WRHA/CCMB Oncology Pharmacotherapeutic (P & T) Subcommittee
Systemic Therapy Summary
Review/Update

STS Title: First-Line Treatment of Locally Advanced or Metastatic Biliary Tract Carcinoma with Cisplatin and Gemcitabine
Protocol Code: (GAST- Cisplatin + Gemcitabine)
Effective: May 2010
Annual Review: February 2014

The above-named CancerCare Manitoba Practice Guideline was under review for the following reason(s) – Please check all applicable:

☐ New evidence exists which affects the recommendation statement(s) and/or clinical content of the guideline

☐ New information exists which necessitates change in other content

☐ The guideline is no longer applicable and is to be retired from use

☑ The guideline is due for review as per P&T Subcommittee protocol

☐ Other

The DSG Chair and/or designated DSG member(s) have reviewed the content of the STS “First-Line Treatment of Locally Advanced or Metastatic Biliary Tract Carcinoma with Cisplatin and Gemcitabine”. Any modifications to the document subsequent to DSG review have been discussed by the P&T Subcommittee STS Working Group.

Review of this CCMB Systemic Therapy Summary is now complete. The updated version is approved for re-distribution and clinical application according to policies and procedures as CCMB, WRHA Community Oncology sites, and Community Cancer Programs Network sites. The next scheduled date of review is:

Approved by:

[Signature]

DSG Chair/Designate

[Signature]

Dr. Ralph PW Wong, BSc, MD, FRCPC
Chair, WRHA/CCMB
Pharmacotherapeutic Subcommittee

[Signature]

Dr. Piotr Czajkowski, BSc, MD, MSc, FRCPC
Lead and Steering Committee Chair,
CCMB Clinical Practice Guidelines Initiative

[Signature]

cc. WRHA/CCMB Oncology P&T Subcommittee
Systemic Therapy Summaries Working Group
Associated Program Directors/Department Heads
Practice Guideline: Systemic Therapy Summary

First-Line Treatment of Locally Advanced or Metastatic Biliary Tract Carcinoma with Cisplatin and Gemcitabine

(GAST- Cisplatin + Gemcitabine)

Effective: May 2010
Required Update: February 2014
Annual Review: February 2013

CCMB Electronic Posting Date:
ACKNOWLEDGEMENT AND SPONSORSHIP DISCLAIMERS
Introduction

This document has been prepared by the Winnipeg Regional Health Authority/CancerCare Manitoba (WRHA/CCMB) Oncology Pharmacotherapeutic (P&T) Subcommittee’s Systemic Therapy Summaries Working Group, as a means of disseminating drug information and formulary decisions made by the Subcommittee. The CCMB Provincial Pharmacy Program, Provincial Oncology Drug Program (PODP), and Clinical Practice Guidelines Initiative (CPGI) have contributed to the development of this summary.

Systemic Therapy Summaries (STS) are being developed for drugs/or indications where clinical benefit has been accepted by the P&T Subcommittee, based on scientific data. All STS documents are approved by the P&T Subcommittee Chair and the CPGI Lead/Advisory Panel Chair.

The content of this STS was in large part adapted from the Formulary Addition Request submitted to the P&T Subcommittee by the CCMB Gastro-Intestinal (GI) Disease Site Group, May, 2010. This document will be reviewed, and updated as necessary, once in every twelve-month period; unless emerging evidence from scientific research dictates otherwise.

Purpose

This document is intended as a guide to facilitate the safe and effective clinical use of cisplatin and gemcitabine for first-line treatment of locally advanced or metastatic biliary tract carcinoma.

For this purpose, it may be used by qualified and licensed healthcare practitioners involved with the care of oncology patients, which may include (but is not limited to): physicians, nurses, and pharmacists at CancerCare Manitoba, Community Cancer Programs Network (CCPN) sites, and WRHA Community Oncology Program sites.

Disclaimer

Use of this document should not preclude the practitioner's independent clinical judgement, nor should it replace consultation with the oncologist.

It is the responsibility of the practitioner to develop an individualized treatment plan for each patient under his/her care, and ideally this should take place within the context of a multidisciplinary team. The unique needs and preferences of the patient and the family should always be reflected in the plan of care.

