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Use of Gemcitabine in the Treatment of Advanced Pancreatic Adenocarcinoma Practice Guideline Report #2-10

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ORIGINAL GUIDELINE: May 22, 1998

MOST RECENT LITERATURE SEARCH: June 2003

NEW EVIDENCE ADDED TO GUIDELINE REPORT: June 24, 2003

New evidence found by update searches since completion of the original guideline is consistent with the original recommendations.

SUMMARY

Guideline Question

Should gemcitabine be offered as treatment to patients with unresectable or advanced pancreatic adenocarcinoma?

Target Population

These recommendations apply to adult patients with unresectable or advanced pancreatic adenocarcinoma.

Recommendations

- Gemcitabine is a reasonable treatment option in patients with advanced or unresectable pancreatic cancer. There is evidence from one randomized controlled trial that gemcitabine improves symptoms and modestly improves survival in patients with advanced or unresectable pancreatic cancer. These patients were symptomatic, had a life expectancy of at least twelve weeks, and a Karnofsky performance status of at least 50% (equivalent to an Eastern Cooperative Oncology Group performance status of less than 3).

Methods

Entries to MEDLINE (through to May, week 2, 2003, CANCERLIT (through to September 2002), and Cochrane Library (Issue 1, 2003) databases and abstracts published in the proceedings of the 1999-2003 annual meetings of the American Society of Clinical Oncology have been searched for evidence relevant to this practice guideline.

Evidence was selected and reviewed by one member of the Practice Guidelines Initiative Gastrointestinal Cancer Disease Site Group and methodologists. This practice guideline has been reviewed and approved by the Gastrointestinal Cancer Disease Site Group, which comprises medical oncologists, radiation oncologists, and surgeons. Patient representatives did not participate in the development of the original guideline report, but two patient

representatives sit on the current Disease Site Group, which is responsible for updating the guideline.

External Review by Ontario practitioners was obtained through a mailed survey. Final approval of the original guideline report was obtained from the Practice Guidelines Coordinating Committee.

The Practice Guidelines Initiative has a formal standardized process to ensure the currency of each guideline report. This consists of the periodic review and evaluation of the scientific literature, and where appropriate, integration of this literature with the original guideline information.

Key Evidence

Two phase I trials, seven phase II trials, one trial with both a phase I and phase II design, and one randomized controlled trial comparing gemcitabine with 5-fluorouracil were reviewed.

In the randomized controlled trial, patients randomized to gemcitabine experienced improved symptomatic clinical benefit (23.8% versus 4.8%; $p=0.0022$), longer median survival (5.65 versus 4.41 months; $p=0.0025$), improved one-year survival rate (18% versus 2%; $p=0.0025$), and longer median progression-free survival (2.33 versus 0.92 months; $p=0.0002$), but there was no significant difference in tumour response (5.4% versus 0%) compared with those randomized to 5-fluorouracil. Gemcitabine and 5-fluorouracil were generally well tolerated by patients in this trial. Myelosuppression, and nausea and vomiting, were more pronounced in patients randomized to receive gemcitabine compared with patients randomized to receive 5-fluorouracil.

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*The Practice Guidelines Initiative is sponsored by:
Cancer Care Ontario & the Ontario Ministry of Health and Long-term Care.*

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PREAMBLE: About Our Practice Guideline Reports

The Practice Guidelines Initiative (PGI) is a project supported by Cancer Care Ontario (CCO) and the Ontario Ministry of Health and Long-Term Care, as part of the Program in Evidence-based Care. The purpose of the Program is to improve outcomes for cancer patients, to assist practitioners to apply the best available research evidence to clinical decisions, and to promote responsible use of health care resources. The core activity of the Program is the development of practice guidelines by multidisciplinary Disease Site Groups of the PGI using the methodology of the Practice Guidelines Development Cycle.¹ The resulting practice guideline reports are convenient and up-to-date sources of the best available evidence on clinical topics, developed through systematic reviews, evidence synthesis, and input from a broad community of practitioners. They are intended to promote evidence-based practice.

This practice guideline report has been formally approved by the Practice Guidelines Coordinating Committee, whose membership includes oncologists, other health providers, patient representatives, and Cancer Care Ontario executives. Formal approval of a practice guideline by the Coordinating Committee does not necessarily mean that the practice guideline has been adopted as a practice policy of CCO. The decision to adopt a practice guideline as a practice policy rests with each regional cancer network that is expected to consult with relevant stakeholders, including CCO.

Reference:

- ¹ Browman GP, Levine MN, Mohide EA, Hayward RSA, Pritchard KI, Gafni A, et al. The practice guidelines development cycle: a conceptual tool for practice guidelines development and implementation. *J Clin Oncol* 1995;13(2):502-12.

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FULL REPORT

I. QUESTION

Should gemcitabine be offered as treatment to patients with unresectable or advanced pancreatic adenocarcinoma? Outcomes of interest are symptom control and overall survival.

II. CHOICE OF TOPIC AND RATIONALE

Pancreatic carcinoma is the fourth leading cause of cancer deaths in North America, with a median survival of three to four months. There is no standard therapy for advanced disease. In the United States of America, gemcitabine is currently being registered for use in non-small cell lung cancer and ovarian cancer. Early studies have suggested a role for the agent in advanced pancreatic cancer. As the agent is now available for clinical use, a review of its potential benefit is warranted.

