AHFS Final Determination of Medical Acceptance:
Off-label Use of Gemcitabine and Cisplatin Therapy for Unresectable Biliary Tract Cancer

Drug/Drug Combination: Gemcitabine and Cisplatin

Off-label Use: Treatment of unresectable locally advanced or metastatic biliary tract cancer (intrahepatic or extrahepatic cholangiocarcinoma, gallbladder cancer, or ampullary cancer), including unresectable recurrent disease following surgical resection, in patients with good performance status (ECOG performance status of 0 or 1)

Criteria Used in Selection of Off-label Use for Review:

- Clinical results from a well-designed and well-conducted phase 3 randomized trial
- Clinical results from a trial demonstrating an improvement in outcome (overall survival) compared with a reasonable standard of care

Strength of Evidence: Level 1 (High strength/quality)

Strength of Study End Point(s): Overall survival

Grade of Recommendation: Recommended (Accepted)

Narrative Summary:

Use in Biliary Tract Cancer:

Gemcitabine has been used in combination with cisplatin for the treatment of unresectable locally advanced or metastatic biliary tract cancer (intrahepatic or extrahepatic cholangiocarcinoma, gallbladder cancer, or ampullary cancer), including unresectable recurrent disease following surgical resection.[1,3]

Evidence concerning efficacy of chemotherapy regimens in the treatment of advanced biliary tract cancer is derived largely from small, nonrandomized, clinical studies and retrospective analyses; few large, randomized, controlled clinical trials have been conducted.[1,2,5] Experts state that, in patients with biliary tract adenocarcinoma (the most common type of biliary tract cancer), chemotherapy can be recommended in individuals with unresectable locally advanced or metastatic disease and in those with recurrent disease following surgical resection,[2] since there is some evidence from a randomized study in patients with unresectable pancreatic or biliary tract cancer indicating that use of chemotherapy for the treatment of unresectable biliary tract cancer is associated with prolonged survival and improved quality of life.[2,4] Chemotherapy is recommended in such individuals with good performance status (ECOG performance status of 0 or 1).[2] However, in patients with poor performance status (ECOG performance status of 2 or 3) or insufficient biliary decompression, the benefits of chemotherapy are limited and use of alternative therapy for palliation of associated symptoms (e.g., pain) and improvement in quality of life is recommended.[2] In one retrospective

analysis comparing chemotherapy with best supportive care in patients with advanced gallbladder cancer, a survival benefit was observed in patients with good performance status but not in those with poor performance status.[2,6]

In a multicenter, randomized, phase 3 trial (Advanced Biliary Cancer [ABC]-02), 410 patients with unresectable locally advanced or metastatic biliary tract carcinoma, including unresectable recurrent disease following surgical resection, were randomized to receive either combination therapy with gemcitabine (1 g/m^2 administered by IV infusion over 30 minutes on days 1 and 8) and cisplatin (25 mg/m^2 administered by IV infusion over 1 hour on days 1 and 8) on a 21-day cycle or gemcitabine alone (1 g/m^2 administered by IV infusion over 30 minutes on days 1, 8, and 15) on a 28-day cycle.[1,3] Patients without evidence of disease progression at 12 weeks could continue to receive their assigned regimen for an additional 12 weeks.[1] Patients enrolled in the study generally had good baseline performance status (ECOG score of 0 or 1 in 88% of patients, score of 2 in 12%).[1] Patients who had received prior systemic chemotherapy for locally advanced or metastatic biliary tract carcinoma (other than low-dose radiosensitizing chemotherapy given in conjunction with radiotherapy) were excluded from the study.[3] At a median follow-up of 8.2 months, patients who received combination therapy with gemcitabine and cisplatin had longer median overall (11.7 versus 8.1 months) and progression-free (8 versus 5 months) survival, a higher 6-month progression-free survival rate (59.3 versus 42.5%), and higher rates of tumor control (complete or partial responses or stable disease) (81.4 versus 71.8%) compared with patients who received gemcitabine alone.[1] Only one patient in each treatment group achieved a complete response.[1] Grade 3 or 4 hematologic toxicity (most commonly neutropenia [25.3 versus 16.6%]) occurred more frequently in patients receiving combination therapy with gemcitabine and cisplatin, whereas grade 3 or 4 abnormalities in liver function (27.1 versus 16.7%), including elevations in serum ALT (SGPT) concentrations, occurred more frequently in patients receiving gemcitabine alone.[1] Grade 3 or 4 infection occurred with similar frequency in both groups.[1] Based on current evidence, combination therapy with gemcitabine and cisplatin is recommended (accepted) for use in the treatment of unresectable locally advanced or metastatic biliary tract cancer (intrahepatic or extrahepatic cholangiocarcinoma, gallbladder cancer, or ampullary cancer), including unresectable recurrent disease following surgical resection, in patients with good performance status (ECOG performance of 0 or 1).

