Accomplishments in 2008 in the Management of Hepatobiliary Cancers

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Hepatocellular Carcinoma

I. EPIDEMIOLOGY

Hepatocellular carcinoma (HCC) is the sixth most common cancer worldwide, and the third most common cause of cancer-related death.[1] While the incidence of HCC is starting to plateau or decrease in Asia,[2] it is increasing in the US and Europe.[3,4] In 2008, HCC and intrahepatic cholangiocarcinoma have risen to rank fifth as a cause of cancer-related mortality in men in the United States.[5] Based on Surveillance, Epidemiology, and End Results (SEER) data, age-adjusted HCC incidence rates tripled between 1975 and 2005.[4] From 2000 to 2005, marked increases in incidence rates occurred among Hispanic, black, and white middle-aged men.

HCC develops in a cirrhotic liver in 80% of cases, and this preneoplastic condition is the strongest predisposing factor.[6] The rising incidence of HCC is largely due to chronic hepatitis C infection

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(HCV). However, metabolic syndrome related to obesity, diabetes mellitus, and non-alcoholic fatty liver disease (NAFLD) has been recognized as another potential risk factor and will likely continue to influence the trend of rising HCC incidence in the coming decades.[7]

II. MANAGEMENT OF HCC — STANDARD APPROACHES AND REPORTS DURING THE PAST YEAR

II-A. Surgery

Surgical resection remains the curative treatment of choice for patients with resectable HCC and adequately preserved liver function. Major resections can only be performed with low rates of life-threatening complications in non-cirrhotic patients. By contrast, in cirrhotic patients, this procedure requires well-defined selection criteria (solitary tumors and Child-Pugh A status without portal hypertension) as well as a skilled surgical team. In these cases, perioperative mortality of < 3%, blood transfusion requirement of <10%, and 5-year survival rates of 50% to 60% have been achieved.[8] The experience of laparoscopic resection of HCC has been reported in several centers with encouraging results.[9,10] In general, laparoscopic resection is only applicable to selected patients and may be associated with better postoperative quality of life than open resection.

Three variables emerge as prognostic factors in patients undergoing resection: size and number of tumors and the presence of vascular invasion. In a large Japanese survey of thousands of HCC patients, tumor size less than 2 cm was shown to be an independent predictor of survival.[9] Five-year survival rates were 66% if HCC was ≤ 2 cm, 52% if tumor size was 2 to 5 cm, 37% for tumors > 5 cm, and 26% if tumors had three or more nodules.

Tumor recurrence complicates 70% to 80% of cases, and there is no established preventive therapy. More than 15 randomized controlled trials (RCTs) assessing locoregional and systemic therapies have been published, including studies of chemoembolization, internal radiation, chemotherapy, adoptive immunotherapy, retinoids, or interferon.[11] Despite positive results with some of these treatments, such as internal radiation with ^{131}I-labeled lipiodol, retinoids, or adoptive immunotherapy, the strength of evidence was not convincing enough to suggest a standard of care.

Liver transplantation is the preferred treatment for patients with small multinodular tumors or those with advanced liver dysfunction.[6] These patients, with single HCC ≤ 5 cm or up to three nodules < 3 cm (Milan criteria), achieve a 5-year survival rate of 70% with a recurrence rate < 15% at major centers. Due to the scarcity of donors, up to 10% to 20% of candidates drop out from the waiting list before undergoing transplantation. None of the treatments that are used at many centers for patients on the waiting list have been tested in the setting of randomized investigations.

Although the Milan criteria are the generally accepted standard worldwide to select patients for transplant,[12] several studies have explored transplant outcomes in patients who exceeded the Milan criteria. In a large retrospective study of more than 1,100 patients undergoing transplantation for HCC who exceeded the Milan criteria, patients without microvascular invasion, but who fell within the up-to-seven criteria (HCC with seven as the sum of the size of the largest tumor in cm and the number of tumors), favorable outcome with 5-year overall survival of 71.2% was achieved.[13] Genomic translational studies are currently being conducted in an attempt to identify the ideal patient subpopulations for transplantation based on molecular profiles.

