

RESEARCH ARTICLE

Treatment Outcome of Palliative Chemotherapy in Inoperable Cholangiocarcinoma in Thailand

Kritiya Butthongkomvong^{1&}, Ekaphop Sirachainan^{2*}, Supattra Jhankumpha¹, Surang Kumdang¹, On-Usa Sukhontharot³

Abstract

Background: Cholangiocarcinoma is the most common cancer in males in Thailand. The outcome is poor although systemic chemotherapy has been used in attempts to improve disease control, quality of life and prolong survival in patient with unresectable and advanced disease. **Materials and Methods:** In this retrospective study the medical records of all patients diagnosed as having unresectable and metastatic cholangiocarcinoma and receiving systemic chemotherapy at Udonthani Cancer Hospital during January 2007 to December 2010 were reviewed. **Results:** Among the total of 105 patients, 21 received gemcitabine-based chemotherapy and 84 5FU-based chemotherapy. Most received platinum doublet regimens. 5FU-based regimens yielded an overall response rate (tumor control) of 23.8% and a median survival of 7.2 months while gemcitabine-based regimens yielded an overall response rate (tumor control) 19.1% and a median survival of 10.0 months. **Conclusions:** Tumor control and survival of patient with advanced cholangiocarcinoma treated with gemcitabine-based and 5FU-based chemotherapy do not markedly differ.

Keywords: Unresectable - inoperable - metastatic cholangiocarcinoma - chemotherapy - outcome

Asian Pacific J Cancer Prev, 14 (6), 3565-3568

Introduction

Cholangiocarcinoma arises from epithelial cells of the intrahepatic and extrahepatic bile ducts (de Groen et al., 1999; Murad et al., 2009). It is a rare cancer in United States and Europe (de Groen et al., 1999; Jemal et al., 2011), but common in Thailand. The reported incidence is one to two cases per 100,000 patients in United States (Murad et al., 2009; Siegel et al., 2012). In Thailand, it is a common cancer. Interestingly, it is the most common cancer in male and third common cancer in female. The reported incidence of primary liver cancer is 38.6 cases per 100,000 patients and remarkable, is highest in north and northeast of Thailand. More than 80% of primary liver cancer in Thailand is cholangiocarcinoma (Khuntikao, 2005; Khuhaprema et al., 2010; Sararat, 2010).

Although surgical resection is the only potential curative treatment, less than 25% of patients are successfully resectable at presentation and among these patients, relapse rate is obviously high (Khan et al., 2002; Thongprasert, 2005; Chaiwerawattana et al., 2011). Patients with unresectable and metastatic cholangiocarcinoma have a poor prognosis, with a median overall survival less than 1 year (Anderson et al., 2004; Yonemoto et al., 2007; Jongha et al., 2009).

Systemic chemotherapy has been used in an attempt to improve disease control, quality of life and prolong survival. Previous studies reported the results in limited

subjects consisting of a mixed bile duct cancers, gall bladder cancer, ampullary cancer and pancreatic cancer with elicited variable outcomes (Thongprasert, 2005; Hezel et al., 2008). Glimelius, et al demonstrated an improvement in quality of life and overall survival for patients treated with palliative chemotherapy compared with best supportive care. Overall survival was significantly longer in the chemotherapy group (median survival 6 vs. 2.5 month) (Glimelius et al., 1996).

5FU-based regimens have overall response rate ranging from 0-40% and a median survival ranging from 2-12 months. The combination of cisplatin with 5FU resulted in a response rate of 10-40% and median overall survival time somewhat better than 5FU alone (Thongprasert, 2005; Hezel et al., 2008).

