Indications for Neoadjuvant, Adjuvant, and Palliative Chemotherapy in the Treatment of Biliary Tract Cancers

Fidel David Huitzil-Melendez, MD[a], Eileen M. O'Reilly, MD[a,b], Austin Duffy, MD[a], Ghassan K. Abou-Alfa, MD[a,b,*]

KEYWORDS

- Biliary tract cancers • Cholangiocarcinoma
- Gallbladder cancer • Chemotherapy
- Regional chemotherapy • Targeted agents
- Adjuvant therapy

Carcinomas arising from the biliary tree epithelium are uncommon malignancies in the United States. According to the Surveillance, Epidemiology and End Results program, gallbladder cancer is the most common biliary tract malignancy, with an age-adjusted incidence of 1.2184 cases per 100,000 in 2005.[1] The incidence of intrahepatic cholangiocarcinoma is lower, but has increased in recent years from 0.13 cases per 100,000 in 1973 to 0.67 cases per 100,000 in 1997.[2] In 2008, 9520 new cases of gallbladder and other bile duct cancers were estimated to occur in the United States. In addition, 21,370 new cases of primary liver cancer, of which approximately 10% are intrahepatic cholangiocarcinomas, were also estimated for 2008.[3]

According to Surveillance, Epidemiology and End Results, the estimated overall 5-year survival rate in year 2000 for gallbladder cancer was 16.65% and that of liver and intrahepatic bile duct cancer was only 11.82%.[1] The poor prognosis is in part explained by advanced disease at presentation in most cases. Only 31% of patients with gallbladder cancer and 36% of patients with liver and bile duct cancer have localized disease at presentation.[1] Even surgically treated patients experience high rates of recurrent disease.[4–6] In this context, it is clear that effective adjuvant treatment strategies are desperately needed for successfully resected patients and that most

[a] Section of Gastrointestinal Oncology, Memorial Sloan-Kettering Cancer Center, 1275 York Avenue, New York, NY 10022, USA
[b] Weill Medical College at Cornell University, New York, NY, USA
* Corresponding author.
E-mail address: abou-alg@mskcc.org (G.K. Abou-Alfa).

Surg Oncol Clin N Am 18 (2009) 361–379
doi:10.1016/j.soc.2008.12.006 **surgonc.theclinics.com**
1055-3207/08/$ – see front matter

patients with biliary tract cancers are candidates for palliative therapy at some point in the course of their disease.

This article reviews the available evidence to support indications of systemic chemotherapy in the palliative and perioperative settings.

SYSTEMIC CHEMOTHERAPY IN ADVANCED DISEASE

Meta-Analysis

Many chemotherapy agents and regimens have been tested in patients with advanced biliary tract cancers. The most comprehensive evaluation of the activity of systemic chemotherapy in advanced biliary tract cancers derives from a pooled analysis of 104 chemotherapy trials published in English from 1985 to 2006, comprising 112 trial arms and 2810 patients.[7] Several aspects of available clinical trials of systemic chemotherapy in advanced biliary tract cancers must be highlighted. Despite evidence that gallbladder, intrahepatic, and extrahepatic bile duct carcinomas differ not only in risk factors and clinical manifestations but also in molecular pathogenesis and prognosis,[8] clinical trials evaluating the activity of systemic therapies often pool these carcinomas under the common denomination of advanced biliary tract carcinomas. As such, possible distinct responses to systemic therapies cannot be discerned with confidence. Most are single-arm phase II trials. Only one phase III trial and two randomized phase II trials were identified in this meta-analysis. Only a minority of the trials reported statistical considerations, such as sample size calculation, null and alternative hypothesis, significance level, and power. The mean number of patients per trial was 25.1 (range, 5–65). Results from well-designed controlled trials evaluating the activity of systemic chemotherapy in advanced biliary tract cancers are lacking, and important questions, such as whether chemotherapy improves survival over best supportive care, whether combination chemotherapy is superior to single-agent therapy in terms of survival, and which is the reference regimen in this disease, remain without a solid evidence-based answer.

Nonetheless, the pooled analysis has defined relevant outcomes for chemotherapy in advanced biliary tract cancers. Response rate defined as complete response and partial response and tumor control rate defined as complete response, partial response, and stable disease showed a weak ($r = 0.2$ and $r = 0.26$, respectively) but significant correlation with time to tumor progression and overall survival. Time to tumor progression showed a strong ($r = 0.73$) and statistically significant ($P = .000$) correlation with overall survival. Although comparisons among regimens evaluated in single-arm phase II trials are not appropriate, the results of the pooled analysis may be the best evidence available regarding the activity of systemic chemotherapy in advanced biliary tract cancers and may define chemotherapy historical controls useful for the design of future clinical trials.

Results of the pooled analysis are summarized in **Table 1**. The pooled response rate was 22.6% (95% confidence interval [CI], 21–24.2; N = 2810) and the pooled tumor control rate was 57.3% (95% CI, 55.3–59.3; N = 2386). Median time to progression was 4.1 months (1543 patients) and median overall survival was 8.2 months (2197 patients). A regression equation showed that a 10% increment in response corresponded to an 8% increase of tumor control rate, a 0.7-month increase of time to progression, and a 0.6-month increase of overall survival. A 1-month increase in time to progression corresponded to a 1.3-month increase of overall survival.

Reliable comparisons among chemotherapy regimens can only be derived from well-designed and well-conducted randomized controlled trials that minimize a myriad of potential biases, including selection bias. Comparisons derived from the pooled