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Fixed-Dose-Rate Gemcitabine: A Viable First-Line Treatment Option for Advanced Pancreatic and Biliary Tract Cancer

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ABSTRACT

Background. **We have already reported on fixed-dose-rate gemcitabine (FDR-Gem) in advanced, inoperable pancreatic ductal adenocarcinoma (PDAC) and biliary tract cancer (BTC) in the context of a formal phase II study; building on that experience, we have now expanded the study to reach a cumulative accrual of 106 patients.**

Methods. **One hundred six patients (PDAC/BTC, 75/31) were treated with weekly FDR-Gem (1,000 mg/m^2 infused at 10 mg/m^2 per minute). Patient characteristics included: male-to-female ratio, 0.83; median age, 63 years (range, 28–82); metastatic disease in 66% of patients; and an Eastern Cooperative Oncology Group performance status (ECOG PS) score of 0–1 in 81% of patients.**

Results. **The median and total number of treatment weeks delivered were 8 (range, 2–22) and 1,154, respectively. Thirteen percent of patients achieved an objective response, 42% experienced a positive clinical benefit response, and 54% achieved a >50% reduction in serum cancer antigen (CA)19.9 levels. The median progression-free survival (PFS) and overall survival (OS) times for the entire population were 4.4 months (95% confidence interval [CI], 3.5–5.1 months) and 7.7 months (95% CI, 6.3–8.8 months), respectively, with 20% of patients alive at 1 year. On multivariate analysis, a CA19.9 reduction >50% and baseline ECOG PS score of 0 were the only independent predictors of PFS and OS, respectively. Treatment was well tolerated, with grade 3–4 neutropenia in 47 of 1,154 treatment weeks (4.1%), and grade 3 anemia and thrombocytopenia in 8 of 1,154 (0.7%) and 16 of 1,154 (1.4%) treatment weeks, respectively.**

Conclusions. **Currently available evidence, including this updated analysis, supports the use of FDR-Gem as a first-line option in advanced PDAC, and possibly in BTC, patients and prompts the continued evaluation of this approach in combination regimens.** ***The Oncologist*** 2010;15:e1–e4

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Table 1. Grade 3–4 toxicities

	Per treatment week (n = 1,154)		Per patient (n = 106)	
Toxicity[a]	**Grade 3, *n* (%)**	**Grade 4, *n* (%)**	**Grade 3, *n* (%)**	**Grade 4, *n* (%)**
Neutropenia	40 (3.5)	7 (0.6)	14 (13.2)	2 (1.9)
Thrombocytopenia	16 (1.4)	–	9 (8.5)	–
Anemia	8 (0.7)	–	3 (2.8)	–
Nausea/vomiting	–	–	–	–
AST	9 (0.8)	2 (0.2)	4 (3.8)	2 (1.9)
ALT	20 (1.7)	2 (0.2)	3 (2.8)	2 (1.9)
Diarrhea	4 (0.3)	–	4 (3.8)	–
Non-neutropenic fever	4 (0.3)	–	4 (3.8)	–
Peripheral neuropathy	NE	NE	1 (0.9)	–
Skin rash	NE	NE	1 (0.9)	–

[a]According to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0 (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/ctcaev3.pdf).
Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; NE, not evaluated.

We read with great interest two papers that appeared in a recent issue of ***The Oncologist*** regarding the use of prolonged infusion gemcitabine [1] and new therapeutic directions for advanced pancreatic cancer [2]. We have already reported on fixed-dose-rate gemcitabine (FDR-Gem) in inoperable pancreatic ductal adenocarcinoma (PDAC) and biliary tract cancer (BTC) patients [3] in the context of a formal phase II study; building on that experience, we have now expanded the study to reach a cumulative accrual of 106 patients treated with weekly FDR-Gem (1,000 mg/m^2 infused at 10 mg/m^2 per minute). Seventy-five patients had PDAC and 31 had BTC; other patient characteristics included: male-to-female ratio, 0.83; median age, 63 years (range, 28–82); metastatic disease in 66% of patients; and an Eastern Cooperative Oncology Group performance status (ECOG PS) score of 0–1 in 81% of patients. The median and total number of treatment weeks delivered were 8 (range, 2–22) and 1,154, respectively. Treatment was well tolerated, with no hospitalizations resulting from severe adverse events and no treatment-related deaths. Grade 3–4 toxicities are summarized in Table 1. Approximately 13% of patients achieved an objective response, 42% experienced a positive clinical benefit response, and 54% achieved a reduction in serum cancer antigen (CA)19.9 levels of >50%, as compared with baseline (Table 2). The median progression-free survival (PFS) and overall survival (OS) times for the entire population were 4.4 months (95% confidence interval [CI], 3.5–5.1 months) and 7.7 months (95% CI, 6.3–8.8 months), respectively, with 20% of patients alive at 1 year (Fig. 1). On multivariate analysis, a CA19.9 reduction >50% and a baseline ECOG PS score of 0 were the only independent predictors of PFS and OS, respectively.

