Original Article

Long term responders to palliative chemotherapy for advanced biliary tract cancer

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Background: Patients with advanced biliary tract cancer (BTC) are often treated with palliative chemotherapy (PC). Standard PC since 2010 is a cisplatin/gemcitabine doublet, with median overall survival (OS) of 11.7 months from the ABC-02 trial. Prior to this, our institutional standard was gemcitabine and fluoropyrimidine. The ABC-02 study used 8 cycles of PC as standard with treatment stopped even in the absence of disease progression, but some patients may benefit from continuing PC longer than 8 cycles.

Methods: Patients treated with at least 2 cycles of PC for advanced BTC in Princess Margaret Cancer Centre between 1987 and 2015 were included, and divided into 2 groups for analysis—long-term responders (LTR) who received 9 or more cycles, and controls (2–8 cycles). Data was collected on demographics, clinicopathological features, PC regimen, toxicities, and survival. The primary outcome measure was OS, with secondary analyses including progression-free survival (PFS) and toxicity rates between groups.

Results: A total of 382 patients were identified, 123 who met the criteria for LTR and 259 who were included as controls. The baseline demographic and clinical characteristics were similar, although more patients in the control group had gallbladder cancer or extrahepatic cholangiocarcinoma than LTR (P=0.024), and more patients in the LTR group were treated with combination chemotherapy regimens (93% *vs.* 82% in controls, P=0.003). The LTR patients had significantly longer PFS (median 13.3 *vs.* 4.1 months, P<0.001) and longer OS than controls (median 22.1 *vs.* 9.2 months, P<0.001). In LTR patients, 15% had a break from chemotherapy of 3 months or more and restarted the same regimen. The LTR patients reported higher rates of nausea, cutaneous and hematologic toxicity, but also more frequently went on to receive second-line chemotherapy (47% *vs.* 33%, P=0.007). In multivariable analysis of OS, LTR, good performance status and intrahepatic site of cancer were associated with better survival.

Conclusions: From this institutional dataset, a significant proportion of patients continued chemotherapy past 8 cycles, and appeared to derive benefit from longer duration of treatment. Toxicity rates were higher in this group, but manageable as evidenced by second-line treatment rates. Discontinuation of chemotherapy for reasons other than toxicity or progression may result in loss of disease control and impact survival in this population; these data suggest the use of continued chemotherapy to disease progression in patients with advanced BTC is a favorable option.

Keywords: Chemotherapy; cholangiocarcinoma; biliary tract cancer (BTC); metastatic; gallbladder cancer

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Introduction

Biliary tract cancer (BTC) encompasses tumors of the gallbladder, intrahepatic and extrahepatic bile ducts. These are rare cancers in most of the world, but significant regional variation in incidence exists with East Asia and Latin America reporting rates higher than international averages (1). Gallbladder cancer is falling in incidence worldwide, but rates of intrahepatic cholangiocarcinoma appear to be rising (2). Curative treatment relies upon surgical excision, but even those with localized disease have survival rates of 30% at 5 years from registry data (3). In patients with metastatic or locally advanced BTC, there has been limited progress in treatment. Early studies of chemotherapy demonstrated responses to 5-fluorouracil (5-FU) and gemcitabine, with response rates ranging from 10–30% (4,5). The combination of gemcitabine and capecitabine has also been studied, with median overall survival (OS) of 14 months in a phase II study (6). In recent years, the standard chemotherapy regimen for advanced BTC has consisted of cisplatin and gemcitabine, based on the results of the randomized phase III ABC-02 study which demonstrated superiority of this regimen with median OS of 11.7 months, compared with median OS of 8.1 months for gemcitabine alone. Progression-free survival (PFS) also favored the doublet over single agent (8 *vs.* 5 months) (7). There is no established second-line chemotherapy regimen in patients with progressive disease on palliative chemotherapy (PC), with studies to date reporting disappointing response rates less than 10% and median PFS times of approximately 3 months (8,9). In the ABC-02 study, patients were treated to 8 cycles of chemotherapy and then discontinued regardless of ongoing response. In clinical practice, patients responding to chemotherapy without significant toxicity often continue chemotherapy for additional cycles. There is a need to consider carefully the balance of quality of life and treatment toxicity with cancer control in the setting of palliative treatment. In breast cancer and lung cancer, there is evidence that continued palliative systemic therapy may impact on patient survival, but the same data are lacking in BTC (10,11).

