Advances in the treatment of metastatic or unresectable biliary tract cancer

J. W. Valle*

Christie Hospital/The University of Manchester, Manchester, UK

The prognosis for advanced/inoperable biliary tract cancer is poor and the management of biliary obstruction and sepsis remains the cornerstone of best supportive care (BSC). Many phase II studies have reported some activity of chemotherapy, usually involving one or more of a fluoropyrimidine, a platinum agent and gemcitabine. No adequately powered study has shown conclusively a benefit for chemotherapy compared with BSC alone although three small randomized studies have suggested an improved survival. Results from the randomized phase III ABC-02 study demonstrated a survival advantage of cisplatin and gemcitabine doublet-chemotherapy over gemcitabine monotherapy (median survival of 11.7 compared with 8.1 months, hazard ratio (HR), 0.64 [95% confidence interval (CI) 0.52 to 0.80]; log rank \( P < 0.001\)) as well as a significantly longer progression-free survival [median 8 compared with 5 months; HR 0.63 (95% CI 0.51 to 0.77); log rank \( P < 0.001\)]. A similar magnitude of benefit was seen in Japanese patients in a second study using the same treatment regimens [the BT-22 study]. Ongoing studies are underway evaluating other chemotherapy regimens in first-line although attention is turning to the addition of targeted therapies; these will be reviewed. Pivotal to success in this process is both the identification of appropriate targets across this heterogeneous group of malignancies (e.g. EGFR, VEGF, MEK inhibition, amongst others) and collaboration between investigators to deliver relevant, timely and adequately powered studies.

Biliary tract cancer (BTC) is a collective term that includes gallbladder cancers, cholangiocarcinomas and ampullary carcinomas depending on their epithelial site of origin. Although considered rare in Europe and the United States, the prevalence is much higher in Asia and Latin America. The incidence of cholangiocarcinoma, which accounts for 3% of all gastrointestinal cancers worldwide [1] is increasing consistently across different populations including North America, Europe, Asia and Australia [2]. These tumours unfortunately carry a poor prognosis; surgery cures a minority of patients with a 5-year survival of 9%–18% for proximal bile duct lesion and 20%–30% for distal lesions [3]. Patients commonly present with advanced disease and may have significant co-morbidity, advanced age, intercurrent sepsis and, consequently, poor performance score. Most treatment is, therefore, palliative and aimed at improving quality of life and survival.

Essential in the management of patients presenting with advanced (inoperable, recurrent or metastatic) BTC is the need for biliary decompression and insertion of stents for the relief of obstructive jaundice, as appropriate [3].

Until recently, the role of chemotherapy for patients with advanced BTC was not clearly established. Results from a number of small phase II studies (with a predominance of 5-fluorouracil (5FU) or gemcitabine-containing regimens) had suggested that these tumours were relatively chemo-sensitive. However, no single regimen had been adopted as the standard of care because of the small size and underpowering of these phase II studies. 5FU-based regimens appear to produce responses of 10%–20%, while gemcitabine-based regimens produce responses of 20%–30%.

There has been a paucity of phase III studies in advanced BTC, particularly adequately powered studies to determine clinical practice. Three small studies have compared chemotherapy against best supportive care alone (see Table 1). Glimelius et al. [4] showed improved overall survival in favour of the chemotherapy arm over best supportive care alone (6 compared with 2.5 months; \( P < 0.001\)), which reached the level of significance for patients with pancreatic cancer (\( n = 53; P = 0.05\)), but did not for BTC (\( n = 37; P = 0.1\)), most likely as a result of the lack of statistical power given the small patient numbers. The chemotherapy in question was the FELV regimen (5FU/etoposide and leucovorin) although the etoposide was omitted in patients of reduced performance score or advanced age [4].

A Japanese phase III study of palliative surgery alone compared with palliative surgery followed by FAM (5FU, doxorubicin and mitomycin C) chemotherapy showed no survival advantage (4.7 months compared with 5 months, respectively), in a mixed patient population (pancreas, \( n = 52\); biliary, \( n = 31\) [5].

