Phase I - II Study of Gemcitabine and Fluorouracil as a Continuous Infusion in Patients with Pancreatic Cancer

Reviewers: John Han-Chih Chang, MD
Source: Journal of Clinical Oncology Volume 17: pages 585 592

Background

Pancreatic cancer is the seventh most commonly diagnosed cancer, but the fourth most common cause of cancer-related deaths. It is very often not amenable to resection and, thus, requires chemotherapy (ChT) along with radiotherapy (RT) to treat this tumor. Even in the cases where surgery is an option (10 ? 20%), postoperative chemotherapy along with radiotherapy improves overall survival (Gastrointestinal Study Group trials). Still, much work needs to be done in perfecting treatment. In resected cases, surgery along with ChT and RT have provided only a small number of long-term survivors (approximately a 20% 5-year survival). In the 3-arm randomized trial comparing RT alone versus RT (at 2 different dose levels) + ChT for unresectable patients, there were no survivors beyond 2 years after treatment. This is truly humbling. This article attempts to focus on the question on how best to improve the ChT for this terrible disease.

5-FU had been the standard of care for pancreatic cancer. It has been shown in other gastrointestinal sites that protracted venous infusion delivery was better than the bolus administration for improving response to treatment. Though 5-FU has been considered the standard, most would agree ? it alone does not seem to be enough. Gemcitabine (Gemzar®) (a nucleoside analog) was the next step. In a small phase III randomized trial (Burris et al, *J Clin Oncol* 15: 2403 ? 13, 1997) of gemcitabine versus 5-FU in mostly stage IV patients, there was a significant survival advantage to utilizing gemcitabine over 5-FU. Thus, the goal of this phase I-II trial was to elucidate the toxicity and efficacy of combining 5-FU (the standard) in a protracted venous infusion delivery with the addition of weekly gemcitabine and to maximize the benefit of both.

Materials and Methods

Patients utilized in this preliminary trial were unresectable locally advanced or metastatic pancreatic cancer patients without previous treatment with ChT or hormonal therapy. Prior RT was allowed if it was palliative in nature and was given over 4 weeks prior to enrollment. One cycle of ChT consisted of gemcitabine given on weekly basis for 3 consecutive weeks. 5-FU was given on a continuous basis for the duration of therapy. A cycle would be repeated every 4 weeks. Those that responded to treatment or remained stable continued for a total of 6 cycles. Those that progressed were taken off study.

The dose escalation applied to the gemcitabine. The starting dose of gemcitabine was 700 mg/m2 per week (5-FU was given at a rate of 200 mg/m2/day). The dose was then increased by 100mg/m2 for each successive cohort. If one patient had a 1st cycle dose limiting toxicity (as defined by the National Cancer Institute criteria in the paper), then 3 more were accrued to that dose level. If 2 or more had a dose limiting toxicity with the 1st cycle, then that dose level would be deemed intolerable and the next dose level down would be called the maximum tolerated dose (MTD).

Results

Twenty-six patients were enrolled with most (2/3rd) having metastatic disease. The dose escalation reached a gemcitabine dose of 1100 mg/m2 before 2 of 3 had a dose limiting toxicity with the first cycle of ChT (septic shock ? fatal and grade 4 thrombocytopenia ? recovered). Thus, the 1000 mg/m2 was considered the MTD. However, calculations were made of the actual dose received, since some subsequent dose reductions were made after the 1st cycle in most cases for toxicity. Based on the calculations, the recommended dose is 900 mg/m2 when given in combination with 200 mg/m2/d of protracted venous infusion 5-FU. Most of the grade 3 ?

4 toxicities were hematological. Of the patients that had received the 900 mg/m2 or more, the grade 3 ? 4 nonhematological toxicities were asthenia (generalized muscle weakness) in one patient, another with a severe cutaneous reaction, two had uncontrolled diarrhea and one presented with mucositis. Dose reductions were performed in over half of the patients, most often in the third week's dose of each cycle. Omission of the third week's dose was performed in 8 patients.

The effectiveness of the treatment was evaluated. The treatment yielded 4 partial responses (PR) and 1 complete response (CR) out of 26 (19.2% response rate). Three patients who had partial responses were in the 900-mg/m2 group. The other patient with PR was given the 800-mg/m2 dose. The patient achieving a CR had been given 700 mg/m2, but he only had locally advanced disease without metastases. Twenty-two had symptomatic disease at the time of entry. Ten of these obtained a "clinical benefit response." This translates into obtaining pain control (in 9 patients with 6 requiring fewer analgesics); improving performance status (7 patients) and increasing body weight (1 patient). The median follow up was 17.7 months. The median progression-free and overall survival was 7.4 and 10.3 months, respectively. The ACTUARIAL 1-year survival in these patients was 39.5%.

Conclusions

The actuarial survival of 39.5% seems to be much better than the 1-year survival seen in the prior randomized trial of 5-FU (2%) versus gemcitabine (18%). We must be careful not to directly compare these results, especially since the numbers are small here (26 patients). It does show some promise. Perhaps, there is synergy as was demonstrated in prior in vitro studies with 5-FU and gemcitabine. There should be tempered excitement, because a response rate of 20% is hardly a home run. It is, albeit, an improvement for this horrible disease. The prior randomized trial touted an 8% response rate for gemcitabine alone (again, direct comparisons are not completely fair).

The direction we should proceed from here is to a randomized trial to prove once and for all that combination therapy is better than single agents alone. OR, perhaps, unresectable locally advanced pancreatic cancer patients should proceed to a phase I and/or II trial with RT + 5-FU followed by gemcitabine + 5-FU. The reasoning for leaving gemcitabine out during radiation therapy stems from data from our institution and others that the combination of gemcitabine with radiation therapy is overly toxic.

The fact that there are so many possibilities for further studies means that we have a long road ahead of us. This article serves to further us along ever so slightly.