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PACLITAXEL AND CONCURRENT RADIATION FOR LOCALLY ADVANCED PANCREATIC CARCINOMA

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1. ABSRACT

An effective local-regional therapy is needed for adenocarcinomas of the pancreas. Paclitaxel (Taxol; Bristol-Myers Squibb Company, Princeton NJ) may enhance the effect of radiation therapy. Paclitaxel synchronizes cells at G2/M, a relatively radiosensitive phase of the cell cycle. We have shown that response to paclitaxel and concurrent radiation (paclitaxel/RT) was not affected by p53 mutations in non-small cell lung cancer (NSCLC). This suggested that paclitaxel/RT was a rationale treatment approach for other malignancies which frequently harbor p53 mutations such as upper gastrointestinal malignancies. We have completed a phase I study of paclitaxel/RT for locally advanced pancreatic and gastric cancers. The maximum tolerated dose (MTD) of paclitaxel was 50 mg/m^2/week for 6 weeks with abdominal radiation. The dose limiting toxicities were abdominal pain within the radiation field, nausea and anorexia. Twenty-five patients with locally advanced pancreatic cancer have now completed treatment at the phase II dose level of paclitaxel 50 mg/m^2/week with 50 Gy concurrent RT. Thus far, the only grade 3/4 toxicities have been hypersensitivity reactions in 2 patients, asymptomatic grade 4 neutropenia in 3 patients, and non-neutropenic biliary sepsis in 1 patient. Of the first 22 assessable patients treated at the phase II study, 8 obtained a partial response (PR) for a preliminary response rate of 36%. These findings demonstrate that paclitaxel/RT is well tolerated with substantial activity for locally advanced pancreatic cancer.

2. INTRODUCTION

An effective local-regional treatment modality is needed for adenocarcinomas of the pancreas. Pancreatic cancer is the fifth leading cause of cancer death in the United States (1). Over half of all newly diagnosed patients with pancreatic cancer are unresectable due to locoregional disease (2,3). An effective local treatment would be of substantial importance. Reducing local tumor extension would diminish morbidity and potentially increaseresectability. An effective local treatment given as neoadjuvant or adjuvant therapy might also decrease the 50-75% local recurrence rate following resection (4).

Unfortunately, conventional local treatments of pancreatic cancer do not have substantial activity. For example, in an Eastern Cooperative Oncology Group phase II trial, there were only four partial responses among 51 eligible patients with potentially resectable pancreatic adenocarcinoma who received preoperative 5-FU, mitomycin and radiation (5). Half of these patients experienced severe toxicity. More active less toxic preoperative combined modality therapies are needed in pancreatic cancer.

Paclitaxel (Taxol; Bristol-Myers Squibb Company, Princeton NJ), is a chemotherapeutic agent extracted from the bark of the Pacific yew (Taxus brevifolia). Paclitaxel interferes with mitotic spindle function by enhancing the rate and yield of microtubule assembly and preventing microtubule depolymerization (6). Paclitaxel has demonstrated modest activity against pancreatic cancer. The Southwest Oncology Group demonstrated an 8% overall response rate of paclitaxel for pancreatic cancer, with one complete response and two partial responses among 39 patients (7). These response rates are comparable to the single agent activity of gemcitabine and 5FU in pancreatic cancer (8). However, paclitaxel's most important role in upper GI malignancies may be as a radiation enhancer.

Paclitaxel was initially studied as a radiosensitizer because it synchronized cells at G2/M, a particularly sensitive phase of the cell cycle (9,10). However, paclitaxel radiosensitization persists well after the relatively brief period of G2/M synchronization, suggesting that other factors may relate to its ability to enhance radiation (11). The p53 gene is required for initiation of apoptosis in response to most chemotherapeutic agents and radiation (12). In vitro, paclitaxel has the exceptional property of causing cancer cell death independent of wild-type p53 (12,13). We have shown in locally advanced NSCLC that response to paclitaxel/RT is not effected by p53 mutations (14). These findings suggest that paclitaxel mediated blockade at G2/M can activate cell cycle control pathways to induce apoptosis independent of p53 (15). Therefore, Paclitaxel/RT is a rationale treatment approach for other

malignancies which frequently harbor p53 mutations such as pancreatic cancer.

Recently it has been demonstrated that stem cells of the gastrointestinal mucosa werre not radiosensitized by paclitaxel (16). This may improve the therapeutic index of paclitaxel/RT by reducing the potential of small bowel toxicity. This may allow for increased dosages of paclitaxel/RT improving the likelihood of local control. Therefore, we performed phase I/II studies of paclitaxel/RT for locally advanced pancreatic cancer.

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

We sought to determine the maximum tolerated dose of weekly paclitaxel with upper abdominal radiation. Therefore, we performed a phase I study of paclitaxel/RT for locally advanced pancreatic and gastric cancers (17). Thirty-four patients were entered on this study; 18 with locally advanced adenocarcinoma of the pancreas and 16 with gastric cancer. The mean age was 70 and two patients were over 80.

