Gallbladder and Biliary Tract Carcinoma: A Comprehensive Update, Part 2

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Gallbladder carcinoma and carcinoma of the bile ducts are relatively rare cancers in the United States. These cancers are often diagnosed in an advanced stage due to their nonspecific symptomatology and until recently have been associated with a dismal prognosis. Recent advances in imaging and surgical techniques along with emerging options in palliative chemotherapy have improved the outlook in these cancers. While complete surgical resection remains the only hope of cure in both these cancers, palliative biliary decompression and chemotherapy result in substantial improvement in quality of life. Part 1 of this review, which appeared in last month’s issue, provided a relevant and comprehensive update of molecular pathology, imaging modalities, and surgical care. In part 2, we examine palliative care and systemic therapy in gallbladder and biliary tract carcinomas, as well as the use of liver transplantation in the treatment of cholangiocarcinomas. These strategies are of relevance to internists as well as oncologists caring for these patients.

ABSTRACT: Gallbladder carcinoma and carcinoma of the bile ducts are relatively rare cancers in the United States. These cancers are often diagnosed in an advanced stage due to their nonspecific symptomatology and until recently have been associated with a dismal prognosis. Recent advances in imaging and surgical techniques along with emerging options in palliative chemotherapy have improved the outlook in these cancers. While complete surgical resection remains the only hope of cure in both these cancers, palliative biliary decompression and chemotherapy result in substantial improvement in quality of life. Part 1 of this review, which appeared in last month’s issue, provided a relevant and comprehensive update of molecular pathology, imaging modalities, and surgical care. In part 2, we examine palliative care and systemic therapy in gallbladder and biliary tract carcinomas, as well as the use of liver transplantation in the treatment of cholangiocarcinomas. These strategies are of relevance to internists as well as oncologists caring for these patients.

Gallbladder carcinoma and cholangiocarcinoma—carcinoma of the bile ducts—are relatively rare cancers in the United States, but have long been associated with a dismal prognosis. Although complete surgical resection is the only hope for cure in both diseases, advances in diagnostic imaging techniques permit earlier diagnosis and have led to improved survival in recent years. The search for appropriate neoadjuvant or adjuvant treatments to improve survival and decrease recurrence rates is ongoing.

In the June issue of *ONCOLOGY*, part 1 of this two-part review summarized improvements in preoperative imaging, staging, and curative surgery. In this concluding part, we address the expanded treatment options available in terms of chemotherapy, radiation therapy, and palliative care, all of which are improving the outlook for patients diagnosed with these cancers.

Adjuvant Treatment

Gallbladder Carcinoma

Few prospective randomized trials have assessed adjuvant therapy in this rare tumor group. The available data derive from small phase II trials in which patients undergoing such treatment have been compared with historical controls.

The only phase III trial of adjuvant chemotherapy included 508 patients with resected gallbladder (n = 140), bile duct (n = 139), ampulla of Vater (n = 56), and pancreatic carcinoma (n = 173).[1] Patients were randomized to surgery alone or with MF (mitomycin [Mutamycin]/fluorouracil [5-FU]). The MF group received mitomycin, 6 mg/m², at the time of surgery and two courses of 5-FU at 310 mg/m² x 5 days in the postoperative period followed by oral 5-FU, 100 mg/m²/d, from postoperative week 5 until recurrence. The 5-year disease-free survival rate (for gallbladder carcinoma patients)
favored adjuvant chemotherapy (20.3% vs 11.6%, \( P = .02 \)), and the 5-year overall survival rate was also improved (26% vs 14.4%, \( P = .03 \)). There were no significant differences in survival or disease-free survival rates in the other cancer groups. A meta-analysis of publications concerning the role of radiation therapy in gallbladder carcinoma from 1974 to 2000 reported a slight improvement in survival after adjuvant or palliative radiotherapy.\[2\] The strongest benefit was for tumors resected with only microscopic residual tissue. This report recommended an intraoperative boost of 15 Gy to the residual lesion or tumor bed with additional postoperative external beam radiation therapy (EBRT) of 45 to 50 Gy. Adjuvant chemoradiation consisting of concurrent 5-FU plus EBRT in 21 resected patients with gallbladder carcinoma was associated with a 5-year survival rate of 64% in the completely resected (negative-margins) group, compared with 33% associated with surgery alone in historical controls.\[3\] Although confirmatory results from large randomized prospective trials are lacking, it is reasonable to offer patients with advanced gallbladder disease postoperative radiotherapy given the low morbidity of radiation compared with the high local recurrence rates and poor survival associated with surgery alone. Adjuvant chemotherapy with 5-FU and mitomycin may be recommended for resected gallbladder cancer.\[1\]