III. METHODS

Guideline Development

This practice guideline report was developed by the Practice Guidelines Initiative (PGI) of Cancer Care Ontario's Program in Evidence-based Care, using the methods of the Practice Guidelines Development Cycle (1u). Evidence was selected and reviewed by one member of the PGI's Gastrointestinal Cancer Disease Site Group (DSG) and methodologists. Members of the Gastrointestinal Cancer DSG disclosed potential conflict of interest information.

The practice guideline report is a convenient and up-to-date source of the best available evidence on the use of gemcitabine in the treatment of unresectable or advanced pancreatic adenocarcinoma, developed through systematic reviews, evidence synthesis, and input from practitioners in Ontario. The body of evidence in this report is primarily comprised of mature randomized controlled trial data; therefore, recommendations by the DSG are offered. The practice guideline report is intended to promote evidence-based practice. The PGI is editorially independent of Cancer Care Ontario and the Ontario Ministry of Health and Long-Term Care.

External review by Ontario practitioners was obtained through a mailed survey consisting of items that address the quality of the draft practice guideline report and recommendations, and whether the recommendations should serve as a practice guideline. Final approval of the original guideline report was obtained from the Practice Guidelines Coordinating Committee (PGCC).

The PGI has a formal standardized process to ensure the currency of each guideline report. This consists of the periodic review and evaluation of the scientific literature, and where appropriate, integration of this literature with the original guideline information.

Literature Search Strategy

MEDLINE (1987 to May 1998), CANCELIT (1988 to May 1998), and the Cochrane Library (1997, Issue 4) were searched using the following terms: "gemcitabine" (text word) and "pancreas" or "pancreatic neoplasms" (subject headings). CARL's UnCover database was searched for articles that had not yet been indexed in MEDLINE using the keywords "gemcitabine" and "pancreatic". The Physician Data Query (PDQ) database was searched to find ongoing trials (both those that are active and those that have recently closed). Recently published journals were searched manually.

Update

The original literature search has been updated using MEDLINE (through May week 2, 2003), CANCELIT (through September 2002), the Cochrane Library (Issue 1, 2003), and the 1999-2003 proceedings of the annual meeting of the American Society of Clinical Oncology. The Physician Data Query (PDQ) database (http://www.nci.nih.gov/search/clinical_trials/) was searched for ongoing trials. The updated literature search was limited to randomized trials only.

Inclusion Criteria

Articles were selected for inclusion in this systematic review of the evidence if they were the following:

1. Fully published articles or abstracts of gemcitabine treatment in patients with pancreatic cancer.
2. Phase I, phase II, and phase III trials were considered in this report.

Update

After the first update in 2002, the decision was that only articles detailing randomized trials of gemcitabine treatment in patients with pancreatic cancer would meet the inclusion criteria for review.

Exclusion Criteria

1. Papers published in a language other than English were not considered.

Synthesizing the Evidence

As overall survival was reported for only one RCT and one phase II trial, no pooled estimate for survival across studies was calculated. Partial response rates were pooled across phase II trials to obtain a more precise estimate of the effect of gemcitabine. The pooled partial response rate provides an estimate of the activity of gemcitabine and should not be interpreted as a surrogate measure for overall survival or quality of life. The data were pooled by summing the number of partial responses across phase II trials and dividing this number by the total number of patients included in all phase II trials. The result was converted to a percentage and the 95% confidence intervals (CI) were calculated.

IV. RESULTS

Literature Search Results

Two phase I trials (1,2), one trial with both a phase I and phase II design (3), six phase II trials (4-9), and one randomized controlled trial (RCT) (10) were reviewed.

Update

Eight new trials have been obtained through updating activities (2u-9u). Two were randomized phase II trials (2u,5u), and six were randomized controlled trials (3u,4u,6u-9u). All trials will be discussed in the appropriate sections.

Randomized Controlled Trial

The RCT (10) was a multicentred, patient-blinded, randomized trial of gemcitabine versus 5-fluorouracil (5-FU) in patients with locally advanced (26% of patients) or metastatic (74% of patients) adenocarcinoma of the pancreas who had received no prior chemotherapy. The primary outcome was "clinical benefit response", which is a composite of measurements of pain (analgesic consumption and pain intensity), Karnofsky performance status, and weight (see Appendix 1). Secondary outcomes of interest were survival, time to progressive disease and tumour response. Results are summarized in Table 1.

One hundred and twenty-six patients were randomized to receive either gemcitabine (n=63) or 5-FU (n=63). The gemcitabine dose and schedule were 1000 mg/m² over 30 minutes intravenously (IV) once weekly for seven weeks, followed by one week of rest, then once weekly for three of every four weeks. The 5-FU dose and schedule were 600 mg/m² over 30 minutes IV once weekly. Patients were unaware of which treatment they received although this was known by the physician.

Patients randomized to gemcitabine experienced improved clinical benefit response compared with those randomized to 5-FU (23.8% versus [v.] 4.8%; p=0.0022), longer median survival (5.65 v. 4.41 months; log-rank p=0.0025), improved one-year survival rate (18% v. 2%;

log-rank $p=0.0025$), longer median progression-free survival (2.33 v. 0.92 months; log-rank $p=0.0002$), and improved progression-free survival at 12 months (9% v. 5%; log-rank $p=0.0002$). The difference in partial tumour response rate between patients randomized to gemcitabine and 5-FU was not significantly different (5.4% v. 0.0%).