II-B. Locoregional Treatment

II-B. 1. Local Ablation

Several locoregional treatment options exist for patients with HCC. Generally, radiofrequency ablation (RFA) and percutaneous ethanol injection (PEI) are the options used most commonly to treat small HCCs that are solitary or limited to a few lesions. Complete responses are achieved in more than 80% of patients with tumors smaller than 3 cm in diameter, but in 50% with tumors of 3 to 5 cm in size.[14] During the past years, six new RCTs comparing different modalities of local ablation have been reported. Based on these reports, there is agreement that RFA provides better local control of HCC than does PEI, and thus is considered the treatment of choice.

II-B. 2. Chemoembolization

Patients with intermediate stages of HCC present a natural outcome of 16 months of median survival.[15] Chemoembolization is generally used in patients with multifocal unresectable HCC without vascular invasion, and can improve median survival to up to 20 months in selected patients, based on data from two randomized studies and a systematic review of six RCTs.[15–17] Subsequent data from a phase II study showed that patients treated with drug-eluting beads containing doxorubicin had objective response rates of 60% to 70% (as compared with 30% to 40% with Gelfoam and lipiodol-doxorubicin), without systemic toxicity.[18] These results provide the rationale to use drug-eluting beads in advanced clinical trials.

II-B. 3. Other Local Treatment Modalities

It is encouraging that many other local treatment modalities have been explored in HCC, including intra-arterial injection of yttrium-90 microspheres, microwave, and cryoablation.

- Kulik and colleagues reported their early experience from a phase II study using radioembolization with yttrium-90 microspheres.[19] About one third of the patients had portal vein thrombosis. Results provided initial evidence that this technique is well tolerated with encouraging signals of antitumor activity.
- The use of radiation to the liver has been explored in Asia, and based on initial encouraging reports, is also being tested in the West.[20]

How these local treatments will compare with trans-arterial chemoembolization (TACE) and whether each technique will find a unique application in selected patient populations remain to be determined in randomized studies.

II-C. Systemic Treatment

2008 represents an important year for the development of systemic therapy in HCC. Several large trials of sorafenib — recently estab-

lished as a standard treatment in advanced HCC — were published. Data from phase II studies of sunitinib were published, and early evidence of antitumor activity was reported for several other molecularly targeted agents including bevacizumab (alone or in combination with erlotinib), brivanib, and ABT-869.

- The mature efficacy and toxicity data from the SHARP study (Sorafenib HCC Assessment Randomized Protocol) were published.[21] Results showed that patients with advanced HCC and underlying Child-Pugh A cirrhosis who were treated with sorafenib had improved overall survival (OS) and time to tumor progression (TTP) compared with the placebo-treated group. Median OS was 10.7 months with sorafenib and 7.9 months with placebo (hazard ratio [HR] of death in the sorafenib group, 0.69; $P < .001$); and median TTP was 5.5 months and 2.8 months, respectively ($P < 0.001$). This study has established sorafenib as the standard treatment for patients with advanced HCC, ie, those with cancer-related symptoms, and/or portal vein thrombosis and/or extrahepatic disease.[21]
- In an Asian-Pacific randomized phase III study, sorafenib treatment also resulted in improved OS in advanced HCC patients, most of whom had hepatitis B infection (HBV) as the primary etiologic factor.[22] Overall survival was 6.5 months in the sorafenib group vs. 4.2 months in the placebo group (HR in the sorafenib group, 0.68; $P = .014$). Safety profiles of sorafenib were similar in this and the SHARP study. Hand-and-foot reactions, diarrhea, and fatigue were the major side effects encountered.[21,22]
- A randomized phase II study compared doxorubicin + sorafenib vs. doxorubicin + placebo, and showed a trend toward improved TTP and OS in the sorafenib arm.[23] Unfortunately, the control arm was doxorubicin, making the relative contribution of doxorubicin, if any, difficult to assess in the sorafenib/doxorubicin arm.
- Sunitinib was tested in two single-arm phase II studies (using 37.5 mg or 50 mg daily, 4 weeks on/2 weeks off schedule). Early evidence of antitumor activity was reported, with progression-free survival (PFS) of 3.9 and 3.7 months in the two trials.[24,25] Safety profiles showed more toxicity for the 50-mg dose (with up to 10% of treatment-related deaths),[25] whereas safety was less problematic for the lower-dose schedule.[24] Despite the lack of direct comparison of sunitinib and sorafenib in the same patient population in a randomized phase II study, a randomized phase III study comparing these two agents in advanced HCC is ongoing worldwide (Table 1).
- Siegel and colleagues conducted a study of single-agent bevacizumab in patients with HCC without portal vein thrombosis,[26] and reported a 13% response rate and PFS of 6.5 months in patients without extrahepatic spread.
- Treatment with the combination of bevacizumab and erlotinib resulted in a median PFS of 9 months and OS of 15.6 months, but the trial population was very heterogeneous.[27]
- Preliminary data for brivanib and ABT-869 were presented at the second International Liver Cancer Association meeting.[28,29]