**Cholangiocarcinoma**

**TABLE 1**

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<th>Adjuvant Radiation/Chemoradiation in Gallbladder/Biliary Tract Carcinoma</th>
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Only 20% to 30% of patients with hilar cholangiocarcinoma are eligible for potentially curative (R0) resection. The median survival associated with an R0 resection is significantly better (22 months) than that of a palliative resection (10.7 months).\[4\] Small studies suggest that neoadjuvant therapy consisting of chemotherapy, radiation, chemoradiation, or photodynamic therapy may increase rates of curative resection. However, the small size of these experiences precludes any definitive conclusion.\[4,5\] Cameron et al reported the Johns Hopkins experience with 96 proximal cholangiocarcinoma patients undergoing either curative or palliative surgery and 66% receiving postoperative radiotherapy. No survival advantage was associated with postoperative radiotherapy in the group undergoing curative resection; however, radiation improved survival in those undergoing palliative surgery (R1 or R2 resection).\[6\] Table 1 summarizes some of the adjuvant and neoadjuvant treatment experiences in gallbladder and cholangiocarcinoma.\[1,3,4,7-10\]

**Liver Transplantation for Biliary Tumors**

**TABLE 2**

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The prospect of liver transplantation as a cure for cholangiocarcinoma is appealing given encouraging results of transplantation in primary sclerosing cholangitis with incidental, small (< 1 cm) cholangiocarcinomas (Table 2).\[11-16\] Unfortunately, the recurrence rate is high within the first few years after transplantation. Using life table analysis, projected 1-, 2-, and 5-year survival estimates of 72%, 48%, and 23% were reported for 207 patients who underwent liver transplantation for unresectable cholangiocarcinoma.\[11,12\] The poor long-term survival rates were secondary to high postoperative mortality and a high
incidence of recurrence (51%). The majority of recurrences (85%) occurred within 2 years of transplant. Sites of recurrence were most commonly in the allograft (47%) and in the lung (30%). No prognostic markers were identified that could help with patient selection. To decrease the rate of posttransplant recurrence, preoperative chemoradiation with 5-FU has been attempted. In a small series, 11 patients successfully completed this therapy, and at a follow-up of 44 months, only 1 had relapsed.[17] Transplantation for hilar cholangiocarcinoma after neoadjuvant chemoradiation with infusional 5-FU and biliary brachytherapy has been evaluated in 17 patients.[18] Five patients had tumor progression during the neoadjuvant phase, precluding transplantation. Among the 11 who completed the protocol, 45% were alive without tumor recurrence at a median follow-up of 7.5 years.

The high risk of recurrence of cholangiocarcinoma after transplantation precludes recommending this procedure as a routine treatment for biliary tract tumors. That said, it seems reasonable to consider liver transplantation for patients with cholangiocarcinomas less than 1 cm.[11,18,19]

