HIGHLIGHT ARTICLE


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SUMMARY

Despite advances in our understanding of the molecular and genetic basis of pancreatic cancer, the outcome for this disease remains dismal. Gemcitabine, the standard chemotherapy for pancreatic cancer, offers modest improvement of tumor-related symptoms and marginal advantage of survival. Many chemotherapeutic and targeted agents have been pitted against or combined with gemcitabine in randomized phase III trials and no drug was shown to be superior to single-agent gemcitabine except two gemcitabine-containing combinations: capecitabine plus gemcitabine vs. gemcitabine and erlotinib. In this article, the author debates: “Is there a standard of care for the treatment of advanced pancreatic cancer?”. In addition, he summarizes the key studies presented at the “Gastrointestinal Cancers Symposium” held in Orlando, FL, USA on January 25-27, 2008. The studies discussed here include the following: i) a phase I study of a chemotherapy doublet gemcitabine plus capecitabine, combined with a biologic doublet (bevacizumab plus erlotinib) in patients with advanced pancreatic adenocarcinoma (abstract #141); ii) a phase II study of gemcitabine, bevacizumab, and erlotinib in locally advanced and metastatic adenocarcinoma of the pancreas (abstract #151); iii) final results of the multicenter phase II study on gemcitabine, capecitabine, and bevacizumab in patients with advanced pancreatic cancer (abstract #198); iv) interim results from a phase II study of volociximab in combination with gemcitabine in patients with metastatic pancreatic cancer (abstract #142); v) a pilot study of combination chemotherapy with S-1 and irinotecan for advanced pancreatic cancer (abstract #155); vi) a multicenter phase II study of gemcitabine and S-1 combination chemotherapy in patients with unresectable pancreatic cancer (abstract #212); vii) a phase I/II study of PHY906 plus capecitabine in patients with advanced pancreatic carcinoma (abstract #260); and viii) the final results of a phase II trial of Genexol-PM®, a novel cremophor-free, polymeric micelle formulation of paclitaxel in patients with advanced pancreatic cancer (abstract #269). Based on the results presented at the meeting, it comes to us that patients with locally advanced vs. metastatic pancreatic cancer should be studied separately, better understanding of the biology of pancreatic cancer is mandatory and evaluation of novel agents is crucial. We, as oncologist, have to change our attitudes towards clinical trials and need to think beyond a trial design such as gemcitabine vs. drug of our choice.

INTRODUCTION

What defines a standard of care is evidence of benefit to a patient, consisting of increased survival, shrinkage of tumor mass, tolerability
of the therapy, and palliation of the tumor-related symptoms. This benefit is based on comparison to current/prior standard therapy or best supportive care. In addition, the determination of a standard is typically performed through a phase III clinical trial that demonstrates statistical improvement. However, statistical improvement does not always transform into clinical improvement. Before gemcitabine’s approval, 5-fluorouracil (5-FU) was presumably a treatment for pancreatic cancer. Rubin et al. performed a phase II study of 5-FU plus leucovorin in thirty-one patients with pancreatic cancer. No objective response was observed with a median overall survival of 5.7 months [1]. To improve the response, three 5-FU-based regimens were evaluated including doxorubicin and mitomycin. An increased toxicity with no significant increase in response or survival benefit was observed [2]. Earlier studies of gemcitabine showed modest activity with a response rate of 6.3% and 11% and median overall survival of 6.3 months and 5.6 months, respectively [3, 4]. The median survival reported in gemcitabine trials was akin to that of the 5-FU. However, the Carmichael et al. study did show clinical benefit in terms of improved performance status (17.2%), decreased pain score (28.6%), and decreased nausea (27.3%) and this study might have led to the randomized phase III study [3]. Burris et al. performed a multi-centered randomized, phase III clinical trial that compared 5-FU to gemcitabine [5]. Treatment with gemcitabine resulted in a relative improvement of 36% in median overall survival compared to 5-FU (5.7 months vs. 4.2 months) and 1-year survival rates (18% vs. 2%). In addition to the survival benefit, gemcitabine was also superior to 5-FU in producing clinical benefit response (24% vs. 5%) (Figure 1). This study led to the approval of gemcitabine for 1st line chemotherapy agent. Using gemcitabine as the control, several investigational drugs (BAY 12-9566, exatecan, SCH 66336) were compared against gemcitabine and no such agent demonstrated superiority over gemcitabine (Figure 2) [6, 7, 8]. Therefore, the study design for clinical trials for pancreatic cancer was directed towards comparing gemcitabine monotherapy or gemcitabine plus the investigational drug. This trial design allows new drugs to be tested in the first-line setting. Over the last decade, multiple cytotoxic (5-FU, capecitabine, irinotecan, cisplatin, oxaliplatin, etc) [9, 10, 11, 12, 13, 14] and targeted agents (bevacizumab, cetuximab) [15, 16] have been combined with gemcitabine in randomized phase III trials and none of such combinations showed superiority over single-agent gemcitabine. Two large randomized phase III studies in pancreatic cancer have demonstrated the superiority of a gemcitabine-containing combination over single-agent gemcitabine: capecitabine plus gemcitabine vs. gemcitabine and erlotinib plus gemcitabine vs. gemcitabine [17, 18]. Preliminary data from a study by Cunningham et al. [17] showed a 7.4
month median survival (95% confidence interval (95% CI): 6.5-8.5 months) for subjects who received gemcitabine plus capecitabine combination therapy (n=267), significantly higher (P=0.026) when compared to 6.0 months (95% CI: 5.4-7.1 months) for those who received gemcitabine alone (n=266) (hazard ratio (HR): 0.80; 95% CI: 0.65-0.98). Moreover, 1-year survival was 19% for subjects on gemcitabine mono-therapy and 26% for those receiving the combination. However, the comparison is not equal. The HR compares the entire survival curve and favors the tail-end of the curve, where there were virtually no subjects. Thus, the HR in this trial is based heavily on these preliminary data without many subjects. However, in comparison, Herrmann et al. [11] reported data from a completed phase III trial; results showed that the combination of gemcitabine plus capecitabine did not significantly (P=0.314) improve overall survival compared with gemcitabine mono-therapy (8.0 vs. 7.3 months, respectively). This discrepancy in outcomes from two trials evaluating the gemcitabine and capecitabine combination indicates that more data are needed before determining the real value of that regimen.