Dosage in Biliary Tract Cancer:

When gemcitabine has been used in combination with cisplatin for the treatment of unresectable locally advanced or metastatic biliary tract cancer in adults, including treatment of unresectable recurrent disease following surgical resection, gemcitabine 1 g/m^2 has been administered by 30-minute IV infusion on days 1 and 8 of each 21-day cycle, and cisplatin 25 mg/m^2 has been administered by 1-hour IV infusion on days 1 and 8 prior to gemcitabine administration.[1,2] Treatment has been continued for 24 weeks (8 cycles of therapy) in the absence of disease progression or unacceptable toxicity.[1,2]

References:

1. Valle J, Wasan H, Palmer DH et al. Cisplatin plus gemcitabine versus gemcitabine for biliary tract cancer. *N Engl J Med.* 2010; 362:1273-81.
2. Furuse J, Takada T, Miyazaki M et al. Guidelines for chemotherapy of biliary tract and ampullary carcinomas. *J Hepatobiliary Pancreat Surg.* 2008; 15:55-62.
3. Gemcitabine with or without cisplatin in treating patients with unresectable locally advanced or metastatic cholangiocarcinoma or other biliary tract tumors. From ClinicalTrials.gov registry (http://clinicaltrials.gov/ct2/show/results/NCT00262769). Accessed 2011 Feb 24.

4. Glimelius B, Hoffman K, Sjoden PO et al. Chemotherapy improves survival and quality of life in advanced pancreatic and biliary cancer. *Ann Oncol*. 1996; 7:593-600
5. Eckel F, Schmid RM. Chemotherapy in advanced biliary tract carcinoma: a pooled analysis of clinical trials. *Br J Cancer.* 2007; 96:896-902.
6. Ishii H, Furuse J, Yonemoto N et al. Chemotherapy in the treatment of advanced gallbladder cancer. *Oncology.* 2004; 66:138-42.

Oncology Expert Committee Voting Results:

Proposed Level of Evidence: Level 1 (High strength/quality); overall survival

Concur with rating: 5 votes

Do not concur with rating: 0 votes

Grade of Recommendation:

Recommended use (Accepted): 5 votes

Reasonable choice (Accepted, treatment option): 0 votes

Not fully established (Unclear risk/benefit or equivocal): 0 votes

Not recommended (Unaccepted): 0 votes

Proposed Consensus Recommendation:
Based on current evidence, combination therapy with gemcitabine and cisplatin is recommended (accepted) for use in the treatment of unresectable locally advanced or metastatic biliary tract cancer (intrahepatic or extrahepatic cholangiocarcinoma, gallbladder cancer, or ampullary cancer), including unresectable recurrent disease following surgical resection, in patients with good performance status (ECOG performance status of 0 or 1).

Concur with recommendation: 5 votes

Do not concur with recommendation: 0 votes

Oncology Expert Committee Members' Comments:

Comments in Support of Vote on Level of Evidence and Grade of Recommendation:
Reviewer #1: Consider limiting to those patients with ECOG PS 0–1 only.

Reviewer #1: Based on the robust primary endpoint chosen (overall survival), and considering the paucity of data in this disease state, I fully agree with the level of evidence and narrative summary provided.

Reviewer #2: Recommend for patients with good performance status (0–1). I don't think that ECOG 2 was adequately represented in this trial (based on small number of patients and hazard ratio – Figure 3 in trial).

Reviewer #2: I support the evidence rate of level 1 despite this study's lack of blinding. The study meets all end points, is a multicenter trial, and is to be used in a cancer that currently has limited data on treatment. I do think that the data would be stronger if the tumor response was determined by an independent review committee instead of investigator-determined. I would limit my recommendation at this time to patients with ECOG performance status of 0–1 (majority of patients in this trial).

Reviewer #3: Multicenter randomized phase III trial with OS as endpoint. Similar treatment compliance of two arms. Single study, but as this is a large well designed study, fell the results can be used for ratings.

Reviewer #4: Based upon the high level of evidence from the phase 3, randomized clinical trial by Valle et al; I agree with the proposed off-label use of cisplatin plus gemcitabine in patients with unresectable locally advanced or metastatic biliary tract cancer.

Comments on Draft Narrative Summary:
Reviewer #1: In the subgroup analysis, those patients with ECOG PS=2 did not derive the same benefit as those with better PS (0–1); it is unclear based on provided information in the NEJM article whether these patients with PS2 had a higher amount of side effects. Based on prior studies/recommendations, I would still be hesitant to use either gem or gem-cis in a patient with PS=2.

Comments on Proposed Consensus Recommendation:
None submitted.

Participants:

AHFS Staff Members (writing and editing): Sarah Donegan, Pharm.D., BCOP; Lily Leu, Pharm.D., BCOP; Jane Miller, Pharm.D.

AHFS Oncology Expert Committee Members (reviewing and voting): Ronald Walters, M.D., M.B.A., M.H.A., M.S.; Rowena Schwartz, Pharm.D., BCOP; James Trovato, Pharm.D., M.B.A., BCOP., FASHP; Danielle Roman, Pharm.D., BCOP; Mandy Gatesman, Pharm.D., BCOP

External Consultants: None

Conflict of Interest Disclosures:

Individuals who substantively participated in the development, review, and/or disposition of this off-label oncology determination were screened for direct and indirect conflicts of interests involving themselves, their spouse, and minor children. No conflicts of interest were identified for this determination.

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