Update

In a phase II/III randomized trial (3u), patients were allocated to receive either gemcitabine $1000\text{mg}/\text{m}^2$ once per week for 7 weeks, followed by a 1 week rest, and then again on days 1, 8, and 15 of a 28-day cycle or ZD9331 (a novel antifolate inhibitor of thymidylate synthase) $130\text{mg}/\text{m}^2$ on days 1 and 8 of a three-week cycle. Both treatments were given by intravenous infusion. Preliminary efficacy results show that the two treatments provide similar outcomes (Table 1). It was not stated in this study whether the differences between the two groups was statistically significant, and no p -values were provided.

In the phase III Eastern Cooperative Oncology Group (ECOG) E2297 trial (4u), patients were allocated to receive gemcitabine $1000\text{mg}/\text{m}^2$ weekly for three weeks, followed by one week of rest (repeat), or to receive gemcitabine $1000\text{mg}/\text{m}^2$, followed by 5-FU $600\text{mg}/\text{m}^2$ weekly for three weeks, followed by one week of rest (repeat). Results appear in Table 1. This study concluded that there is no clinically meaningful difference between the two treatments, and future research should explore different treatment combinations with gemcitabine.

In an RCT by Heinemann et al (6u), patients were randomized to receive either gemcitabine alone at $1,000\text{mg}/\text{m}^2$ days 1, 8, and 15 every 28 days or gemcitabine at $1,000\text{mg}/\text{m}^2$ plus cisplatin at $50\text{mg}/\text{m}^2$ days 1 and 15 every 28 days. While mature efficacy data are still pending, progression-free survival was superior in the combined treatment arm compared to gemcitabine alone. There was a significant increase in nausea and vomiting in the combined treatment arm.

In an RCT by Li et al (7u), reported in abstract form, patients were randomized to receive either gemcitabine at $600\text{mg}/\text{m}^2$ weekly every six weeks plus concurrent chemoradiotherapy (CCRT) 50.4-61.2 Gy in 1.8 Gy daily fractions or 5-FU at $500\text{mg}/\text{m}^2$ three times daily every 2 weeks for six weeks plus CCRT 50.4-61.2 Gy in 1.8 Gy daily fractions. While both treatment regimens showed comparable toxicity profiles, gemcitabine combined with radiotherapy had improved clinical benefit response ($p=0.034$), median survival ($p<0.027$), and median progression-free survival ($p<0.016$).

In a preliminary report of an RCT by Louvet et al (8u), patients were randomized to receive either gemcitabine at $1,000\text{mg}/\text{m}^2$ day 1 or gemcitabine at $1,000\text{mg}/\text{m}^2$ day 1 plus oxaliplatin at $100\text{mg}/\text{m}^2$ two-hour infusion day 2. The investigators have no toxicity or efficacy data to report at this time.

In an RCT by Rocha Lima et al (9u), patients were randomized to receive either gemcitabine at $1,000\text{mg}/\text{m}^2$ plus irinotecan at $100\text{mg}/\text{m}^2$ days 1 and 8 every 3 weeks or gemcitabine at $1,000\text{mg}/\text{m}^2$ alone seven weeks out of eight for cycle 1, then days 1, 8, and 15 every 4 weeks thereafter. While no improvement in long-term survival was detected, the investigators conclude that gemcitabine plus irinotecan has a comparable toxicity profile and more active tumour regression response than gemcitabine alone.

Table 1. Randomized trials of gemcitabine in pancreatic cancer.

| Treatment Allocation (ref) | Total Enrolled (Evaluable) | Clinical Benefit Response | Median Survival (months) | One-year Survival | Median Progression-Free Survival (months) | Partial Response Rate |
|---|----------------------------|---------------------------|------------------------------|----------------------------|---|--------------------------|
| Gemcitabine | 63 (56) | 23.8% | 5.65 | 18% | 2.33 | 5.4% |
| 5-FU (10) | 63 (57) | 4.8% p=0.0022 | 4.41 p=0.0025 log-rank | 2% p=0.0025 log-rank | 0.92 p=0.0002 log-rank | 0% p>0.05 |
| Gemcitabine | 25 | 14.3% | 3.5 | NR | NR | 8% |
| ZD9331 (3u) | 30 | 15.0% p=NR | 5.0 p=NR | NR p=NR | NR p=NR | 3% p=NR |
| Gemcitabine | 162 | NR | 5.4 | 13.8 | 2.2 | 5.6% |
| Gemcitabine + 5-FU (4u) | 160 | NR | 6.7 p=0.09 | 19.5 p=NS log-rank | 3.4 p=0.022 log-rank | 6.9% p=NS log-rank |
| Gemcitabine | 96 | NR | 8.3 | NR | 2.8 | NR |
| Gemcitabine + Cisplatin (6u) | 99 | NR | 6.0 Log-rank p=0.12 | NR | 5.4 Log-rank p<0.01 | NR |
| Gemcitabine + 50-61 Gy in 1.8 Gy/d fractions | 18 | 50% | 14.5 | NR | 7.1 | NR |
| 5-FU + 50-61 Gy in 1.8 Gy/d fractions (7u) | 16 | 19% p=0.034 | 6.7 p<0.027 | NR | 2.7 p<0.016 | NR |
| Gemcitabine | 74 | NR | NR | NR | NR | NR |
| Gemcitabine + L-OHP (8u) | 76 | NR | NR | NR | NR | NR |
| Gemcitabine | 180 | NR | 6.6 | 22 | 3 | 4.4 |
| Gemcitabine + CPT-11 (9u) | 180 | NR | 6.3 | 21 | 3.4 | 14.4 p<0.001 |