On the other hand, 569 patients were randomly assigned to receive either gemcitabine with or without erlotinib. Patients treated with the combination of gemcitabine and erlotinib had an improved overall survival with a statistically significant HR of 0.82 [18]. The median and 1-year survival rates were better for the combination treatment: 6.24 vs. 5.91 months and 23 vs. 17%, respectively. In the Moore et al. study, the difference, although significant, shows about 12 to 14 days of gain with erlotinib therapy. Is this clinically meaningful? Do we want to add a drug that adds toxicity with only 2 weeks of gain? In most cancers, this difference would be considered as not clinically relevant, but in pancreatic cancer, this difference becomes more meaningful because of the poor outcome of advanced pancreatic cancer, the absence of impact of most other treatment options, the relatively limited impact of the reference treatment of gemcitabine monotherapy, and the acceptable toxicity profile.

**HIGHLIGHTS FROM THE GI CANCERS SYMPOSIUM 2008**

Many abstracts pertaining to pancreatic cancer were presented at this meeting. The main highlights include the following studies pertaining to the advanced pancreatic cancer.

**A. Two Drug Combination**

*Volociximab + Gemcitabine*

Interim results from a phase II study of volociximab in combination with gemcitabine in patients with advanced pancreatic cancer were also presented [19]. Volociximab is a chimeric monoclonal antibody that inhibits the functional activity of alpha5-beta1 integrin, a protein found on activated endothelial cells that are involved in the formation of blood vessels. Preclinical data suggest a direct antitumor effect. The study was a multicenter open-label, 2-cohort, single arm, phase II study. Twenty patients in cohort 1 received volociximab 10 mg/kg i.v. every 2 weeks with gemcitabine 1,000 mg/m2 on days 1, 8, 15 of a 28 day cycle. An additional twenty patients in cohort 2 received volociximab 15 mg/kg every week on days 1, 8, 15, and 22 with gemcitabine on days 1, 8, and 15. In cohort 1, one patient had partial response (5%) and 10 had stable disease (50%) with an overall survival at 1 year of 34%. In cohort 2, two patients had partial response (10%) and 7 (35%) patients had stable disease with an overall survival of 4.8 months. Most frequent toxicities included nausea (75%), constipation (60%), diarrhea (55%), abdominal pain (50%) and pulmonary embolism (20%).