Fifteen of the 18 patients with pancreatic cancer were locally unresectable, including 13 with vascular or loco-regional extension, one with a local recurrence, and one who had a medical contraindication to surgery. The three other patients with pancreatic cancer had undergone pancreaticoduodenectomy; one had positive margins and two had multiple involved lymph nodes.

Of the patients with gastric cancer, ten were unresectable or borderline resectable including three with retroperitoneal adenopathy, two with linitis plastica, and five with extensive cancers involving the body of the stomach that extended proximally to involve the lower half of the esophagus. The six other patients with gastric cancer included in this study had undergone gastrectomy; four had residual adenopathy and two had involved margins.

Radiation therapy to a total dose of 50 Gy was delivered in 28 fractions of 1.8 Gy per fraction to the tumor and draining lymph nodes. The initial dose of paclitaxel was 30mg/m^2 by 3 hour intravenous (IV) infusion repeated every week for 6 weeks with concurrent radiation. Doses were escalated at 10mg/m^2 increments in successive cohorts of three new patients until dose limiting toxicity was observed.

Treatment was well tolerated up to the 60mg/m^2/week paclitaxel dose level when dose limiting toxicities occurred. Abdominal pain within the radiation field, nausea and anorexia were the dose limiting toxicities. CT scan and endoscopy suggested that these toxicities were due to inflammation and edema within the esophagus, stomach and small bowel. In general, gastrointestinal toxicities occurred in the fifth and sixth week of treatment and resolved within 2-4 weeks of completing therapy.

Treatment was well tolerated at paclitaxel dosages of $\leq$50 mg/m^2/week. Patients who received treatment after gastrectomy or Whipple procedure tolerated paclitaxel/RT as well as those who were primarily unresectable. Pretreatment performance status and ability to maintain adequate nutrition were the most important predictors of toxicity. Myelosuppression was uncommon and generally mild.

4. PHASE II STUDY OF PACLITAXEL/RT FOR PANCREATIC CANCER

Twenty-five patients with locally advanced pancreatic cancer have completed treatment at the phase II dose level of paclitaxel, 50mg/m^2/week, for six weeks with 50 Gy. The median age was 65 (42-86). Four patients were deemed unresectable at exploratory laparotomy. Twenty patients were judged to be unresectable by CT scan due to encasement of major blood vessels. One patient was medically unresectable due to coexistent cardiac disease.

Two patients developed grade 4 hypersensitivity reactions with dyspnea and hypotension following their first paclitaxel treatment and were removed from the study. Of the remaining 23 patients, three developed asymptomatic grade 4 neutropenia, and one had non-neutropenic biliary sepsis. No other grade 3 or grade 4 toxicities developed.

Three patients were unevaluable for response; 2 due to hypersensitivity reactions and one did not have radiographically assessable disease. Of the remaining 22 patients, 8 had a partial response for a preliminary response rate of 36%. Stable disease was observed in 7 patients (32%). Only 1 patient (5%) had local progression after completion of treatment and 6 (27%) developed distant metastases.

Ten initially unresectable patients with stable or improved local disease assessed by computerized tomographic (CT) scan underwent exploratory laparotomy after paclitaxel/RT. Three underwent complete resection with negative margins. One patient had extensive fibrosis without visible tumor and was not resected. Six patients were found, at surgical exploration, to have microscopic disease within the liver that had not been detected during restaging CT scan.

5. PERSPECTIVE

Paclitaxel/RT is well tolerated and has substantial activity in locally advanced pancreatic cancer. It is particularly encouraging that some patients with vascular encasement prior to paclitaxel/RT have subsequently been able to undergo surgical resection following paclitaxel/RT. To improve on these results, Future studies could involve the addition of other radiosensitizers such as gemcitabine and 5-FU.

Future studies are needed to improve the radiographic assessment of response and resectability. Conventional CT scans may be unable to differentiante viable tumor from post-treatment fibrosis. Unsuspected microscopic disease, not detected by CT, has been detected at surgical exploration. Clearly novel agents are needed to prevent or delay the growth of metastatic deposits. It is unlikely that currently available chemotherapy such as paclitaxel, gemcitabine and 5-FU may not have sufficient systemic activity to prevent distant metastases. Therefore, The Brown University Oncology Group has begun evaluating the addition of matrix metalloproteinase

inhibitors in patients with locally advanced pancreatic cancer after completion of paclitaxel/RT.

