REVIEW

Systemic Therapy for Locally Advanced and Metastatic Cholangiocarcinoma

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Abstract

Cholangiocarcinoma, the typical bile duct epithelium neoplasm, is most commonly reported in the Northeast of Thailand. Surgical intervention is the only possible curative treatment in the early stage of disease. Unfortunately, most patients are advanced at the time of diagnosis and not appropriate for curative surgical treatment. The prognosis of advanced CCA is extremely poor and chemotherapy is the only approved treatment for this stage of disease. This article reviews the state-of-art chemotherapy for locally advanced or metastatic cholangiocarcinoma.

Keywords: Antineoplastic agents - bile duct neoplasms - liver neoplasms - systemic treatment

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Introduction

The only curative treatment for cholangiocarcinoma (CCA) is surgery. However, most of the tumors are too advanced to operate or already spread to other organs. These patients are classified as locally advanced/ metastatic diseases, which the prognosis is extremely poor. The overall survival usually does not exceed one year. Even though it is common in the northeastern part of Thailand, the worldwide incidence is low. As a result, data on treatment strategies, sizes of study population, and study design was limited and varied. Herein, we reviewed a systemic therapy in advanced CCA, mostly the intrahepatic type, for which curative surgery is not an option.

Does Chemotherapy Improve Overall Survival Rate in Advanced or Unresectable CCA?

The only phase III randomized study, which compared 5FU/LV to best supportive care, has resulted in the adoption of chemotherapy as the current standard of care (Glimelius et al., 1996). A combined total of 90 patients with CCA, gall bladder cancer, and pancreatic tumors were enrolled. Overall survival and quality-adjusted survival were statistically superior in the treatment arm (6 months vs. 2.5 months and 4 months vs. 1 month respectively; $p<0.01$ in both). Moreover, quality of life was statistically better in the chemotherapy group. Since then, no phase III randomized trial has ever been conducted but there are many phase II studies that identify the most effective agent for CCA. Noted that the study population was not only CCA patients.

What is/are the Most Effective Chemotherapeutic Agent(s)?

The most studied antineoplastic agents for CCA are 5-FU and gemcitabine. Both drugs were evaluated as a single agent and combination chemotherapy. The results are shown in Tables 1 and 2.

As the samples in phase II studies were small, and the characteristics of study population varied considerably, the response rate and the median survival time varied could not be compared directly. In general, the response rate from 5-FU or gemcitabine is less than 30% and the median overall survival is approximately 6-10 months. One-year survival is a rare event (Thongprasert, 2005).

What is the Standard Chemotherapy Regimen for CCA?

Since there was no randomized phase III trial in CCA, a pooled analysis of phase II studies was conducted in

Table 1. Studies of 5FU in Locally Advanced/Metastatic CCA

Study	Drug or Drug combination	No. of patients	Overall response (%)	Survival Median
Falkson et al., 1984	5-FU	30	10	26 weeks
Choi et al., 2000	5-FU/leucovorin	28	32	6 months
Gebbia et al., 1996	5-FU/leucovorin/hydroxyurea	30	30	8 months
Patt et al., 1996	5-FU/IFN alpha	32	34	12 months
Raderer et al., 1999	5-FU/leucovorin/mitomycin C	20	25	9.5 months
Ducreux et al., 1998	5-FU/cisplatin	25	24	10 months
Taieb et al., 2002	5-FU/leucovorin/cisplatin	29	34	9.5 months
Ellis et al., 1995	5-FU/epirubicin/cisplatin	20	40	11 months
Lee et al., 2004	5-FU/epirubicin/cisplatin	20	10	5 months

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2007. One hundred and four studies from 1985-2006 were included with the total number of 2,810 patients. Fifteen percent of studies were conducted between 1993 and1999, while the rest were conducted after 2000 (Eckel and Schmid, 2007). The mean study sample size was 25.1 (5-65) patients per study, which was a relatively small number. The overall response rate (ORR=Complete remission rate plus partial remission rate or CR+PR) from chemotherapy was 22.6% and when considering stable disease (SD) as one of the outcomes, the tumor control rate (TCR=CR+PR+SD) was 57.3%. Time to progression was 4.1 months and the median overall survival was 8.2 months.