The aim of this study was to review the clinical features and outcomes of patients who had longer than expected treatment with PC for BTC, and to compare these features and outcomes with other patients at our institution who were treated with PC. It was hypothesized that patients treated with 9 or more cycles would have better survival than those treated with fewer cycles, and that some clinical or demographic features may be identifiable to predict which patients derive greater benefit.

Methods

This retrospective study included patients treated with 2 or more cycles of PC for BTC at Princess Margaret Cancer Centre between 1987 and 2015. These data were collected as part of the institutional database of BTC patients, including all patients treated at Princess Margaret Cancer Centre. Included patients were required to have a pathological or cytological diagnosis of gallbladder carcinoma, intrahepatic or extrahepatic cholangiocarcinoma. Patients with mixed hepatocellular/cholangiocarcinoma were excluded, as were peri-ampullary cancers and those who discontinued chemotherapy after only one cycle. Institutional Review Board approval was obtained for the study (07-0376-CE).

The following baseline data were collected from the records of included patients: age, sex, date of diagnosis, primary tumor site (intrahepatic, hilar, distal bile duct, gallbladder), Eastern Cooperative Oncology Group (ECOG) performance status at diagnosis, symptoms at diagnosis (pain, jaundice, weight loss, nausea/vomiting), tumor stage, tumor grade and differentiation, history of definitive surgical resection, previous adjuvant chemotherapy, history of biliary stenting, date of recurrence, and pattern of recurrence. Data regarding PC were also collected: start and end date of PC, chemotherapy regimen, number of cycles, toxicities (neutropenia, thrombocytopenia, skin toxicity, nausea/vomiting, diarrhea, peripheral neuropathy, nephropathy, anemia), response to chemotherapy, reason for discontinuation, date of progression, and details of second-line chemotherapy (if used). Toxicities were not graded as per CTCAE, but recorded if considered clinically significant by the following measures: resulted in delay, dose reduction or discontinuation of chemotherapy, or required specific intervention (for example, transfusion for anemia).

Pathological and clinical staging was based on the seventh edition, American Joint Committee on Cancer Tumor Node Metastasis staging system, even for the earliest period in which tumors were retrospectively staged (12). Tumor regression was defined as any tumor shrinkage from baseline prior to commencement of chemotherapy as per radiology reporting. As most of these patients were treated outside of a clinical trial, formal response evaluation was not performed, but standard reporting followed RECIST

practice. Long term responders (LTR) were defined as those who had received 9 or more cycles of first-line PC, and those who had 2–8 cycles were included as a control group. No matching of cases and controls was performed as this was a retrospective study. Regarding chemotherapy regimens, the fluoropyrimidines 5-FU and capecitabine were used and these were grouped together for this analysis. Patients treated with selumetinib as an experimental agent with cisplatin and gemcitabine as part of a clinical trial were also included.

Patient demographics and clinical characteristics were summarized using descriptive methods, and differences between treatment groups at baseline were evaluated using Chi-square, Fisher's exact test and t-tests as appropriate. The two primary event outcomes were PFS and OS. PFS in this study was defined as time from start of PC to disease progression, as per treating physician or death from any cause. OS was defined as the time from start of PC to death from any cause. T Survival probabilities were estimated using the Kaplan-Meier method. Survival differences between groups were examined using log rank tests. Cox proportional hazard models were developed using relevant clinicopathological variables to determine the association of each with OS. Variables with a P<0.05 in univariable analysis were included in a multivariable model. Results were expressed as hazard ratios (HRs) with 95% confidence intervals (CIs). All tests were two-sided. A P value of <0.05 was considered statistically significant. Analyses were performed using SAS (Statistical Analysis System, version 9.4) and R 3.0.0.

Results

Patient characteristics

Between 1987 and 2015, a total of 1558 patients were identified as having been treated for BTC (all stages) at Princess Margaret Cancer Centre. Of these, 382 had 2 or more cycles of PC for advanced disease and were included in this study. Patients were divided into two groups for analysis: 123 patients who had 9 or more cycles of first-line chemotherapy (LTR), and 259 who had 2–8 cycles (controls). There were no significant differences in age, sex, period of diagnosis, presence of biliary stent, tumor grade or ECOG performance status at diagnosis (*Table 1*). There was a difference in distribution of patients across biliary cancer subtypes, with more patients in the LTR group with intrahepatic and hilar cholangiocarcinoma, and more distal bile duct and gallbladder cancers in the control group (P=0.024). More patients in the control group had previous definitive surgery before recurrence (39% *vs.* 26%, P=0.016), but rates of adjuvant chemotherapy and median time to recurrence after surgery in these patients were similar.

