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DQTC-SOS Advice Report 1 EDUCATION AND INFORMATION 2012

The Role of Gemcitabine in the Treatment of Cholangiocarcinoma and Gallbladder Cancer

B. Dingle, R.B. Rumble, M. Brouwers,
and members of the Gastrointestinal Cancer Disease Site Group

Report Date: April 26, 2005

This DQTC-SOS Advice Report was put in the Education and Information section in 2012. The PEBC has a formal and standardized process to ensure the currency of each document (PEBC Assessment & Review Protocol).

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The Role of Gemcitabine in the Treatment of Cholangiocarcinoma and Gallbladder Cancer

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The 2005 guideline recommendations were put in the

Education and Information section

This means that the recommendations will no longer be maintained but may still be useful for academic or other information purposes.

SUMMARY

Question
What is the role of gemcitabine in the treatment of cholangiocarcinoma and gallbladder cancer? Outcomes of interest include overall response rates, overall survival, adverse effects, and quality of life.

Target Population
These recommendations apply to adult patients with advanced or metastatic cancer of the gallbladder, or with cholangiocarcinoma, for whom therapy with gemcitabine is being considered.

Recommendations
See Appendix 1 for recommended regimens and dosages

- In appropriate patients with gallbladder cancer or cholangiocarcinoma, surgical resection offers the best chance for survival and should be the first treatment of choice.

- For patients who are not considered candidates for surgery with curative intent, but who are willing and able to tolerate treatment with chemotherapy, considering the lack of an effective standard treatment option, gemcitabine, either alone or in combination with a fluoropyrimidine such as 5-fluorouracil (5-FU) or capecitabine, is a reasonable alternative to best supportive care, although this conclusion has not been confirmed with a randomized controlled trial.
- Patients should be encouraged to enrol in randomized controlled trials comparing promising new treatments, such as gemcitabine in combination with a fluoropyrimidine against other treatments with proven response.

Evidence

In appropriate patients with gallbladder cancer or cholangiocarcinoma, surgical resection offers the best chance for survival and should be the first treatment of choice.

- Five-year survival rates after surgical resection of stage I gallbladder cancer may be greater than 85%, but drops to 25%, 10%, and 2% for stage II, III, and IV tumours. For patients with non-resectable disease who are offered palliative chemotherapy only, the five-year survival rate approaches 0%.

For patients who are not considered candidates for surgery with curative intent, but who are willing and able to tolerate treatment with chemotherapy, considering the lack of an effective standard treatment option, gemcitabine, either alone or in combination with a fluoropyrimidine such as 5-FU or capecitabine, is a reasonable alternative to best supportive care, although this conclusion has not been confirmed with a randomized controlled trial.

- Gemcitabine either alone, or in combination with fluoropyrimidines, cisplatin, oxaliplatin, or carboplatin has shown positive activity and response in phase II trials treating advanced biliary cancer. Given the more favourable toxicity profile of fluoropyrimidines (either 5-FU/leucovorin [LV] or capecitabine) compared with the alkylating platinum compounds cisplatin, oxaliplatin, or carboplatin, and the apparent improved response rates and survival in combination therapy, the use of gemcitabine and a fluoropyrimidine is favoured.
- The expert opinion of the Gastrointestinal Cancer Disease Site Group is that some benefit may accrue from complete and partial responses, if not also from stabilization of the disease. In some of the phase II trials reviewed, the extension of median survival to over one year exceeds current results with best supportive care by as much as six months.

Future Research

Patients with cancers of the biliary tree should be encouraged to enrol in clinical trials. Future trials should be designed to assess the efficacy, adverse effects, and quality-of-life scores of gemcitabine, either alone or in combination, compared directly against other treatments with proven response.

Related Guidelines

The Program in Evidence-based Care Practice Guideline Report #2-10: *Use of Gemcitabine in the Treatment of Advanced Pancreatic Carcinoma*.

FULL REPORT

I. QUESTION

What is the role of gemcitabine in the treatment of cholangiocarcinoma and gallbladder cancer? Outcomes of interest include overall response rates, overall survival, adverse effects, and quality of life.