Table 1. Representative active or completed phase III trials in hepatocellular carcinoma*

Trial ID No.	Region or Sponsor	Drug of Interest	Sample Size	Phase of the Study	Date of Completion or Expected Completion	Comments
NCT00105443	Llovet et al,[21] Bayer	Sorafenib	602	III	Completed. Trial stopped early, in Feb 2007	Sorafenib vs. placebo, first-line, advanced disease
NCT00492752	Cheng et al,[22] Bayer	Sorafenib	271	III	Completed, March 2007	Sorafenib vs. placebo, first-line, advanced disease, in Asia
NCT00699374	Pfizer	Sunitinib	1200	III	Ongoing, July 2012	Sunitinib vs. sorafenib, first-line, advanced disease
NCT00858871	Bristol-Myers Squibb	Brivanib	1050	III	Ongoing, March 2012	Brivanib vs. sorafenib, first-line, advanced disease
NCT00901901	Bayer, Onyx, OSI	Sorafenib/ Erlotinib	700	III	Ongoing, July 2011	Sorafenib + erlotinib vs. sorafenib + placebo, first-line, advanced disease
NCT00471965	Sanofi-Aventis	FOLFOX4	440	III	Ongoing, March 2009	FOLFOX4 vs. doxorubicin, first-line, advanced disease, in Asia
NCT00825955	Bristol-Myers Squibb	Brivanib	340	III	Ongoing, January 2011	Brivanib + BSC vs. placebo + BSC in advanced, second-line (progressed on/after or intolerant to sorafenib)
NCT00692770	Bayer	Sorafenib	1100	III	Ongoing, April 2014	Sorafenib vs. placebo as adjuvant treatment for HCC after surgical resection or local ablation
NCT00561522	Fudan University, Shanghai, China	Capecitabine	290	III	Ongoing, November 2011	Randomized controlled trial to assess capecitabine as adjuvant therapy for HCC following surgical resection

*Source: www.clinicaltrials.gov. Accessed on July 30, 2009.
Abbreviations: BSC = best supportive care; FOLFOX = oxaliplatin in combination with 5-fluorouracil/leucovorin; HCC = hepatocellular carcinoma.

III. CLINICAL TRIAL DESIGN

The active development of molecularly targeted agents in HCC has presented unparalleled challenges on many key issues in clinical trial design in this disease. Examples of questions that need to be addressed include the following: How should response be assessed? What would be the optimum end points in phase I, II, and III studies? What populations should be targeted to examine potential efficacy and minimize toxicity due to the underlying cirrhosis that afflicts most HCC patients? Realizing an urgent need for high-quality trials in HCC, an expert panel was convened to develop guidelines that will serve as a common framework for designing HCC trials to facilitate comparability of results. This has led to a consensus paper discussing these issues as well as other general recommendations.[30]

IV. BASIC SCIENCE AND BIOMARKERS

IV-A. Basic and Translational Science

Better understanding of the mechanism of hepatocarcinogenesis holds promise to develop new diagnostic and prognostic markers and identify potential targets for therapeutic interventions. Several scientific reports in 2008 continued to shed light in this field.