This document is not a comprehensive drug monograph. Practitioners must refer to other sources for complete drug information.
First-Line Treatment of Locally Advanced or Metastatic Biliary Tract Carcinoma with Cisplatin and Gemcitabine

Protocol Code: **GAST- Cisplatin + Gemcitabine**

Developed by: Gastro-Intestinal (GI) Disease Site Group

Date of Presentation to P&T Subcommittee: May 2010

**Treatment Recommendation**

The Gastro-Intestinal (GI) Disease Site Group recommends cisplatin in combination with gemcitabine for the first-line treatment of locally advanced or metastatic biliary tract cancer in patients who meet the inclusion criteria (see below).

**Treatment Intent**

- Non-curative
- Prolongation of progression-free survival and overall survival

**Rationale**

Biliary tract carcinomas are a heterogeneous group of tumours which include intrahepatic and extrahepatic cholangiocarcinomas, gallbladder cancer, and ampullary carcinomas. They are relatively uncommon. Unfortunately, the majority of patients with biliary tract carcinoma present with advanced and inoperable disease. Phase II trials had identified a number of active drugs, but no phase III trials were previously available. Gemcitabine has been utilized as first-line treatment for metastatic biliary tract carcinoma. This is due in part to its activity in pancreatic cancer, and also to its favorable toxicity profile. The response rates range between 30-36% with median survival ranging from 30–56 weeks.²
Clinical Benefit (Level 1b Evidence see Appendix I)

Support for the use of gemcitabine in combination with cisplatin in the treatment of cholangiocarcinoma comes primarily from the Advanced Biliary Cancer (ABC)-02 Trial. This is a randomized phase III trial involving 410 patients with locally advanced or metastatic cholangiocarcinoma, gall bladder cancer, or ampullary cancer, comparing cisplatin in combination with gemcitabine to gemcitabine alone. The primary overall end point of this trial was survival. After a median follow-up of 8.2 months and 324 deaths, median overall survival was 11.7 months for the 204 patients in the cisplatin/gemcitabine group and 8.1 months for the 206 in the gemcitabine only group (HR = 0.64, P < 0.001). Median progression-free survival was 8.0 months in the gemcitabine/cisplatin group and 5.0 months in the gemcitabine only group (P < 0.001).

Patient Population and Selection Criteria

Inclusion Criteria (May 2010)

- Diagnosis of nonresectable, recurrent, or metastatic biliary tract carcinoma, and
- Eastern Cooperative Oncology Group (ECOG) performance status 2 or less and life expectancy greater than 3 months (see Appendix II), and
- Adequate bone marrow function (ANC greater than or equal to $1.5 \times 10^9/L$, platelets greater than $100 \times 10^9/L$) and adequate renal function.

CCMB Formulary Status

1. Formulary definition
   - Formulary*
   - * Approved and funded by CCMB, provided that criteria for use are met. A Drug Request Form is NOT required.

2. Adjudication Process: None

3. Restrictions: None
### Treatment Regimen – GAST- Cisplatin + Gemcitabine

1 cycle = 21 days (planned treatment 8 cycles)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>CCMB Administrative Guideline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cisplatin</td>
<td>25 mg/m² Days 1, 8</td>
<td>IV in 250 mL NS over 1 hour</td>
</tr>
<tr>
<td>Gemcitabine</td>
<td>1000 mg/m² Days 1, 8</td>
<td>IV in 250 mL NS over 30 minutes</td>
</tr>
</tbody>
</table>

### Premedications and Supportive Care

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>CCMB Administrative Guideline</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>fluids</strong></td>
<td>600-900 mL Days 1, 8</td>
<td>Oral pre-hydration the morning of cisplatin treatment</td>
</tr>
<tr>
<td><strong>Dexamethasone</strong></td>
<td>12 mg Days 1, 8</td>
<td>Orally 30 minutes before chemotherapy</td>
</tr>
<tr>
<td><strong>Ondansetron</strong></td>
<td>8 mg on Days 1, 8</td>
<td>IV in 50 mL NS over 15 minutes prior to chemotherapy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Orally 30 minutes before chemotherapy</td>
</tr>
</tbody>
</table>
Clinical Monitoring and Follow-Up Recommendations

**Laboratory Tests**

- Prior to Day 1: CBC with differential, serum creatinine, bilirubin, AST, ALT, LDH, GGT, alkaline phosphatase, sodium, potassium, chloride, magnesium, calcium, albumin, urea, glucose
- Prior to Day 8: CBC with differential, serum creatinine, sodium, potassium, chloride, magnesium, calcium, albumin, urea, glucose
- Optional Day 1: CA 19-9

**Clinical Toxicity Assessment (CTCAE v.4.0 see Appendix III)**

Prior to each cycle: assess for nausea and vomiting, pulmonary toxicity, ototoxicity, and neurotoxicity

**Assessment of Treatment Response**

Clinical follow-up with CT scans or appropriate diagnostic imaging should be repeated every 4 cycles (or 3 months). If there is evidence of response or stable disease, therapy may be continued. If imaging shows progressive disease, cisplatin plus gemcitabine therapy should be discontinued.

