Optimal & Ideal Drainage of Hilar Cancer:
Palliative Therapy for Better Drainage

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Cholangiocarcinoma arises from the ductal epithelium of the biliary tree. It is one of the most lethal cancers defying long-term control of disease. Cholangiocarcinomas arising from ductular epithelium within the liver are called as intrahepatic cholangiocarcinoma, while cholangiocarcinomas arising from ductal epithelium of extrahepatic bile ducts are extrahepatic cholangiocarcinoma. Hilar cholangiocarcinoma (Klatskin tumor) which occur at the confluence of right and left hepatic ducts are getting special attention for these tumors are especially difficult to manage, bear technical challenge in palliative drainage, and have worse prognosis than other cholangiocarcinomas. Though surgical resection has been the only option for cure, radical resection rate in hilar cholangiocarcinoma is as low as 10-15% due to frequent intrahepatic spread along bile ducts. In those patients with unresectable hilar cholangiocarcinoma, liver failure and recurrent sepsis secondary to biliary obstruction occupy substantial proportion of cause of death.

For patients with unresectable hilar cholangiocarcinoma and obstructive jaundice, palliative treatment is mandatory to improve quality of life. Relief of biliary obstruction is one of the main options, and aims to relieve jaundice, decrease pain and pruritus, and prevent cholangitis and sepsis. Relief of jaundice improves quality of life as well as survival by preventing liver failure. Effective palliative drainage is obtained by endoscopic stent placement and percutaneous transhepatic biliary drainage. Although effective biliary drainage has been made, hilar obstruction, unlike distal biliary obstruction, often resists long-term patency. Bilateral hepatic duct obstruction and more often obstruction of secondary branch add the difficulty of effective long-term biliary drainage. Considering that the median survival of patients with advanced hilar cancer is 7-8 months, current practice of endoscopic or percutaneous drainage is not enough to maintain biliary patency for the remaining life. Further treatment to provide better biliary drainage and prolong biliary patency is additional option for these patients. Additional treatment includes systemic chemotherapy, radiation therapy, and photodynamic therapy. All of these are aimed to decrease tumor volume, thus preventing tumoral ingrowth or overgrowth into the established stents.

Chemotherapy
The low-resection rate and high recurrence after surgery render most patients with hilar cholangiocarcinoma as potential candidates for systemic chemotherapy. The role of systemic chemotherapy in the palliation of cholangiocarcinoma is not defined yet. Despite the poor response rate of cholangiocarcinoma to chemotherapy, systemic chemotherapy remains as the only viable anticancer treatment option in large proportion of the patients during the course of the disease.

Patients having locally advanced or metastatic disease are candidates for palliative systemic chemotherapy. So far, no single agent or combination regimen has achieved significant survival advantage. During the period of 70s through 90s, 5-fluorouracil and mitomycin have been the main chemotherapeutic agents for cholangiocarcinoma. Though earlier studies reported encouraging response rate of 47% with single agent MMC chemotherapy in biliary cancer, later studies could not reproduce comparable outcomes. In an EORTC trial of MMC for advanced biliary tract cancers, the objective response rate was only 10% in 30 patients. Subsequent phase I or II studies were carried out using 5-fluorouracil alone or in combination with other agents reported similar outcomes.

Most of the clinical trials of chemotherapy for biliary tract cancers were carried out in the form of phase I or II single-armed regimen in a small number of patients. Thus any single trial was not large enough to draw meaningful conclusion. This limitation attributes to the relative rarity of biliary tract cancer. Moreover, majority of the patients with biliary tract cancers are not suitable for systemic chemotherapy due to their medical condition such as obstructive jaundice, cholangitis, and deranged liver function.
In those patients with biliary obstruction and cholangitis, adequate palliative biliary drainage holds the first priority.