- Schlaeger and colleagues attempted to identify etiology-dependent DNA copy number aberrations and genes relevant to hepatocarcinogenesis by performing an array-based comparative genomic hybridization of 63 HCCs of well-defined etiology and four HCC cell lines, followed by gene expression profiling and functional analyses of candidate genes. For a 10-megabase chromosome region on 8q24, they observed etiology-dependent copy number gains and Myc overexpression in viral and alcohol-related HCCs, resulting in up-regulation of Myc target genes.[31]
- The importance of liver cancer stem cells is increasingly being recognized. Yang and colleagues presented evidence to support the involvement of Wnt/beta-catenin pathway in activation and expansion of oval cells in normal rodent models and human HCCs.[32] Two reports from the University of Hong Kong have identified CD45(-)CD90(+) cancer stem cells in both HCC tumor tissues and in the circulation, suggesting this cell population could be used as a marker for human liver cancer and as a target for diagnosis and therapy.[33,34] The CD90+CD44+ cells demonstrated a more aggressive phenotype than the CD90+CD44(-) counterpart, and formed metastatic lesions in the lung of immunodeficient mice. Evidence of involvement of aberrant transforming growth factor (TGF)-beta and IL-6 signaling in liver progenitor/stem cells in hepatocarcinogenesis was also presented.[35] Despite these interesting reports, many details about HCC stem cells remain poorly understood. These include the precise cell(s) of origin, molecular genetics, and the mechanisms responsible for the highly aggressive nature of HCC. Exploration of the differences between cancer stem cells and normal stem cells is crucial, not only for understanding tumor biology but also for the development of specific therapies that effectively target these cells in patients.
- Identification of key molecular genetic changes and molecular classification of HCC remain active areas of investigation. By characterizing the copy number alterations and gene expression profiles from HCC with underlying HCV-related cirrhosis, Chiang and colleagues identified multiple genetic alterations, including focal gains at 6p21 incorporating vascular endothelial growth factor A (VEGFA).[36] The importance of the mTOR (mammalian target of rapamycin) pathway in HCC was examined in a comprehensive study with 314 HCC and 37 nontumoral tissues, using a series of molecular techniques to assess mutations, DNA copy number changes, messenger RNA and gene expression, and protein activation.[37] Aberrant mTOR signaling (p-RPS6) was present in half the cases, and chromosomal gains in rapamycin-insensitive companion of MTOR (RICTOR) (25% of patients) and positive p-RPS6 staining correlated with HCC recurrence following resection.[37]
- Several studies continued to assess the use of animal model systems for testing novel molecular targeted agents that inhibit VEGF/R, mTOR, epidermal growth factor receptor (EGFR), and many other key pathways involved in hepatocarcinogenesis.[38–41] These studies provided important insights on the rationale for moving these agents and regimens into clinical trials.

IV-B. Prognostic and Predictive Markers

The most widely applied staging systems for HCC, such as the Barcelona Clinic Liver Cancer (BCLC) staging system or the Japan Integrated Staging (JIS), do not currently include any molecular biomarkers of prognosis or predictive of treatment response.[42–43] The importance of developing molecular-based classification systems and novel markers that will help to determine patient prognosis and predict clinical outcome has been increasingly recognized.

IV-B. 1. Prognostic Markers

Several publications in 2008 on molecular profiling of tumor and surrounding nontumor liver tissues have provided important insights into the mechanisms of tumor recurrence and potential strategies to target patients at risk.

- Hoshida and colleagues carried out genome-wide expression profiling of more than 6,000 human genes in formalin-fixed, paraffin-embedded tissues from 307 HCC patients, and demonstrated that a reproducible gene-expression signature correlating with survival was present in liver tissue adjacent to the tumor.[44] These findings indicate the existence of a field effect, in which environmental exposure (eg, viral infection) increases risk for future malignant transformation, and suggest that a gene-expression signature can serve as a sensitive "readout" of the liver's biologic state in at-risk patients.
- Investigators from Liver Cancer Institute in Shanghai examined the expression of macrophage colony-stimulating factor (M-CSF) and density of macrophages (M Phi) by immunohistochemistry in tissue microarrays containing paired tumoral and peritumoral liver tissue from 105 patients who had undergone hepatectomy for HCC, and demonstrated that high peritumoral M-CSF and M Phi were associated with HCC progression, disease recurrence, and poor survival after hepatectomy.[45]
- Woo and colleagues examined gene expression profiles in 65 HCC patients with HBV, and identified a gene expression signature that effectively predicted early HCC recurrence independent of microarray platforms and cohorts.[46]

IV-B. 2. Predictive Markers

Identification of potential predictive and surrogate markers in patients receiving sorafenib and other targeted agents has been an area of active investigation.

