Second-line chemotherapy in advanced biliary cancer: a systematic review

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The randomized NCRN phase III ABC-02 trial provided level-A evidence for first-line chemotherapy with cisplatin and gemcitabine combination in advanced biliary cancer (ABC). This systematic literature review aims to evaluate the level of evidence for the use of second-line chemotherapy for patients with ABC in terms of overall survival (OS), response, toxicity and quality of life. Eligible studies were identified using Medline, ASCO, ESMO and the World Gastrointestinal Congress databases. Searches were last updated on 15 December 2013. Eligible studies reported survival and/or response data for patients with ABC receiving second-line systemic chemotherapy. This systematic review was registered in the PROSPERO database (No. CRD42013004205). Five hundred and fifty-eight studies were identified from the searches in Medline (n = 342), ASCO (n = 160), ESMO (n = 27) and World Gastrointestinal Congress (n = 29). Twenty-five studies were eligible: 14 phase II clinical trials, 9 retrospective analyses and 2 case reports. In total, data from 761 patients were reported with median number of patients included in each study of 22 (range 9–96). The mean OS was 7.2 months [95% confidence interval (CI) 6.2–8.2] [phase II: 6.6 (95% CI 5.1–8.1); retrospective analysis: 7.7 (95% CI 6.5–8.9)]. The mean progression-free survival (PFS), response rate (RR) and disease control rate were 3.2 months (95% CI 2.7–3.7), 7.7% (95% CI 4.6–10.9) and 49.5% (95% CI 41.4–57.7), respectively. The best correlations were between OS and PFS for all studies (r = 0.54; P = 0.01) and between OS and PFS (r = 0.61; P = 0.04) and OS and RR (r = 0.62; P = 0.03) for phase II studies, respectively. Biliary tract cancer is known to be a chemo-responsive disease. There is insufficient evidence (level C) to recommend a second-line chemotherapy schedule in ABC, although the available data suggest that a cohort of patients may benefit. Further prospective and randomized studies are needed to clarify the relative value of second-line chemotherapy in this setting.

Key words: advanced biliary cancer, chemotherapy, second-line, systematic review

introduction

The term ‘biliary tract cancer’ (BTC) is a collective term to include tumours of the gallbladder, cholangiocarcinoma (intra-hepatic and extra-hepatic bile duct) and the ampulla of Vater with a relative frequency of 41%, 42% and 17%, respectively [1]. Cholangiocarcinoma and ampullary carcinomas are more frequent in males, while gallbladder tumours have a higher incidence in women [2]. Most patients are aged between 50 and 70 years at diagnosis, and the large majority of tumours (>90%) are adenocarcinomas [2, 3]. Although BTCs are uncommon, accounting for ~0.7% of all malignant tumours in adults, clinical studies from the past 25 years suggest that both incidence and mortality are increasing, predominantly due to a rise in intra-hepatic cholangiocarcinoma [4]. In the United States, 10,310 people were anticipated to be diagnosed with a BTC during 2013 [5], while the annual incidence in England and Wales is ~1,200 new cases [6]. Epidemiological studies across Europe, employing data from the World Health Organisation (WHO) over the period 1990–2010, matched with previously published studies, showing an increase of the European mortality from intra-hepatic cholangiocarcinoma by around 9% in both sexes from 1990 to 2008 (reaching rates of 1.1/100,000 in men and 0.75/100,000 in women): the highest rates were in UK, Germany and France [7].

Surgical resection, preferably carried out in a specialist centre, offers the only chance of long-term cure in BTC. However, due to their aggressive course, most patients (>65%) are diagnosed with non-resectable disease and are only suitable for palliative chemotherapy or supportive care.

Advanced biliary cancer (ABC) includes patients with unresectable locally advanced (stage III) and metastatic (stage IV) disease, and carries a poor prognosis with 5-year overall survival (OS) of 10% and 0%, respectively [8]. For this reason, active symptom control (ASC) addressing the development of biliary


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obstruction and its complications is pivotal in the successful management of ABC from the time of diagnosis.

In addition to ASC, first-line palliative chemotherapy for advanced ABC has shown an improvement in OS and quality of life. An early clinical trial including 90 patients with bile duct or pancreatic carcinomas randomized patients to receive best supportive care (BSC) with or without chemotherapy [a combination of 5-fluorouracil (5-FU), etoposide and leucovorin] [9]. Chemotherapy-treated patients experienced an improvement in OS and quality of life compared with those managed with BSC alone. A number of subsequent phase II studies followed, with 5-FU, gemcitabine and platinum analogues emerging as the most active agents [10, 11]. In 2010, based on phase III randomized data, a reference regimen for first-line therapy of cisplatin and gemcitabine was established by the UK NCRN ABC-02 study [12]. This study demonstrated an OS advantage for the cisplatin–gemcitabine doublet over gemcitabine alone (11.7 versus 8.1 months; hazard ratio 0.64, 95% confidence interval (95% CI) 0.52–0.80; P < 0.001). A similar magnitude of benefit was seen in a Japanese randomized phase II study (BT22) using the same treatment regimen, with a median survival of 11.2 months with cisplatin and gemcitabine [13].