Gemcitabine-based chemotherapy yield the overall response rate ranging from 8-50% with the median survival ranging from 5-15.4 months (Thongprasert, 2005; Thongprasert et al., 2005; Chaiyut et al., 2007; Hezel et al., 2008; Valle, 2009). According to the randomized controlled phase III trial (ABC-02 trial), gemcitabine in combination with cisplatin significantly improved the median overall survival over gemcitabine alone (11.7 vs. 8.1 months) in locally advanced and metastatic cholangiocarcinoma, gallbladder cancer, ampullary cancer (Valle et al., 2010).

To our knowledge, there is no randomized controlled trial demonstrated the efficacy of gemcitabine based

¹Medical Oncology Unit, ³Cancer Registry Unit, Udonthani Cancer Hospital, ²Medical Oncology Unit, Ramathibodi Hospital, Thailand &Equal contributors *For correspondence: raesr@mahidol.ac.th

over 5FU-based regimens in unresectable and metastatic cholangiocarcinoma.

In Udonthani Cancer Hospital, unresectable and metastatic cholangiocarcinoma patients were treated by systemic chemotherapy. Both gemcitabine based and 5FU-based regimens have been used. This study is the retrospective analysis of the treatment outcome of palliative chemotherapy in unresectable and inoperable cholangiocarcinoma at medical oncology unit, Udonthani Cancer Hospital during 2007-2010.

Materials and Methods

After approval by the institutional review board, the medical records of all patients, who were diagnosed unresectable and metastatic cholangiocarcinoma and treated by systemic chemotherapy at Udonthani Cancer Hospital from January 2007 through December 2010, were reviewed for patient characteristics, tumor response, time to disease progression, survival and toxicity of treatment. The data from total 105 patients were collected in this retrospective cohort study. The statistical analysis was performed using statistical software. Frequency and percentage were used for general data. The survival rate and time to progression were analyzed according to Kaplan-Meier methodology.

Treatment and dose modifications

In clinical practice at Udonthani Cancer Hospital from January 2007 through December 2010, all patients suspected of having cholangiocarcinoma with good performance status and organ functions, were undergone biopsy in order to verify the diagnosis. In addition, working up for staging was done. If the disease was surgical unresectable or metastatic, the patients would received systemic chemotherapy. Gemcitabine-based or 5FU-based regimens have been used depending on the drug cost affordability of patients. Gemcitabine-based regimens included gemcitabine single agent, gemcitabine plus cisplatin, gemcitabine plus carboplatin, gemcitabine plus capecitabine. 5FU-based regimens included 5FU plus cisplatin, 5FU plus carboplatin and 5FU plus leucovorin. During the course of chemotherapy, if patients developed renal impairment or electrolyte imbalance, cisplatin was switched to carboplatin. The dose of chemotherapy was reduced about 10-20% in subsequent cycles in the cases developed grade ≥ 3 neutropenia and thrombocytopenia in association with bleeding or febrile neutropenia. No further chemotherapy was given in patients with complete course (6 cycles) or progressive disease or unacceptable toxicity whichever came first. WHO criteria was applied to define the degree of treatment response.

Results

Patient characteristics

Demographic characteristics are listed in Table 1. Twenty one patients received gemcitabine-based regimens. 5FU-based regimen have been used in the rest eighty-four patients. The mean age of patients receiving gemcitabine-based and 5FU-based regimens were 55 years

(range 44-70) and 57 years (range 31-85), respectively. All patients had the baseline performance status 0-2 according to Eastern Cooperative Oncology Group (ECOG). Baseline patient characteristics were similar in both groups. The most common presenting symptom was abdominal pain. Majority of patients had intrahepatic cholangiocarcinoma and 80% had metastatic diseases at diagnosis 1 or 2 metastatic sites which were abdominal

