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## EVIDENCE-BASED ONCOLOGY

# Adding irinotecan to first-line gemcitabine improves tumour response in advanced pancreatic cancer

*Abstracted from: Rocha Lima CM, Green MR, Rotche R et al. Irinotecan plus gemcitabine results in no survival advantage compared with gemcitabine monotherapy in patients with locally advanced or metastatic pancreatic cancer despite increased tumour response rate. J Clin Oncol 2004;22:3776–83.*

## Background

There is limited evidence to support the use of irinotecan plus gemcitabine (IRINOGEN) in patients with locally advanced or metastatic pancreatic cancer.

## Objective

To determine if IRINOGEN prolongs survival compared with gemcitabine alone in chemotherapy-naïve people with locally advanced or metastatic pancreatic cancer.

## Setting

Six hospitals in the US, Canada and New Zealand; recruitment from 10 February 2000 to 28 December 2001.

## Method

Multicentre, randomised controlled trial.

## Participants

Three hundred and sixty people with locally advanced ( $n = 51$ , 14%) or metastatic pancreatic cancer ( $n = 293$ , 81%) and an Eastern Cooperative Oncology Group performance status of 0 ( $n = 93$ , 25.8%), 1 ( $n = 181$ , 50.3%), 2 ( $n = 70$ , 19.4%) or 3 ( $n = 1$ , 0.3%) and unknown ( $n = 18$ , 5%). People were excluded if they had: prior systemic chemotherapy or radiotherapy; active inflammatory bowel disease; significant bowel obstruction; chronic diarrhoea; known brain or leptomeningeal disease; myocardial infarction within 6 months; uncontrolled high blood pressure; unstable angina; symptomatic congestive heart failure; serious uncontrolled arrhythmia, HIV infection or AIDS-related disease, other secondary malignancies or severe concurrent diseases, mental illness, or if they were pregnant or breastfeeding.

## Intervention

Participants were randomised to receive IRINOGEN chemotherapy (gemcitabine  $1000 \text{ mg/m}^2$ , followed by irinotecan  $100 \text{ mg/m}^2$ , on days 1

and 8 of a 3-week treatment cycle), or gemcitabine alone (gemcitabine 1000 mg/m<sup>2</sup>, every 7 days for 7 weeks of an 8-week induction period, followed by gemcitabine 1000 mg/m<sup>2</sup>, every 7 days for 3 weeks of a repeated 4-week treatment cycle). Median duration of therapy: 12.1 weeks, 95% CI 3–8.9 with IRINOGE M vs. 12.9 weeks, 95% CI 6.6–88.0 weeks with gemcitabine.

## Main outcomes

Median survival; time to progression; tumour response.

## Main results

**Effectiveness.** There were no significant differences in survival outcomes between gemcitabine alone and IRINOGE M. IRINOGE M significantly increased tumour response compared with gemcitabine alone (see Evidence Profile: Benefits).

**Safety.** IRINOGE M significantly increased diarrhoea events compared with gemcitabine alone (see Evidence Profile: Harms). No treatment-related deaths were reported.

Evidence Profile: Benefits			
	IRINOGE M; <i>n</i> = 180	Gemcitabine alone; <i>n</i> = 180 (95% CI)	Significance
Median survival	6.3 months (4.7–7.5 months)	6.6 months (5.2–7.8 months)	<i>P</i> = 0.79
Time to progression	3.5 months (2.8–4.2 months)	3.0 months (2.5–3.7 months)	<i>P</i> = 0.352
Complete or partial tumour response <sup>a</sup>	16.1% (11.1–22.3%)	4.4% (1.9–8.6%)	<i>P</i> < 0.001
Complete tumour response <sup>a</sup>	1.7% (not stated)	0% (not stated)	Not stated
Partial tumour response <sup>a</sup>	14.4% (not stated)	4.4% (not stated)	Not stated

IRINOGE M, irinotecan plus gemcitabine.  
<sup>a</sup> Confirmed more than 4–6 weeks after initial objective response.