Notes: 5-FU, 5-fluorouracil; NR, not reported; NS, not significant

Phase II Trials

The results of the phase II trials are summarized in Table 2. The small numbers of patients in each study were further reduced by the relatively high proportion of unevaluable patients. Some patients were enrolled too recently to evaluate response, while others were stated to be unevaluable because of premature death or progression of disease, pointing out the limitations of tumour response as a clinically meaningful endpoint. The pooled estimate of the partial response rate was 12.9% (95% CI, 8.5 to 18.6; n=186). The most recently published phase II trial by Rothenberg et al (9) was designed to assess clinical benefit because most patients were symptomatic. This study reported a clinical benefit response of 27% in a group of patients who were pretreated with a 5-FU-containing regimen. The partial tumour response rate was 10%, and the median survival was 3.85 months.

Update

Two randomized phase II trials have been obtained through updating procedures (2u,5u). A randomized phase II trial (2u) of dose-intense gemcitabine by standard infusion versus fixed-dose rate has been published in abstract form. A total of 93 patients with metastatic pancreatic adenocarcinoma were randomized to 2200 mg/m² over standard 30-minute infusion or 1500 mg/m² at a rate of 10 mg/m²/minute once weekly for three weeks of every four weeks. In an early analysis of 67 evaluable patients, the objective response was 2.7% for standard infusion compared with 16.6% for fixed-dose rate, time to disease progression was 1.9 months versus 2.2 months, and median survival was 4.7 months versus 6.1 months, respectively.

A second randomized phase II trial (5u) performed by the European Organization for Treatment and Research of Cancer - Gastrointestinal (EORTC-GI) group of docetaxel/gemcitabine versus docetaxel/cisplatin has also been published in abstract form. A total of 96 patients with advanced pancreatic carcinoma were randomized to receive either docetaxel 85 mg/m² on day 8 plus gemcitabine 800 mg/m² on days 1 and 8 every three weeks or docetaxel 75 mg/m² plus cisplatin 75 mg/m² on day 1 every 3 weeks. In an early analysis of evaluable patients, partial response rates (16% versus 16%), progression-free survival (3 months versus 3.9 months), and median survival (7.6 months versus 7.1 months) were comparable between the two regimens. P-values were not reported for any of the outcomes.

Phase I Trials

Activity was noted in two phase I trials in patients with pancreatic cancer. The response rate was not stated in one (1) and was three out of seven (43%) in another (2). In a dose-escalation study in previously untreated patients (3), a partial and a minor response were noted in five evaluable patients, both of whom had symptomatic improvement.

Adverse Effects

In the randomized controlled trial (10), gemcitabine and 5-FU were generally well tolerated. Myelosuppression, and nausea and vomiting, were more pronounced with patients randomized to gemcitabine.

Update

In the randomized phase II/II trial (3u), withdrawal from treatment due to adverse effects occurred in 33.3% of the ZD9331 patients, but only 20% of the patients receiving gemcitabine (p-value not reported). Two patients in the ZD9331 group died as a result of treatment, while no patients died as a result of treatment in the gemcitabine arm of the trial. It was not noted in the trial report whether the differences between the treatment arms were statistically significant, and p-values were not reported.

In the phase III randomized ECOG E2297 trial (4u), adverse effects caused 3% of patients to withdraw in the gemcitabine-only treatment arm, and 8% of patients to withdraw in the gemcitabine-plus-5-FU treatment arm. Each treatment arm had a single case of death that was attributed to treatment. One patient in the gemcitabine- only arm died of bacteremia while

under treatment, and one patient in the gemcitabine-plus-5-FU treatment arm died of renal failure while under treatment. For both treatment arms, the most common grade 3-4 adverse effects were hematologic and gastrointestinal. With the exception of nausea and vomiting, more pronounced adverse effects were observed in the gemcitabine- plus-5-FU treatment arm. Adverse effects for the gemcitabine compared to the gemcitabine- plus-5-FU arms were, respectively, leucopenia, 16% and 29%, granulocytopenia, 5% and 7%, thrombocytopenia, 11% and 19%, anemia, 10% and 10%, nausea, 11% and 8%, vomiting, 8% and 7%, and diarrhea, 4% and 10%.

In the second randomized phase II trial (5u), adverse effects were evaluated on all patients once treatment was completed. The most common effect was neutropenia (grade 3, 24%; grade 4, 16%). The gemcitabine arm of the trial also had a single case of febrile neutropenia. Other adverse effects include anemia (20%), thrombopenia (8%), diarrhea (8%), mucositis (8%), and dyspnoe (8%). The trial did not indicate whether these values were significantly different from the arm that did not receive gemcitabine therapy.