- In a presentation at the 2008 meeting of the American Association for the Study of Liver Diseases, Llovet and colleagues reported early results of an assessment of potential predictive markers in the SHARP study.[47] They found that sorafenib treatment resulted in significantly decreased plasma levels of c-Kit, sVEGFR2, and sVEGFR3, and increased VEGF levels at 12 weeks. HCC patients with high baseline c-Kit levels showed a trend of better response to sorafenib in terms of OS and TTP.
- In an attempt to evaluate sunitinib mechanisms of action and identify useful biomarkers, extensive correlative studies have been performed in the two phase II studies of this agent in HCC. Zhu and colleagues compared clinical outcome with DCE-MRI imaging parameters (eg, K^{trans} at baseline and day 14 post-treatment) and circulating biomarkers involved in angiogenic and inflammatory pathways at baseline and post-treatment, to search for biomarkers that might correlate with clinical efficacy.[24] Sunitinib treatment induced significant and sustained increases in plasma VEGF, PlGF, and SDF1α, and decreases in plasma sVEGFR2, sVEGFR3, and circulating progenitor cells. In addition, sunitinib treatment tended to decrease plasma levels of VEGF-C and soluble c-Kit. Significantly higher baseline plasma levels of the inflammatory cytokines IL-8, IL-6, SDF1α, and TNF-α were found in patients with rapid tumor progression and/or mortality after sunitinib therapy ($P < .05$). Moreover, patients with decreased levels of plasma IL-6 and soluble c-Kit after 14 days of sunitinib treatment had significantly improved PFS and OS ($P < .05$). Data from the other phase II study are consistent with these, showing that sunitinib at a higher dose induced significant elevations in plasma VEGF and decreases in plasma sVEGFR2, sVEGFR3, VEGF-C, and soluble c-Kit.[48] Collectively, these circulating biomarker data suggest a critical role for the balance between angiogenic and inflammatory pathways in HCC response and resistance to sunitinib treatment. Successful modulation of these inflammatory markers might be critical for achieving treatment response with sunitinib and potentially other antiangiogenic agents. The findings of these hypothesis-generating studies need to be validated in large prospective trials.

V. ACCOMPLISHMENTS AND FUTURE DIRECTIONS

V-A. Application of the Accomplishments

Results of the SHARP study, demonstrating an OS improvement in patients treated with sorafenib vs. placebo, have led to approval of sorafenib for the treatment of advanced HCC and represent a breakthrough in the management of this disease. Sorafenib is now the standard of care and the new reference for future development of novel agents and regimens for advanced HCC.

V-B. Future Directions

Several phase III trials of potential new treatment approaches are ongoing in patients with HCC. Table 1 lists representative active (or completed) phase III trials in this disease.

Prevention of HCC through HBV vaccination and lifestyle modification, and early diagnosis through increased awareness and improved screening methods, remain the best strategies to lower HCC incidence and improve treatment outcomes. For patients with established HCC, surgical resection and transplantation remain the optimal curative approaches. In the setting of early– and intermediate–stage HCC, better definition of the indications for, and outcomes with, various local treatment modalities should lead to improved results for these patients. Furthermore, studies of sorafenib in patients following surgical resection, high-risk RFA, or TACE will help to define potential adjuvant strategies. For advanced-stage HCC, combinations of sorafenib with other targeted agents or chemotherapy, and development of other targeted agents, hold promise to improve outcomes further.

It is imperative that efforts continue to focus on identifying and validating surrogate and predictive biomarkers of clinical efficacy, toxicity, and treatment resistance for antiangiogenic and other targeted agents being developed for HCC. Better understanding of the mechanism of hepatocarcinogenesis and molecular profiling of HCC will help to identify additional diagnostic and screening markers and novel therapeutic targets. Such efforts will bring us closer to individualized medicine in HCC in the coming decade.