## Evidence Profile: Harms

Adverse events (%)	IRINOGE M; <i>n</i> = 173 (%)	Gemcitabine alone; <i>n</i> = 169 (%)
<i>Non-haematological</i>		
Diarrhoea	32 (18.5)	3 (1.8)
Nausea	29 (16.8)	17 (10.1)
Fatigue	29 (16.8)	26 (15.4)
Abdominal pain	31 (17.9)	31 (18.3)
Vomiting	24 (13.9)	14 (8.3)
Dehydration	21 (12.1)	15 (8.9)
Deep vein thrombosis or pulmonary embolism	26 (15.0)	23 (14.0)
<i>Haematological</i>		
Neutropenia	65 (37.6)	54 (32.0)
Leukopenia	45 (26.0)	25 (14.8)
Thrombocytopenia	34 (19.7)	24 (14.2)
Anaemia	28 (16.2)	22 (13.0)
Febrile neutropenia	6 (3.5)	9 (5.3)

Grades 3 and 4; IRINOGE M, irinotecan plus gemcitabine.

## Authors' conclusions

IRINOGE M safely improved tumour response rates compared with gemcitabine alone, but did not alter overall survival in people with locally advanced or metastatic pancreatic cancer.

## Method notes

<i>Random error</i>	
Power calculation	85% power with a sample size of 350 participants in each group ( $\alpha = 0.05$ ) to detect a 40% improvement in median survival
<i>Bias</i>	
<i>Measures to prevent bias</i>	
<i>Comparator bias</i>	
Was true uncertainty about relative effects of competing treatments acknowledged?	Adequate: authors report on a previous phase II trial where gemcitabine plus irinotecan was active and had an acceptable toxicity profile

<i>Selection bias</i>	
Selection method	Adequate
Generation of allocation sequence	Adequate: randomisation performed with stratification for East Coast Oncology Group performance status, disease extent and prior radiotherapy
Allocation concealment	Adequate
Balanced groups	Adequate: well balanced with respect to age, sex, performance status, extent of disease and prior radiotherapy
<i>Performance bias</i>	
Blinding	Open label
<i>Detection bias</i>	
Assessors blinded	Not clear
<i>Attrition bias</i>	
Withdrawals and dropouts described	Yes
<i>Analysis</i>	
Intention to treat analysis	Kaplan–Meier analysis and the log-rank test
Other statistical methods used	Proportional hazard techniques or logistic regression used to test the influence of stratification factors on the primary and secondary endpoints. Confirmed and unconfirmed response rates were analysed by the $\chi^2$ test

the publication of the pivotal Burris study<sup>1</sup> comparing this drug to bolus 5-fluorouracil (5FU). This trial demonstrated a longer median survival (5.7 months vs. 4.4 months,  $P = 0.0025$ ), 1-year survival (18% vs. 2%) and better clinical benefit (22.2% vs. 4.8%,  $P = 0.0022$ ).

Irinotecan, a camptothecin, has demonstrated pre-clinical synergy with gemcitabine and also safety and some efficacy in phase II studies in advanced pancreatic cancer. Rocha Lima compared this combination (IRINOGEM) with single agent gemcitabine in a phase III study of 360 patients with advanced pancreatic cancer.<sup>2</sup> The median duration of treatment in both arms was about 12 weeks and similar numbers of patients in each withdrew due to adverse events. Diarrhoea was more common in the combination arm (grades 3, 4: 18.5% vs. 1.8%) but only led to five patients discontinuing in this arm. Haematological toxicity in both arms was similar except for higher grades 3, 4 leucopenia in the combination (26% vs. 14.2%). Responses were measured radiologically using RECIST criteria and confirmed at 4–6 weeks after initial objective response. Overall response (PR + CR) was significantly higher for IRINOGEM compared to gemcitabine (16.1% vs. 4.0%,  $P < 0.001$ ). No differences in median survival (6.3 vs. 6.6 months,  $P = 0.79$ ) nor time to progression (3.5 vs. 3.0 months) were observed. One-year survival was 20% on both arms. Patients were stratified on entry by performance status, disease extent and prior radiation therapy. Exploratory analysis was performed on the patients with locally advanced disease suggesting a trend towards favouring IRINOGEM with time to progression, while median survival numerically favoured the gemcitabine group. This subgroup of patients was small (27 and 24, respectively), thus giving rise to wide overlapping confidence intervals. Quality of life was measured using the FACT-Hep scale, with good compliance overall. No significant difference was seen in any of the domains measured in the two arms.