**Palliative Treatment**

**Biliary Decompression**

Malignant biliary obstruction results in much of the morbidity of biliary tract and gallbladder carcinomas. Relief of biliary obstruction palliates symptoms including jaundice and associated pruritis, pain, and weight loss. Quality-of-life parameters have been evaluated in 50 patients undergoing endoscopic biliary drainage for malignant biliary obstruction. Weight loss and hyperbilirubinemia were strongly predictive of poor quality of life.[20] Successful biliary drainage was associated with improvement in quality of life, although less so in those with baseline bilirubin over 13 mg/dL. Patients with malignant biliary tract obstruction attain significant improvement in emotional, cognitive, and global health scores after endoscopic stent placement.[21] Biliary decompression can be achieved with equivalent efficacy by operative biliary-enteric bypass or endoscopic or percutaneous stenting of the biliary tree.[22,23] Surgical decompression is recommended during an unsuccessful attempt at curative resection or in patients in whom nonsurgical decompression is not feasible. Self-expanding metallic stents produce a longer duration of patency—8 to 10 months, compared with 4 to 5 months using polyethylene endoprostheses.[24] Survival expectations may therefore be used to guide stent selection. Reoccclusion is usually secondary to tumor ingrowth or sludging.[25]

With improvement in radiologic techniques, the results of percutaneous stenting are as good if not superior to endoscopic stenting.[26] Percutaneous procedures may be preferable in type II-IV hilar cholangiocarcinomas, as endoscopic drainage in these cases is often difficult and results in high rates of cholangitis due to inadequate drainage.[27,28]

To improve the duration of stent patency and overall survival, adjuvant radiation and chemotherapy has been tried. In a study in 32 patients, intraluminal brachytherapy with iridium (Ir)-192 along with stent insertion was found to yield 2-year survival rates of up to 27% in those with Klatskin's tumor and up to 50% in those with carcinoma of the ampulla of Vater, along with a stent patency duration of more than 1 year.[29] Another study in 22 patients had similar results, with mean stent patency duration of 19.5 months after treatment with Ir-192.[30] The significance of these findings is unclear given the potential patient selection bias associated with small sample size.

**Palliative Chemotherapy**

Patients with cholangiocarcinoma or gallbladder carcinoma typically present late in the course of their disease and often are not candidates for curative surgical resection. In cases where surgical intervention is not warranted, palliative chemotherapy has been used to diminish symptoms and possibly to extend survival. Only one large randomized trial has addressed the role of palliative chemotherapy in advanced biliary tract cancer. Glimelius et al randomized patients with pancreatic cancer and biliary tract cancer to a regimen of 5-FU/leucovorin with or without etoposide, or best supportive care, and evaluated these strategies for disease response and quality-of-life indicators. Of 90 enrolled patients, 37 had advanced biliary tract carcinoma. Marked although short-term improvements in survival (6.5 vs 2.5 mo) and quality of life (measured with the European Organization for Research and Treatment of Cancer [EORTC] QLQ-C30 instrument) were noted in the treatment group, establishing a role for
Several phase I and II trials, as well as numerous case and series reports, have assessed the efficacy and toxicity profiles of various chemotherapy regimens in the palliative treatment of biliary tract tumors. A variety of single-agent and multiagent chemotherapy regimens have yielded modest results in palliating patients with advanced carcinomas. Response rates have ranged from 0% to 47%. No consensus has been reached regarding standard of care.

Many drugs including 5-FU/leucovorin, cisplatin, oxaliplatin (Eloxatin), carboplatin (Paraplatin), mitomycin C (Mutamycin), doxorubicin, interferon-alpha 2b (Intron A), gemcitabine (Gemzar), epirubicin (Ellence), capecitabine (Xeloda), irinotecan (Camptosar), and docetaxel (Taxotere) continue to be evaluated alone and in combination for the treatment of advanced biliary cancer. While the results of these phase II trials do not permit conclusive recommendations for a particular regimen, they do indicate that progression of advanced carcinoma of the biliary tract can in many cases be temporarily controlled. Partial responses consistently ranging from 10% to 30% and disease stabilization rates from 10% to 50%, as well as improving median time to progression and median overall survival time, indicate that investigation of palliative treatment warrants continued attention. This section summarizes recent phase I and II trials in the management of biliary tract tumors. Small sample sizes in each trial and the small number of trials preclude the development of statistically significant findings in cross-study analyses. Furthermore, studies seldom examine identical dosing and delivery schedules, making cross-study comparison difficult. However, analyzing the results of these trials can provide guidance in the clinical management of patients and suggest new avenues for investigation.