Biliary Tract Cancers

I. OVERVIEW OF THE DISEASE

Biliary tract cancers (BTC) represent a heterogeneous group of tumors that arise in the gallbladder, the intrahepatic bile ducts (intrahepatic cholangiocarcinoma [IHCC]), the biliary bifurcation (hilar cholangiocarcinoma), or distally in the biliary tree (extrahepatic cholangiocarcinoma [EHCC]). Most patients with gallbladder cancer or cholangiocarcinoma present with advanced disease that is not amenable to surgical resection, a situation in which the administration of palliative chemotherapy has become common practice.

II. MANAGEMENT OF BILIARY TRACT CANCERS—CURRENT APPROACHES AND REPORTS DURING THE PAST YEAR

Historically, advances in the treatment of biliary cancers have been limited by small studies, the heterogeneity of the tumors clinically and biologically, the poor understanding of biliary carcinogenesis, and the complex clinical scenarios encountered, such as biliary obstruction, infections, and poor nutritional status.

II-A. Surgical Resection and Adjuvant Therapy

Surgical resection offers the only chance for cure in patients with BTC. However, the number of patients in whom a successful curative R0 resection can be achieved is limited. For example, in a series of 225 patients with hilar cholangiocarcinoma, only 28% underwent an R0 resection, with a median overall survival of 42 months.[49] In other surgical series of extra-hepatic cholangiocarcinoma, median survival ranges between 5 and 32 months, with locoregional failure rates in excess of 50%. These results highlight the need for effective adjuvant therapeutic options. To date, there is no

established standard adjuvant therapy for patients with resected gallbladder carcinoma or cholangiocarcinoma.

In 2008, several small retrospective reports of adjuvant chemoradiotherapy were published, which, unfortunately, do not alter the current landscape.[50–52] One such retrospective report of 91 patients with extrahepatic cholangiocarcinoma who underwent surgical resection noted an additional benefit on overall and disease-free survival from the continuation of systemic 5-FU chemotherapy for 6 to 12 months beyond the initial period of chemoradiotherapy.[52] The Southwest Oncology Group (SWOG) 0809 trial is an ongoing single-arm cooperative group study of adjuvant gemcitabine in combination with capecitabine in patients with resected gallbladder carcinoma or extrahepatic cholangiocarcinoma (Table 2). Patients are treated with gemcitabine and capecitabine for 4 months followed by a period of concurrent capecitabine and radiotherapy. This study will provide prospective data on a uniform group of patients with high-quality control measures of central pathologic and radiation planning review. The data from this trial may facilitate the planning of a prospective randomized trial in the near future.

II-B. Systemic Therapy for Unresectable or Metastatic BTC

II-B. 1. Cytotoxic Chemotherapy

Cytotoxic chemotherapy has limited efficacy in patients with unresectable or metastatic BTC. Most of the available data derive from phase II studies, which are limited by small numbers of patients and heterogeneous patient populations. The regimens commonly used have been 5-fluorouracil– or gemcitabine–based, which have resulted in variable response rates of up to 40% and median OS durations of 6 to 11 months.[53] A meta-analysis had suggested that the gemcitabine and platinum combinations provided the highest response rate and tumor control rate.[54]

This reality did not change significantly in 2008 with the continued absence of randomized studies and the lack of uniformity in the inclusion criteria among the multiple smaller studies conducted. Most of the trials reported in 2008 that evaluated cytotoxic chemotherapy combinations continued to focus on gemcitabine, platinum compounds, and thymidylate synthase inhibitors such as 5-fluorouracil and S-1.

- The combination of gemcitabine with a platinum compound was tested in at least three phase II studies. Gemcitabine plus cisplatin resulted in a response rate of 24%, PFS of 4 months, and OS of 6.5 months in a multicenter phase II study.[55] Gemcitabine and oxaliplatin manifested a variable response rate (RR) and OS depending on the phase II study.[56,57] Of particular interest is a multicenter phase II study of gemcitabine and oxaliplatin in which patients were stratified based on the location of the tumor along the biliary tree[57]; patients with gallbladder carcinoma or EHCC had a 27% RR, while none of the patients with IHCC had an objective response. Similarly, median OS duration was 12.8 months for patients with gallbladder carcinoma, or EHCC, vs. 5.2 months for those with IHCC. The OS of patients with EHCC and gallbladder carcinoma reported in this study needs to be confirmed, especially as it appears to be longer than in other phase II reports. Nonetheless, the findings contribute to an emerging body of literature suggesting that the location of the tumor may influence patient response to various treatments. Furthermore, recent investigations into the biology of biliary tract carcinogenesis support the clinical observations of differential outcome based on tumor location (see Section III).
- In the absence of prospective randomized trials in this patient population, larger retrospective studies have been used to derive preliminary lessons and generate hypotheses. For example, researchers at Seoul National University Hospital in Korea retrospectively studied 243 patients who were treated with either gemcitabine-based (n=99) or fluoropyrimidine-based (n = 144) chemotherapy.[58] Among patients treated with gemcitabine regimens, 95% of them received gemcitabine combined with a platinum agent; in the fluoropyrimidine-treated patients, 58% received fluoropyrimidine combined with platinum. The authors concluded that there was no difference in efficacy between the fluoropyrimidine- and gemcitabine-based treatments. The addition of a plat-