The trial was powered to detect an improvement in overall survival of 40% over gemcitabine, which would be considered clinically meaningful. The authors point out that the two groups were evenly matched and that only 8% of gemcitabine patients crossed over to irinotecan. Second-line therapy was given to 39% of IRINOGEM patients and 46% of gemcitabine patients, and cannot explain the results. The survival curves were almost identical, making the chance of finding a smaller difference unlikely, even with a larger sample size.

Why was there no improvement in survival commensurate with the higher response? Table 1

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## Commentary

Progress in the management of advanced inoperable pancreatic cancer has been slow compared with developments in advanced colorectal cancer and breast cancer. Gemcitabine, a nucleoside analogue, has remained the standard of care since

**Table 1** Randomised phase III studies of single agent gemcitabine vs. gemcitabine cytotoxic combination regimens in advanced pancreatic cancer

Study	N	Treatment arms	ORR (CR + PR)	CBR/QOL	1 yr survival	PFS (months)	Median survival (months)
Rocha Lima et al. <sup>2</sup>	360	Gemcitabine Gemcitabine + irinotecan	4.4% vs 16.1% ( <i>p</i> < 0.001)	FACT-Hep: No significant difference	22% vs 21%	3.0 vs 3.5 ( <i>p</i> = 0.352)	6.6 vs 6.3 ( <i>p</i> = 0.79)
Berlin et al. <sup>3</sup>	322	Gemcitabine Gemcitabine + 5 FU	5.6% vs 6.9%		20% vs 20% ( <i>p</i> = ns)	2.2 vs 3.4 ( <i>p</i> = 0.022)	7.1 vs 9.0 ( <i>p</i> = 0.09)
Wang et al. <sup>4</sup>	42	Gemcitabine Gemcitabine + cisplatin	6.3% vs 11%	Clinical benefit: 87.5% vs 70%	31% vs 11%		9.0 vs 7.1
Collucci et al. <sup>5</sup>	107	Gemcitabine Gemcitabine + cisplatin	9.2% vs 24.4% ( <i>p</i> = 0.02)	Clinical benefit: 49% vs 52.6% ( <i>p</i> = ns)	11% vs 11.3%	2.0 vs 5.0 ( <i>p</i> = 0.048)	5.0 vs 6.0 ( <i>p</i> = 0.43)
Heineman et al. <sup>6</sup>	198	Gemcitabine Gemcitabine + cisplatin	8.0% vs 10.2% ( <i>p</i> = ns)			2.8 vs 5.4 ( <i>p</i> < 0.01)	6.0 vs 7.6 ( <i>p</i> = ns)
Li and Chao <sup>7</sup>	46	Gemcitabine Gemcitabine + cisplatin	12% vs 10% ( <i>p</i> = ns)	Clinical benefit 36% vs 29% ( <i>p</i> > 0.05)	6.3% vs 13.6%	2.8 vs 2.8 ( <i>p</i> = 0.9)	4.6 vs 5.6 ( <i>p</i> = 0.75)
Louvet et al. <sup>8</sup>	313	Gemcitabine Gemcitabine + oxaliplatin	17.3% vs 26.8% ( <i>p</i> = 0.04)	Clinical benefit: 26.9% vs 38.2% ( <i>p</i> = 0.03)	27.8 vs 34.5%	3.7 vs 5.8 ( <i>p</i> = 0.04)	7.1 vs 9.0 ( <i>p</i> = 0.13)
O'Reilly et al. <sup>9</sup>	349	Gemcitabine Gemcitabine + exetecan	7.1% vs 8.2%	Improvement in time to deterioration of analgesic consumption and performance score	21% vs 23%	3.8 vs 3.7 ( <i>p</i> = 0.22)	6.2 vs 6.7 ( <i>p</i> = 0.52)
Richards et al. <sup>10</sup>	565	Gemcitabine Gemcitabine + pemetrexed	9.1% vs 18.3% ( <i>p</i> = 0.006)	EORTC QLQ C30: well preserved both arms	20% vs 21%	3.3 vs 3.9 ( <i>p</i> = 0.11)	6.3 vs 6.2 ( <i>p</i> = 0.08)
Reni et al. <sup>11</sup>	104	Gemcitabine Cisplatin, epirubicin, gemcitabine, 5FU	8.5% vs 40% ( <i>p</i> < 0.001)		22% vs 38% ( <i>p</i> = 0.06)		
Ohkawa <sup>12</sup>	19	Gemcitabine Gemcitabine + UFT	33% vs 0%	Clinical benefit: 33% vs 25%		5.0 vs 1.9 ( <i>p</i> = 0.04)	7.6 vs 5.0 ( <i>p</i> = ns)

