Review Article

Systemic therapy of gallbladder cancer: review of first line, maintenance, neoadjuvant and second line therapy specific to gallbladder cancer

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Abstract: Gallbladder cancer is the most common malignant cancer of the biliary tract and is distinct from other forms of biliary tract cancer in several of its risk factors and molecular aberrations. Locally advanced, unresectable and metastatic gallbladder cancer is associated with a poor prognosis and systemic chemotherapy is the main form of treatment available to these patients. This review is focused on the available evidence supporting the use of first-line chemotherapy specifically for gallbladder cancer. Numerous non-randomised studies have been published and certain forms of monotherapy and combination therapy can both lead to response rates (RRs) of approximately 40% and may prove to affect overall survival, most notably a recent phase II study of triplet therapy with gemcitabine, cisplatin and nab-paclitaxel. There are however relatively few randomised phases II and III studies on which to base recommendations, but they do demonstrate significant survival advantages of gemcitabine-containing combination therapies over best supportive care and chemotherapeutic monotherapy. The ABC-02 trial established the combination of gemcitabine and cisplatin as standard therapy in 2010, but more recent phase III studies reported as conference papers may support alternative, gemcitabine-containing doublet chemotherapy regimens such as gemcitabine in combination with oxaliplatin or S1. This manuscript also highlights the available data from studies examining maintenance chemotherapy, biomarkers, neoadjuvant therapy and second line studies in gallbladder cancer; unfortunately, there is insufficient evidence to make recommendations in these regards. The prognosis for unresectable and metastatic gallbladder cancer remains poor, and biomarkers for stratifying patients to particular first line therapies are not defined. This might be improved by gallbladder cancer specific analysis and reporting, and making histological primary specific data available publicly for further analysis.

Keywords: Gallbladder; chemotherapy; systemic therapy; metastatic; unresectable

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Introduction

Gallbladder cancer the sixth most common cancer of the gastrointestinal tract and the most common malignant cancer of the biliary system (1,2). It is mostly associated with late diagnosis, an aggressive disease course and poor prognosis (1).

There is marked international variation in incidence; the top five countries are in South America and East Asia: Bolivia, Chile, Thailand, South Korea and Nepal [age-standardised rate (ASR) per 100,000 of 14.0, 9.3, 7.4, 6.8 and 6.7 respectively] (3). There is also great variation within countries, for example, the indigenous populations of North and South America have an increased risk of gallbladder cancer, as do the people of Northern India. Recent reports calculate an ASR of 7.16 per 100,000 for Northern India's Gwalior district, however historical data suggests that the ASR could be even higher (21.5 per 100,000) for women in Delhi (1,4,5). The United States of America (US), India and the United Kingdom (UK) have much lower rates of gallbladder cancer (with an ASR of 1.5–2.0 per 100,000) (6,7).

The predominant histological type of gallbladder cancer is adenocarcinoma (approaching 98%) and two thirds of these are moderately or poorly differentiated (8-10). The remaining histological variants are papillary, mucinous, squamous and adenosquamous alongside extra-pulmonary small cell and neuroendocrine tumours (8). Risk factors for gallbladder cancer include age, female sex, ethnicity, gallstones, gallbladder polyps, chronic cholecystitis, chronic infection with *Salmonella typhi*, an abnormal pancreatobiliary duct junction, obesity and diabetes (11,12). Many of these are distinct from the risk factors for cancers arising elsewhere in the biliary tract (11). Gallbladder cancer development is associated with several molecular aberrations, some of which are distinct to gallbladder cancer, such as *EGFR*, *ERBB3*, *PTEN*, *ARID2*, *MLL2*, *MLL3*, *TERT* promotor mutations, and others, such as *TP53*, *BRCA1*, *BRCA2*, *PIK3CA* mutations, which are common to all forms of biliary tract cancer (13,14).