Table 2. Treatment outcomes

Outcome	***n* of patients (%)**
Objective response[a]	
Eligible/evaluable	106/100
CR	0 (0)
PR	14 (14)
SD	43 (43)
PD	43 (43)
ITT-ORR (95% CI)	13.2% (4%–26%)
CBR[b]	
Evaluable	86
Yes	36 (42)
No	50 (54)
CBR rate (95% CI)	42% (31%–52%)
Tumor marker response	
Evaluable	56
>75% decrease	17 (30)
51%–75% decrease	13 (23)
25%–50% decrease	3 (5)
No change	6 (11)
>25% increase	17 (30)

[a]According to standard World Health Organization criteria.
[b]According to the definition of Burris et al. [8].
Abbreviations: CBR, clinical benefit response; CI, confidence interval; CR, complete response; ITT-ORR, intent to treat objective response rate; PD, progressive disease; PR, partial response; SD, stable disease.

With all the limits of indirect comparisons, these results compare favorably with those reported for standard infusion gemcitabine in both the analysis performed by Stor-

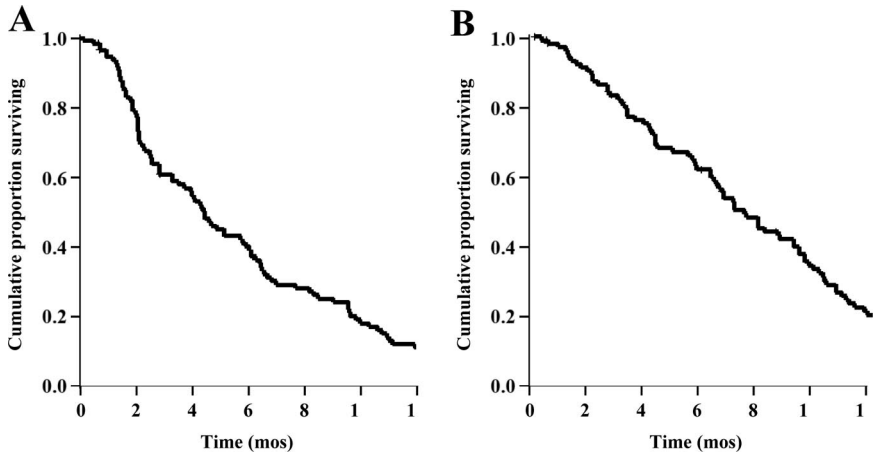

Figure 1. Kaplan–Meier estimates of progression-free survival **(A)** and overall survival **(B)** for the intent-to-treat population (n = 106).

niolo et al. [4] in a cohort of >1,500 patients treated under an investigational new drug program (objective response rate, 13%; median PFS time, 2.8 months; median OS time, 5.1 months) and the control arms of randomized trials of gemcitabine-based combinations (reviewed in [2]), and add to current evidence supporting the use of FDR-Gem in advanced PDAC patients. Indeed, the phase II randomized study by Tempero et al. [5] and the ECOG phase III trial E6201 (reported in part at the American Society of Clinical Oncology 2006 meeting [6]) both suggest that the FDR infusion strategy may lead to longer survival than with standard 30-minute infusion gemcitabine. Similar considerations may be applied to the use of FDR-Gem for the treatment of advanced BTC patients [7], although in this setting no randomized comparisons have been reported.

In contrast to the trial Tempero et al. [5] and the ECOG trial [6], both employing FDR-Gem at its maximum-tolerated dose of 1,500 mg/m^2 per week as established in phase I studies, we applied the FDR infusion strategy without modifying the standard dose schedule of 1,000 mg/m^2 per week. This resulted in a sensibly lower hematologic toxicity rate; indeed, in the study by Tempero et al. [5] and in the ECOG trial [6], the incidences of severe neutropenia and thrombocytopenia were 50%–60% and 30%–40%, respectively, whereas in our series the same toxicities were observed in approximately 15% and <10% of patients, respectively. This, in turn, suggests that, when the total gemcitabine dose administered is not increased, the FDR strategy per se does not result in worse toxicity than with standard infusion, while apparently maintaining the activity.

Overall, we appreciate the excellent review of the pharmacological and clinical rationale for modulating gemcitabine infusion by Veltkamp et al. [1] and find it thought provoking that treatment of advanced PDAC was reviewed in the same issue of ***The Oncologist***. We believe that the currently available evidence, including the updated analysis of a large series of 106 patients presented herein, supports the hypothesis that the FDR infusion strategy may increase the gemcitabine therapeutic index in advanced PDAC, and possibly in BTC, and prompts the continued evaluation of this approach in combination regimens.

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Michele Milella and Alain J. Gelibter contributed equally.

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Conception/Design: Michele Milella, Alain J. Gelibter
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