Interestingly, the studies were then furthered classified to three groups. First, studies with low response rate (RR), identified by RR lesser than the lower limit of 95%CI of the pooled analysis. There were 22 studies in this group including the studies using taxanes, irinotecan, single agent gemcitabine, single agent 5-FU, novel agents and targeted therapy: erlotinib, lapatinib, exatecan, dolostatin, and lanreotide. The RR in this group was approximately below 10%. The second group was classified as middle RR group, of which the pooled analysis RR was 22.6%, and a high RR group, whose response rate was higher than the upper limit of 95%CI. This included the studies with gemcitabine/cisplatin, 5-FU/cisplatin, and single agent gemcitabine. Response rate in this group was more than 30%. There is a correlation between RR, TCR, TTP and overall survival. If the response rate increases 10%, the TTP will be 0.7 months longer and the overall survival was increased 0.6 month. And if the TTP increases for a month, the overall survival would be longer 1.3 months.

In the subgroup analysis, patients with gall bladder cancer responded to chemotherapy more than CCA patients significantly, with the RR of 35.5% compared with 17.7%, respectively. Nevertheless, the mean overall survival of gall bladder cancer patients was 7.2 months compared with 9.3 months in CCA patients.

A two-drug regimen was significantly better in RR, TCR, and TTP than single agent regimen. The overall survival also favored the two-drug regimen but only with marginal significance. When comparing a multi-drug regimen to the two-drug regimen, the latter was better in RR but the overall survival was not different. The multi-drug regimen was better in TCR and TTP than single agent and there was a trend to prolong overall survival (Table 3).

The effective chemotherapy regimen for CCA should be a two-drug regimen, which was significantly better than single agent. Adding the third agent did improve neither RR nor OS. Chemotherapeutic agents that produced the most responses were gemcitabine and platinum compounds, which significantly increased the RR than regimens without them. The important results from this study which answer the questions to which chemotherapy is the best for CCA are: 1) There was no difference in efficacy between single agent 5-FU and single agent gemcitabine. 2) Combination regimen: a. 5-FU/gemcitabine was better in RR than single agent 5-FU but the RR was lesser than gemcitabine/platinum. b. 5-FU/platinum was better in RR than single agent 5-FU without statistical significance. c. Gemcitabine/platinum was the regimen with the highest RR, significantly higher than 5-FU/gemcitabine (p value=0.013) and 5-FU/platinum (p value=0.011).

From this pooled analysis, there are three important agents in the treatment of CCA: 5-FU, gemcitabine, and platinum. There was no difference between single agent gemcitabine and single agent 5-FU. The two-drug regimen was preferred to single agent. The combination of platinum and gemcitabine was more effective than 5-FU plus platinum. Therefore, the best chemotherapy for CCA which should be considered the standard of

Table 2. Studies of Gemcitabine in Locally Advanced/Metastatic CCA

References	Drug and drugs combination	No. of patients rate	Overall response	Median survival
Arroyo et al., 2001	Gemcitabine 1000 mg/m^2/week x3 q 4 wks	39%	36 months	6.5
Gebbia et al., 2001	Gemcitabine 1000 mg/m^2/week x3 q 4 wks	18%	22 months	8
Raderer et al., 1999	Gemcitabine 1200 mg/m^2/week x3 q 4 wks	19%	16 months	6.5
Penz et al., 2001	Gemcitabine 2200 mg/m^2/week q 2 wks	32%	22 months	11.5
Gebbia et al., 2001	Gemcitabine/5-FU/leucovorin	22%	36 months	11
Carraro et al., 2001	Gemcitabine/cisplatin D1,8,15 q 4 weeks	11%	50 months	11.3
Thongprasert et al., 2005	Gemcitabine D1,8/cisplatin D1 q 3 weeks	40%	27.5 months	9
Andre et al., 2004	Gemcitabine/oxaliplatin q 2 weeks	33%	36 months	15.4
Bhargava et al., 2003	Gemcitabine/irinotecan D1,8 q 3 weeks	14%	14 months	NR
Knox et al., 2003	Gemcitabine D1,8/capecitabine D1-14 q 2 weeks	17%	33 months	NR