Table 1. Patient Characteristics

Characteristic	Gemcitabine based (N=21)	5FU based (N=84)	P-value
Sex			0.63
Male	15 (71.43)	44 (52.38)	
Female	6 (28.57)	40 (47.62)	
Age (years)			0.65
Mean	55.71	57.46	
Range	44-70	31-85	
ECOG performance status -no. (%)			0.55
0	14 (66.67)	40 (47.62)	
1	7 (33.33)	40 (47.62)	
2	0	4 (4.76)	
3	0	0	
4	0	0	
Presenting symptom- N (%)			
Abdominal pain	19 (90.48)	63 (75.00)	0.47
Anorexia	2 (9.52)	24 (28.57)	0.72
Fever	1 (4.76)	4 (4.76)	0.57
Jaundice	1 (4.76)	3 (3.57)	0.98
Palpable mass	3 (14.29)	14 (16.67)	0.48
Others	0	17 (20.24)	-
Initial status -N (%)			0.87
Recurrence, locoregional	0	0	
Recurrence, distant metastasis	1 (4.76)	2 (2.38)	
Initial locally advanced	2 (9.52)	10 (11.90)	
Initial metastasis	18 (85.72)	72 (85.72)	
Primary tumor site - N (%)			0.08
Intrahepatic	20 (95.24)	74 (88.10)	
Extrahepatic	1 (4.76)	1 (1.19)	
Perihilar	0	9 (10.71)	
Mixed	0	0	
Metastatic site - N (%)			
Lung	5 (23.81)	18 (21.43)	0.53
Liver	9 (42.86)	30 (35.71)	0.47
Bone	0	6 (7.14)	-
Cervical LN	3 (14.29)	13 (15.48)	0.43
Abdominal LN	12 (57.14)	39 (46.43)	0.82
Peritoneum	2 (9.52)	7 (8.33)	0.42
Other	0	3(3.57)	-
Number of metastaticsite-no. (%)			0.29
0	2 (9.52)	10 (11.91)	
1	9 (42.86)	41 (48.81)	
2	8 (38.10)	25 (29.76)	
3	2 (9.52)	7 (8.33)	
4	0	1 (1.19)	
Histologic grade - N (%)			0.18
Well differentiated	10 (47.62)	24 (28.57)	
Moderately differentiated	3 (14.29)	16 (19.05)	
Poorly differentiated	2 (9.52)	9 (10.71)	
Unspecified	6 (28.57)	35 (41.67)	
Previous therapy -N (%)			0.99
No	17 (80.95)	70 (83.33)	
Yes	4 (19.05)	14 (16.67)	
Type of previous therapy -N (%)			-
Curative surgery	1 (4.76)	1(1.19)	
Palliative surgery/Bypass	2 (9.52)	8 (9.52)	
Laparotomy	1 (4.76)	3 (3.57)	
Biliary Stenting/Drainage	0	0	
Palliative Radiotherapy	0	2 (2.38)	
Adjuvant Chemotherapy	1 (4.76)	1 (1.19)	
Radiofrequency ablation	0	1 (1.19)	

lymph node and/or intrahepatic metastasis. All patients were chemotherapy treatment naive.

Treatment and response to treatment

Treatment and responses are listed in Table 2. In gemcitabine-based use, eighteen patients received gemcitabine plus cisplatin (85.71%). In 5FU-based use, 5FU plus cisplatin and 5FU plus carboplatin were used in sixty eight patients (80.78%). More than 80% of patients in both group received chemotherapy without dose or drug modification. Median number of chemotherapy was three cycles. Four patients (19.05%) in gemcitabine-based group achieved controlled disease (partial response and stable disease). Twenty patients (23.81%) in 5FU-based group achieved controlled disease (partial response and stable disease). None of the patient in both groups achieved clinically complete response.

Survival and time to progression

Of all 105 patients, 103 patients died. Notably, one patient who received 5FU-based chemotherapy was alive with disease progression. Unfortunately, there was no vital status of another one patient receiving gemcitabine-based chemotherapy. The one-year overall survival was 24.42% (95%-CI 16.66 to 33.00) with the median overall survival of 7.77 months (95%CI 6.46 to 9.08) as shown in Figure 1.