Table 2. Summary of results of phase II trials of gemcitabine in pancreatic cancer.

| Trial (Reference) | Total Enrolled | Number Unevaluable | # Too Early to Evaluate | Total Evaluable | Partial Response (# of patients) | Symptomatic Response | Previous Treatment |
|--|----------------|--------------------|-------------------------|-----------------|----------------------------------|----------------------|--------------------|
| Tempero et al (3), 1994 | 15 | 5 | 5 | 5 | 1 | 40% | No |
| Casper et al (4), 1990 | 18 | 0 | 9 | 9 | 3 | 10% | No |
| Casper et al (5), 1991 | 43 | 0 | 4 | 39 | 5 | 13% | No |
| Carmichael et al (6), 1993 | 32 | 5 | 4 | 23 | 2 | 9% | n/s |
| Casper et al (7), 1994* | 45 | 10 | 0 | 35 | 5 | 14% | No |
| Carmichael et al (8), 1992 | 26 | 5 | 3 | 18 | 2 | NR | No |
| Rothenberg et al (9), 1996 | 63 | 6 | 0 | 57 | 6 | 27% | Yes (5-FU) |
| Lutz et al (5u) (gemcitabine arm only) | 49 | 0 | 17 | 32 | 16% | NR | NR |

Notes: 5-FU, 5-fluorouracil; NR, not reported.

* Median survival was 5.6 months, and one-year survival was 23%.

V. INTERPRETIVE SUMMARY

The randomized controlled trial demonstrated that patients randomized to gemcitabine had greater symptomatic clinical benefit, longer median survival and an improved one-year survival rate, and longer progression-free survival than did those randomized to 5-FU, but there was no difference in tumour response between the two treatments. The pooled estimate of the partial response rate from seven phase II trials was 12.9% (95% CI, 8.5 to 18.6; n=186).

Update

This single report, published in abstract form, reveals response rates and median survival rates consistent with the previously published data. No quality-of-life data was available. Thus, there is no further information that would alter the conclusions of the original guideline report.

VI. ONGOING TRIALS

| Protocol ID | Description of ongoing trial | Stage |
|---|--|-------------------|
| E-R9704, RTOG-9704, SWOG-R9704 | Phase III randomized study of adjuvant fluorouracil-based chemoradiotherapy preceded and followed by fluorouracil versus gemcitabine in patients with resected adenocarcinoma of the pancreas (summary last modified 10/2002) <ul style="list-style-type: none"> • Randomized, multicentre trial • A total of 518 patients will be accrued for this study over 8.6 years • NCI cooperative group program, NCI-sponsored, New Jersey-approved | Closed to accrual |
| DAIICHI-8951A-PRT031, MSKCC-02011 | Phase III randomized study of exatecan mesylate and gemcitabine versus gemcitabine alone in patients with chemotherapy-naive locally advanced or metastatic cancer of the exocrine pancreas (summary last modified 09/2001) <ul style="list-style-type: none"> • Randomized, open-label, multicentre trial • A total of 340 patients (170 per arm) will be accrued over 18 months • Pharmaceutical sponsorship | Closed to accrual |
| CECOG/ PAN-1.3.001, EU-20142, SWS-SAKK-44/00 | Phase III randomized study of gemcitabine with or without capecitabine in patients with advanced pancreatic cancer (summary last modified 02/2002) <ul style="list-style-type: none"> • Randomized, multicentre trial • A total of 300 patients (150 per arm) will be accrued over 3 years • Central European Cooperative Oncology Group/ Swiss Institute for Applied Cancer Research clinical trials group sponsorship | recruiting |
| CRUK-GEM-CAP, EU-20116 | Phase III randomized study of gemcitabine with or without capecitabine in patients with locally advanced or metastatic pancreatic cancer (summary last modified 07/2002) <ul style="list-style-type: none"> • Randomized, open-label, multicentre trial • A total of 508 patients (254 per arm) will be accrued for this trial • Cancer Research UK sponsorship | recruiting |
| NCI-5012, NCI-CCC-99-45, NCI-P02-0212, URCC-2200 | Phase III randomized study of gemcitabine with or without dalteparin in patients with unresectable or metastatic pancreatic cancer (summary last modified 12/2002) <ul style="list-style-type: none"> • Randomized, multicentre trial • A total of 400 patients (200 per arm) will be accrued for this study • NCI sponsorship | recruiting |
| CAN-NCIC-PA3, OSI-CAN-NCIC-PA3 | Phase III randomized study of gemcitabine with or without erlotinib in patients with unresectable locally advanced or metastatic pancreatic cancer (summary last modified 04/2003) <ul style="list-style-type: none"> • Randomized, double-blind, placebo-controlled, multicentre trial • A total of 800 patients (400 per arm) will be accrued for this study • NCIC-Clinical Trials Group and pharmaceutical sponsorship | Closed to accrual |
| LORUS-LOR-VIR-P03-002 | Phase III randomized study of gemcitabine with or without virulizin followed by optional second-line therapy with virulizin or placebo with or without fluorouracil in patients with chemotherapy-naive locally advanced or metastatic pancreatic cancer (summary last modified 09/2002) <ul style="list-style-type: none"> • Randomized, double-blind, parallel group, multicentre trial • A total of 350 patients (175 per arm) will be accrued for this study over 1.5 years • Pharmaceutical sponsorship | recruiting |