Details of treatment for advanced disease

Patients in the LTR group were more frequently treated with combination chemotherapy regimens than those in the control group (93% *vs.* 82%, respectively, P=0.003). In both groups, most patients were treated with either gemcitabine and cisplatin or gemcitabine and a fluoropyrimidine (capecitabine or 5-FU, *Table 2*). There was a difference in the distribution of chemotherapy regimens between groups, with more patients in the LTR group receiving fluoropyrimidine-gemcitabine combinations, and more patients in the control group treated with platinum-gemcitabine combinations (P=0.007). In the LTR group, the median number of chemotherapy cycles was 12 (range 9–47), compared with 4 in the control group (range 2–8, P<0.001). The reasons for stopping chemotherapy were not different between LTR and control groups: disease progression (radiological and/or clinical) was the commonest reason (56% and 58%), followed by planned discontinuation and toxicity. In both groups, 6% stopped due to other reasons. These included episodes of sepsis, surgical procedures and upper gastrointestinal hemorrhage. More frequent hematologic toxicity was observed in the LTR group than in controls, in the form of neutropenia (30% *vs.* 14%, P<0.001) and thrombocytopenia (26% *vs.* 17%, P=0.056, *Table 2*). There was also more frequent skin toxicity in this group (32% *vs.* 12%, P<0.001), which may relate to the increased proportion of patients treated with a fluoropyrimidine in the LTR group or from overall treatment exposure. In analysis of toxicity by chemotherapy regimen, there was a significantly higher rate of skin toxicity (34%) in patients treated with gemcitabine/fluoropyrimidine chemotherapy (34%) than other regimens (P<0.001, *Table S1*). In contrast, neuropathy and nephropathy were more common with gemcitabine/cisplatin chemotherapy, as expected (P=0.002 for both). In both groups, a small number of patients treated with combination regimens were changed to single agent chemotherapy—6 (5%) in the LTR group (at a median of 8 cycles) and 7 (3%) in the control group (at a median of 5 cycles). In the LTR group, 24 patients (20%) stopped first-line chemotherapy for 3 months or more, and restarted the

Table 1 Baseline characteristics and treatment details of included patients

Characteristic	All patients [N=382]	Long-term responders [N=123]	Controls [N=259]	P value
Median age [range]	62 [23-86]	61 [27-80]	62 [23-86]	0.15
Sex N, [%]				0.12
Female	173 [45]	63 [51]	110 [42]	
Male	209 [55]	60 [49]	149 [58]	
Year of diagnosis N, [%]				0.25
1987–2005	133 [35]	48 [39]	85 [33]	
2006–2015	249 [65]	75 [61]	174 [67]	
Site of Cancer N, [%]				0.024
Distal bile duct	71 [19]	13 [11]	58 [22]	
Gallbladder	104 [27]	31 [25]	73 [28]	
Intrahepatic bile duct	130 [34]	47 [38]	83 [32]	
Hilar	64 [17]	27 [22]	37 [14]	
Bile duct NOS	13 [3]	5 [4]	8 [3]	
Tumor grade[†]				0.33
Grade 1	49 [19]	18 [22]	31 [18]	
Grade 2	126 [50]	35 [43]	91 [53]	
Grade 3/4	77 [31]	28 [35]	49 [29]	
Missing	130	42	88	
ECOG performance status N, [%]				0.11
0–1	355 [94]	119 [97]	236 [92]	
2–3	24 [6]	4 [3]	20 [8]	
Missing	3	0	3	
Symptoms at diagnosis N, [%]				
Pain	197 [52]	64 [52]	133 [52]	0.99
Weight loss	153 [40]	47 [38]	106 [41]	0.66
Jaundice	179 [47]	56 [46]	123 [47]	0.74
Nausea/vomiting	43 [11]	6 [5]	37 [14]	0.006
Biliary stent insertion N, [%]	192 [50]	62 [50]	130 [50]	0.99
Definitive surgery N, [%]	110 [29]	26 [21]	84 [32]	0.029
Adjuvant chemotherapy* N, [%]	34 [31]	5 [19]	29 [35]	0.16
Median time to recurrence				0.60
Months, [range]	10.7 [1-110]	14.9 [1-100]	9.7 [1-110]	
Disease status at palliative chemotherapy				0.042
Locally advanced unresectable	50 [13]	21 [17]	29 [11]	
Metastatic	222 [58]	76 [62]	146 [56]	
Recurrence after prior surgery	110 [29]	26 [21]	84 [32]	

*, in patients with definitive surgery; [†], tumor grade as per WHO criteria. ECOG, Eastern Cooperative Oncology Group.