Table 2. Treatment and Response

Characteristics	Gemcitabine based (N=21)	5FU based (N=84)	P-value
	N (%)	N (%)	
Gemcitabine-based regimens			
Gemcitabine/Cisplatin	18 (85.71)		
Gemcitabine/Capecitabine	2 (9.52)		
Gemcitabine weekly	1 (4.76)		
5FU-based regimens			
5FU/leucovorin		16 (19.05)	
5FU/cisplatin		57 (67.86)	
5FU/carboplatin		11 (13.10)	
Dose modification			0.89
No	20 (95.24)	82 (97.62)	
Yes	1 (4.76)	2 (2.38)	
Drug modification*			0.92
No	17 (80.95)	80 (95.24)	
Yes	4 (19.05)	4 (4.76)	
Type of clinical reponse			0.15
Complete response (CR)	0	0	
Partial response (PR)	3 (14.29)	11 (13.10)	
Stable disease (SD)	1 (4.76)	9 (10.71)	
Progressive disease (PD)	12 (57.14)	54 (64.29)	
Loss to follow up	4 (19.05)	10 (11.90)	
Toxic death	1 (4.76)	0	
Number of chemotherapy cycle			0.84
1	3 (14.29)	13 (15.48)	
2	4 (19.05)	10 (11.90)	
3	4 (19.05)	22 (26.19)	
4	3 (14.29)	7 (8.33)	
5	1 (4.76)	7 (8.33)	
6	6 (28.57)	25 (29.76)	
Mean	3.62	3.71	
Cause of chemotherapy termination			0.73
Progressive disease	7 (33.33)	45 (53.37)	
Unacceptable toxicity	2 (9.52)	0	
Loss to follow up	5 (23.81)	12 (14.29)	
Complete treatment	7 (33.33)	27 (32.14)	

*Cisplatin was replaced by carboplatin

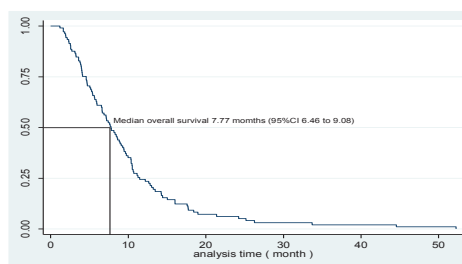


Figure 1. Overall Survival (months)

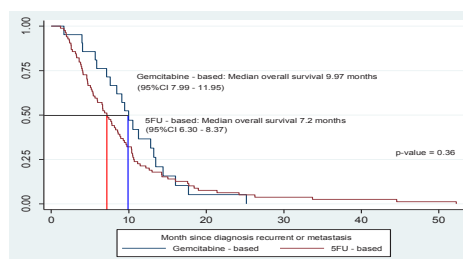


Figure 2. Overall Survival between Two Groups of Patients

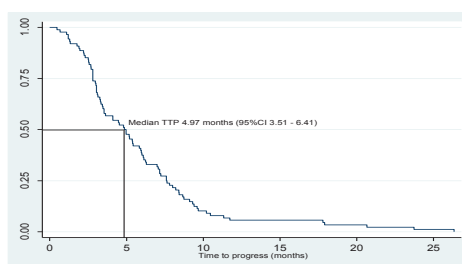


Figure 3. Time to Progression for All Patients

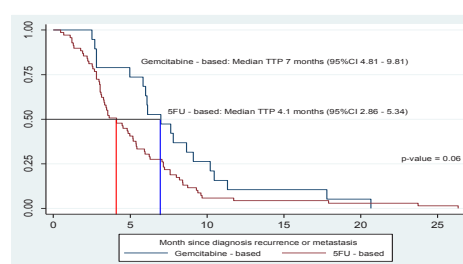


Figure 4. Time to Progression (TTP) between Two Groups of Patients

In gemcitabine-based chemotherapy, the median overall survival of these patients was 9.97 months (95%CI 7.99 to 11.95) and one year survival was 36.67% (95%CI 16.86 to 56.81). In 5FU-based patients, the median overall survival was 7.2 months (95%CI 6.03 to 8.37) and one year survival was 21.43% (95%CI 13.41 to 30.70) (Figure 2).