In contrast, to date, there is no phase III evidence supporting the use of second-line chemotherapy after failure of first-line chemotherapy in ABC; thus, ASC is the standard of care. In the ABC-02 trial [12], only 63 patients (15.3%) were treated with second-line chemotherapy [14]. In contrast, 63 of the 84 patients (75%) included in the Japanese BT22 trial [13] received second-line chemotherapy, predominantly with S1. Despite this difference in the rate of patients receiving second-line chemotherapy, the median OS in both studies was similar (11.7 and 11.2 months in ABC-02 and BT22, respectively) thus questioning the benefit of second-line chemotherapy.

In order to synthesize the current knowledge regarding second-line chemotherapy for ABC and to inform on the value of developing randomized trials in this setting, we conducted a systematic review of the literature to evaluate the level of evidence supporting the use of second-line chemotherapy for patients with ABC in terms of OS, response and quality of life.

methods

participants
This systematic review focused on patients with ABC and progressive disease after a first-line chemotherapy schedule (any regimen) and who were treated with second-line chemotherapy.

interventions
Eligible studies were required to include patients treated with second-line treatment; both prospective studies and retrospective series or case reports were included. Eligible interventions included any systemic chemotherapy regimens without other local therapies except when used for ASC.

search strategy
This systematic review was registered in the PROSPERO database, number CRD42013004205 [15]. A search (dated 15 December 2013) to identify eligible studies was undertaken using the Medline database [16]. Abstracts of the Proceedings of the Annual Meeting of the American Society of Clinical Oncology (ASCO), the biannual European Society of Medical Oncology Congress since 2002 (ESMO) and the annual World Gastrointestinal Congress since 2006 were also searched manually [17–19]. Key words used to identify eligible publications in Medline were [([(biliary tract AND chemotherapy AND second) OR (biliary tract AND chemotherapy AND refractory)]) OR (gallbladder AND chemotherapy AND refractory]) OR (cholangiocarcinoma AND chemotherapy AND refractory)] while BTC was employed for searching in ASCO, ESMO and World GI Congress meetings. No dates of publication or language limits were applied.

end points
The primary end point of this review was OS (defined as time since starting second-line chemotherapy until death or last follow-up). Secondary outcome measures included time to progression (TTP)/progression-free survival (PFS) (both defined as time since starting second-line chemotherapy until progression or last follow-up), response rate (RR, defined as rate of partial responses and complete responses), disease control rate (DCR, defined and rate of partial responses, complete response and stabilization) and toxicities. Quality-of-life data were also collected if available. Details of the administered first-line chemotherapy regimen were also reviewed.

selection of eligible studies
For selection, studies included patients receiving second-line systemic chemotherapy for ABC and reported survival and/or response data (for the subgroup of ABC patients in the event of a mixed-cohort study). Meta-analyses, systematic reviews, clinical trials, retrospective analysis or case reports were included, with at least an abstract or full text in English available (although no language exclusion criteria were applied).

Studies were excluded if no systemic chemotherapy was employed or if systemic chemotherapy was employed in combination with local therapies such as radiotherapy, surgery or photodynamic therapies. Phase I clinical trials including ABC but with no data available for response/survival for the ABC patients subgroup were also excluded.

data extraction, synthesis and actual level of evidence assessment
Clinical and methodological data were extracted from the eligible studies by employing the ‘Standards, Options and Recommendations’ project data collection forms [20]. The following definitions of level of evidence were used [20]: level A: there exists a meta-analysis of high standard or several randomized trials with consistent results; level B: if randomized studies (level B1), therapeutic trials, quasi-experimental trials or comparisons of populations (level B2) provide consistent results when considered together; level C: there exist studies, therapeutic trials, quasi-experimental trials or comparisons of populations, of which the results are not consistent when considered together; level D: if either scientific data do not exist or there are only a series of cases; expert agreement: data do not exist but the experts are unanimous in their judgement.
The Stata/MP 13 package was used for the statistical analysis. Weighted mean and the 95% CI of the mean were calculated for median OS and median PFS according to the number of patients included in the studies (analytic weighting). Although weights are usually chosen to be inversely proportional to the variances of the individual study estimates, such variance estimates were not available from the published reports and so the crude proxy of sample size was used instead. The derived CIs should be treated only as rough approximations. Numerators and denominators were reported for RR and DCR however, and hence information on the variances of study specific estimators was available for these outcomes. There was evidence of heterogeneity in the rates between studies and so logistic regression incorporating a random intercept (i.e. a random-effects analysis) was used for these outcomes. Weighted pairwise correlations (weighted simply by the number of patients included in each study) between OS and RR/DCR/PFS were also calculated. Case reports were excluded from the statistical analysis.

results

eligible studies

Figure 1 summarizes the PRISMA flow diagram for selection of eligible studies [21]; 558 results were obtained from the searches in Medline (n = 342), ASCO (n = 160), ESMO (n = 27) and World Gastrointestinal Congress (n = 29). Of these, 44 were duplicates and 475 did not meet the inclusion criteria and were therefore excluded. Of the 39 studies which appeared to be eligible after the initial screen, a full text search was carried out. Fourteen studies were removed after the full text search [22–35]; see supplementary data, available at Annals of Oncology online, for more detail.

Twenty-five studies were included in the final analysis: 14 phase II clinical trials (Table 1) [36–49], 9 retrospective analyses (Table 2) [14, 50–57] and 2 case reports [58, 59]. No phase III clinical trials, systematic reviews or meta-analyses were available.

phase II clinical trials

Only 14 phase II clinical trials involving the salvage treatment of ABC met the inclusion criteria; these included patients after failure of first-line chemotherapy (mostly gemcitabine and/or 5-FU). They are summarized in Table 1.