*S-1 plus Gemcitabine and S-1 plus Irinotecan*

Two studies of combination of S-1, a novel oral fluoropyrimidine pro-drug combined with dihydropyrimidine dehydrogenase (DPD) inhibitor, with gemcitabine and irinotecan were presented with summary results shown in Table 1 [20, 21].
B. Three Drug Combination

Gemcitabine + Bevacizumab + Erlotinib

A phase II study of gemcitabine, bevacizumab, and erlotinib in locally advanced and metastatic adenocarcinoma of the pancreas who received gemcitabine 1,000 mg/m² on days 1, 8, and 15, erlotinib 100 mg orally days 1-28, and bevacizumab 10 mg/kg i.v. days 1 and 15, every 28 days [22]. Twenty-eight patients with no prior therapies were enrolled and the response was evaluable in 23. Five patients achieved a confirmed partial response (22%) and 13 patients had stable disease (57%). The median time to progression was 3.4 months while median overall survival was 6.8 months. Initial report in the abstract indicated that the grade 3/4 toxicities were neutropenia 38%, thrombocytopenia 16%, thromboembolic events 14%, nausea 14%, hypertension 8%, and GI bleeding 8%. One treatment-related death occurred (hemorrhage).

Gemcitabine + Capecitabine + Bevacizumab

Final results of the phase II study of gemcitabine, capecitabine, and bevacizumab in patients with advanced pancreatic cancer were presented [23]. Patients received bevacizumab 15 mg/kg i.v. day 1, capecitabine 650 mg/m² bid days 1-14, and gemcitabine 1,000 mg/m² i.v. days 1 and 8; cycles repeated every 21 days. Among 50 patients, one patient achieved complete response (2%), 10 partial response (20%), and 30 stable disease (60%). Median progression free survival and overall survival were 5.8 and 9.8 months, respectively. Grade 3/4 toxicities included neutropenia 38%, thrombocytopenia 16%, thromboembolic events 14%, nausea 14%, hypertension 8%, and GI bleeding 8%. One treatment-related death occurred (hemorrhage).

C. Four Drug Combination

Gemcitabine + Capecitabine + Bevacizumab + Erlotinib

A phase I study of a chemotherapy doublet (gemcitabine plus capecitabine), combined with a biologic doublet (bevacizumab plus erlotinib) in patients with advanced pancreatic adenocarcinoma was presented (the TARGET trial) [24]. Patients with advanced (including locally advanced) were treated at 4 cohorts of escalating capecitabine doses (days 1-21): 910 mg/m², 1,160 mg/m², 1,400 mg/m², and 1,660 mg/m². The doses of co-administered gemcitabine (1,000 mg/m² days 1, 8, and 15), bevacizumab (5 mg/kg days 1 and 15), and

Table 1. Results of two studies of combination of S-1 plus gemcitabine or S-1 plus irinotecan.

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<th>S-1 + gemcitabine [20]</th>
<th>S-1 + irinotecan [21]</th>
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<tr>
<td>No. of patients</td>
<td>38</td>
<td>16</td>
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<tr>
<td>Schema</td>
<td>Gemcitabine 1,000 mg/m² over 30 min on days 1 and 8; S-1 40 mg/m² orally twice daily from day 1 to day 14, repeated every 3 weeks</td>
<td>Irinotecan 100 mg/m² on days 1 and 15; S-1 80 mg/m² for 14 consecutive days, followed by a 14-day rest period</td>
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<td>Response rate</td>
<td>23.5%</td>
<td>43.7%</td>
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<td>Time to progression or progression free survival</td>
<td>Progression free survival: 5.4 months</td>
<td>Time to progression: 4.9 months</td>
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<td>Median survival</td>
<td>9.3 months</td>
<td>11.3 months</td>
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<td>Grade 3-4 toxicities</td>
<td>Neutropenia: 10.0%</td>
<td>Neutropenia: 31%</td>
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<td></td>
<td>Leucopenia: 2.8%</td>
<td>Diarrhea: 6%</td>
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<td>Thrombocytopenia: 0.9%</td>
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<td>Anemia: 1.4%</td>
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<td>Anorexia: 4%</td>
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<td>Rash: 2%</td>
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erlotinib (100 mg/day) every 28 days were constant. Dose-limiting toxicity occurred in one patient at 910 mg/m² (grade 3 epistaxis) and two patients at 1,660 mg/m² (grade 3 diarrhea, and grade 3 skin rash for more than 7 days). No patient developed GI perforation or pneumonitis; while a GI bleed (grade 1) was seen in one patient. Among evaluable 14 patients, there were 5 confirmed partial responses (36%) and a 50% decrease in CA 19-9 by 8 weeks was seen in 9 patients (64%). The maximal tolerable dose of capecitabine in this four drug cytotoxic/biologic combination is 1,660 mg/m² and a follow-on phase II study is planned.