Table 2 Details of treatment for advanced disease

Characteristic	All patients [N=382]	Long-term responders [N=123]	Controls [N=259]	P value
First-line chemotherapy cycles				<0.001
Median [range]	6 [2-47]	12 [9-47]	4 [2-8]	
First-line chemotherapy regimen N, [%]				0.007
Fluoropyrimidine	11 [3]	9 [3]	2 [2]	
Gemcitabine- Fluoropyrimidine	156 [41]	93 [36]	63 [51]	
Gemcitabine-Platinum	155 [41]	109 [42]	46 [37]	
Gemcitabine-Platinum + Selumetinib	10 [3]	5 [2]	5 [4]	
Gemcitabine	43 [11]	37 [14]	6 [5]	
Other	7 [2]	6 [2]	1 [1]	
Radiographic response N, [%]				<0.001
Complete regression	3 [1]	3 [2]	0	
Partial regression	116 [32]	71 [59]	46 [19]	
Stable imaging	142 [40]	47 [39]	95 [40]	
Disease progression	97 [27]	0	96 [41]	
Missing	24	2	22	
Chemotherapy toxicity N, [%][†]				
Neutropenia	74 [19]	37 [30]	37 [14]	<0.001
Thrombocytopenia	77 [20]	32 [26]	45 [17]	0.056
Neuropathy	11 [3]	6 [5]	6 [2]	0.21
Nephropathy	11 [3]	6 [5]	5 [2]	0.19
Nausea/vomiting	105 [27]	45 [37]	60 [23]	0.007
Sepsis/infection	73 [19]	24 [20]	49 [19]	0.89
Skin toxicity	69 [18]	39 [32]	30 [12]	<0.001
Reason for stopping N, [%]				0.96
Disease progression	219 [57]	69 [56]	150 [58]	
Toxicity	48 [13]	17 [14]	31 [12]	
Planned/patient request	76 [20]	24 [19]	52 [20]	
Other	39 [10]	13 [11]	26 [10]	
Chemotherapy break >3 months N, [%]	20 [5]	19 [15]	1 [1]	<0.001
Second-line chemotherapy N, [%]	142 [37]	58 [47]	84 [33]	0.007
Median cycles [range]		3 [1-21]	3 [1-18]	
Third-line chemotherapy [N, %]	48 [13]	22 [18]	26 [10]	0.046
Radiotherapy details[‡]				0.09
Stereotactic/fractionated RT to primary tumor	33 [9]	15 [12]	18 [7]	
Palliative RT	40 [10]	11 [9]	29 [11]	

[†], Any cycle; [‡], for advanced disease, either before or after first-line palliative chemotherapy. RT, radiotherapy.

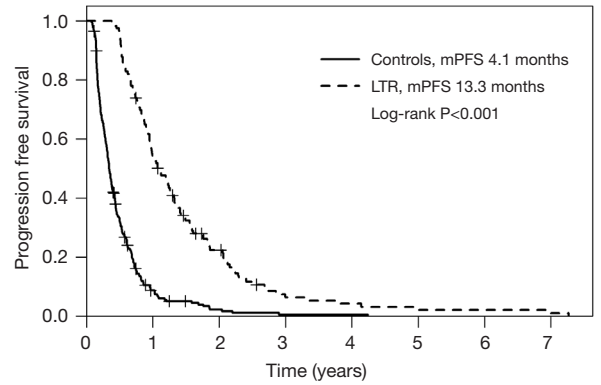

Figure 1 PFS in LTR and controls. LTR, long term responders; mPFS, median progression-free survival.