Newer agents developed in late 90s and early 2000s include oral 5-fluorouracil such as capecitabine and S-1, taxane, CPT11, and gemcitabine. Uracil-tegafur, capecitabine, and S-1 belong to oral 5-fluorouracil prodrugs and have been evaluated in advanced biliary tract cancers. Uracil-tegafur, when administrated with leucovorin, achieved 14% of tumor response rate with median survival of 5 months in 14 patients.1 Capcitabine possesses relative tumor selectivity, producing 125 times higher concentration in tumor cells than normal cells. In 18 patients with cholangiocarcinoma, capcitabine stabilized tumor in 28% with a partial response rate of 6% and a median survival of 8.1 months.2 When combined with cisplatin, capcitabine produced an overall response rate of 21.4% and a median survival of 9.1 months.3 S1 also has been tried in 19 patients and achieved a response rate of 21.1% and a median survival of 8.3 months.4 Taxanes such as paclitaxel and docetaxel seem to have minimal activity against biliary tract cancer.5 Likewise, irinotecan, a topoisomerase inhibitor exerted minimal activity with a response rate of 8% in 36 patients with biliary tract cancer.6

The most promising anticancer drug for cholangiocarcinoma is gemcitabine which has showed obvious response in patients with pancreatic cancer. In a series of single agent chemotherapy with gemcitabine in patients with biliary tract cancer, overall response rate has been reported to be around 30% (8-60%) with a median survival of 10 months.7 Clinical trials of gemcitabine-based combination chemotherapy also revealed variable results with overall response rates in the range of 27.5-50% and median survival rates in the range of 5-11.3 months.8 Compared to gemcitabine alone, gemcitabine-based combination chemotherapy achieved slightly better or similar response. Cisplatin was one of the most commonly combined drugs with gemcitabine and produced overall response rates of 27.5-50% and median survival of 5-11.3 months. When capcitabine was combined with gemcitabine, it was well-tolerated in patients with deranged liver function and showed 30% of overall response rate.9 Oxaliplatin, when combine with gemcitabine, also achieved similar response rate of 35.5%.10 Available data are still lacking to determine the role of adjuvant chemotherapy alone in patients with biliary tract cancers. Likewise systemic chemotherapy for advanced biliary tract cancers, most studies of adjuvant setting are small, retrospective, and single-centered. In a recent trial relative large number of 139 patients were randomly assigned as surgery alone and surgery plus adjuvant chemotherapy using 5-fluorouracil and mitomycin. There was no difference in the rate of lymph node involvement. According to the results, there was no difference in survival rate, survival time, and recurrence rate between surgery alone and adjuvant group.

**Targeted Therapy**

The idea that tumor growth is absolutely dependent on tumor vessel formation for its nutritional support has been the basis for development of therapeutic agent targeting tumor vessel for anti-angiogenic therapy. The VEGF and VEGF receptor families comprise several members and play pivotal role in both physiologic and pathologic angiogenesis. Among VEGF, VEGF-A which binds to both VEGFR-1 and -2 plays a key role in angiogenesis and is frequently over-expressed in a variety of tumors. The level VEGF expression has positive correlation with disease progression and metastasis, and has inverse correlation with patients’ survival and prognosis.

The bevacizumab, a well-known anti-VEGF antibody, has been tried for cholangiocarcinoma in combination with other agents or radiation therapy. In a phase II trial, combination of bevacizumab with gemcitabine and oxaliplatin produced 45% PR and 34% SD with median progression free survival 7 months and overall survival 13.2 months.11 Some of the studies are still ongoing. The soraﬁnib is an oral multi-kinase inhibitor and targets Raf kinase, VEGFR-2, 3 kinase, and PDGFR. An interim analysis of an ongoing trial of soraﬁnib for biliary tract cancer revealed that soraﬁnib was well tolerated and produced 6% PR and 29% SD.12 AZD2171 is a small molecule with pan-VEGFR-tyrosine kinase inhibiting activity for VEGFR-2 and -3, PD-GFR-β and c-Kit. Currently, phase I trial is being investigated.

Though some trials showed promising results, novel treatment strategies need further trials including combination with other targeting agents, chemotherapy, or radiation therapy.