Median time to progression was 4.97 months (95%-CI 3.51 to 6.41) in all patients. In patients with gemcitabine-based chemotherapy, the median time to progression was 7 months (95%CI 4.81 to 9.18) while it was 4.1 months (95%CI 2.86 to 5.34) in patients receiving 5FU-based chemotherapy. Between two groups of patients, the median times to progression were not statistically significant (p=0.06) (Figure 3 and 4).

Toxicity

Toxicity data were shown in Table 3. There was one treatment-related death in a 55-years old woman with locally advanced disease receiving gemcitabine

Table 3. Toxicity

Adverse event	Gemcitabine based (N=21)		5FU based (N=84)	
	Grade 3,4	Grade 5	Grade 3,4	Grade 5
	N (%)	N (%)	N (%)	N (%)
Leukopenia	1 (4.76)	0	0	0
Anemia	1 (4.76)	0	2 (2.38)	0
Thrombocytopenia	2 (9.52)	0	0	0
Neutropenia	3 (14.29)	0	1 (1.19)	0
Mucositis	0	0	1 (1.19)	0
Vomiting	0	0	0	0
Increased creatinine	1 (4.76)	0	0	0
Infection without Neutropenia	0	0	1 (1.19)	0
Infection with Neutropenia	1 (4.76)	1(4.76)	0	0
Biliary sepsis	0	0	0	0
Hyponatremia	2 (9.52)	0	1(1.19)	0
Hypokalemia	1 (4.76)	0	0	0

*This table can not calculate P-value due to very small number in each parameter

plus cisplatin. After twenty two days of first cycle of chemotherapy, she developed the febrile neutropenia (absolute neutrophil count 570/mm³) complicated with septic shock, thrombocytopenia (platelet count 5,000/mm³), acute renal failure and electrolyte disturbance. She expired within 24 hour after admission. Myelosuppression and electrolyte disturbance were evidently observed in gemcitabine-based regimen.

Discussion

Cholangiocarcinoma has been the leading cancer in Thailand, especially in northern and northeastern regions (Khuntikao, 2005; Khuhaprema et al., 2010; Sararat, 2010). Generally, more than 80% of primary liver cancer in Thailand is cholangiocarcinoma. The treatment outcome in this biliary tract cancer is poor. Tumor removal is the main treatment modality. In general, patients with cholangiocarcinoma present with advanced disease which are basically beyond surgery. Chemotherapy was therefore given to probable cases of having cholangiocarcinoma. Unfortunately, there is no chemotherapy with approved superior efficacy. In addition, there has been limited numbers of studies in histologically verified patient. All patients included in this study were histologically confirmed. As of our recent knowledge, no randomized controlled trial demonstrated the efficacy of gemcitabine-based chemotherapy and 5FU-based regimens in unresectable and metastatic cholangiocarcinoma. Most previous data seem to elicit that gemcitabine-based may be superior than 5FU-based chemotherapy. In our study, four out of five patients have been treated with 5FU based regimen because of patients' affordability. The median overall survival of all our patients received chemotherapy was 7.77 months. It is slightly longer than historically data that showed 6 months overall survival while comparing with 2.5 months in best supportive care group (Glimelius et al., 1996).

In our study, majority of patients received 2 drugs. 5FU-based regimens achieved overall response rate (tumor control) 23.81% and a median survival 7.2 month. Gemcitabine-based regimens achieved overall response rate (tumor control) 19.05% and a median survival 9.97 month. All were identical to historical data (Thongprasert,

2005; Hezel et al., 2008). These survival data were not statistically different.