- Eleven patients diagnosed with ABC were treated with a combination of docetaxel and erlotinib [36]. With the limitation of small numbers of patients, grade ≥2 rash was associated with higher PFS and OS.
- A cisplatin and gemcitabine schedule was selected to treat 20 patients after progression on gemcitabine and S1 [37]. Thirty percent of the patients included received cisplatin and gemcitabine as third-line treatment.
- Oh et al. treated 32 ABC patients with second-line gemcitabine after progression to 5-FU [38]. According to prognostic factor analysis, poor performance status (PS >1) and albumin level <3.5 g/dl had an independent influence on poor TTP and OS.
- A phase II trial treated 50 ABC patients with infusional 5-FU, doxorubicin and mitomycin C-C (iFAM) [42]; based on multivariate analysis, ECOG performance status, serum albumin and response to previous chemotherapy were significantly associated with OS.
- Three phase II trials with S1 after progression on first-line chemotherapy included 16 [39], 41 [40] and 22 [41] patients suggesting that S1 single agent appears to be feasible and moderately efficacious second-line chemotherapy.
- Nine patients were treated with a combination of gemcitabine, oxaliplatin and cetuximab [43]. The reported DCR was 33% with a median OS of 7 months.
- In 2013, Sasaki et al. reported a pilot study of 13 patients treated with irinotecan after failure of previous treatment with gemcitabine, cisplatin and oral fluoropyrimidine [44]. Irinotecan monotherapy (100 mg/m² on days 1, 8 and 15, repeated every 4 weeks) had modest anti-tumour effect in this scenario with high rate of grade 3/4 toxicities: received dose intensity was only 55% due to this reason.
- Thirty-seven patients were treated in context of a phase II clinical trial with FOLFOX-4 regimen [45]. Median TTP was 3.1 months (95% CI 2.3–3.6), with DCR of 62.2%.
- Three different phase II trials have evaluated the targeted therapies sunitinib [47], everolimus [60] or imatinib [48]. No important clinical activity was found in 56 patients treated with sunitinib or in 9 patients treated with imatinib. However, the data with everolimus in 37 patients showed encouraging anti-tumour activity (DCR: 55.5%, which was long-lasting in some cases).
- Bortezomib, a proteasome inhibitor, showed a DCR of 50% with PFS and OS of 1.6 and 9.4 months, respectively in 20 ABC second-line patients [49]. However, 65% of patients had grade 3–4 side-effects.

retropective analyses

Several retrospective analyses have been published analysing the survival and response data of patients treated with second-line chemotherapy. The most important ones are summarized here, while Table 2 collects the data of all the publications up-to-date with available data of survival and response.

- Walter et al. reported the tolerance, survival and prognostic factors in a large retrospective study of 378 ABC patients [56]. Several prognostic factors correlated with improved OS among the 96 second-line chemotherapy patients: performance status ≤1, non-gallbladder tumours, objective response during the first-line chemotherapy and a PFS longer than 6 months after first-line treatment.
- In another study, 96 patients were analysed retrospectively for survival and tumour response in 2012 [55]; 46 patients received second-line therapy. For patients who received a 5-FU combination after failure of gemcitabine-based schedule, the DCR, median PFS and median OS (since starting chemotherapy included 16 [39], 41 [40] and 22 [41] patients
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Differences in DCR, PFS and OS were not statistically significant.

Finally, a retrospective analysis was carried out of 63 patients treated with second-line chemotherapy after receiving the combination of cisplatin and gemcitabine in the context of the ABC-02 trial (regimens included: gemcitabine, 5-FU, FOLFOX or cisplatin–gemcitabine) [14]. Only 15.3% of the 410 patients included in the trial received second-line schedule; and 72% of these were PS 0–1 (representing 11% of all the patients treated with the first-line treatment).

case reports

Two case reports met the inclusion criteria:

- Two patients treated with second-line capecitabine after first-line 5-FU combination [58]. Patients had stable disease on reassessment scan after 4.5 and 3 months of starting treatment. No OS data were presented.
- A series of four cases, second-line cisplatin and gemcitabine (gemcitabine 1000 mg/m² on days 1 and 8 for 30 min, cisplatin 75 mg/m² on day 1 for 90 min, given every 21 days) was administered after 5-FU failure [59]. Two patients had a partial response and the remaining two had stable disease. The median PFS and OS were 5 and 9 months, respectively.

statistical analysis

Case reports were excluded from the statistical analysis; the 23 retrospective and phase II studies included a total of 761 patients for evaluation.

The median number of second-line ABC patients included in each study overall was 22 (range 9–96) [phase II: 20 (range 9–56) and retrospective analyses: 49 (range 10–96)]. The weighted mean ‘median OS’ in the 20 studies with survival data available (including retrospective analysis and phase II trials) was 7.2 months (95% CI 6.2–8.2) from commencement of second-line chemotherapy treatment (see supplementary Figure S1, available at Annals of Oncology online). Twelve of the 14 phase II trials included data for OS: the weighted mean was 6.6 months (95% CI 5.1–8.1). The weighted mean OS for the eight retrospective analyses with available survival data was 7.7 months (95% CI 6.5–8.9). The weighted mean ‘median PFS’ for