D. Newer Agents

**Genexol-PM® (GPM): A Novel Cremophor-Free, Polymeric Micelle Formulation of Paclitaxel**

GPM is a novel micellar formulation of paclitaxel in a low molecular weight biodegradable synthetic polymer. The maximal tolerable doses for GPM in preclinical and phase I studies are higher than that for cremophor-based paclitaxel. At maximal tolerable dose for each formulation, GPM was more effective than cremophor-based paclitaxel or gemcitabine against several tumor models including 2 pancreatic cancer xenografts. The rationale for development of GPM is synthesized in Figure 3.

We presented the final results of a phase II study of GPM in patients with chemo-naïve pancreatic cancer who were treated with 3-h i.v. GPM every 3 weeks [25]. Among 56 evaluable patients, overall response rate was 6.7% with median time to progression of 3.0 months and median overall survival of 6.2 months. The most common grade 3 toxicities were neutropenia (17.8%), fatigue (17.8%), infection (13.3%), and peripheral sensory neuropathy (11.1%). The results of this study suggests that treatment with GPM at a dose of 300 mg/m² given every 3 weeks was well tolerated and resulted in progression free survival similar to that seen historically with gemcitabine. Future studies of GPM in combination with gemcitabine are being planned.

**PHY906: A Traditional Chinese Medicine Botanical**

PHY906 is a formulation of traditional Chinese medicine botanicals which has shown synergistic antitumor activity with capecitabine in PANC-1 cell lines and is a potent inhibitor of NF-kappaB [26]. In addition, studies in other tumor types have shown that PHY906 may reduce chemotherapy-induced GI toxicities, in particular nausea, vomiting, and diarrhea. Moreover, earlier data also suggested that PHY906 does not alter pharmacokinetics of capecitabine. These data prompted us to perform a phase I/II study of a dose intense weekly (7/7) schedule for capecitabine plus PHY906 (funded by the National Comprehensive Cancer Network; NCCN). We presented results of the phase I part of the study in which we were able to escalate dose to 1,750 mg/m² without any dose-limiting toxicity [27]. The ongoing phase II study is assessing efficacy and quality of life in gemcitabine-refractory pancreatic cancer patients. Correlative chemokine (IL-2, IL-4, IL-5, IL-10, TNF-alpha, IFN-gamma) levels, as surrogates for NF-kappaB expression, will be quantified by cytometric bead array in order to help to elucidate PHY906 mode of action.

**DISCUSSION**

Although we have made incremental progress in the treatment of pancreatic cancer, the prognosis of patients with this disease remains extremely poor. Gemcitabine remains
the standard of care for treating patients with pancreatic cancer. Apparently, many oncologists are still using single-agent gemcitabine in pancreatic cancer due to lack of a shift to the gemcitabine-erlotinib or gemcitabine-capecitabine combination. On the other hand, many trials are still ongoing that were designed to evaluate gemcitabine plus an investigational drug or add another to gemcitabine-erlotinib combination. Moreover, the US Food and Drug Administration still allows trials with a gemcitabine monotherapy arm.

So, some questions arise regarding the identification of the standard therapy (Figure 4) [28]:

- Is there a standard of care for advanced pancreatic cancer?
- Is gemcitabine really a standard?
- Do we need to continue to compare everything to gemcitabine? Or, do we need to start over again and find newer, better agents? (Since gemcitabine has offered only a modest benefit to our patients, other than it arguably helps in improving symptoms, at least in terms of pain scores).

Gemcitabine was approved based on symptom improvement, and there has been no rigorous assessment of survival with gemcitabine therapy. I think that gemcitabine is not a meaningful backbone for the addition of other anticancer therapies for pancreas cancer and that we need to explore newer agents. We definitely need to identify surrogates for survival. We need to learn from our mistakes and patients with locally advanced pancreatic cancer should be studied separately from metastatic pancreatic cancer in future studies. In addition, the oncologists need to change their attitudes towards clinical trials. Development of novel agents and approaches are urgently needed in conjunction with improvement in access to clinical trials for patients. In short, there is no current clear standard of care for the treatment of advanced pancreatic cancer.

Keywords Antibodies, Monoclonal; bevacizumab; capecitabine; cetuximab; erlotinib; Fluorouracil; gemcitabine; irinotecan; Pancreatic Neoplasms; Protein Kinase Inhibitors; Protein-Tyrosine Kinase; Receptor, Epidermal Growth Factor; S 1 (combination)

Abbreviations DPD: dihydropyrimidine dehydrogenase; GPM: Genexol-PM®; HR: hazard ratio

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Can Oncologists Change?

Figure 4. We, as oncologist, have to change our attitudes towards clinical trials and need to think beyond a trial design such as gemcitabine vs. drug of our choice.

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fluorouracil and leucovorin in patients with metastatic gastric or pancreatic carcinoma. Cancer 1996; 78:1888-91. [PMID 8909307]