According to this retrospectively collected data, we are unable to draw any conclusion whether gemcitabine or 5FU-based regimens showed better efficacy in the treatment of unresectable or metastatic cholangiocarcinoma. With less cost, this 5FU-based chemotherapy may be efficient to treat advanced cholangiocarcinoma and an appropriate use in resource-limited country.

References

- Anderson CD, Wright PC, Berlin J, et al (2004). Diagnosis and treatment of cholangiocarcinoma. *Oncologist*, **9**, 43-57.
- Chaiwerawattana A, Sukarayodhin S, Karalak A, et al (2011). Screening, diagnosis and treatment of liver cancer and bile duct cancer. 2nd ed. National cancer Institute, Thailand
- Chaiyut C, Thongprasert S, Busyamas C, et al (2007). Experience with gemcitabine and cisplatin in the therapy of inoperable and metastatic cholangiocarcinoma. *World J Gastroenterol*, **13**, 2852-4.
- de Groen PC, Gores GJ, LaRusso NF, et al (1999). Biliary tract cancers. *N Engl J Med*, **341**, 1368-78.
- Glimelius B, Hoffman K, Sjoden P-O, et al (1996). Chemotherapy improves survival and quality of life in advanced pancreatic and biliary cancer. *Ann Oncol*, **7**, 593-600.
- Hezel AF, Zhu AX (2008). Systemic therapy for biliary tract cancers. *Oncologist*, **13**, 415-23.
- Jemal A, Bray F, Center MM, et al (2011). Global cancer statistics. *CA Cancer J Clin*, **61**, 69-90.
- Jongha P, Myung-Hwan K, Kyu-pyo Kim, et al (2009). Natural history and prognostic factors of advanced cholangiocarcinoma without surgery, chemotherapy, or radiotherapy: a large-scale observational study. *Gut Liver*, **3**, 298-305.
- Khan SA, Davidson BR, Goldin R, et al (2002). Guidelines for the diagnosis and treatment of cholangiocarcinoma: consensus document. *Gut*, **51**, 1-9.
- Khuhaprema T, Srivatanakul P, Attasara P, et al (2010). Cancer incidence in Thailand, liver and bile duct. *Cancer in Thailand*, **5**, 31-4
- Khuntikao N (2005). Current concept in management of cholangiocarcinoma. *Srinagarind Med J*, **20**, 143-9.
- Murad A, Mark JW, Michele M (2009). Advances in diagnosis, treatment and palliation of cholangiocarcinoma: 1990-2009. *World J Gastroenterol*, **15**, 4240-62.
- Sararat C (2010). Hospital based cancer registry 2009. Cancer registry unit, Udonthani cancer center, Thailand
- Siegel R, Naishadham D, Jemal A (2012). Cancer statistics, 2012. *CA Cancer J Clin*, **62**, 10-29.
- Thongprasert S (2005). The role of chemotherapy in cholangiocarcinoma. *Ann Oncol*, **16**, 93-6.
- Thongprasert S, Napapan S, Charoentum C, et al (2005). Phase II study of gemcitabine and cisplatin as first-line chemotherapy in inoperable biliary tract carcinoma. *Ann Oncol*, **16**, 279-81.
- Valle J, Wasan H, John E, et al (2009). Gemcitabine alone or in combination with cisplatin in patients with advanced or metastatic cholangiocarcinomas or other biliary tract tumours: a multicentre randomised phase II study – The UK ABC-01 Study. *Br J Cancer*, **101**, 621-7.
- Valle J, Wasan H, Palmer DH, et al (2010). Cisplatin plus gemcitabine versus gemcitabine for biliary tract cancer. *N Engl J Med*, **362**, 1273-81.
- Yonemoto N, Furuse J, Okusaka T, et al (2007). A multi-center retrospective analysis of survival benefits of chemotherapy for unresectable biliary tract cancer. *Jpn J Clin Oncol*, **37**, 843-51.