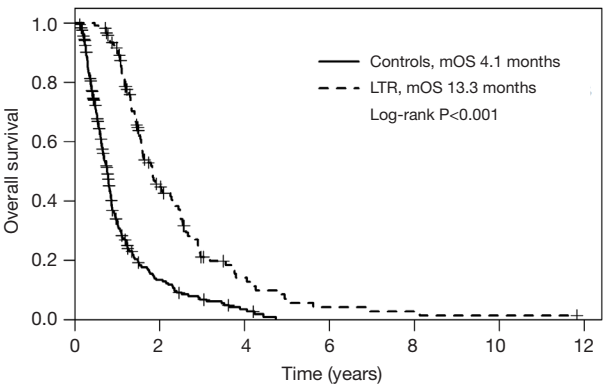

Figure 2 Overall survival in LTR and controls. LTR, long term responders; mOS, median overall survival.

same regimen on progression and achieved disease control again; no patients in the control group had such a break. More patients in the LTR group went on to have second-line chemotherapy regimens (49% *vs.* 33%, P=0.002), although patients in both groups had a median of 3 cycles of second-line chemotherapy. A group of patients in both LTR and control cohorts (12% and 7%, respectively, P=0.08) were treated with stereotactic radiotherapy to their primary tumors, or high-dose fractionated radiotherapy.

PFS, radiographic response and OS

At a median follow up time of 10.7 months (range, 1.3–142 months), the PFS in the entire study cohort was 6.3 months (95% CI, 5.5–7.2). PFS was significantly longer in LTR patients at 13.3 months (95% CI, 11.4–15.4) than in the control group at 4.1 months (95% CI, 3.7–4.6; P<0.001, *Figure 1*). There was significantly higher rate of radiological regression from baseline prior to commencement of PC in the LTR group than in controls (62% *vs.* 19%, P<0.001), a similar rate of stable imaging as best response (39% *vs.* 40%) and a lower rate of disease progression (0 *vs.* 41%) as best response. The absence of patients with progression as best response was expected given the selection of LTR patients as those treated with 6 months of chemotherapy—patients with progression at first response assessment would have stopped first-line chemotherapy at this early time point.

Median OS in the entire study cohort was 12.9 months (95% CI, 11.3–14.2) and was longer in the LTR group at 22.1 months (range, 6–142 months) compared with 9.2 months (range, 1–57 months) in the control group (95% CI, 8.0–10.0; P<0.001, *Figure 2*). In addition, a small number of patients had true long term survival following PC, with 9 patients in the LTR group alive at 4 years, and 2 alive at 8 years. This analysis did not conform to the proportional hazards model, as long term response was a time-dependent variable. As such, HRs for LTR survival at 1 year and 2 years were 0.29 (95% CI, 0.21–0.40) and 0.69 (95% CI, 0.47–1.01), respectively. Other variables associated with better OS in univariable models included intrahepatic site of primary tumor (with gallbladder cancer associated with the worst outcomes), good performance status at diagnosis, treatment with second-line chemotherapy, and treatment break (defined as >3 months with no treatment, followed by re-initiation of the same regimen); these results are summarized in *Table 3*. Survival in patients with locally advanced disease was not different to those with distant metastases or recurrence after surgery (P=0.37), and no significant differences were seen between chemotherapy regimen (P=0.16). Variables found to be significant at a univariable level were included in a multivariable regression model, and long term response remained significantly associated with better OS at this level (P<0.001). Receipt of second line chemotherapy was also independently associated with longer OS on multivariable analysis (P<0.001). Poor performance status (ECOG 2–3) was independently associated with shorter OS (HR 2.06, P=0.003), and the association between site of cancer and survival was maintained in the multivariable model (P<0.001). Patients in the control group, who received second-line chemotherapy, still had shorter OS than LTR patients (P<0.001, *Figure S1*), illustrating that the effect of continued first-line chemotherapy was greater than two separate treatment lines.

Table 3 Univariable and multivariable regression analyses of overall survival

Covariate	HR (95% CI)	P-value	HR (95% CI)	P value
Age (continuous)	1.00 (0.99–1.01)	0.87		
Male gender	1.09 (0.87–1.36)	0.46		
Tumor grade		0.717		
Grade 1	Reference	–		
Grade 2	1.12 (0.78–1.62)	0.530		
Grade 3/4	1.18 (0.79–1.74)	0.420		
Presence of biliary stent	1.17 (0.93–1.46)	0.172		
Jaundice at diagnosis	1.15 (0.92–1.44)	0.209		
Weight loss at diagnosis	1.09 (0.87–1.37)	0.451		
Long-term responder[†‡]	NA	<0.001	NA	<0.001
ECOG PS 2–3	2.02 (1.28–3.2)	0.002	2.06 (1.28–3.30)	0.003
Combination chemotherapy regimen	0.71 (0.52–0.98)	0.035	0.88 (0.64–1.22)	0.44
Site of Cancer		<0.001		<0.001
Intrahepatic	Reference		Reference	
Distal bile duct	1.51 (1.10–2.07)	0.011	1.23 (0.89–1.70)	0.21
Gallbladder	1.71 (1.28–2.28)	<0.001	1.83 (1.35–2.48)	<0.001
Hilar	0.95 (0.68–1.34)	0.78	0.99 (0.70–1.38)	0.93
Bile duct NOS	0.95 (0.49–1.81)	0.87	0.69 (0.34–1.41)	0.30
Treatment break[†*]	–	0.001	NA	
Second-line chemotherapy[†*]	–	<0.001	NA	