II. CHOICE OF TOPIC AND RATIONALE

Cancers of the biliary tree, including cholangiocarcinoma and gallbladder cancer, are difficult to treat with curative intent for several reasons. First, they are rare in the population (1), making adequate accrual into randomized controlled trials (RCTs) difficult and time-consuming; second, many patients present with unresectable disease and are eligible for palliative treatment only (1), and third, no chemotherapy (CT) or radiotherapy (RT) options tested to date have shown any substantial activity (1). Past single-arm studies examining CT regimens for the treatment of gallbladder cancer involving between 13 and 87 patients reported the following response rates by intervention: 5-FU/nitrosurea, 9%; F-FU/doxorubicin/mitomycin (FAM), 28%; mitomycin C alone, 10%; cisplatin, 8%, and 5-FU/epirubicin/methotrexate/leucovorin, 0% (1). A two-arm trial comparing 5-FU alone against FAM in gallbladder cancer reported no response in either treatment arm (1). Past treatments for cholangiocarcinoma typically combined RT with any CT administered. Four single-arm studies examining RT+CT (CRT) involving between nine and 20 patients reported the following median survival rates by intervention: 5-FU/mitomycin C/65 Gray RT, 17 months; mitomycin C/32-40 Gray RT, 30 months; floxuridine/35-66 Gray RT, 19 months; and 5-FU/59 Gray RT, 12 months (1). A two-arm trial comparing various CT regimens with either an RT dose < 40 Gray versus various CT regimens with an RT dose > 40 Gray reported median survival rates of 8 and 16 months respectively (1). Currently, the treatment of choice for these cancers is surgery, but surgery is dependent upon the cancer being detected at an earlier, resectable stage. Recently, the role of radiation therapy in combination with chemical radiosensitizers has been investigated (1).

In Canada, gallbladder cancer represented 0.28% of all new cancers in 2000 (381 of 134,413 total) and 0.41% of all cancer deaths (259 of 62,672 total) (2). Gallbladder cancer affected females at 2.3 times the rate for males for both incidence and mortality (2). Incidence, mortality, and gender-specific data were not available for cholangiocarcinoma.

Gemcitabine is a newer drug available to Ontario clinicians that has demonstrated a treatment response in pancreatic cancer patients (3,4) and is also indicated for the treatment of non-small cell lung cancer (4). Gemcitabine is an intravenous (IV) drug that is metabolized within tumour cells by nucleoside kinases to the active gemcitabine diphosphate and gemcitabine triphosphate nucleosides. These gemcitabine nucleosides inhibit DNA synthesis via two processes. In the first, gemcitabine diphosphate inhibits ribonucleotide reductase, an enzyme responsible for catalyzing reactions that generate the deoxynucleoside triphosphates for DNA synthesis. In the second, gemcitabine triphosphate competes with deoxycytidine 5'-triphosphate (dCTP) for incorporation into DNA. By using these two mechanisms, gemcitabine induces a programmed cell-death response by blocking the progression of dividing cells through the G1/S-phase boundary.

Considering the demonstrated treatment response of gemcitabine in similar cancers, the lack of effective alternative treatment options, and the interest by some Ontario clinicians to have access to this drug, the Drug Quality Therapeutic Committee's Standing Oncology Subcommittee (DQTC-SOS) approached Cancer Care Ontario's Program in Evidence-based Care (PEBC) to provide advice, informed by the clinical evidence, as to the role of gemcitabine for cancers of the biliary tree. This advice report, developed by the PEBC Gastrointestinal Disease Site Group (DSG), provides a systematic review of the

available evidence, data synthesis, clinical interpretation, and recommendations and will be used by the DQTC–SOS to make funding and policy recommendations.

III. METHODS

This advice report, produced by the PEBC's Gastrointestinal Cancer DSG, is a convenient and up-to-date source of the best available evidence on the role of gemcitabine in the treatment of gallbladder cancer developed through systematic reviews of the available evidence. Members of the DSG disclosed any potential conflicts of interest. The PEBC is editorially independent of Cancer Care Ontario and the Ontario Ministry of Health and Long-Term Care.