**5-FU/Leucovorin**

Either in combination or as a single agent, 5-FU has been used in the management of biliary carcinomas for almost 30 years. Single-agent studies have met with variable success. From 1974 to 1994, four small studies (enrolling between 7 and 30 patients) investigated the efficacy of singleagent 5-FU. Response rates ranged from 0% to 24% in a total of 78 patients.[31]

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Table 3 summarizes the results of the Glimelius et al randomized trial and three additional 5-FU/leucovorin trials.[32-35] Response rates in these trials appear better than those reported for 5-FU alone.[32] The toxicity of 5-FU/leucovorin regimens is tolerable and easily managed. Grade 3/4 toxicities have included mucositis, diarrhea, hematologic toxicity, asthenia, and abdominal pain.

**5-FU Combination Regimens**

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<th>Fluorouracil Combination Regimens</th>
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Given the poor responses with 5-FU/leucovorin alone, investigators have evaluated 5-FU-based combinations in a number of phase I and II clinical trials. These trials are summarized in Table 4.[36-47] Outcomes have been mixed, with partial response rates ranging between 0% and 64% and disease stabilization rates from 0% to 50%. Complete responses have been rare. Reported median time to progression ranges from 3 to 10 months, while reported median survival ranges from 5 to 32 months.
**5-FU and Mitomycin**—Single-agent mitomycin has been used in several trials, with response rates ranging from 0% to 47%.[31] The FAM regimen (5-FU, doxorubicin [Adriamycin], mitomycin) demonstrated a disease control rate (complete and partial responses plus disease stabilization) of 81%.[36] Unfortunately, other mitomycin-based trials have shown unacceptable toxicity. A trial of mitomycin, 10 mg/m² every 8 weeks, together with weekly 5-FU at 2,600 mg/m² plus leucovorin at 150 mg/m² was stopped after treatment-related deaths exceeded 10% in the first 25 patients.[48] Given the potential toxicity of mitomycin and the availability of other agents, further investigation of mitomycin regimens is probably not warranted.

**5-FU and Platinum**—Cisplatin has minimal activity as a single agent against biliary tract carcinomas.[31] The combination of 5-FU and cisplatin has been assessed in several trials with variable success. An overall response rate of 24% was attained in a 25-patient trial evaluating 5-FU, 1,000 mg/m² intravenous infusion daily for 5 days, plus a 1-hour infusion of cisplatin, 100 mg/m² on day 2.[37] The PIAF regimen (cisplatin, interferon alfa-2b, doxorubicin, 5-FU) produced response rates of 35% and 9.5% in 19 gallbladder carcinoma patients and 22 cholangiocarcinoma patients, respectively. Although the median survival of 14 months was encouraging, the significant toxicity profile of PIAF, which included grade 3/4 neutropenia (41%), nausea and vomiting (34%), thrombocytopenia (20%), and anemia (15%), precludes future use.[38] In addition, it is impossible to discern the contribution, if any, of interferon in this regimen.

**Gemcitabine as a Single Agent**

**TABLE 5**

| Trials of Gemcitabine as a Single Agent |

Gemcitabine is a deoxycytidine analog related to cytarabine with demonstrated success in the palliative treatment of patients with advanced pancreatic cancer.[49] Hence, clinical investigators were eager to develop this agent in the treatment of biliary tract neoplasms. A number of small clinical trials summarized in Table 5 have examined the palliative effects of gemcitabine on biliary tract carcinomas.[42,50-57]

In general, gemcitabine therapy has produced moderate disease-control rates, time to progression, and median survival. These trials have shown objective response rates up to 60%, with disease-control rates ranging from 50% to 93%.[42,57,58] Clinical benefit with relief of tumor-related symptoms and weight gain has also been attained in more than 60% of evaluable patients.[51,52] A unique schedule consisting of larger gemcitabine doses (2,200 mg/m² as a 30-minute infusion every 2 weeks for 6 months) was administered to 30 patients with biliary tract tumors. The partial response and disease stabilization rates were 22% and 44%, respectively. Median time to progression and median overall survival were 5.6 and 11.5 months.[57] The tolerance was excellent, with minimal myelosupression despite the increase in dosage. These results with gemcitabine are comparable to, or better than, those achieved with 5-FU/leucovorin. Single-agent gemcitabine treatments are remarkably well tolerated and result in encouraging progression-free and overall survivals. Grade 3/4 hematologic toxicity is rarely observed, with thrombocytopenia the most common event, affecting 0% to 18% of patients.