### Common or Clinically Important Adverse Events

(Refer to individual drug monographs for full details of adverse events)

<table>
<thead>
<tr>
<th>Myelosuppression</th>
<th>Neutropenia and thrombocytopenia are amongst the most frequently reported grade 3 or 4 drug-related adverse effects of treatment with cisplatin combined with gemcitabine. In the Phase III ABC-02 trial the incidence of grade 3 or 4 neutropenia in patients treated with cisplatin and gemcitabine was 25.3%, thrombocytopenia 8.6%, and anemia 7.6%. Severe hematologic toxicity occurred in 32.3% of the study patients. The incidence of grade 3 or 4 infections reported in the trial was 18.2%.1 Because this group of patients is high risk for developing cholangitis, fever or other evidence of infection must be assessed and treated promptly.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal toxicities</td>
<td>Emetogenic potential of regimen = High (&gt; 90%) Nausea and/or vomiting are common side effects of treatment, primarily due to the emetogenicity of cisplatin. Severe nausea and/or vomiting symptoms were present in about 5% of study patients in the Phase III ABC-02 trial.1 Severe stomatitis, anorexia, and diarrhea</td>
</tr>
</tbody>
</table>
### Common or Clinically Important Adverse Events – cont’d

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Fever/flu-like symptoms</strong></td>
<td>Gemcitabine treatment has been associated with flu-like symptoms which are usually mild, and short in duration. If necessary, acetaminophen may be used to manage fever.</td>
</tr>
<tr>
<td><strong>Neurotoxicity</strong></td>
<td>Cisplatin has also been associated with peripheral neuropathies that often present as paresthesias of the upper and lower extremities. Peripheral neuropathy is cumulative and usually reversible, although recovery is often slow. Nervous system effects can also include motor difficulties such as gait, reduced or absent deep-tendon reflexes and leg weakness.</td>
</tr>
<tr>
<td><strong>Ototoxicity</strong></td>
<td>Auditory impairments including tinnitus, with or without clinical hearing loss, are potential side effects of cisplatin. Ototoxicity is cumulative and irreversible and results from damage to the inner ear.</td>
</tr>
<tr>
<td><strong>Nephrotoxicity (may include SIADH)</strong></td>
<td>Nephrotoxicity is a common dose-related side effect of cisplatin, and can be life-threatening. Renal dysfunction may manifest as renal insufficiency, hypokalemia and hypomagnesemia. Hydration is required to minimize the risk for nephrotoxicity. Patients should be encouraged to maintain oral intake of 2000mL (8 glasses) daily at home. They should be instructed to return for IV hydration if nausea and vomiting precludes oral intake.</td>
</tr>
<tr>
<td><strong>Increase in bilirubin/LFTs</strong></td>
<td>Gemcitabine can cause transient and reversible elevations of liver transaminases in greater than 60% of patients, though these increases are rarely of clinical significance. There is no evidence to suggest increasing hepatic toxicity with greater duration of treatment or increasing cumulative dose. Dosing modifications are not required in these instances. Abnormal liver function tests were reported 16.7% of study patients treated with gemcitabine in combination with cisplatin.</td>
</tr>
<tr>
<td><strong>Skin rash</strong></td>
<td>Skin rash can occur from gemcitabine, and is typically mild to moderate in severity. The rash presents as a macular or finely granular maculopapular pruritic eruption on the trunk and extremities.</td>
</tr>
<tr>
<td><strong>Electrolyte abnormalities</strong></td>
<td>Cisplatin treatment can cause electrolyte disturbances, most commonly hypomagnesemia, hypocalcemia, and hypokalemia.</td>
</tr>
<tr>
<td><strong>Other common adverse effects</strong></td>
<td>Fatigue, lethargy, hematuria, proteinuria, edema/peripheral edema.</td>
</tr>
</tbody>
</table>
### Precautions