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

Literature Search Strategy

The MEDLINE database was searched from 1996 to March (week 2) 2005. The following Medical subject headings (MeSH) "gemcitabine" and "gallbladder neoplasms" were combined, and results were limited to English only. In addition, conference proceedings from the 1998-2004 meetings of the American Society of Clinical Oncology were searched for abstracts of relevant trials, including the 2004 Gastrointestinal Cancers Symposium abstracts. The Canadian Medical Association Infobase (http://mdm.ca/cpgsnew/cpgs/index.asp) and the National Guidelines Clearinghouse (http://www.guideline.gov/index.asp) were also searched for existing evidence-based practice guidelines. An additional article not found in the literature search, as it was too recent to be indexed, was obtained from a Gastrointestinal Cancer DSG member.

Relevant articles and abstracts were selected and reviewed by two reviewers, and the reference lists from those sources were searched for additional trials.

Inclusion Criteria

Articles were selected for inclusion in the systematic review of the evidence if they were fully published English-language reports or published abstracts of:

1. Randomized controlled trials (RCTs) comparing gemcitabine, either alone or in combination, with best supportive care or other therapy in the treatment of cholangiocarcinoma or gallbladder cancer.
2. Phase II trials reporting on the efficacy or adverse effects detected in treatment with gemcitabine, alone or in combination, in the treatment of cholangiocarcinoma or gallbladder cancer.

Exclusion Criteria

1. Letters and editorials were not eligible.

Synthesizing the Evidence

As none of the trials obtained were RCTs, no pooling of outcome data was possible.

IV. RESULTS

Literature Search Results

A total of thirteen trial reports were obtained (5-17). None of the reports obtained were randomized controlled trials; all were single-arm phase II studies. The sample sizes of the studies were small, ranging from 11 to 45 patients. Ten reports were available in fully published form (5-7,9-14,17), and three reports were available as abstracts only (8,15,16). Seven of the trials reported hospitals, government agencies, or clinical trials groups as the sole source of funding (5,7-10,13,14), and five reported pharmaceutical sponsorship, three by Eli Lilly & Company (6,12,16), one by Sanofi-Synthelabo (11), and one by both Eli Lilly Canada and Hoffman-La Roche (17). One trial did not report the source of funding (15).

Of the trials obtained, three described gemcitabine monotherapy (5-7), and ten described gemcitabine in combination with other drugs (8-17). None of the trials delineated between patients with gallbladder cancer versus those with cholangiocarcinoma.

Gemcitabine Monotherapy

Efficacy outcomes

Three single-arm, phase II trials investigating gemcitabine monotherapy were obtained (5-7) (Table 1). The dosages used appear in Appendix 1. Response rates ranged from 30% in two trials (6,7) to 36% (5); however, none of the patients across those trials (n=78) experienced a complete response. Median survival rates reported ranged from a low of 30 weeks (5) to a high of 56 (7). One-year survival rates ranged from 16% (5) to 57% (7).

Adverse effects

Adverse effects observed in the trials of gemcitabine monotherapy are described as follows: one trial (5) reported no grade 3-4 adverse effects, and one trial (7) reported no grade 4 adverse effects. Two trials reported either grade 3 or grade 4 neutropenia (6,7). At least one trial reported the following grade 3-4 effects: anemia (6), nausea (6), flu-like symptoms (6), hemolytic uremic syndrome (6), and anorexia (7). Generally, the gemcitabine monotherapy trials reported that any adverse effects observed were mild and manageable. See Appendix 2 for details of the observed adverse effects by trial.

Quality of life

None of the trials on gemcitabine monotherapy reported data on quality of life.