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**Figure 1.** PRISMA flow diagram.
<table>
<thead>
<tr>
<th>Trial (ref)</th>
<th>Drug</th>
<th>Non-ABC cancers included?</th>
<th>Number of total patients included in the trial</th>
<th>First line specified?</th>
<th>Number of ABC patients</th>
<th>Primary end point</th>
<th>CR (%)</th>
<th>PR (%)</th>
<th>RR (%)</th>
<th>SD (%)</th>
<th>DCR (%)</th>
<th>Median TTP/PFS (months)</th>
<th>Median OS (months)</th>
<th>Toxicity G1/2</th>
<th>Toxicity G3/4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chiorean et al. [36]</td>
<td>Docetaxel and erlotinib</td>
<td>Yes (HCC)</td>
<td>25</td>
<td>No</td>
<td>11</td>
<td>PFS</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>64</td>
<td>64</td>
<td>4</td>
<td>5.7</td>
<td>Rash, diarrhoea (56%), fatigue (52%)</td>
<td>NR</td>
</tr>
<tr>
<td>Sasaki et al. [37]</td>
<td>Cisplatin and gemcitabine</td>
<td>No</td>
<td>20</td>
<td></td>
<td>20</td>
<td>RR</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>70</td>
<td>70</td>
<td>3.6</td>
<td>5.9</td>
<td>Anaemia, thrombocytopenia and constipation</td>
<td>Leucopenia (35%), neutropenia (35%), anaemia (20%) and thrombocytopenia (15%)</td>
</tr>
<tr>
<td>Oh et al. [38]</td>
<td>Gemcitabine and S1 single agent</td>
<td>No</td>
<td>32</td>
<td></td>
<td>32</td>
<td>RR</td>
<td>0</td>
<td>6.9</td>
<td>6.9</td>
<td>20.7</td>
<td>27.6</td>
<td>1.6</td>
<td>4.1</td>
<td>Anaemia, thrombocytopenia and nausea</td>
<td>Neutropenia, febrile neutropenia and thrombocytopenia</td>
</tr>
<tr>
<td>Sasaki et al. [39]</td>
<td>Gemcitabine</td>
<td>Yes (first-line patients)</td>
<td>45</td>
<td></td>
<td>16</td>
<td>RR</td>
<td>0</td>
<td>18.8</td>
<td>18.8</td>
<td>25</td>
<td>43.8</td>
<td>5.5</td>
<td>8</td>
<td>Leucopenia (31.3%), neutropenia (12.5%), anaemia (31.3%), thrombocytopenia (31.3%) and anorexia (18.8%)</td>
<td>No</td>
</tr>
<tr>
<td>Suzuki et al. [40]</td>
<td>Gemcitabine</td>
<td>No</td>
<td>41</td>
<td></td>
<td>41</td>
<td>RR</td>
<td>0</td>
<td>7.5</td>
<td>7.5</td>
<td>55</td>
<td>62.5</td>
<td>2.5</td>
<td>7.5</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>Sasaki et al. [41]</td>
<td>Gemcitabine</td>
<td>No</td>
<td>22</td>
<td></td>
<td>22</td>
<td>RR</td>
<td>0</td>
<td>22.7</td>
<td>22.7</td>
<td>27.3</td>
<td>50</td>
<td>5.4</td>
<td>13.5</td>
<td>Anorexia (55%), anaemia (54%), thrombocytopenia (41%), neutropenia (36%) and pigmentation (32%)</td>
<td>Neutropenia (5%) and anaemia (5%)</td>
</tr>
<tr>
<td>Lim et al. [42]</td>
<td>iFAM</td>
<td>No</td>
<td>50</td>
<td></td>
<td>50</td>
<td>OS</td>
<td>0</td>
<td>4.2</td>
<td>4.2</td>
<td>18.7</td>
<td>22.9</td>
<td>2.2</td>
<td>5.6</td>
<td>Alopecia (34%), stomatitis (28%), vomiting (24%) and diarrhoea (12%)</td>
<td>Neutropenia (10%), thrombocytopenia (8%) and anaemia (2%)</td>
</tr>
<tr>
<td>Paule et al. [43]</td>
<td>GemOx</td>
<td>No</td>
<td>9</td>
<td></td>
<td>9</td>
<td>RR</td>
<td>11.1</td>
<td>11.1</td>
<td>22.2</td>
<td>11.1</td>
<td>33.3</td>
<td>4</td>
<td>7</td>
<td>Rash</td>
<td>Neutropenia (11.1%)</td>
</tr>
<tr>
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<td>Cetuximab</td>
<td>No</td>
<td>13</td>
<td></td>
<td>13</td>
<td>Not -specified</td>
<td>0</td>
<td>7.7</td>
<td>7.7</td>
<td>15.4</td>
<td>23.1</td>
<td>1.8</td>
<td>6.7</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>He et al. [45]</td>
<td>FOLFOX-4</td>
<td>No</td>
<td>37</td>
<td></td>
<td>37</td>
<td>TTP</td>
<td>0</td>
<td>21.6</td>
<td>21.6</td>
<td>40.6</td>
<td>62.2</td>
<td>3.1</td>
<td>NR</td>
<td>37.8%: Neutropenia and fatigue 21.6%</td>
<td>Anemia (11%), thrombocytopenia (22%), transient AST/ALT elevation (5.5%), fatigue (11%).</td>
</tr>
<tr>
<td>Buzzoni et al. [46]</td>
<td>Everolimus</td>
<td>No</td>
<td>37</td>
<td></td>
<td>37</td>
<td>DCR</td>
<td>5.5</td>
<td>5.5</td>
<td>5.5</td>
<td>50</td>
<td>55.5</td>
<td>NR</td>
<td>NR</td>
<td>Anemia (11%), thrombocytopenia (22%), transient AST/ALT elevation (5.5%), fatigue (11%).</td>
<td></td>
</tr>
<tr>
<td>Yi et al. [47]</td>
<td>Sunitinib</td>
<td>No</td>
<td>56</td>
<td></td>
<td>56</td>
<td>TTP</td>
<td>0</td>
<td>8.9</td>
<td>8.9</td>
<td>41.1</td>
<td>50</td>
<td>2.4</td>
<td>4.8</td>
<td>Stomatitis (30%), thrombocytopenia (42.9%), fatigue (39.3%), hand-foot syndrome (35.7%) and neuropathy (19.6%)</td>
<td>Neutropenia (21.4%), thrombocytopenia (21.4%), hand-foot syndrome (10.7%) and anaemia (5.4%)</td>
</tr>
<tr>
<td>Roth et al. [48]</td>
<td>Imatinib</td>
<td>No</td>
<td>9</td>
<td></td>
<td>9</td>
<td>RR</td>
<td>0</td>
<td>0</td>
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<td>2.6</td>
<td>4.9</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>Costello et al. [49]</td>
<td>Bortezomib</td>
<td>No</td>
<td>20</td>
<td></td>
<td>20</td>
<td>RR</td>
<td>0</td>
<td>5</td>
<td>5</td>
<td>45</td>
<td>50</td>
<td>1.6</td>
<td>9.4</td>
<td>65%: fatigue (20%), thrombocytopenia (15%), hyperbilirubinemia (15%) and hypotension (10%)</td>
<td></td>
</tr>
</tbody>
</table>

