

## LETTER

# Options for the Treatment of Gemcitabine-Resistant Advanced Pancreatic Cancer: Are We There Yet?

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Dear Sir:

We read with interest the review article by Gounaris *et al.* entitled 'Options for the Treatment of Gemcitabine-Resistant Advanced Pancreatic Cancer', published in the March issue of JOP. J Pancreas (Online) [1]. The authors searched the OVID and MEDLINE databases from 1950 to present using the MeSH terms "pancreatic neoplasms", "drug treatment", and "gemcitabine". In addition to 31 published studies identified, these results were supplemented by abstracts published in the last three (2007-2009) American Society of Clinical Oncology (ASCO) proceedings of annual meetings. They found that the evidence for second line treatments of metastatic pancreatic cancer consists mainly of single arm, small phase II studies. Only oxaliplatin-fluoropyrimidine combinations have been compared against supportive care and seem promising. However, we will add that oral capecitabine seems to be a very convenient and an optimal therapy too [2].

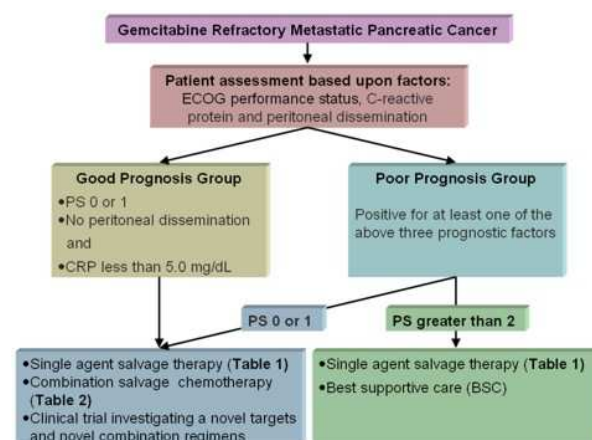
We agree with the authors that there is growing evidence supporting benefit of chemotherapy after gemcitabine failure in selected patients with good performance status as we published similar data earlier in JOP. J Pancreas (Online) [2]. Lack of data to support second-line treatment strategy in advanced pancreatic cancer is probably due to the fact that we still do not have an effective first-line treatment that renders true survival benefit [3]. In order to establish a much needed effective second-line treatment options for advanced pancreatic cancer, we need cooperative efforts among institutions and community practices in enrolling gemcitabine refractory patients in clinical

trials. Moreover, development of novel therapeutic agents should be an obvious area of our focus in the future. We must improve study design and be more rigorous in scrutinizing phase II data before moving forward with large phase III randomized trials that require enormous resources. One solution would be more frequent implementation of randomized phase II trials to test agents with encouraging activities before undertaking phase III trials.

Patient selection and individualized medicine is another area of increased interest at present. While it is still at a very early stage before we can see clinical application, pharmacogenomics in pancreatic cancer is an important area to watch. There are various preclinical studies investigating polymorphisms and expression levels of genes associated with gemcitabine sensitivity and/or resistance [4].

In brief, selected advanced pancreatic cancer patients with good performance status should be considered for second-line chemotherapy after first-line gemcitabine failure. With better patient selection, we can improve clinical outcomes of advanced pancreatic cancer in second-line settings, which will ultimately improve the

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**Figure 1.** Proposed selection guideline for second-line therapy after gemcitabine failure [2].

ECOG: Eastern Cooperative Oncology Group; PS: performance status

**Table 1.** Possible single agent treatment options for gemcitabine refractory patients.

Capecitabine or 5-fluorouracil plus leucovorin [12, 13]
Irinotecan [14]
Erlotinib (if not given previously) [17] <sup>a</sup>
<u>Docetaxel (limited data) [16] <sup>b</sup></u>
<sup>a</sup> Very limited data (generally not recommended)
<sup>b</sup> No clear benefit; however, few patients may have stable disease

over all survival. It is also important to consider the quality of life measurements in this setting as obviously patients are more symptomatic when receiving second-line chemotherapy. Prospective clinical trials investigating clinical outcomes in association with published prognostic factors such as performance status, C-reactive protein, and peritoneal dissemination may improve patient selection for second-line treatment as we previously suggested (Figure 1; Tables 1 and 2).

**Conflict of interest** The authors declare no conflicts of interest

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**Table 2.** Possible combination treatment options for gemcitabine refractory patients.

Oxaliplatin plus 5-fluorouracil plus leucovorin (FOLFOX) or capecitabine plus oxaliplatin (XELOX) [5, 6., 7, 8, 9]
Gemcitabine plus docetaxel plus capecitabine (GTX) [11] <sup>a</sup>
Capecitabine plus erlotinib [15]
5-fluorouracil plus leucovorin plus irinotecan (FOLFIRI) [7]
<u>Gemcitabine and oxaliplatin (GemOx) [10]</u>
<sup>a</sup> It should be reserved for young and excellent performance status (PS) patients because it is a toxic regimen

therapy in patients with advanced pancreatic cancer previously treated with gemcitabine-based chemotherapy. *J Clin Oncol* 2009; 27(15 Suppl.):4618.

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