Gemcitabine in Combination with Other Drugs

Efficacy outcomes

Ten single-arm, phase II trials investigating gemcitabine in combination with other drugs were obtained (8-17) (Table 1). Gemcitabine was tested in combination with cisplatin (8,12,15), docetaxel (9), 5-fluorouracil/leucovorin (5-FU/LV) (10,13), oxaliplatin (11), mitomycin-C (14), carboplatin (16), and capecitabine (17). The dosages used are in Appendix 1.

Response rates ranged from lows of 9.3% with gemcitabine plus docetaxel (9) to highs of 50% (8), 37% (12), and 48% (15) with gemcitabine in combination with cisplatin. Only patients receiving gemcitabine in combination with cisplatin (8,12,15), oxaliplatin (11), carboplatin (16), or capecitabine (17) demonstrated complete responses (11 out of 85 for gemcitabine with cisplatin [13%], 1 out of 22 with oxaliplatin [5%], 1 out of 13 with carboplatin [8%], and 2 out of 45 with capecitabine [4%]).

Adverse effects

A variety of grade 3-4 adverse effects were observed in the trials of gemcitabine in combination with other drugs. The three trials investigating gemcitabine in combination

with cisplatin (8,12,15) reported granulocytopenia (8), thrombocytopenia (8,12,15), fever (8), asthenia (8), anorexia (8), neutropenia (12,15), anemia (12,15), and leukopenia (15). The trial investigating gemcitabine in combination with docetaxel (9) reported alopecia, nausea/vomiting, mucositis, leukopenia, thrombocytopenia, and anemia. The trial investigating gemcitabine in combination with 5-FU/LV (10,13) reported dyspnea, nausea/vomiting, fatigue, thrombocytopenia, diarrhea, infection, leukopenia, anemia, and elevation of liver enzymes. The trial investigating gemcitabine in combination with oxaliplatin (11) reported neutropenia, thrombocytopenia, nausea/vomiting, and peripheral neuropathy. The trial investigating gemcitabine in combination with mitomycin-C reported leukopenia and thrombocytopenia. The trial investigating gemcitabine in combination with carboplatin (16) reported nausea/vomiting, elevation of liver enzymes, proteinuria, hematuria, edema, and fatigue. The trial investigating gemcitabine in combination with capecitabine (17) reported neutropenia (one case of febrile neutropenia), thrombocytopenia, hand-foot rash, infection, fatigue, and thromboembolitis. See Appendix 2 for details of the observed adverse effects by trial.

Quality of life

None of the trials on gemcitabine combination therapy reported data on quality of life.

Table 1. Treatment outcomes by study.

Study author, (reference), [location], protocol ID, year	**Regimen**	**Number of patients** [eval. response] (eval. toxicity)	**Response rate % (RR) [CR + PR]**	**Median number of courses delivered**	**Median follow-up (weeks)**	**Median survival (weeks)**	**1-year survival %**
Monotherapy with gemcitabine							
Gallardo et al (5) [Chile] 2001	GEM	26 [25]	36 [0 + 9]	4.2	21.9	30.0	16
Kubicka et al (6) [Germany] 2001	GEM	23	30 [0 + 7]	3.75	NR	37.2	NR
Tsavaris et al (7) [Greece] 2004	GEM	30	30 [0 + 9]	14	NR	56	56.7
Combination therapy with gemcitabine							
Carraro et al (8) [Argentina] 2001 Abstract	GEM+CIS	11 [10]	50 [3 + 2]	4.1 (mean)	5.2	45.2	NR
Kuhn et al (9) [Germany] 2002	GEM+DOC	43	9.3 [0 + 4]	NR	58.8	44	40
Alberts et al (10)	GEM+ 5-FU/LV	42	9.5 [0 + 5]	4	80	38.8	14

