surgery following completion of paclitaxel/RT, although resection was not possible due to extensive inflammation and fibrosis. Of two other responding patients who have been explored, one had unsuspected liver metastases and the other had an involved para-aortic lymph node. Nausea, anorexia and abdominal pain continue to be the major toxicities seen, with NCI grade 3-4 toxicities in two patients. Preliminary response and toxicity data for both studies are contained in Tables 2 and 3, respectively.

4.2. Activity of paclitaxel/RT in pancreatic and gastric tumors with p53 mutations

We are now evaluating our treated gastric and pancreatic cancers for the presence of p53 mutations as described previously (27). As shown in Table 4, responses to paclitaxel/RT have been seen in gastric and pancreatic cancers both without and with p53 mutations.

The ability to cause tumor cell death by a p53-independent pathway may help explain the activity of paclitaxel in a wide variety of tumors as well as its demonstrated radiosensitizing activity.

5. FUTURE DIRECTIONS

Paclitaxel/RT appears to have substantial activity in locally advanced gastric and pancreatic cancers. As we continue our phase II studies, one of our goals is to stage patients more accurately pretreatment by using laparoscopy, to exclude patients with peritoneal implants or surface hepatic metastases, and endoscopic ultrasound, to more accurately assess depth of invasion, vascular encasement, and nodal involvement, particularly for gastric cancers. Acknowledging that even responding patients who are able to undergo potentially curative resection remain at high risk of local and distant disease recurrence, future investigations may involve the addition of cytotoxic or non-cytotoxic agents following completion of paclitaxel/RT/surgery to try to prevent growth of micrometastatic deposits. Matrix metalloproteinase inhibitors, ras inhibitors, anti-angiogenesis agents, or other biologic response modifiers may have a role in this setting. However, our first goal, and one that remains daunting, is to render these patients grossly free of disease with effective preoperative therapy and potentially curative surgery.

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