| Protocol ID | Description of ongoing trial | Stage |
|--|--|--------------|
| PRONEURON-401.00.001, UAB-0105, UAB-F010524008, WELLSTAT-401.00.001 | <p>Phase III randomized study of triacetyluridine and high-dose fluorouracil versus gemcitabine in patients with unresectable locally advanced or metastatic pancreatic cancer. (summary last modified 12/2002)</p> <ul style="list-style-type: none"> • Randomized, open-label, multicentre trial • A total of 260 patients (130 per arm) will be accrued for this study over 16 months • Pharmaceutical sponsorship | recruiting |
| CPMC-IRB-8544, NCCAM, NCI-V99-1538 | <p>Phase III study of gemcitabine versus intensive pancreatic proteolytic enzyme therapy with ancillary nutritional support in patients with stage II, III, or IV adenocarcinoma of the pancreas (summary last modified 10/2002)</p> <ul style="list-style-type: none"> • Open-label trial • Approximately 72-90 patients will be accrued for this study within 3 years • National Center for Complementary and Alternative Medicine, National Institute of Health sponsorship | recruiting |
| EORTC-05962 | <p>Phase III randomized multicentre trial of infusional fluorouracil with or without cisplatin and with or without chronomodulation against locally advanced or metastatic pancreatic cancer (summary last modified 12/2002)</p> <ul style="list-style-type: none"> • Randomized, multicentre study • 200 patients will be accrued • EORTC Chronotherapy Group sponsorship | recruiting |
| URCC-2200, NCI-5012, NCI-CCC-99-45, NCI-P02-0212 | <p>Phase III randomized study of gemcitabine with or without dalteparin in patients with unresectable or metastatic pancreatic cancer (summary last modified 12/2002)</p> <ul style="list-style-type: none"> • Randomized, multicentre study • A total of 400 patients (200 per treatment arm) will be accrued for this study within 40 months • NCI sponsorship | recruiting |
| E-4201 | <p>Phase III randomized study of gemcitabine with or without radiotherapy in patients with locally advanced, unresectable pancreatic cancer (summary last modified 04/2003)</p> <ul style="list-style-type: none"> • Randomized, multicentre study • Approximately 332 patients will be accrued for this study within 2 years • NCI sponsorship | recruiting |
| E-6201 | <p>Phase III Randomized Study of Prolonged Infusion Gemcitabine With Versus Without Oxaliplatin Versus Standard Infusion Gemcitabine in Patients With Locally Advanced or Metastatic Pancreatic Cancer (summary last modified 03/2003)</p> <ul style="list-style-type: none"> • Randomized trial • A total of 666 patients (222 per treatment arm) will be accrued for this study within 37 months • NCI sponsorship | recruiting |

DISEASE SITE GROUP CONSENSUS PROCESS

The Gastrointestinal Cancer DSG discussion centred around the one available randomized controlled trial (10). The DSG was concerned that the methodology used to assess clinical benefit had not been independently validated. Group members also felt that the potential for bias existed because trial physicians were aware of the treatment that patients received. The possibility that 5-FU may have worsened outcome, compared to no treatment, could have been addressed by having a no-treatment control arm, although a worsened outcome was considered unlikely. The DSG generally agreed that the study was clinically sound and that gemcitabine appears to be useful in the treatment of advanced pancreatic cancer, possibly benefiting asymptomatic patients by prolonging progression-free survival (10). The DSG was aware of the limitations of the data because only one trial has been published but thought that the final design was generally sound and that this trial remains the best available evidence to date for a patient population for which no other effective treatment exists. The emerging literature on this topic will be followed closely.

VII. EXTERNAL REVIEW OF THE PRACTICE GUIDELINE REPORT

This section describes the external review activities undertaken for the original guideline report.

Draft Practice Guideline

Based on the evidence described in the original report above, the Gastrointestinal DSG drafted the following recommendations:

Draft Recommendations

Gemcitabine is a reasonable treatment option in patients with advanced or unresectable pancreatic cancer. There is evidence from one randomized controlled trial that gemcitabine improves symptoms and modestly improves survival in patients with advanced or unresectable pancreatic cancer. These patients were symptomatic and had a life expectancy of at least twelve weeks and a Karnofsky performance status of at least 50% (equivalent to an ECOG performance status of less than 3).

Practitioner Feedback

Based on the evidence described in the original report above and the draft recommendations presented above, feedback was sought from Ontario clinicians.

Methods

Practitioner feedback was obtained through a mailed survey of 63 practitioners in Ontario. The survey consisted of items evaluating the methods, results and interpretive summary used to inform the draft recommendations and whether the draft recommendations above should be approved as a practice guideline. Written comments were invited. Follow-up reminders were sent at two weeks (post card) and four weeks (complete package mailed again). The results of the survey were reviewed by the Gastrointestinal Cancer DSG.

Results

Results of the practitioner feedback survey of the original draft guideline report are summarized in Table 3. Thirty-two (51%) surveys were returned. Twenty-six (81%) respondents indicated that the evidence-based recommendation was relevant to their clinical practice and completed the survey.

Table 3. Practitioner responses to the practitioner feedback survey.

| Item | Number (%)* | | |
|--|-------------------------|----------------------------|-------------------------------|
| | Strongly agree or agree | Neither agree nor disagree | Strongly disagree or disagree |
| The rationale for developing this evidence-based recommendation, as stated in the “Choice of Topic” section of the report, is clear. | 25 (96%) | 0 | 1 (4%) |
| A practice guideline on this topic will be useful to clinicians. | 24 (92%) | 2 (8%) | 0 |
| The literature search is relevant and complete. | 24 (92%) | 0 | 2 (8%) |
| The summary of the evidence is acceptable to me. | 24 (92%) | 1 (4%) | 1 (4%) |
| I agree with this evidence-based recommendation as stated. | 23 (89%) | 1 (4%) | 2 (8%) |
| In your opinion, this recommendation should serve as a practice guideline. | 20 (77%) | 4 (15%) | 2 (8%) |
| If this evidence-based recommendation were to become a practice guideline, would you use it in your own practice? | Yes | Unsure | No |
| | 20 (77%) | 3 (12%) | 2 (8%) |

*Some percentages do not add to 100 because of missing data.