NR, not reported; 5-FU, 5-fluorouracil; CR, complete response; PR, partial response; RR, response rate (CR + PR); SD, stable disease; DCR, disease control rate (RR + SD); PFS, progression-free survival; TTP, time to progression; OS, overall survival; G, grade; GemOx, combination of gemcitabine and oxaliplatin; iFAM, infusional; 5-FU, combined with doxorubicin and mitomycin C-C; FOLFOX-4, combination of oxaliplatin; 5-FU, leucovorin; HCC, hepatocellular carcinoma.
Table 2. Retrospective series analysis of second-line chemotherapy in ABC

<table>
<thead>
<tr>
<th>Series (ref)</th>
<th>Drug</th>
<th>Non-ABC cancers included?</th>
<th>Number of total patients included in the trial</th>
<th>First-line specified?</th>
<th>Number of second-line ABC patients</th>
<th>CR (%)</th>
<th>PR (%)</th>
<th>RR (%)</th>
<th>SD (%)</th>
<th>DCR (%)</th>
<th>Median TTP/PFS (months)</th>
<th>Median OS (months)</th>
<th>Toxicity G1/2</th>
<th>Toxicity G3/4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kameda et al. [50]</td>
<td>Cisplatin and gemcitabine</td>
<td>No</td>
<td>10</td>
<td>Gemcitabine</td>
<td>10</td>
<td>0</td>
<td>30</td>
<td>30</td>
<td>60</td>
<td>4</td>
<td>6.4</td>
<td>NR</td>
<td>Neutropenia (30%), anaemia (30%)</td>
<td></td>
</tr>
<tr>
<td>Kiba et al. [51]</td>
<td>Gemcitabine</td>
<td>Yes (first-line)</td>
<td>39</td>
<td>Other than gemcitabine (5-FU, cisplatin, CPT11)</td>
<td>17</td>
<td>5.9</td>
<td>17.6</td>
<td>28.5</td>
<td>52.9</td>
<td>92.9</td>
<td>NR</td>
<td>NR</td>
<td>Neutropenia, thrombocytopenia, renal failure, fatigue</td>
<td></td>
</tr>
<tr>
<td>Katayose et al. [52]</td>
<td>S1</td>
<td>No</td>
<td>11</td>
<td>Gemcitabine</td>
<td>11</td>
<td>0</td>
<td>9.1</td>
<td>9.1</td>
<td>27.3</td>
<td>36.4</td>
<td>3</td>
<td>15</td>
<td>Anaemia (91%), thrombocytopenia (55%), AST increased (36%), neutropenia (18%) and nausea (18%)</td>
<td></td>
</tr>
<tr>
<td>Brandi et al. [53]</td>
<td>Gemcitabine combination</td>
<td>No</td>
<td>49</td>
<td>Gemcitabine combination</td>
<td>49</td>
<td>NR</td>
<td>NR</td>
<td>10.2</td>
<td>NR</td>
<td>30.6</td>
<td>3.5</td>
<td>8.1</td>
<td>NR</td>
<td>Neutropenia, thrombocytopenia, renal failure, fatigue</td>
</tr>
<tr>
<td>Kobayashi et al. [54]</td>
<td>S1</td>
<td>No</td>
<td>55</td>
<td>Gemcitabine combination</td>
<td>55</td>
<td>0</td>
<td>4</td>
<td>4</td>
<td>38</td>
<td>42</td>
<td>2.3</td>
<td>6</td>
<td>Anaemia (72.2%), anorexia (41.8%) and thrombocytopenia (34.5%)</td>
<td></td>
</tr>
<tr>
<td>Bridgewater et al. [14]</td>
<td>Platinum combination</td>
<td>No</td>
<td>63</td>
<td>Cisplatin and gemcitabine combination</td>
<td>63</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>4</td>
<td>8.1</td>
<td>NR</td>
<td>Asthenia (18%), dizziness (9%), diarrhea (9%), nausea (9%)</td>
</tr>
<tr>
<td>Croitoru et al. [55]</td>
<td>Gemcitabine/5-FU combination</td>
<td>Yes (first-line)</td>
<td>96</td>
<td>5-FU or gemcitabine combined with cisplatin</td>
<td>46</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>76.7</td>
<td>76.7</td>
<td>5.5</td>
<td>8.8</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Walter et al. [56]</td>
<td>Gemcitabine/5-FU combination</td>
<td>No</td>
<td>96</td>
<td>Gemcitabine/5-FU combination</td>
<td>96</td>
<td>0</td>
<td>9</td>
<td>9</td>
<td>34</td>
<td>43</td>
<td>2.8</td>
<td>7.5</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Sasaki et al. [57]</td>
<td>Cisplatin and gemcitabine</td>
<td>No</td>
<td>60</td>
<td>Gemcitabine ± S1</td>
<td>60</td>
<td>0</td>
<td>1.7</td>
<td>1.7</td>
<td>56.7</td>
<td>58.4</td>
<td>3.5</td>
<td>6.7</td>
<td>Haematological toxicities (62% anaemia, 53% thrombocytopenia, 32% neutropenia); nausea (26%), anorexia (48%), constipation (28%)</td>
<td></td>
</tr>
</tbody>
</table>