[†], variable violated proportional hazard assumption; [‡], LTR was modeled as a time-dependent variable, so HR is not interpretable; [*], included in multivariable analysis as stratification factor. ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; NA, not available; NOS, not otherwise specified.

Discussion

The best results from clinical trials of chemotherapy in advanced BTC suggest a median survival of less than 1 year, even with the use of multi-agent regimens (7). In this large cohort of patients treated with chemotherapy for advanced BTC, 30% of patients were treated with 9 or more cycles of first-line therapy. This was a group of patients who were symptomatic or had significant disease progression, some with deteriorating performance status at the start of PC. In spite of this, a considerable proportion had significantly longer than expected progression-free and OS with continued chemotherapy, at the cost of some increased rates of some toxicities. Analysis of clinical characteristics did not reveal any prominent features predictive of benefit from chemotherapy. If chemotherapy had been stopped at 8 cycles (as per trial data), it is likely that some of this benefit would have been missed. In addition, a small number of patients in the LTR group had continued benefit from chemotherapy, with 9 alive at 4 years, and 2 alive at 8 years. In this study population, other factors associated with differences in survival included site of primary tumor and performance status.

Recently, a sub-group of patients with long-term survival have been reported from the ABC-02 study (13). Of 410 total patients, 45 (approximately 11%) had continued study follow-up for more than 24 months, with a median survival of 31.4 months. Factors associated with longer survival in that population were chemotherapy regimen (cisplatin/gemcitabine doublet compared with gemcitabine alone), locally advanced disease (compared with metastatic disease),

and better ECOG performance status. They did not report data on number of treatment cycles, use of treatment breaks or second-line chemotherapy. In contrast to our population they did not note a significant difference by primary tumor site, although they did not sub-categorize cholangiocarcinoma into intra- or extrahepatic. Our cohort of long-term survivors was a larger proportion of total patients with BTC receiving chemotherapy (30%), and in contrast to the ABC-02 cohort, these patients were treated to disease progression. In the treatment of other cancers, the use of chemotherapy to disease progression has been associated with longer survival. In patients with metastatic breast cancer, a systematic review of studies reported that continuing chemotherapy to disease progression was associated with a modest but significant effect on OS (HR 0.91, 95% CI, 0.84–0.99) (10). Studies of "maintenance" chemotherapy to disease progression in lung cancer have also shown improvements in survival with this strategy (HR 0.78, P=0.0195 for pemetrexed) (14). In patients with metastatic colon cancer, the use of maintenance 5-FU chemotherapy after combination 5-FU, leucovorin and oxaliplatin (FOLFOX) was associated with longer disease control than a chemotherapy-free interval (13.1 *vs.* 9.2 months, P=0.46), but no significant difference in OS was noted (15).

Although tumors of the biliary tract are treated similarly, there is now a significant body of evidence demonstrating significant differences in the molecular pathogenesis and clinical outcomes of cholangiocarcinomas of the intrahepatic bile ducts, extrahepatic bile ducts and cancer of the gallbladder (16,17). There have been a number of reports of distinct molecular drivers in tumors of different sites, with *IDH1/2* (isocitrate dehydrogenase 1/2) mutations and *FGFR* (fibroblast growth factor receptor) fusion events in intrahepatic tumors, *PRKACA* (Protein Kinase CAMP-Activated Catalytic Subunit Alpha) fusions and *ARID1B* (AT-Rich Interaction Domain 1B) mutations in extrahepatic cholangiocarcinoma, and *EGFR* (epidermal growth factor receptor) and *ERBB3* (Erb-B2 Receptor Tyrosine Kinase 3) mutations seen in gallbladder cancers. In our study, patients with gallbladder cancer had worse outcomes than patients with intrahepatic cholangiocarcinoma (HR 1.81), although patients with other BTC subtypes had similar survival times. This finding is consistent with previous reports across biliary cancer subtypes, with a prior pooled analysis of clinical trials of chemotherapy in advanced BTC reporting better response rates in gallbladder cancer but shorter OS (18).