**Gemcitabine in Combination Regimens**

**TABLE 6**
Trials of Gemcitabine in Combination Regimens

Table 6 summarizes the dosing schedules and outcomes of 12 phase II trials of gemcitabine-based combinations.[55,59-73] Gemcitabine has been combined with 5-FU, docetaxel, irinotecan, cisplatin, and capecitabine. The efficacy of combination treatments has varied, but some of these phase II trials have shown encouraging activity as compared with single-agent gemcitabine. Several of these trials have been associated with improved survival outcomes of 11 months. However, in order for these regimens to be acceptable in clinical practice, they need to demonstrate tolerable toxicity profiles and reproducible survival benefits.

**Gemcitabine and Cisplatin**—Gemcitabine/cisplatin regimens have been well tolerated with few grade 4 toxicities. Response rates have ranged from 47.6% to 57% and disease stabilization rates from 28% to 41%.[60-62] The efficacy of this combination needs to be further assessed in larger randomized trials.

**Gemcitabine and Capecitabine**—Single-agent capecitabine at a dosage of 2,000 mg/m²/d has been evaluated in a study of 26 patients with biliary and gallbladder cancers.[74] A 50% response rate and 1-year overall survival rate of 70% was attained. These encouraging outcomes prompted studies of capecitabine-based combination regimens. In one such trial, gemcitabine at 1,000 mg/m² on days 1 and 8 and capecitabine at 650 mg/m² po bid on days 1 to 14 was administered every 21 days.[63] Of 15 patients assessable for response, 33% attained a partial response and 33% had stable disease. The regimen was well tolerated, with less than 5% of patients developing grade 3/4 toxicity.

**Gemcitabine and Irinotecan**—The combination of gemcitabine at 1,000 mg/m² and irinotecan at 100 mg/m² on days 1 and 8 every 21 days has been evaluated in a small trial including 13 patients.[64] Objective responses were observed in 18.2% of patients, with stable disease in 54.5%. Grade 3/4 toxicities were rare and tolerable. The regimen appears to be feasible in the treatment of biliary cancers, but it is not clear whether irinotecan adds appreciably to treatment with gemcitabine alone.[64]

**Gemcitabine and 5-FU**—Two trials have examined the efficacy of gemcitabine/ 5-FU combinations for the treatment of biliary tract tumors. Gemcitabine at 1,000 mg/m² followed by 5-FU at 500 mg/m² once a week for 3 weeks on a 4-week cycle has been evaluated in nine patients; three experienced a partial response.[59] Gemcitabine at 1,000 mg/m² in combination with 5-FU/leucovorin has been evaluated in 42 patients.[65] Patients were treated on days 1, 8, and 15 of 4-week cycles, and partial responses were attained in 9.5% of patients. Median time to progression and median overall survival were 3.8 and 6.8 months, respectively. The combination was well tolerated, with few grade 3/4 toxicities. Based on these data, however, the combination of 5-FU and gemcitabine appears to have little benefit.

**Gemcitabine and Docetaxel**—On the basis of the activity and safety profile of gemcitabine plus docetaxel in non-small-cell lung cancer, a phase II study of this combination administered weekly was conducted in 43 patients with unresectable biliary tract cancers.[66] A 9% partial response rate, 53% disease stabilization, and median overall survival of 11 months were attained with this well tolerated combination. The regimen is undergoing further investigation in a randomized multicenter study.

**Gemcitabine, 5-FU/Leucovorin, Irinotecan, and Cisplatin**—The novel combination known as G-FLIP (gemcitabine, 5-FU bolus plus infusion, leucovorin, irinotecan, and cisplatin [Platinol]) makes use of clinical evidence of known sequence-dependent synergy among these four drugs, while
avoiding known sequence-dependent toxicity.[75] A phase I study included five patients with gallbladder cancer; three achieved a partial response.[67] The regimen was well tolerated, with largely hematologic toxicities consisting of anemia (9%), thrombocytopenia (9%), neutropenia (19%), and neutropenic fever (14%). These results require further evaluation in a phase II study in gallbladder cancer patients.