NR, not reported; 5-FU, fluoropyrimidine; CR, complete response; PR, partial response; RR, response rate (CR + PR); SD, stable disease; DCR, disease control rate (RR × SD); PFS, progression-free survival; TTP, time to progression; OS, overall survival; G, grade; CPT11, irinotecan; AST, aspartate aminotransferase.
all the studies (21 with data available) was 3.2 months (95% CI 2.7–3.7). In the 22 studies (including retrospective and phase II trials) with RR data and the 21 studies reporting DCR, the weighted mean RR and DCR were 7.7% (95% CI 4.6–10.9) and 49.5% (95% CI 41.4–57.7), respectively. These results are summarized in Table 3.

Correlation between the OS and DCR/RR/PFS was assessed; results are summarized in Table 4 and Figure 2. It should be noted that the calculated correlation coefficients are quite sensitive to the two studies reporting median OS over 13 months. When all the studies included in the statistical analysis were included for the weighted correlation index determination, the strongest correlation was shown between OS and PFS ($r = 0.54$); this correlation was statistically significant ($P = 0.01$) (Figure 2C). This significance was maintained in the phase II trials subgroups ($r = 0.61; P = 0.04$) (Figure 2E). Correlation between OS and RR was significant only in the phase II trials subgroup ($r = 0.62; P = 0.03$) (Figure 2D); showing weaker correlation when all the studies were included ($r = 0.34; P = 0.16$) (Figure 2B). No marked correlation was found between OS and DCR ($r = 0.19; P = 0.45$) (Figure 2A).

We analysed the impact in OS of switching type of chemotherapy (from gemcitabine based to 5-FU based or vice-versa). For this analysis, studies employing targeted therapies and those with no data available regarding the employed first-line chemotherapy were excluded. There was no difference in OS between the studies that switched the type of treatment (mean 8.6 months) and those which did not (mean 7 months). No differences were found either in PFS (mean 3.2 versus 3.6 months), DCR (mean 48.9% versus 49.4%) nor RR (mean 14% versus 9.6%).

**Table 3. Response and survival data in the 23 studies analysed**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Subgroup</th>
<th>Studies with data available</th>
<th>Total studies</th>
<th>Weighted mean</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>OS (months)</td>
<td>Overall</td>
<td>20</td>
<td>23</td>
<td>7.2</td>
<td>6.2–8.2</td>
</tr>
<tr>
<td></td>
<td>Phase II</td>
<td>12</td>
<td>14</td>
<td>6.6</td>
<td>5.1–8.1</td>
</tr>
<tr>
<td></td>
<td>Retrospective analysis</td>
<td>8</td>
<td>9</td>
<td>7.7</td>
<td>6.5–8.9</td>
</tr>
<tr>
<td>PFS (months)</td>
<td>Overall</td>
<td>21</td>
<td>23</td>
<td>3.2</td>
<td>2.7–3.7</td>
</tr>
<tr>
<td></td>
<td>Phase II</td>
<td>13</td>
<td>14</td>
<td>2.8</td>
<td>2.1–3.5</td>
</tr>
<tr>
<td></td>
<td>Retrospective analysis</td>
<td>8</td>
<td>9</td>
<td>3.5</td>
<td>2.8–4.2</td>
</tr>
<tr>
<td>RR (%)</td>
<td>Overall</td>
<td>22</td>
<td>23</td>
<td>7.7</td>
<td>4.6–10.9</td>
</tr>
<tr>
<td></td>
<td>Phase II</td>
<td>14</td>
<td>14</td>
<td>8.2</td>
<td>3.9–12.4</td>
</tr>
<tr>
<td></td>
<td>Retrospective analysis</td>
<td>8</td>
<td>9</td>
<td>7.2</td>
<td>2.7–11.7</td>
</tr>
<tr>
<td>DCR (%)</td>
<td>Overall</td>
<td>21</td>
<td>23</td>
<td>49.5</td>
<td>41.4–57.7</td>
</tr>
<tr>
<td></td>
<td>Phase II</td>
<td>13</td>
<td>14</td>
<td>46.6</td>
<td>36.6–57</td>
</tr>
<tr>
<td></td>
<td>Retrospective analysis</td>
<td>8</td>
<td>9</td>
<td>53.9</td>
<td>41.4–66.8</td>
</tr>
</tbody>
</table>

Bold is showing the data for phase II and retrospective studies combined (“overall”)

RR, response rate (complete response + partial response); DCR, disease control rate (RR + stable disease); PFS, progression-free survival; OS, overall survival.