Table 3. A Comparison of Single Drug, 2-Drug Combinations, and 3 or More Drugs Combinations in Pooled Analysis

Comparison	RR (%), p value	TCR (%), p value	TTP (months), p value	OS (months), p value
2 drugs vs 1 drug	28.0 vs. 15.3, p=0.000	61.0 vs. 50.4, p=0.000	4.4 vs. 3.4, p=0.015	9.3 vs .7.5, p=0.061
≥3drugs vs 1 drug		58.9 vs. 50.4, p=0.028	5.3 vs. 3.4, p=0.016	9.0 vs. 7.5, p=0.086
≥3drugs vs 2 drugs	19.1 vs. 28.0, p=0.000			9.0 vs. 9.3, p=NS

Table 4. Summary of Phase III Randomized Controlled Trial in CCA

Reference	Comparison	No. of patients	TCR* (%), p value	TTP (months), p value, HR	OS (months), p value, HR
UK ABC 02	Gemcitabine/cisplatin vs gemcitabine	410	81.4vs71.8, p=0.049	8.0vs5.0, p<0.001, HR=0.63	11.7vs8.3, p<0.001, HR=0.70

care is gemcitabine plus platinum (cisplatin/carboplatin/oxaliplatin).

Important Phase III Randomized Controlled Trial in CCA

The recently published phase III UK ABC-02 trial (Valle et al., 2010) which compared single agent gemcitabine to the combination of gemcitabine and cisplatin has established the standard of care for biliary tract cancers at present. A total of 410 patients were enrolled with advanced inoperable intra- and extrahepatic cholangiocarcinoma (59%), gallbladder cancer (36%), and ampullary cancer (5%). This study demonstrated a significant benefit in time-to-progression and overall survival favoring gemcitabine/cisplatin arm (Table 4).

Targeted Agents

Since the effects of cytotoxic chemotherapies are limited in CCA, many new targeted agents are being actively investigated. Erlotinib, an oral tyrosine kinase inhibitor of epidermal growth factor receptor (EGFR), is one of the first studied agents. In a phase III randomized trial of 268 patients, there was a trend toward a PFS benefit from adding erlotinib to gemcitabine and oxaliplatin, but OS was not different at 9.5 months (Lee et al., 2012). Moreover, adding cetuximab, a monoclonal antibody to EGFR, to gemcitabine/oxaliplatin produced a 63% response rate in one phase II trial (Gruenberger et al., 2010). Because adding angiogenesis inhibitor to chemotherapy has improved overall survival in other cancers such as colon cancer, the investigators have added bevacizumab to gemcitabine and oxaliplatin in one phase II study. The median PFS and OS were 7.0 and 12.7 months (Zhu et al., 2010). Nevertheless, sorafenib, multiple tyrosine kinase inhibitors target both Raf kinase and vascular endothelial growth factor, did not result in a significant objective response rate as a first-line therapy for CCA (El-Khoueiry et al., 2007).

Many attempts have been made to optimize the use of combination targeted agents. One phase II study of erlotinib and bevacizumab showed promising result. The partial response was 12% from 53 patients and the OS was 9.9 months (Lubner et al., 2010). On the contrary, sorafenib combined with erlotinib as a first line for advanced CCA failed to demonstrate benefit in terms of response rate, PFS, and OS in a phase II study (El-Khoueiry et al., 2012).

Understanding the biology of biliary tract cancer will guide us to investigate more phase II trials and better use the new targeted therapies in the near future.

Conclusion

Palliative chemotherapy is considered the standard treatment for advanced/inoperable or metastatic CCA patients if the performance status is good and the biliary obstruction can be drained. The cytotoxic agents can prolong survival as compared with best supportive care. Evidences supported two-drug combination: gemcitabine/cisplatin as the standard of care. As of targeted agents, none has been demonstrated improved overall survival. Better understanding the pathways of the disease would improve the development of the new agents and the outcome of the disease.

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