Summary of Main Findings

Nine (28%) respondents provided written comments. Concerns were raised regarding the availability of only one RCT as the basis of a guideline.

Modifications/Actions

The Gastrointestinal Cancer DSG noted the concerns from the practitioner feedback but no modifications to the evidence-based recommendation were considered necessary.

Approved Practice Guideline Recommendations

This practice guideline reflects the integration of the draft recommendation with feedback obtained from the external review process. The recommendation has been approved by the Gastrointestinal Cancer DSG and the Practice Guidelines Coordinating Committee.

- Gemcitabine is a reasonable treatment option in patients with advanced or unresectable pancreatic cancer. There is evidence from one randomized controlled trial that gemcitabine improves symptoms and modestly improves survival in patients with advanced or unresectable pancreatic cancer. These patients were symptomatic, had a life expectancy of at least twelve weeks, and a Karnofsky performance status of at least 50% (equivalent to an ECOG performance status of less than 3).

IX. PRACTICE GUIDELINE

This practice guideline reflects the most current information reviewed by the Gastrointestinal Cancer DSG.

Target Population

These recommendations apply to adult patients with unresectable or advanced pancreatic adenocarcinoma.

Recommendations

- Gemcitabine is a reasonable treatment option in patients with advanced or unresectable pancreatic cancer. There is evidence from one randomized controlled trial that gemcitabine improves symptoms and modestly improves survival in patients with

advanced or unresectable pancreatic cancer. These patients were symptomatic, had a life expectancy of at least twelve weeks, and a Karnofsky performance status of at least 50% (equivalent to an ECOG performance status of less than 3).

X. JOURNAL REFERENCE

Germond C, Maroun J, Moore M, Zwaal C, Wong S, and the Gastro-intestinal Cancer Disease Site Group. Use of gemcitabine in the treatment of advanced pancreatic adenocarcinoma. *Curr Oncol* 1999; 6: 224-7.

XI. ACKNOWLEDGMENTS

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The Gastrointestinal Cancer Disease Site Group would like to thank Dr. J. Maroun and Mr. R.B. Rumble for taking the lead in updating this practice guideline report.

For a complete list of the Gastrointestinal Disease Site Group members and the Practice Guidelines Coordinating Committee members, please visit our website at http://www.cancercare.on.ca/access_PEBC.htm.

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Update

This section includes all references from the review and updating activities.

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Appendix 1. Primary measurements of clinical benefit response.

The primary measures of clinical benefit were pain (assessed by pain intensity and analgesic consumption) and functional impairment (assessed by Karnofsky performance status). Weight change (assessed by body weight) was a secondary measure.

Patients were classified as responders if they had improvement in both primary measures or were stable in one, with improvement in the other. Patients who were stable in both primary measures were classified as responders if they had a positive weight change.