ORR = overall response rate; CBR = clinical benefit response; QOL = quality of life; PFS = progression free survival.

summarises the phase III trials comparing gemcitabine vs. gemcitabine combination regimens that have been published or presented.<sup>2–12</sup> A consistent finding in these trials is that response rate does not correlate with survival in advanced pancreatic cancer. Even in combinations that have a very high response rate such as gemcitabine–oxaliplatin (26.8%),<sup>8</sup> gemcitabine–pemetrexed (18.3%)<sup>10</sup> and PEGF (cisplatin, epirubicin, gemcitabine and 5FU, 40%)<sup>11</sup> there is no impact on overall survival. Clinical benefit or quality of life has been compared in most of these trials and only two<sup>8,9</sup> show some superiority of the combination regimen in this aspect.

Two lessons seem to present themselves in pancreatic cancer. Response rate is far less reliable in this disease, reflecting perhaps the high incidence of peritoneal disease that is poorly imaged similar to ovarian cancer, as well as the stromal reaction around the tumour. In addition, the rate of 1-year survival in excess of 20% is increasing in the trials. This could be due to improved supportive care or it could reflect an increased willingness to offer second-line therapy to a subgroup of patients whose overall condition, performance status and initial response allow it to be given.

The National Cancer Institute considers the strongest endpoint for clinical studies in oncology to be overall survival – the most easily defined outcome measure and least subject to investigator bias. Tumour response rate is considered to be an indirect surrogate that is subject to investigator interpretation and is not automatically translatable into survival. A meta-analysis in 2000 showed that response to 5FU-based chemotherapy in advanced colorectal cancer is a valid surrogate marker endpoint for survival.<sup>13</sup> This has also been shown to be the case from multivariate analysis of 1430 patients with metastatic breast cancer enrolled in eight consecutive trials of anthracycline chemotherapy.<sup>14</sup> From the results of the Rocha Lima trial and other recent studies, it seems that gemcitabine-combination chemotherapy regimens can increase response rate over gemcitabine alone. However, this does not produce statistically better overall survival rates or consistently better clinical benefits in advanced pancreatic cancer. A meta-analysis would be required to determine whether there may be a small advantage in survival that the individual trials could not detect, but this difference is not likely to be clinically meaningful.

Further progress in the management of advanced pancreatic cancer is likely to lie with the addition of biological agents to gemcitabine,

rather than other cytotoxic agents. Although two randomised trials of biological agents marimastat<sup>15</sup> (a metalloproteinase inhibitor) and tipifarnib<sup>16</sup> (a farnylsyltransferase inhibitor) have been negative with respect to survival, recent data have been announced from a trial of the tyrosine kinase inhibitor erlotinib.<sup>17</sup> This placebo-controlled trial of 569 patients found a modest improvement in median survival with the combination of gemcitabine and erlotinib over gemcitabine alone (6.4 vs. 5.9 months,  $P = 0.025$ ) and 1-year survival of 24% vs. 17%. Progression-free survival was also significantly increased and, interestingly, there was no difference in the response rates between the arms. Other phase III trials adding targeted therapy to gemcitabine including cetuximab (a monoclonal antibody to the epidermal growth factor receptor (EGFR)) and bevacizumab (a monoclonal antibody against vascular endothelial growth factor (VEGF)) are also likely to report initial results soon.

The Rocha Lima study will not change clinical practice. The higher response rate at a cost of increased toxicity does not produce an improved clinical benefit or improvement in survival. This regimen, however, may be considered in the rare situation where down-staging chemotherapy is required to make a locally advanced pancreatic cancer operable, where a high tumour response rate is desirable. Where a high dose response rate is desirable to make a locally advanced pancreatic cancer operable with downstaging chemotherapy. In this setting however the gemcitabine/oxaliplatin regimen<sup>8</sup> which has an improved progression free survival and 12-month survival is likely to be the optimal protocol.

Quality assessment (1 = fair; 4 = excellent)	
Relevance	4
Validity	4
Applicability	1
Feasibility	3
Impact	2
Knowledge context	3

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