Table 2. Representative active or completed trials in biliary tract cancers

Trial ID No.	Region or Sponsor	Drug of Interest	Sample Size	Phase of the Study	Date of Completion or Expected Completion	Comments
NCT00789958	SWOG/NCI	Gemcitabine, capecitabine, and radiation	80	II (adjuvant)	Ongoing, December 2010	Study to evaluate adjuvant therapy in patients with resected gallbladder carcinoma or EHCC
NCT00753675	AstraZeneca	Vandetanib	174	II (randomized)	February 2010	Gemcitabine + placebo vs. Gemcitabine + vandetanib
NCT00356889	Mayo Clinic/ NCI	Bevacizumab, erlotinib	55	II	Completed, April 2009	Bevacizumab + erlotinib combination in advanced BTC
NCT00090025	Helsinn Healthcare SA	XL119	248	III	Completed, January 2009	XL119 vs. 5-FU/leucovorin in advanced BTC
NCT00262769	UK ABC-02	Gemcitabine/ cisplatin vs. gemcitabine	410	III	Completed	For gem/cis vs. gem in advanced BTC: Median PFS: 8.4 vs. 6.5 mo, $P = .003$ Median OS: 11.7 vs. 8.3 mo, $P = .002$

Abbreviations: BTC = biliary tract cancer; EHCC = extrahepatic cholangiocarcinoma; 5-FU = 5-fluorouracil; NCI = National Cancer Institute; OS = overall survival; PFS = progression-free survival; SWOG = Southwest Oncology Group

inum agent to the fluoropyrimidine or gemcitabine therapy appeared to result in a trend toward a superior RR and disease control rate, but had no effect on PFS and OS. Our ability to draw conclusions from this study is limited by its retrospective and non-randomized nature, and by the multiple potential biases in patient and treatment selection. However, this study highlights the need for prospective randomized trials and highlights another unanswered question related to the superiority of combination chemotherapy compared with single-agent therapy in some or all patients with BTC.

II-B. 2. Cytotoxic Chemotherapy in Combination With Targeted Agent

Preliminary results from a small ongoing phase II study of gemcitabine, oxaliplatin, and cetuximab revealed a promising RR of 58% and PFS of 9 months in 22 patients. Six patients thought to have unresectable disease were converted to resectable.[59] Longer follow-up and mature survival data are necessary to obtain a preliminary efficacy assessment of this combination in BTC and to determine if additional larger studies are warranted.

II-B. 3. Single-Agent Targeted Therapy

Sorafenib has been evaluated as a single agent in two phase II studies for patients with advanced cholangiocarcinoma. One study, reported in 2008, accrued 46 patients and reported a stable disease rate of 50% and PFS of 76 days.[60] These data are consistent with those from SWOG 0514, a phase II study of single-agent sorafenib reported by El-Khoueiry et al in 2007, in which the SD rate was 32%, PFS was 3 months, and OS was 9 months.[61] Studies of sorafenib combined with cytotoxic chemotherapy, or combined with other targeted agents, are ongoing or planned.

II-B. 4. Combination of Targeted Agents

An interim report of a phase II study of bevacizumab in combination with erlotinib in 34 patients noted a promising RR of 20% and a TTP of more than 7 months.[62] Final results are pending.