Study author, (reference), [location], protocol ID, year	**Regimen**	**Number of patients [eval. response] (eval. toxicity)**	**Response rate % (RR) [CR + PR]**	**Median number of courses delivered**	**Median follow-up (weeks)**	**Median survival (weeks)**	**1-year survival %**
[USA] 2004 NCCTG							
André et al (11) [France] 2004 GERCOR	GEM+ L-OHP	33 23	35.5 [0 + 11] 22 [1 + 4]	8 8	NR NR	61.6 30.4	57 30.8
Doval et al (12) [India] 2004	GEM+CIS	30	36.6 [4 + 7]	4.5	NR	20	18.6
Hsu et al (13) [Taiwan] 2004	GEM+ 5-FU/LV	30 [28] (29)	21.4 [0 + 6]	4	174.4	18.8	20
Kornek et al (14) [Austria] 2004	GEM+MMC	25	20 [0 + 5]	4	NR	26.8	23
Reyes-Vidal et al (15) [Chile] 2004 GOCCHI-2000-13 Abstract	GEM+CIS	44 [42]	48 [4 + 16]	NR	NR	28	NR
Tan et al (16) 2004 Abstract	GEM+ CARBO	15 [13]	30.8 [1 + 3]	NR	NR	NR	NR
Knox et al (17) [Canada] 2005	GEM+CAPE	45	31 [2 + 12]	7	44	56	49

Note: RR, objective response rate; CR, complete response; PR, partial response; GEM, gemcitabine; GEM+CIS, gemcitabine plus cisplatin; GEM+DOC, gemcitabine plus docetaxel; GEM+5-FU/LV, gemcitabine plus 5-fluorouracil; GEM+L-OHP, gemcitabine plus oxaliplatin; GEM+MMC, gemcitabine plus mitomycin-C; GEM+CARBO, gemcitabine plus carboplatin; GEM+CAPE, gemcitabine plus capecitabine.

V. INTERPRETIVE SUMMARY

The most effective treatment for cancer of the gallbladder is surgical resection of the primary tumour along with any local spread (1), but surgery is dependent upon the patient presenting at an earlier, resectable stage. Curative resection of cholangiocarcinoma is more complex and is dependent on the site and extent of the tumour (1). Five-year survival after the surgical resection of stage I gallbladder cancer should be greater than

85% (1), but drops to 25%, 10%, and 2% for stage II, III, and IV tumours (1). For patients with resectable cholangiocarcinoma, five-year survival rates range from 35% to 45% (1). There is no generally accepted standard chemotherapy for advanced, non-resectable, cancer of the gallbladder or biliary tree. In advanced disease, median survival with best supportive care is approximately six months (1), and five-year survival rates approach 0% (1). In past phase II studies, response rates for the use of fluoropyrimidines in this population ranged from 10% to 28% (1).

Gemcitabine either alone or in combination with other commonly used drugs such as fluoropyrimidines (10,13,17) or cisplatin (8,12,15) has shown positive activity and response in phase II trials for the treatment of advanced biliary cancer. Single studies of gemcitabine in combination with oxaliplatin (11) and carboplatin (16) also suggest a similar response.

Considering the low incidence rate of these types of tumours and the poor performance status of many patients presenting with biliary cancer, conducting large trials to establish a standard of care is unlikely. Indeed, a search of the National Cancer Institute's Internet clinical trials database (http://www.cancer.gov/search/clinical_trials/) on March 23, 2005 for reports of new or ongoing trials revealed only two small Phase II trials (Appendix 3). Information on a third phase II trial (SAKK-44/02) was submitted by an Ontario clinician. Therefore, treatment decisions must be based on the balance of predictable toxicities and benefits. While none of the studies included in this systematic review measured and evaluated quality-of-life scores, the assumption that some benefit may accrue from complete and partial responses, if not also from stabilization of the disease, seems reasonable. Certainly the extension of median survival to over one year in some studies compares favourably with best supportive care by as much as six months.

Therefore, administering a trial of gemcitabine in selected patients, either as a single agent, or in combination with other drugs that have demonstrated a response in this treatment population, seems reasonable. In general, fluoropyrimidines have a more favourable toxicity profile compared with the alkylating platinum compounds (cisplatin, oxaliplatin, and carboplatin). Considering the improved response rates and survival in combination therapy, the use of gemcitabine and a fluoropyrimidine appears to be favoured. Knox et al (17), in their most recent article, stated that a previous retrospective review of gemcitabine and continuous infusion 5-fluorouracil (5-FU) (18) showed a similar benefit in terms of response but with increased line-related infections and thromboembolitic complications, which suggests that when gemcitabine is given with a fluoropyrimidine, the fluoropyrimidine of choice should be capecitabine.