<table>
<thead>
<tr>
<th>Precaution</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemolytic uremic syndrome</td>
<td>Hemolytic uremic syndrome has been reported with the use of gemcitabine and is characterized by microangiopathic hemolytic anemia, thrombocytopenia and renal failure. The syndrome can present either acutely with severe hemolysis, thrombocytopenia and rapidly progressive renal failure, or more insidiously with mild or no thrombocytopenia and slowly progressive renal failure. The etiology is unknown at present. The onset of this syndrome has been observed during and shortly after gemcitabine therapy. If not treated promptly, the patient may suffer irreversible renal failure and require dialysis. Patients with impaired renal function should be monitored closely while being treated with gemcitabine.</td>
</tr>
<tr>
<td>Severe pulmonary toxicity</td>
<td>Acute dyspnea is observed in approximately 8% of patients that receive gemcitabine, but is usually self-limiting. Rarely, severe pulmonary toxicities such as pulmonary edema, interstitial pneumonitis, and acute respiratory distress syndrome (ARDS) have been reported. Toxicities usually occur after several cycles of gemcitabine, but have also been seen as early as the first cycle.</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>Serious cardiovascular toxicities have been rarely observed. Cisplatin is associated with increased risk of thromboembolic events.</td>
</tr>
</tbody>
</table>

---

Hemolytic uremic syndrome has been reported with the use of gemcitabine and is characterized by microangiopathic hemolytic anemia, thrombocytopenia and renal failure. The syndrome can present either acutely with severe hemolysis, thrombocytopenia and rapidly progressive renal failure, or more insidiously with mild or no thrombocytopenia and slowly progressive renal failure. The etiology is unknown at present. The onset of this syndrome has been observed during and shortly after gemcitabine therapy. If not treated promptly, the patient may suffer irreversible renal failure and require dialysis. Patients with impaired renal function should be monitored closely while being treated with gemcitabine.

Acute dyspnea is observed in approximately 8% of patients that receive gemcitabine, but is usually self-limiting. Rarely, severe pulmonary toxicities such as pulmonary edema, interstitial pneumonitis, and acute respiratory distress syndrome (ARDS) have been reported. Toxicities usually occur after several cycles of gemcitabine, but have also been seen as early as the first cycle.

Serious cardiovascular toxicities have been rarely observed. Cisplatin is associated with increased risk of thromboembolic events.
## Dose Modifications

<table>
<thead>
<tr>
<th>Hepatic dysfunction</th>
<th>Drug</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cisplatin</td>
<td>No dosage adjustment required.</td>
<td></td>
</tr>
<tr>
<td>Gemcitabine</td>
<td>Use with caution; no specific recommendation found.</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Renal dysfunction</th>
<th>Drug</th>
<th>Creatinine Clearance*</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cisplatin</td>
<td>Greater than or equal to 60 mL/min</td>
<td>100%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Between 45-59 mL/min</td>
<td>75%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Less than 45 mL/min</td>
<td>Consider omitting cisplatin. Carboplatin may be considered in place of cisplatin in patients who cannot tolerate cisplatin.</td>
<td></td>
</tr>
<tr>
<td>Gemcitabine</td>
<td>Although current evidence indicates gemcitabine is not nephrotoxic, care should be exercised in the use of this agent in patients with renal dysfunction, as risk of developing hemolytic uremic syndrome may be increased in this group. Patients with renal dysfunction should be monitored closely while being treated with gemcitabine.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

---

* Cockcroft-Gault GFR = N* x (140-age) x IBW (kg) */sCR in umol/L

Ideal Body Weight (IBW)
- Male = 50 kg + [(Ht in cm – 152 cm) x 0.91]
- Female = 45.5 kg + [(Ht in cm – 152 cm) x 0.91] (see Reference 10)
<table>
<thead>
<tr>
<th>ANC</th>
<th>Platelets</th>
<th>Chemotherapy Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Greater than or equal to $1.5 \times 10^9 /L$</td>
<td>and Greater than or equal to $100 \times 10^9 /L$</td>
<td>100%</td>
</tr>
<tr>
<td>Less than $1.5 \times 10^9 /L$</td>
<td>and Less than $100 \times 10^9 /L$</td>
<td>Consider dose reductions**</td>
</tr>
<tr>
<td>Less than $1 \times 10^9 /L$</td>
<td>or Less than $50 \times 10^9 /L$</td>
<td>Omit</td>
</tr>
</tbody>
</table>

**Chemotherapy dose adjustments for decreased blood counts are made at the discretion of the medical oncologist on a case-by-case basis.
References