Epidermal growth factor receptor (EGFR) plays a central role for tumor cell proliferation. This has been the rationale for developing targeted agents in the form of either monoclonal antibodies or small molecular tyrosine kinase inhibitors. Several clinical trials are ongoing to evaluate anti-EGFR therapy in patients with biliary tract cancer. Erlotinib monotherapy demonstrated 7% PR and 17% 6-month progression free survival.14 A phase II trial of combination of cetuximab and GEMOX demonstrated 63% RR, 8.3 months PFS, and 12.7 months median OS.15 Though several studies are still ongoing, anti-EGFR therapies seems to be effective in biliary tract cancers.
Lots of targeted agents have already been developed and more are under development. Their developments are rationalized by molecular changes found in cholangiocarcinomas by study on tumor biology. Strategies to target signals involved in carcinogenesis of cholangiocarcinomas include AKT/mTOR pathway, Ras/Raf/MAPK pathway, proteosomes, angiogenesis, and growth factor receptors. Some of the agents have very specific activity against certain molecules and some have broader activity inhibiting multiple kinases. The avalanche of targeted agents mandates clinical trials with rational strategies by combining these agents together or with chemotherapeutic drugs.

Radiation Therapy

Radiation therapy has been tried in patients with hilar cholangiocarcinoma in the form of external beam irradiation or intraluminal brachytherapy. Effective biliary decompression either by percutaneous or by endoscopic drainage is prerequisite before administration of radiation therapy, because unrelieved biliary obstruction may result in serious cholangitis and sepsis. Brachytherapy has theoretical advantage as it can provide high dose delivery to a well-defined volume while minimizing the exposure to adjacent normal tissue. Brachytherapy can be delivered either by intra-operative or percutaneous or endoscopic route. Only a few studies have utilized high dose rate (HDR) intraluminal brachytherapy (ILBT) for these patients. Some of studies have dealt with intraluminal brachytherapy as an adjunct to metal stent to prevent tumor ingrowth and prolong biliary patency in patients with advanced disease. Addition of intraluminal brachytherapy using Ir-192 to metallic stenting provides favorable outcome and is effective in preventing tumor ingrowth and prolonging biliary patency. In a retrospective study, biliary stenting plus external and intraluminal radiation therapy produced median survival of 10 months which was superior to 7 months of stenting alone. However the rarity of hilar tumor has precluded large clinical trials and there is no randomized trial comparing biliary drainage alone with biliary drainage and radiation therapy.

Photodynamic Therapy

PDT is based on the intravenous injection of photosensitizers which selectively accumulate in cancer cells, followed by delivery of light to kill tumor cells through activation of photosensitizers. PDT-induced anti-tumor effect is usually evident up to 5mm of depth. Unresectable hilar cholangiocarcinomas are indicated for PDT as a palliative treatment.

In a series of uncontrolled studies, the combination of PDT and biliary drainage has shown favorable results for the palliation in patients with nonresectable hilar cholangiocarcinoma. Two prospective randomized trials compared PDT and biliary stenting with biliary stenting alone. In both studies, exclusion criteria were porphyria, previous chemotheraphy or radiotherapy, recent use of photosensitizing or dermatotoxic drugs, prior insertion of metal stent, peritoneal carcinomatosis and diagnostic endoscopic retrograde choalngio-pancreatography (ERCP) more than 1 month previously. In the first trial, patients with large (>3 cm) advanced hilar tumors were included. Patients with successful biliary stenting were randomized as stenting alone or stenting plus PDT. Interim analysis revealed superior survival in PDT group (median survival 493 days vs 98 days, p<0.0001), necessitating premature termination of study. Biliary stenting and PDT group also demonstrated improved biliary drainage and better quality of life.

In the second trial, 32 patients with nonresectable bile duct cancer were randomized. In this study, Photosan-3 was used as photosensitizer instead of Photofrin. Median survival was 630 days with additional PDT and 210 days with biliary stenting alone (p=0.019). Infectious complications, however, were more often in PDT group, which was controllable by prolonged antibiotic coverage. In the majority of subsequent trials either carried out as a randomized comparison or single arm, PDT offered superior biliary drainage, quality of life, and survival. PDT can be applied in neoadjuvant setting to downstaging of unresectable tumor to resectable one.

PDT is still an evolving treatment. Earlier studies used sodium porfimer as a photosensitizer which was activated by 630 nm laser. The depth of laser penetration depends on wavelength, that is, the longer the wavelength the deeper the penetration into tissue. A newer photosensitizer, mTHPC has an absorption in the near-infrared spectrum (652 nm) thus induces deeper tumor necrosis. The formulation of photosensitizers can be modified by loading into nanoparticles such as liposome to enhance tumoral uptake. Currently, PDT is a viable option for palliation of unresectable hilar cholangiocarcinomas. Its application is being
REFERENCES