Our study has some limitations. The retrospective nature of this analysis introduces bias, and limits the applicability of its results. In addition, there is heterogeneity in the chemotherapy regimens used in these patients, but most patients received doublet chemotherapy with gemcitabine and either a fluoropyrimidine or platinum agent. Relatively few patients in the LTR group received single agent chemotherapy, but documentation of reason for choice of chemotherapy agent was not always possible to collect. Toxicity rates were higher in the LTR group, as expected with longer chemotherapy exposure. No quality-of-life data are available for this group, but almost half went on to receive second-line chemotherapy, demonstrating that their performance status and willingness to have treatment was intact. Some patients in this study had next-generation sequencing of their tumors performed, but the numbers were small in each group and could not be used to draw any comparisons. There has not yet been a report of any molecular characteristic that can predict response or long-term disease control from chemotherapy for BTC, and further biomarker discovery in this population is warranted.

In summary, we report the outcomes of patients treated with PC for advanced BTC at our institution, and describe a significant size group that appear to derive benefit from continuing chemotherapy for more than 8 cycles. No major clinical features were noted to distinguish this group from other patients treated with similar chemotherapy regimens other than the lack of disease progression at 8 cycles. Clinicians should be aware of potential for longer-term benefit from chemotherapy in a subset of patients with BTC, and consider the rationale for continued treatment in the absence of cumulative toxicity. Prospective studies with molecular correlates are necessary to further explore this finding and develop better treatment strategies for those who experience limited benefit from current therapies.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: Institutional Review Board approval was obtained for the study (07-0376-CE).

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Supplementary

Table S1 Treatment related toxicities by chemotherapy regimen

Toxicity	All patients [n=382]	Fluoropyrimidine [n=11]	Gemcitabine/ fluoropyrimidine [n=156]	Gemcitabine/ cisplatin [n=155]	Gemcitabine/ cisplatin + Selumetinib [n=10]	Gemcitabine [n=43]	Other [n=7]	P value
Neutropenia	74 [19]	3 [27]	28 [18]	30 [19]	4 [40]	7 [16]	2 [29]	0.46
Sepsis	73 [19]	2 [18]	30 [19]	26 [17]	1 [10]	12 [28]	2 [29]	0.58
Nausea/vomiting	105 [27]	3 [27]	38 [24]	49 [32]	4 [40]	9 [21]	2 [29]	0.54
Skin toxicity	69 [18]	2 [18]	53 [34]	6 [4]	2 [20]	3 [7]	3 [43]	<0.001
Thrombocytopenia	77 [20]	2 [18]	20 [13]	36 [23]	5 [50]	12 [28]	2 [29]	0.012
Diarrhea	44 [12]	2 [18]	23 [15]	15 [10]	0 [0]	4 [9]	0 [0]	0.51
Neuropathy	12 [3]	1 [9]	0 [0]	10 [6]	0 [0]	0 [0]	1 [14]	0.002
Nephropathy	11 [3]	0 [0]	0 [0]	9 [6]	2 [20]	0 [0]	0 [0]	0.002

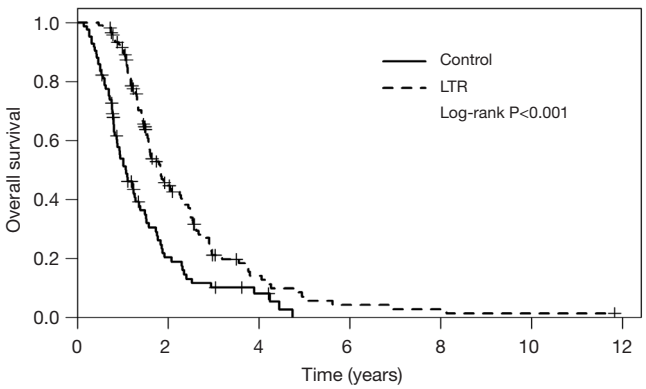

Figure S1 Overall survival in all long term responders, and controls who received second-line chemotherapy. LTR, long term responders.