VI. RECOMMENDATIONS AND EVIDENCE

Recommendations

See Appendix 1 for recommended regimens and dosages.

- In appropriate patients with gallbladder cancer or cholangiocarcinoma, surgical resection offers the best chance for survival and should be the first treatment of choice.
- For patients who are not considered candidates for surgery with curative intent, but who are willing and able to tolerate treatment with chemotherapy, considering the lack of an effective standard treatment option, gemcitabine, either alone or in combination with a fluoropyrimidine such as 5-fluorouracil (5-FU) or capecitabine, is a reasonable alternative to best supportive care, although this conclusion has not been confirmed with a randomized controlled trial.
- Patients should be encouraged to enrol in randomized controlled trials comparing promising new treatments, such as gemcitabine in combination with a fluoropyrimidine against other treatments with proven response.

Evidence

In appropriate patients with gallbladder cancer or cholangiocarcinoma, surgical resection offers the best chance for survival and should be the first treatment of choice.

- Five-year survival rates after surgical resection of stage I gallbladder cancer may be greater than 85%, but this drops to 25%, 10%, and 2% for stage II, III, and IV tumours. For patients with non-resectable disease who are offered palliative chemotherapy only, the five-year survival rate approaches 0%.

For patients who are not considered candidates for surgery with curative intent, but who are willing and able to tolerate treatment with chemotherapy, considering the lack of an effective standard treatment option, gemcitabine, either alone or in combination with a fluoropyrimidine such as 5-fluorouracil (5-FU) or capecitabine, is a reasonable alternative to best supportive care, although this conclusion has not been confirmed with a randomized controlled trial.

- Gemcitabine either alone or in combination with fluoropyrimidines, cisplatin, oxaliplatin, or carboplatin has shown positive activity and response in phase II trials treating advanced biliary cancer. Given the more favourable toxicity profile of fluoropyrimidines (either 5-FU/LV or capecitabine) compared with the alkylating platinum compounds cisplatin, oxaliplatin, or carboplatin, and the apparent improved response rates and survival in combination therapy, the use of gemcitabine and a fluoropyrimidine is favoured.
- The expert opinion of the Gastrointestinal Cancer Disease Site Group is that some benefit may accrue from complete and partial responses, if not also from stabilization of disease. In some of the phase II trials reviewed, the extension of median survival to over one year exceeds current results with best supportive care by as much as six months.

Future Research

Patients with cancers of the biliary tree should be encouraged to enrol in clinical trials. Future trials should be designed to assess the efficacy, adverse effects, and quality-of-life scores of gemcitabine, either alone or in combination, compared directly against other treatments with proven response.

Related Guidelines

The PEBC Practice Guideline Report #2-10: *Use of Gemcitabine in the Treatment of Advanced Pancreatic Carcinoma*.

VII. CONFLICTS OF INTEREST

The members of the PEBC Gastrointestinal Cancer DSG declared that there were no potential conflicts of interest related to the topic of this DQTC-SOS advice report.

VIII. JOURNAL REFERENCE

Dingle B, Rumble RB, Brouwers MC; Cancer Care Ontario's Program in Evidence-based Care's Gastrointestinal Cancer Disease Site Group. The role of gemcitabine in the treatment of cholangiocarcinoma and gallbladder cancer: a systematic review. Can J Gastroenterol. 2005 Dec;19(12):711-716.

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For a complete list of the Gastrointestinal Cancer Disease Site Group members, please visit the CCO website at http://www.cancercare.on.ca/.

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Appendix 1. Dosing by trial.