**Table 4. Correlation index analysis**

<table>
<thead>
<tr>
<th>Correlation between</th>
<th>Subgroup</th>
<th>Studies with data available</th>
<th>Total studies</th>
<th>$r$ (correlation index)</th>
<th>$P$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>OS/DCR</td>
<td>Overall (Figure S1A)</td>
<td>18</td>
<td>23</td>
<td>0.19</td>
<td>0.45</td>
</tr>
<tr>
<td></td>
<td>Phase II</td>
<td>11</td>
<td>14</td>
<td>0.27</td>
<td>0.42</td>
</tr>
<tr>
<td></td>
<td>Retrospective analysis</td>
<td>7</td>
<td>9</td>
<td>0.01</td>
<td>0.98</td>
</tr>
<tr>
<td>OS/RR</td>
<td>Overall (Figure S1B)</td>
<td>19</td>
<td>23</td>
<td>0.34</td>
<td>0.16</td>
</tr>
<tr>
<td></td>
<td>Phase II</td>
<td>12</td>
<td>14</td>
<td>0.62</td>
<td>0.03</td>
</tr>
<tr>
<td></td>
<td>Retrospective analysis</td>
<td>7</td>
<td>9</td>
<td>0.04</td>
<td>0.93</td>
</tr>
<tr>
<td>OS/PFS</td>
<td>Overall (Figure S1C)</td>
<td>20</td>
<td>23</td>
<td>0.54</td>
<td>0.01</td>
</tr>
<tr>
<td></td>
<td>Phase II</td>
<td>12</td>
<td>14</td>
<td>0.61</td>
<td>0.04</td>
</tr>
<tr>
<td></td>
<td>Retrospective analysis</td>
<td>8</td>
<td>9</td>
<td>0.33</td>
<td>0.43</td>
</tr>
</tbody>
</table>

Bold is showing the significant correlations.

RR, response rate; DCR, disease control rate; PFS, progression-free survival; OS, overall survival.

discussion

ASC (including prompt identification and resolution of biliary tract obstruction and infection, and multidisciplinary management of other symptoms arising from tumour progression...
including pain) is the current standard of care for patients with ABC that has progressed following first-line chemotherapy. The aim of this approach is to improve the quality of life for these patients, in which a rapidly worsening performance status and short median OS is expected.

The rapid decline in performance status on progression following first-line chemotherapy in patients with ABC, and the lack of quality data supporting the efficacy of second-line chemotherapy may be reasons for the low number of patients that seem to receive any salvage treatment. Published data suggest that between 15% and 25% of patients might be fit enough to receive second-line chemotherapy [12, 14, 56]. Moreover, several studies indicate that second-line chemotherapy may be of value for selected patients with good performance.

Figure 2. Correlation between overall survival and DCR (A), RR (B) and PFS (C) for the total of 23 studies included in the final analysis. (D) Correlation between OS and RR for the subgroup of phase II trials. (E) Correlation between OS and PFS for the phase II trials. The area of the markers is proportional to the size of each study.
status [35, 38, 56, 61]. However, no consensus exists for the most suitable second-line chemotherapy to be employed in these fit patients.

Therefore, further research evaluating the most suitable management of these patients is both necessary and timely. In order to analyse the currently available data in this setting, we carried out a systematic review of publications regarding second-line chemotherapy in advanced biliary tract patients.

chemotherapy appears to improve the survival expected with ASC only, after failure of first-line chemotherapy—however, this may be due to selection bias

In the ABC-02 trial (first-line cisplatin–gemcitabine versus gemcitabine single agent), the OS after progression to first-line cisplatin and gemcitabine was around 4 months (OS since starting first line = 11.7 months; PFS since starting first line = 8.1) [12]. Taking into account that only 15% of the patients included in the ABC-02 trial received second-line treatment, we can assume that the expected OS after progression to first-line treatment with BSC only is around 4 months [14]. When comparing the results of our analysis [mean OS 7.2 months (95% CI 6.2–8.2), see Table 3] with the expected 4 months of survival with BSC only, salvage chemotherapy after progression on first-line appears to be beneficial.