CCMB Contributors

Dr. Ralph Wong, Medical Oncologist Chair, Gastro-Intestinal Disease Site Group
Mr. Pat Trozzo, BSc (Pharm), Site Manager, Pharmacy Program
Ms. Kimberly Watkinson, BSc (Pharm), Provincial Oncology Drug Program
Ms. Kristi Hofer, BSc (Pharm), Community Cancer Programs Network
Mr. Robert Hardy, BSc (Pharm), Gastro-Intestinal Disease Site Group

Contact Physician

Dr. Ralph Wong, Medical Oncologist
Chair, Gastro-Intestinal Disease Site Group

Approved By

Dr. Sri Navaratnam, Medical Oncologist
Chair, WRHA/CCMB Oncology Pharmacotherapeutic Subcommittee

Dr. Piotr Czaykowski, Medical Oncologist
Lead and Advisory Panel Chair, CCMB Clinical Practice Guidelines Initiative

We gratefully acknowledge the support of CancerCare Manitoba, and the CancerCare Manitoba Foundation.
The Provincial Oncology Clinical Practice Guidelines Initiative
## Appendix I

### Levels of Evidence

<table>
<thead>
<tr>
<th>Level</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ia</td>
<td>Evidence obtained from meta-analysis of randomised controlled trials</td>
</tr>
<tr>
<td>Ib</td>
<td>Evidence obtained from at least one randomised controlled trial</td>
</tr>
<tr>
<td>Iia</td>
<td>Evidence obtained from at least one well-designed controlled study without randomisation</td>
</tr>
<tr>
<td>Iib</td>
<td>Evidence obtained from at least one other type of well-designed, quasi-experimental study</td>
</tr>
<tr>
<td>III</td>
<td>Evidence obtained from well-designed, non-experimental descriptive studies, such as comparative studies, correlation studies and case studies</td>
</tr>
<tr>
<td>IV</td>
<td>Evidence obtained from expert committee reports or opinions and/or clinical experience of respected authorities</td>
</tr>
</tbody>
</table>

## Appendix II

### ECOG Performance Status Scale

<table>
<thead>
<tr>
<th>Status</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Fully active, able to carry on all pre-disease activities without restriction (Karnofsky 90-100)</td>
</tr>
<tr>
<td>1</td>
<td>Restricted in physical strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, for example, light housework or office work (Karnofsky 70-80)</td>
</tr>
<tr>
<td>2</td>
<td>Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about greater than or equal to 50% of waking hours (Karnofsky 50-60)</td>
</tr>
<tr>
<td>3</td>
<td>Capable of only limited self-care, confined to bed or chair greater than or equal to 50% of waking hours (Karnofsky 30-40)</td>
</tr>
<tr>
<td>4</td>
<td>Completely disabled, cannot carry on any self-care, totally confined to bed or chair (Karnofsky 10-20)</td>
</tr>
</tbody>
</table>

### Appendix III

**Common Terminology Criteria for Adverse Events (CTCAE) version 4.0**

**Publish Date: 18 May 2009**

<table>
<thead>
<tr>
<th>Grades</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1</td>
<td>Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.</td>
</tr>
<tr>
<td>Grade 2</td>
<td>Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL*.</td>
</tr>
<tr>
<td>Grade 3</td>
<td>Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care ADL**.</td>
</tr>
<tr>
<td>Grade 4</td>
<td>Life-threatening consequences; urgent intervention indicated.</td>
</tr>
<tr>
<td>Grade 5</td>
<td>Death related to AE.</td>
</tr>
</tbody>
</table>

A semi-colon indicates 'or' within the description of the grade.
A single dash (-) indicates a grade is not available.
Not all grades are appropriate for all AEs. Therefore, some AEs are listed with fewer than five options for grade selection.

**Grade 5:** Grade 5 (Death) is not appropriate for some AEs and therefore is not an option

**Activities of Daily Living (ADL):**
* Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
** Self care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

CancerCare Manitoba Practice Guideline:
Systemic Therapy Summary

CancerCare Manitoba
675 McDermot Avenue
Winnipeg, Manitoba, Canada
R3E 0V9
www.cancercare.mb.ca

CCMB STS: GAST-Cisplatin + Gemcitabine
May 2010

Effective: May 2012
Approved: April 2013

CancerCare Manitoba,
February 2013. All rights reserved.
This material may be freely reproduced for educational and not-for-profit purposes.
No reproduction by or for commercial organization, or for commercial purposes is allowed without written permission of CancerCare Manitoba.