6. REFERENCES

1. S.H. Landis, T. Murray, S. Bolden, & P.A. Wingo: *CA Cancer J Clin* 48, 6-29 (1998)

2. D.B. Evans, J.L. Abbruzzese, & T.A. Rich: In: Cancer-Prinicples and practice of oncology. 5th ed Eds: Devita v.T., Hellman S., Rosenberg S.A., Lippincott-Raven Press, Philadelphia, 1054-1087 (1997)

3. M. Mohiuddin, F. Rosato, A. Schuricht, D. Barbot,W. Biermann, & R. Cantor: Carcinoma of the pancreas-the Jefferson experience. *Eur J Surg Oncol* 20, 13-20 (1994)

4. M. P. Vezeridis, & H.J. Wanebo: Pancreatic cancer in 1994: Diagnosis and treatment. *RI Med* 77, 115-118 (1994)

5. J.P. Hoffman, S. Lipsitz, T.M. Pisansky, Weese J.L. Solin L, & Benson A.B: Phase II trial of preoperative radiation therapy and chemotherapy for patients with localized resectable adenocarcinoma of the pancreas: An Eastern Cooperative Oncology Group Study. *J Clin Oncol* 16, 317-323 (1998)

6. R. Donehower, E.K. Rowinsky, L. Grochow, S.M. Longnecker, & D.S. Ettinger: Phase I trial of Taxol in patients with advanced cancer. *Cancer Treat Rep* 71, 1171-7 (1987)

7. R.P. Whitehead, J. Jacobson, T.D. Brown, S.A. Taylor, G.R. Weiss, & J.S. Macdonald: Phase II trial of paclitaxel and granulocyte colony-stimulating factor in patients with pancreatic carcinomas: A Southwest Oncology Group study. *J Clin Oncol* 15,2414-2419 (1997)

8. H.A. Burris, M.J. Moore, J. Andersen, M.R. Green, M.L. Rothenberg, M.R. Modiano, M.C. Cripps, R.K. Portenoy, A.M. Storniolo, P. Tarassoff, R. Nelson, F.A. Dorr, C.D. Stephens, D.V. & D. Von Hoff: Improvements in survival and clinical benefit with gemcitabine as first-line therapy for patients with advanced pancreas cancer: A randomized trial. *J Clin Oncol* 15,2403-2413 (1997)

9. C.R. Geard, J.M. Jones, & P.B. Schiff. Taxol and radiation. *J Natl Cancer Inst* 15, 89-94 (1993)

10. H. Choy, F.F. Rodriguez, S. Koester, S. Hilsenbeck, & D. Von Hoff Investigation of Taxol as a potential radiation sensitizer. *Cancer* 71, 3774-3778 (1993)

11. N. Gupta, L.J. Hu, & D.F. Deen. Cytotoxicity and cell-cycle effects of paclitaxel when used as a single agent and in combination with ionizing radiation. *Int J Rad Oncol Biol Phys* 37,885-895 (1997)

12. P.M. O'Connor, J. Jackman, I. Bae, T.G. Myers, S. Fan, M. Mutoh, D.A. Scudiero, A. Monks, E.A. Sausville, J.N. Weinstein, S. Friend, A.J. Fornance, & K.W. Kohn. Characterization of the p53 tumor suppressor pathway in cell lines of the National Cancer Institute anticancer drug screen and correlations with the growth-inhibitory potency of 123 anticancer agents. *Cancer Res* 57, 4285-4300 (1997)

13. A.F. Wahl, K.L. Donaldson, C. Fairchild, F.Y.F. Lee, S. Foster, G.W. Demers, & D.A. Galloway: Loss of normal p53 function confers sensitization to taxol by increasing G2/M arrest and apoptosis. *Nature Med* 2, 72-79 (1996)

14. H. Safran, T. King , H. Choy, A. Gollerkeri, H. Kwakwa, F. Lopez, B. Cole B, J. Myers, J. Tarpey, & A. Rosmarin: p53 mutations do not predict response to paclitaxel/radiation for non-small cell lung cancer. *Cancer* 78, 1209-1216 (1996)

15. Y. Saito, C.G. Milross, W.N. Hittelman, L. Donghui, T. Jibu, L.J. Peters,& L. Milas. Effect of radiation and paclitaxel on p53 expression in murine tumors sensitive or resistant to apoptosis induction *Int J Radiat Oncol Biol Phys* 38, 623-631 (1997)

16. K.A. Mason, L. Milas, & L.J. Peters. Effect of paclitaxel (taxol) alone and in combination with radiation of the gastrointestinal mucosa. *Int J Rad Oncol Biol Phys* 32, 1381-1389 (1995)

17. H. Safran, T. King, H. Choy, P. Hesketh, B. Wolf, E. Altenhein, W. Sikov, A. Rosmarin, W. Akerley, K. Radie-Kayne, G. Cicchetti, F. Lopez, K. Bland, H. Wanebo. Paclitaxel and Concurrent Radiation for Locally Advanced Pancreatic and Gastric Cancer: A Phase I Study. *J Clin Oncol* 15, 901-907 (1997)

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