Monotherapy regimens
Gallardo et al (5), 2001 Gemcitabine 1000 mg/m^2 IV for 30 minutes weekly for 3 weeks out of every 4
Kubicka et al (6), 2001 Gemcitabine 1000 mg/m^2 IV for 30 minutes weekly for 3 weeks out of every 4
Tsavaris et al (7), 2004 Gemcitabine 800 mg/m^2 as a 30-minute IV infusion weekly without cessation until one of severe toxicity, disease progression, or patient refusal arose
Combination therapy regimens
Carraro et al (8), 2001 Gemcitabine 1000 mg/m^2 as a 30-minute infusion followed by cisplatin 30 mg/m^2 IV bolus injection, administered on days 1, 8, and 15 of each cycle, repeated every 28 days
Kuhn et al (9), 2002 Gemcitabine 1000 mg/m^2 followed by docetaxel 35 mg/m^2 weekly for 3 weeks followed by 1 week of rest
Alberts et al (10), 2004 Gemcitabine 1000 mg/m^2 30-minute IV infusion followed by leucovorin calcium 25 mg/m^2 IV push followed immediately by 5-fluorouracil 600 mg/m^2 IV push, on days 1, 8, and 15, repeated every four weeks
André et al (11), 2004 Gemcitabine 1000 mg/m^2 as a 10 mg/m^2/min infusion on day 1, followed by oxaliplatin 100 mg/m^2 as a 2-hour infusion on day 2, every two weeks
Doval et al (12), 2004 Gemcitabine 1000 mg/m^2 30-60–minute infusion and cisplatin 70 mg/m^2 2-hour infusion were given on day 1, and gemcitabine 1000 mg/m^2 alone was given on day 8, in a 21-day cycle
Hsu et al (13), 2004 Gemcitabine 800 mg/m^2 IV infusion for 30 minutes followed by 5-FU 2000 mg/m^2 and leucovorin 3000 mg/m^2 IV for 24 hours on day 1,8,15 repeated every four weeks
Kornek et al (14), 2004 Gemcitabine 2000 mg/m^2 on days 1 and 15 with MMC 8 mg/m^2 on day 1 only, repeated every four weeks
Reyes-Vidal et al (15), 2004 Gemcitabine 1250 mg/m2 and cisplatin 35 mg/m2 on days 1, 8 every 21 days for a total of 6 courses
Tan et al (16), 2004 Gemcitabine 1000 mg/m2 IV infused over 30 minutes on days 1, 8 with carboplatin at AUC 5 IV on day 1 only of a 21-day cycle
Knox et al (17), 2005 Gemcitabine 1000 mg/m^2 IV infused over 30 minutes on days 1, 8 with capecitabine 650 mg/m^2 orally twice a day for 14 days, 3-week cycle, where treatment was continued until disease progression, unacceptable toxicity, or withdrawal of consent.

Appendix 2. Adverse effects.

Monotherapy with gemcitabine
Gallardo et al (5), 2001 - no gastrointestinal toxicity or grade 3-4 (WHO) hematological episodes were recorded
Kubicka et al (6), 2001 -grade 3-4 toxicity reports: • neutropenia, 1 patient (13%) • anemia, 1 patient (4%) • nausea, 3 patients (13%) • flu-like symptoms, 1 patient (4%) • hemolytic uremic syndrome, 1 patient (4%)
Tsavaris et al (7), 2004 - no grade 4 (WHO) toxicities reported - no treatment-related deaths reported - WHO grade 3: • neutropenia, 1 patient (3.3%) • anorexia, 1 patient (3.3%)
Combination therapy with gemcitabine
Carraro et al (8), 2001 - two patients died during treatment; one from cerebral ischemia after cycle 1, and one from an undetermined cause - NCIC-CTC grade 3 toxicity reports: • granulocytopenia, 1 patient (9%) • thrombocytopenia, 2 patients (18%) • fever, 1 patient (9%) • asthenia, 1 patient (9%) • anorexia, 1 patient (9%) - no episodes of neutropenia fever or thrombocytopenia-related bleeding were reported
Kuhn et al (9), 2002 - WHO grade 3-4 toxicity reports: • alopecia, 28 patients (65.1%) • nausea/vomiting, 8 patients (18.6%) • mucositis, 2 patients (4.6%) - WHO grade 3 toxicities: • leukopenia, 4 patients (9.3%) • thrombocytopenia, 1 patient (2.3%) • anemia, 1 patient (2.3%)
Alberts et al (10), 2004 - no treatment-related deaths occurred Grades 3-4 toxicity reports: • dyspnea, 4 patients • nausea, 4 patients • fatigue, 7 patients • thrombocytopenia, 6 patients • vomiting, 4 patients • diarrhea, 4 patients
André et al (11), 2004 NCIC-CTC grade 3-4 toxicities included: • neutropenia, 14% • thrombocytopenia, 9% • nausea/vomiting, 5% • peripheral neuropathy, 7%