In a recent study by Dwary et al. [6] patients with gallbladder cancer were randomized to one of three arms: best supportive...
Table 1. Chemotherapy compared with best supportive care studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Eligibility</th>
<th>Regimen</th>
<th>n</th>
<th>MS(months)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>B: FELV: 5FU</td>
<td>18</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td></td>
<td>500 mg/m² + LV 60 mg/m² + etoposide</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>120 mg/m² days 1, 2, 3 q3weeks</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>B: palliative surgery +</td>
<td>42</td>
<td>5.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>FAM (5FU 200 mg/m² + doxorubicin</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>15 mg/m² + mitomycin C 5 mg/m² days 1, 8, 15, 22 q2w &gt;2</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>B: 5FU 425 mg/m²</td>
<td>28</td>
<td>5.3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>bolus + folic acid 20 mg/m² weekly</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>bolus up to 30 weeks</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>C: gemcitabine</td>
<td>26</td>
<td>9.3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>900 mg/m² day 1, 8 + oxaliplatin</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>80 mg/m² days 1, 8 q21d</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

FAM, 5FU, doxorubicin and mitomycin C; 5FU, 5-fluorouracil; LV, leucovorin; MS, median survival.

care, weekly bolus 5FU and folic acid, or gemcitabine plus oxaliplatin (GemOx). This study found improved progression-free survival (PFS) and overall survival in patients receiving chemotherapy, and GemOx in particular (PFS 2.8, 3.5 and 8.5 months; \( P = 0.039 \); median overall survival: 4.5, 5.3 and 9.3 months; \( P = 0.0001 \), in each arm respectively). The chemotherapy was reported to have been tolerated well although toxic effects, details of patient crossover and symptomatic benefit are not yet available [6]. These studies support the premise that BTCs are chemosensitive although, due to lack of statistical power, no individual regimen can be considered a standard.

More recently, a phase III study compared the FELV regimen from the Glimelius study with epirubicin, cisplatin and continuous infusion 5FU (ECF). This study was terminated early because of slow patient accrual (accrued 54 of 166 planned patients). The ECF regimen appeared less toxic without a detectable improvement in survival [7].

The UK ABC-01 study was initiated as a randomized phase II study with 6-month PFS as the primary end point. It demonstrated improved tumour control rate, time to progression and PFS in favour of CisGem (cisplatin 25 mg/m² followed by gemcitabine 1000 mg/m², each on days 1 and 8 of a 21-day cycle) compared with Gem alone (gemcitabine 1000 mg/m² on days 1, 8 and 15 of a 28-day cycle). It also demonstrated the feasibility of undertaking such a study, with 86 patients recruited from 15 institutions [8]. The overall survival data were not released to investigators by the Independent Data Monitoring Committee in view of the planned expansion of the study into a phase III study with identical eligibility and treatment arms, ABC-02.

In ABC-02 an additional 324 patients (for a combined total of 410 patients) were recruited; treatment continued until 24 weeks in each arm, in the absence of disease progression. Seventy-five per cent of patients had metastatic disease, 87% had Eastern Cooperative Oncology Group performance score 0–1, 36% had gallbladder cancer and 59% had bile duct cancer with only 5% of patients with ampullary tumours, evenly distributed between the two treatment arms. The overwhelming majority of patients had adenocarcinomas [with three patients having either squamous cell carcinoma (\( n = 1 \)) or adenosquamous (\( n = 2 \)) histologies]. Patients receiving the CisGem combination had a significantly longer PFS [median PFS 8 compared with 5 months; hazard ratio (HR) 0.63 (95% CI 0.51 to 0.77); log rank \( P < 0.001 \)] and overall survival [11.7 compared with 8.1 months; HR 0.64 (95% CI 0.52 to 0.80); log rank \( P < 0.001 \)] (see Figure 1), with an acceptable toxicity profile, thus setting a standard for patients with advanced BTCs [9].