Other Gemcitabine-Based Combinations—Some multidrug combinations, especially those with cisplatin and gemcitabine, show improved activity compared with single-agent gemcitabine. Most combinations have been well tolerated and have produced improved response rates, but survival outcomes from randomized multicenter trials are lacking. Thus, while activity and survival outcomes are encouraging, definite confirmatory randomized trials are warranted before they can be recommended outside of a clinical trial.

New Anticancer Agents

TABLE 7

New Anticancer Agents Being Studied in Advanced Biliary and Gallbladder Cancers

Table 7 shows the results of clinical trials with several new anticancer agents being studied in advanced biliary and gallbladder cancers.[74,76-78] Dowlati et al reported an 11.1% partial response and 33.3% disease stabilization in 27 patients treated with the antitumor antibiotic rebeccamycin analog.[76] Rebeccamycin analog has both topoisomerase I and II activity and DNA intercalating properties. The 6-month survival rate in this study was 76%, with a median survival of 10 months. Grade 3/4 toxicity consisted of neutropenia (52%), thrombocytopenia and anemia (28%), and neutropenic fever (11.1%).[76]

An ongoing study by Philip et al involves 30 patients with advanced biliary carcinoma being treated with the epidermal growth factor receptor inhibitor erlotinib (Tarceva). To date, only toxicity data are available and only 4% grade 3/4 toxicity with nausea/vomiting has been noted. Efficacy data are pending.[77]

Ueno et al recently reported preliminary data on the use of S-1 in 19 patients with advanced biliary and gallbladder cancers.[78] S-1 is a new oral anticancer agent that contains tegafur (a prodrug of 5-FU), 5-chloro-2,4-dihydroxypyridine (dihydropyrimidine dehydrogenase inhibitor), and potassium oxonate (orotate phosphoribosyl transferase inhibitor). A total of 21% of patients treated with 40 mg/m² bid for 28 consecutive days in 6-week cycles experienced a partial response and 47.4% had disease stabilization, with few grade 3/4 toxicities. Median overall survival was over 8 months. S-1 seems to be well tolerated and active in this disease and will be examined in a larger phase II trial.

Conclusions

Complete surgical resection is the only hope for cure in both gallbladder and cholangiocarcinomas. While a simple cholecystectomy is usually curative for T1 gallbladder tumors, radical cholecystectomy is required for T2 and more invasive lesions. Radical resection should be considered for stage I-III gallbladder carcinomas. Complete tumor resection for cholangiocarcinoma, including partial hepatectomy for hilar carcinomas, is necessary to achieve long-term survival.

Adjuvant radiotherapy with or without concurrent 5-FU and mitomycin may improve survival, especially in gallbladder tumors resected with microscopic residual disease. Large randomized prospective studies on the use of adjuvant therapy are lacking, and any recommendations are based on small studies and metaanalyses. Liver transplantation can provide long-term survivals for cholangiocarcinomas less than 1 cm in diameter but cannot be recommended routinely for all biliary tract tumors due to the high rate of recurrence and postoperative mortality. Although advances in imaging techniques have improved preoperative diagnosis, most patients are diagnosed late and are not candidates for curative resection. Palliation in these patients includes relief of biliary obstruction with endoscopic or percutaneous stent placement as well as palliative chemotherapy, which improves both survival and quality of life. Gemcitabine probably offers the most favorable single-agent profile with respect to disease response and toxicity. Trials of gemcitabine/cisplatin combinations offer encouraging results and a tolerable toxicity profile. Other
combinations including gemcitabine plus capetibabine or docetaxel seem promising but await confirmatory data from larger trials. Until conclusive disease-specific phase III data become available, single-agent therapy with gemcitabine is a reasonable standard of care for palliation of biliary tract tumors.

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