Doval et al (12), 2004 - WHO grades 3-4 toxicity reports: • neutropenia, 10 patients (33.2%) • thrombocytopenia, 5 patients (16.6%) • anemia, 11 patients (36.6%)
Hsu et al (13) -WHO grades 3-4 toxicities included: • infection, 9 patients (31%) • leucopenia, four patients (14%) • thrombocytopenia, three patients (10%) • anemia, three patients (10%) • nausea/vomiting, two patients (7%) • elevation of liver transaminases, three patients (10%)
Kornek et al (14), 2004 -WHO grades 3-4 toxicities included: • leukocytopenia, four patients (17%) • thrombocytopenia, three patients (13%)
Reyes-Vidal et al (15), 2004 - two patients died following the first course of treatment, one due to renal toxicity and one due to disease progression - no WHO grade 4 adverse events were reported - WHO grade 3 toxicity reports: • thrombocytopenia, 2% • neutropenia, 23% • anemia, 14% • leukopenia, 7%
Tan et al (16), 2004 - no grade 4 toxicities were reported - grade 3 hematological toxicities were rare (3 ANC, 1 platelet) - non-hematological toxicities were considered mild and included, nausea, vomiting, elevated LFTs, proteinuria, hematuria, edema, fatigue
Knox et al (17), 2005 NCIC-CTC grade 3-4 toxicities included: • neutropenia, 15 patients (34%) • febrile neutropenia, 1 patient (2%) • thrombocytopenia, 5 patients (11%) • hand-foot rash, 4 patients (9%) • infection, 2 patients (4%) • fatigue, 2 patients (4%) • thromboembolitic, 1 patient (2%)

Note: ANC, absolute neutrophil count; NCIC-CTC, National Cancer Institutes of Canada-Common Toxicity Criteria; WHO, World Health Organization.

Appendix 3. Ongoing trials.

Phase II study of gemcitabine and capecitabine in patients with unresectable, locally advanced or metastatic gallbladder cancer or cholangiocarcinoma.	
Protocol ID:	SWOG-S0202, NCT00033540
Date last modified:	September 1, 2004
Type of trial:	Multicentre Phase II
Accrual:	20-40 patients will be accrued for this study within approximately 10-20 months
Sponsorship:	NCI sponsored SWOG trial
Status:	Open and recruiting
Phase II study of 3-AP (Triapine®) and gemcitabine in patients with unresectable or metastatic biliary duct or gallbladder cancer	
Protocol ID:	NYWCCC-0803945, NCT00075504, NCI-6254
Date last modified:	November 15, 2004
Type of trial:	Multicentre Phase II
Accrual:	31-78 patients (10-29 with liver dysfunction and 21-49 without liver dysfunction) will be accrued for this study within 10-24.5 months
Sponsorship:	NCI sponsorship
Status:	Open and recruiting
Phase II study of adjuvant palliative capecitabine and gemcitabine in patients with locally advanced or metastatic biliary tract cancer	
Protocol ID:	CDR0000340978, SWS-SAKK-44/02, EU-20322, NCT00073905
Date last modified:	December 6, 2004
Type of trial:	Open-label, multicentre study
Accrual:	19-44 patients within 3 years
Sponsorship:	Swiss Institute for Applied Cancer Research (SAKK)
Status:	Open and recruiting