These findings are consistent with a parallel 83-patient Japanese study using the same eligibility and treatment schedule demonstrating an improved PFS from 3.7 to 5.8 months, and improved median survival from 7.7 to 11.2 months with the addition of cisplatin to gemcitabine [10]. The CisGem regimen appears, therefore, to provide consistent benefits across Western and Japanese patients and is a new point of reference for further studies.

Eckel and Schmid [11], in a pooled analysis of 112 studies, with a total of 2810 patients and a mean of 25.1 patients per trial, demonstrated that time to tumour progression had a good correlation with survival in phase II studies (\( r = 0.73; P = 0.000 \)). Moreover, response rate showed poor correlation with survival (\( r = 0.2; P = 0.043 \)) reflecting the difficulties of assessing radiological response with current imaging, particularly in patients with localized, non-metastatic, disease. The authors found that platinum compounds increased the activity of both fluoropyrimidines and gemcitabine.

Recent treatment regimens reported in phase II studies predominantly involve doublet combinations from the triad of a fluoropyrimidine (oral or i.v.), a platinum agent (variously
cisplatin, carboplatin or oxaliplatin) and gemcitabine, e.g. GemOx [12], GemCap [13], CapOx [14] with comparable outcomes reported (response rates 27%–36% and median survival of 12.8–15.4 months). None of these, however, has been validated in a prospective phase III study.

Interest is now turning to investigation of targeted therapies for patients with advanced BTCs. For example, a recent interim analysis from a randomized phase II study of gemcitabine and oxaliplatin (GemOx) with, or without the epithelial growth factor receptor targeted monoclonal antibody, cetuximab, suggests that the median PFS may be improved by the addition of cetuximab (7.0 compared with 5.0 months; P value not available) to chemotherapy. These are preliminary data, however, with PFS rates not obviously higher that that seen in the ABC-02 study. Importantly, correlation of response or survival with k-ras status is awaited and the study has been extended to enroll an additional 50 patients [15].

Another target of interest includes vascular endothelial growth factor (VEGF) inhibition. Cholangiocarcinoma cells stimulate the development of a rich vascular network, which sustains the metabolic needs and ensures adequate supply of oxygen and nutrients to malignant cells [16]. Human BTC cells express both bFGF and VEGF with higher expression of VEGF in both cell lines and tissues [17]. VEGF expression is stimulated by β-catenin [18] and TGF-β; the latter being expressed by surrounding mesenchymal tissue (compared with malignant cells) thus setting up an autocrine/paracrine mechanism of VEGF overproduction [19]. VEGF expression (detected in 75.6% of 33 resected specimens) is associated with significantly higher levels of microvessel density [20]. In a retrospective review of 236 resected cases, VEGF expression was significantly associated with the presence of intrahepatic metastases in intrahepatic cholangiocarcinomas (P = 0.0224) [21].

Recent phase II data using AZD6244 [an orally available inhibitor of the activity of isolated mitogen activated protein kinase kinase (MEK) to phosphorylate extracellular signal-regulated kinase (ERK)-2] in 29 patients with advanced BTC demonstrated a 12% response rate (the primary end point) in monotherapy (nearly 40% of patients had been pre-treated). Tissue levels of pERK and AKT were assessed by immunohistochemistry and tumours were also genotyped for the presence of BRAF or RAS activating mutations. KRAS analysis was performed in 26 patients, 2 of whom harboured mutations in this gene. No BRAF mutations were found. pERK levels were associated with improved PFS [22].

BTCs are sensitive to chemotherapy and additional regimens in first and subsequent lines of treatment need to be established, along with optimal use of chemotherapy in the adjuvant and neoadjuvant setting. In addition, future studies should continue to focus on gaining a better understanding of the underlying processes in the development and establishment of BTCs with the introduction of agents targeting these numerous pathways. A number of such studies are either planned or underway.

disclosures
The author has declared no conflict of interest.

references
6. Dwary AD, Sharma A, Mohanti BK et al. A randomized controlled trial (RCT) comparing best supportive care (BSC), 5-FU plus folinic acid and...