III. BIOLOGY

Given the modest response rates with combination cytotoxic chemotherapy and the lack of an established treatment regimen that clearly influences survival of patients with BTC, recent efforts have focused on improving our understanding of the molecular carcinogenesis of biliary cancers. These efforts have led to the identification of several genes that may play a role in the development of BTC, and that present potential therapeutic targets as well as possible prognostic and predictive markers. Some of these genes, such as EGFR, HER2, and VEGF, have an established role in the carcinogenesis and prognosis of multiple solid tumors and have become clinically established therapeutic targets in colon cancer, non-small cell lung cancer, head and neck cancer, and others.

- In a recent study, immunohistochemical expression of EGFR, HER2, and VEGF was assessed retrospectively in 236 cases of cholangiocarcinoma; associations between the expression of these molecules and clinicopathologic factors or clinical outcome were also examined.[63] The proportions of positive cases for EGFR, VEGF, and HER2 overexpression were 27.4%, 53.8%, and 0.9% in IHCC, and 19.2%, 59.2%, and 8.5% in EHCC, respectively. Clinicopathologically, EGFR overexpression was associated with macroscopic type (P = .0120), lymph node metastasis (P = .0006), tumor stage (P = .0424), lymphatic vessel invasion (P = .0371), and perineural invasion (P = .0459) in EHCC; and VEGF overexpression with intrahepatic metastasis (P = .0224) in IHCC. Multivariate analysis showed that EGFR expression was a significant prognostic factor (HR 2.67; 95% confidence interval [CI] 1.52–4.69; P = .0006) and also a risk factor for tumor recurrence (HR 1.89; 95% CI 1.05–3.39, P = .0335) in IHCC. These results suggest that EGFR expression is associated with tumor progression, and VEGF expression may be involved in hematogenic metastasis in cholangiocarcinoma.
- In another report, microvessel density was identified as an independent prognostic factor for survival on multivariate analysis in a cohort of patients with resected hilar cholangiocarcinoma.[64]
- MicroRNAs are non-coding RNA sequences involved in post-transcriptional gene regulation, and are noted to have differential expression in several tumor types, and between malignant and normal tissues. Chen et al reported the identification of a cluster of 38 microRNAs, which was markedly distinguishable between cholangiocarcinoma samples and normal tissues.[65] Moreover, the exogenous expression of mir-320 or mir-204 could negatively regulate Mcl-1 or Bcl-2 expression and facilitate chemotherapeutic drug-triggered apoptosis.

In summary, the emerging body of literature describing the biology of BTCs will greatly influence the planning of future clinical trials through the identification of new therapeutic targets and through the incorporation of prognostic and predictive markers into more tailored therapeutic options for patients.

IV. FUTURE DIRECTIONS

At the time of the preparation of this manuscript, a large randomized study in patients with advanced BTC receiving gemcitabine and cisplatin vs. gemcitabine alone was reported at the 2009 American Society of Clinical Oncology annual meeting (Table 2). This phase III study, conducted in 410 patients, demonstrated that the addition of cisplatin to gemcitabine afforded a significant benefit in terms of PFS (median, 8.4 vs. 6.5 months; HR 0.72 [95% CI 0.57– 0.90], P = .003) and OS (median, 11.7 vs. 8.3 months; HR 0.70 [95% CI 0.54–0.89], P = .002).[66] While discussion of the limitations of this study is beyond the scope of this manuscript, the results are likely to influence standard practice and the planning of future clinical trials. Future studies may need to include a control arm of gemcitabine and cisplatin or may aim at improving the efficacy of this combination with the addition of targeted agents. This does not preclude the development of other novel combinations, especially the combination of two targeted agents based on a well-developed scientific rationale. In this context, several studies combining targeted agents are planned, such as the combination of sorafenib and erlotinib. Moreover, future studies need to better account for the complexity and diversity of this disease clinically and biologically. In this context, stratification by disease site (intrahepatic vs. extrahepatic vs. gallbladder origin) along with the incorporation of the appropriate biologic correlative studies are two fea-

sible and practical considerations for planned clinical trials.

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Disclosures of Potential Conflicts of Interest

Dr. Zhu has served as an advisor to Genentech and Bayer.

Dr. El-Khoueiry and Dr. Llovet have indicated no potential conflicts of interest.