However, we need to be cautious when interpreting these results. First, patients who are eligible for and receive second-line chemotherapy have a better performance status and therefore, a better prognosis; this has been shown in multiple retrospective and phase II trials [35, 38, 61]. Secondly, although the mean OS overall was higher than the expected four months seen with BSC, the mean OS for the subgroup of the phase II trials was 6.6 months (95% CI 5.1–8.1) compared with 7.7 months (95% CI 6.5–8.9) for the subgroup of retrospective analyses (see Table 3). A potential reason for this apparent discrepancy is the higher quality of data collection that would be expected in the context of phase II trials in comparison to retrospective analyses. The same pattern was observed for DCR and PFS; outcomes in the phase II trials were inferior to those observed in retrospective analysis (see Table 3). In contrast, higher RR was reported in the phase II clinical trials, which could be related with a more accurate radiological follow-up in the context of a prospective study, usually employing objective criteria (e.g., RECIST).

correlation between overall survival and PFS/RR

In our analysis, the best correlation was observed between OS and PFS ($r = 0.54$; $P = 0.01$), which was also significant in the phase II trials subgroup ($r = 0.61$; $P = 0.04$). Although the robustness of this correlation is limited by the heterogeneity of the studies, it is important to note that these results concur with data from the pooled analysis carried out by Eckel and Schmid with studies of first-line chemotherapy in ABC, where the best correlation was shown between PFS and survival; thus making PFS a more suitable surrogate endpoint for studies of systemic therapy in first-line, and now in the second-line settings [10]. In addition, a statistically significant correlation between RR and OS for the subgroup of phase II trials was found ($r = 0.62$; $P = 0.03$) (Table 4 and Figure 2D).

our analysis’ weaknesses: poor level of evidence and heterogeneity

We carried out this review to examine systematically the evidence for administering second-line chemotherapy in patients with ABC who have progressed on a first-line treatment. No phase III clinical trials, systematic reviews or meta-analysis were available; 14 phase II trials, 9 retrospective analyses and 2 case reports met the inclusion criteria and were included in the final analysis. This demonstrates a poor level of evidence (level C) which increases the challenge of drawing quality conclusions. Moreover, due to the lack of randomized trials and the high number of retrospective analysis, there is a high risk of selection bias and over-interpretation of uncontrolled studies in this systematic review; the available data are not solid enough as a basis for clinical decision-making. In an attempt to minimize this problem, the case reports were excluded for the statistical analysis.

In this review, the particularly prolonged survivals observed in two studies are noteworthy (Figures S1 and 2 and Tables 1 and 2). Sasaki et al. [41] reported a phase II trial with S1 chemotherapy in 22 patients and Katayose et al. [52] published a retrospective series of 11 patients treated with gemcitabine with median OS of 13.5 and 15 months, respectively. The favourable outcomes observed in these two studies may be related to several factors. First, the RR reached in the first study (22.7%) was one of the highest RR reported outside of case reports and may have favourably influenced survival. Second, both studies included a high percentage of patients with recurrent disease after resection (64% and 100%, respectively), which is a subgroup of advanced disease with a known favourable prognosis. Third, the second study included patients who had received adjuvant chemotherapy with gemcitabine. Therefore, patients from the study of Katayose et al. were highly selected: relapse disease after resection and adjuvant gemcitabine followed by second-line chemotherapy with a different drug (S1, in patients who developed resistance to gemcitabine).

Marked heterogeneity with respect to the first and second-line chemotherapy used is present in these studies. Moreover, some of the trials have no data specified for first-line treatment. This makes it difficult to conclude regarding the most appropriate schedule for second-line chemotherapy. After progressing on a first-line gemcitabine-based chemotherapy switching to a fluoropyrimidine-based schedule is considered appropriate; however, this has not been validated in prospective studies. In this systematic review, we analysed the impact of switching the type of chemotherapy after progression (gemcitabine based to 5-FU based and vice-versa); no benefit nor in OS, PFS, RR or DCR was found. Therefore, no conclusions regarding the most suitable second-line chemotherapy or approach can be drawn with these data.

No quality-of-life data were available in any of the included studies. With respect to toxicity, most of the trials showed a high incidence of grade 3 and 4 toxicities; haematologic toxicity was the most frequent one (Tables 1 and 2). However, the impact of this toxicity in patient’s life or treatment is not specified in the
trials and the heterogeneity of the reporting detail makes difficult to conclude its real incidence.

**the next step: prospective randomized studies**

As detailed above, even though a detailed systematic review has been undertaken, the quality of the data is too poor to assess the real magnitude of benefit of second-line chemotherapy or the most suitable schedule to use. Therefore, well-designed prospective randomized studies are important to address this question.

Walter et al. reported the largest series of second-line treated patients including 96 subjects [56]. In this analysis, young patients, females and patients with a PFS >6 months following completion of first-line chemotherapy were more likely to receive a second-line treatment. Moreover, several factors had a significant prognostic influence in patients who received second-line chemotherapy: performance status ≤1, non-gallbladder cancer, objective response as best response with first-line treatment and PFS with first-line longer than 6 months. These prognostic factors could help on the development and design of future prospective analyses for a better selection of the patients with more chances to benefit from rescue chemotherapy.

The UK National Cancer Research Institute (NCRI) ABC-06 clinical trial (NCT 01926236, opened in January 2014) is a phase III randomized trial aiming to determine whether patients with ABC benefit from the addition of mFOLFOX chemotherapy over ASC in the second-line setting, after progression to first-line treatment with cisplatin and gemcitabine. Response, survival, toxicity, health economic and quality-of-life data will be collected. It will be the first randomized phase III in this scenario.

**conclusions**

Although level A evidence is available to support the use of first-line chemotherapy in ABC, there is little evidence (level C) to recommend the use of a second-line chemotherapy schedule for these patients. Nevertheless, the available data suggest that second-line chemotherapy in ABC may be of potential benefit in selected patients, particularly those with well-maintained performance status despite disease progression following first-line chemotherapy. Prospective randomized trials are needed to clarify the benefit of second-line chemotherapy in these patients.

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**disclosure**

The authors have declared no conflicts of interest.

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