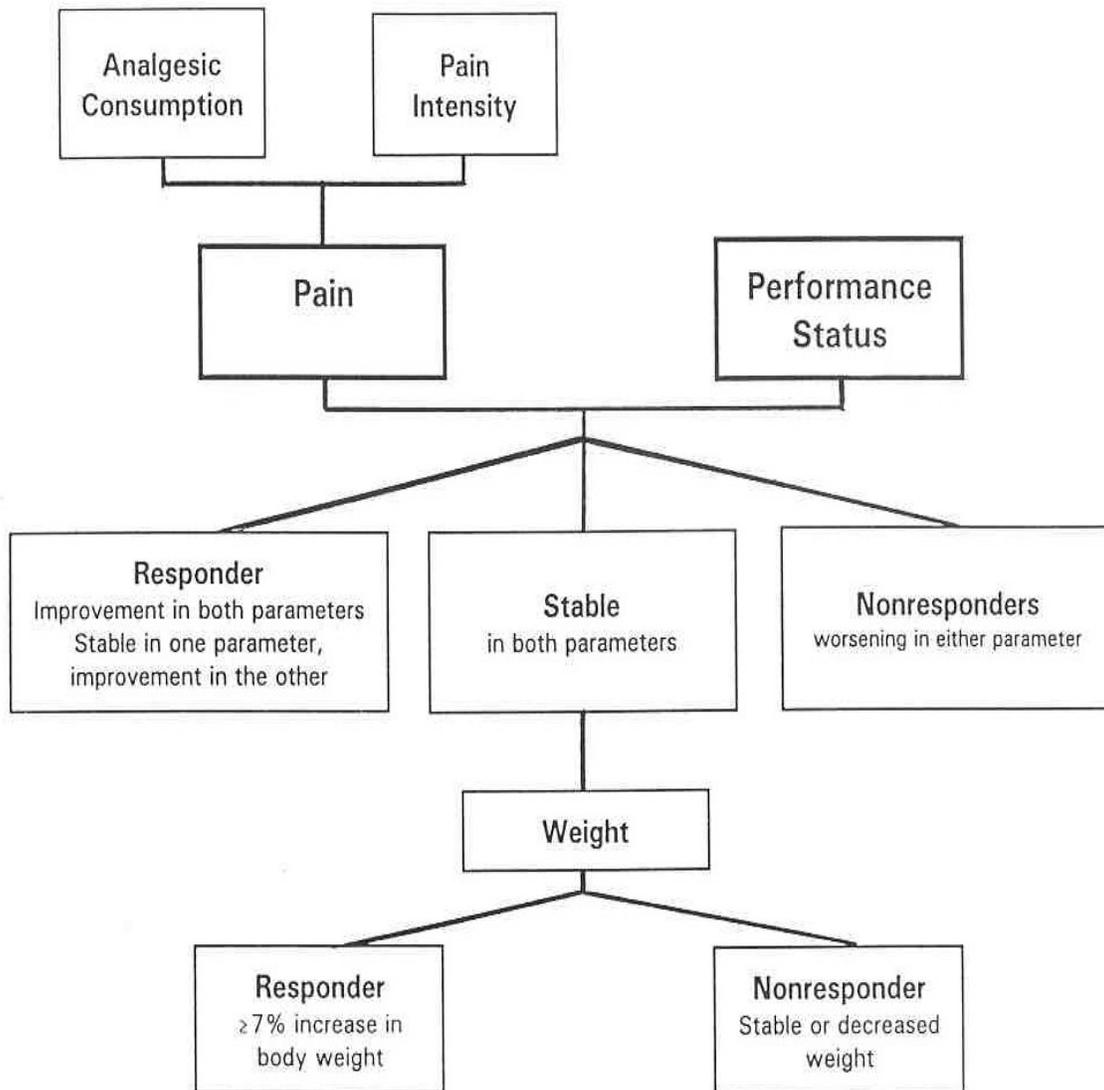


Figure 1.0 Flow diagram for assessment of clinical benefit

From: Burris HA, Moore MJ, Andersen J, et al. Improvements in survival and clinical benefit with gemcitabine as first-line therapy for patients with advanced pancreas cancer: a randomized trial. *J Clin Oncol* 1997;15:2403-13.

Appendix 1 (continued).

Composite measurements of clinical benefit response.

I. Pain Measures:

| | | Gemcitabine | | |
|----------------|----------|-----------------------|--------|-------|
| | | Analgesic Consumption | | |
| Pain Intensity | Positive | P (6) | P (4) | N (7) |
| | Stable | P (5) | S (25) | N (2) |
| | Negative | N (0) | N (2) | N (6) |

Total positive = 15 (23.8%)

| | | 5-Fluorouracil | | |
|----------------|----------|-----------------------|--------|--------|
| | | Analgesic Consumption | | |
| Pain Intensity | Positive | P (0) | P (2) | (0) N |
| | Stable | P (1) | S (38) | (14) N |
| | Negative | N (0) | N (1) | (7) N |

Total positive = 3 (4.8%)

Notes: P = Positive pain
N = Negative pain
S = Stable pain

Analgesic consumption response was positive if there was a $\geq 50\%$ improvement over baseline in analgesic consumption for at least four weeks without a concomitant increase in pain intensity.

Pain intensity response was positive if there was a $\geq 50\%$ improvement over baseline in pain intensity, maintained for at least four weeks, without a concomitant increase in analgesic consumption.

II. Primary Measures of Clinical Benefits:

| | | Performance Status | | |
|------|----------|--------------------|---------|----------|
| | | Positive | Stable | Negative |
| Pain | Positive | R (4) | R (11) | NR (0) |
| | Stable | R (0) | S (25) | NR (0) |
| | Negative | NR (4) | NR (18) | NR (1) |

Total positive = 15 (23.8%)

| | | Performance Status | | |
|------|----------|--------------------|---------|----------|
| | | Positive | Stable | Negative |
| Pain | Positive | R (0) | R (2) | (1) NR |
| | Stable | R (1) | S (37) | (0) NR |
| | Negative | NR (2) | NR (19) | (1) NR |

Total positive = 3 (4.8%)

Notes: R = Clinical benefit responder
NR = Clinical benefit nonresponder
S = Stable under primary measures

Performance status response was positive if there was at least a 20 point improvement over baseline with the Karnofsky performance status, for at least four weeks.

III. Clinical Benefit:

| | | Primary Measures | | |
|--------|-------------|------------------|---------|----------|
| | | Positive | Stable | Negative |
| Weight | Positive | R (1) | R (0) | NR (0) |
| | Nonpositive | R (14) | NR (25) | NR (23) |

Clinical benefit = 15 (23.8%)
No clinical benefit = 48 (76.2%)

| | | Primary Measures | | |
|--------|-------------|------------------|--------|----------|
| | | Positive | Stable | Negative |
| Weight | Positive | R (0) | R (0) | R (0) N |
| | Nonpositive | R (3) | R (37) | R (23) N |

Clinical benefit = 3 (4.8%)
No clinical benefit = 60 (95.2%)

Notes: R = Clinical benefit responder
NR = Clinical benefit nonresponder

Weight change response was positive if there was at least a 7% increase over baseline maintained for at least four weeks.

Patients who were stable for both pain improvement and performance status were considered to be responders if they had a positive weight change response.