Gallbladder cancer is staged in accordance with the TNM categories of the American Joint Committee on Cancer (AJCC) Union for International Cancer Control (UICC) 8th edition (15,16). The primary tumour might invade the lamina propria (T1a) or the muscular layer (T1b) of the gallbladder wall. The primary tumour might invade further into the perimuscular connective tissue without involvement of the serosa (T2a) or into the perimuscular connective tissue on the hepatic side with no extension into the liver (T2b), further into the liver, into the serosa or an adjacent organ (T3) or into the main portal vein, hepatic artery or several extrahepatic organs or structures (T4). Disease is further categorised by regional lymph node spread: no regional lymph node metastasis (N0), metastases to one or three regional lymph nodes (N1) or metastases to four or more regional lymph nodes (N2), and by distant metastasis: no distant metastatic spread (M0) or distant metastases (M1). If there is no regional or distant spread (N0M0) then gallbladder cancer is staged according to the primary tumour: T1, T2a, T2b, T3 disease is categorised as stage I, IIA, IIB and IIIA respectively. Stage IIIB disease corresponds to T1-3 with N1 M0 disease, stage IVa to T4 N0-1 M0 and stage IVB to T1-4 with N2 or M1 disease.

Surgery can be attempted in patients with up to stage IVa disease, but gallbladder cancer is usually diagnosed at an unresectable locally advanced or metastatic stage (6,9). Gallbladder cancer is usually diagnosed as either an incidental finding in patients with cholelithiasis who are treated with cholecystectomy, in patients investigated for localising symptoms such as jaundice or right upper quadrant pain, or with systemic symptoms such as anorexia or weight loss (6,9). Even if extensive surgical resection is performed, gallbladder cancer frequently recurs and is associated with a poor prognosis of less than 4–5 months without systemic therapy (6,9). Therefore, many gallbladder cancer patients will be candidates for and could benefit from systemic chemotherapy, which is the focus of this article.

Systemic chemotherapy for locally advanced or metastatic gallbladder cancer

Advanced, unresectable and metastatic gallbladder cancer commonly infiltrates into the hepatic duct and therefore the first treatment step is frequently palliative endoscopic or percutaneous stenting or drainage (17-19). Functioning biliary drainage improves symptoms of jaundice, nausea, vomiting and itch, reduces the risk of death by cholangitis or liver failure and is frequently part of best supportive care treatment (17,18). Best supportive care may well be best option for some gallbladder cancer patients with locally advanced, unresectable or metastatic disease, particularly those with multiple co-morbidities, poor end-organ function, and a poor Eastern Cooperative Oncology Group (ECOG) performance score (PS) >2 (6).

As well as systemic chemotherapy, alternatives such as chemoradiation with a concomitant fluoropyrimidine in selected cases of locally advanced, unresectable or metastatic gallbladder cancer and immunotherapy in patients with microsatellite instability (MSI-) high tumours may be considered (20). Chemoradiotherapy and immunotherapy will be considered in separate articles within this edition. This article is focused on the role of systemic chemotherapy in advanced gallbladder cancer, and focuses on response rates (RRs) and survival data specifically reported for gallbladder cancer patients. In the referenced studies, the histological sub-types within cohorts are frequently incompletely reported, but we have aimed to present studies which either select for adenocarcinoma. A brief discussion of the management of gallbladder neuroendocrine carcinomas is also provided.

Best supportive care

To provide a reference point for the survival of patients on the multiple regimens described in the literature, we will describe examples of first-line patients managed with best supportive care. In 2010, Sharma *et al.* published a single centre randomised study in which 82 patients with unresectable or metastatic adenocarcinoma of the gallbladder were allocated to the systemic chemotherapy or best supportive care arm (21). The aim of the study was to assess the role of chemotherapy in this setting. Twenty-seven patients were randomized into the best supportive care arm, one patient (3.7%) had stable disease as best response (first CT scan was performed at 15 weeks) and the rest showed progressive disease (96.3%); the median progression free survival (PFS) was 2.8 months (95% CI, 1.8–3.8) and median overall survival (OS) was 4.5 months (95% CI, 0.2–8.8) (21). A retrospective case series from Ji *et al.* in Japan reported OS data for 35 gallbladder cancer patients who had an ECOG PS of 0-2 and were advised to have best supportive care (the reasons for this clinical decision were not reported) (22). The reported median OS was 4.4 months (95% CI, 2.90–5.90), which similar to Sharma *et al.* (21) Singh *et al.* described an even poorer survival from 20 patients in an Indian prospective case series; median OS was 3.25 months (95% CI, 2.75–3.75) (23). However, a proportion of the patients who were included in this cohort were unfit for systemic chemotherapy which could explain the poorer prognosis of the whole series (23).

Clinical data: non-randomised studies of monotherapy

Gemcitabine

First-line gemcitabine monotherapy has shown RRs between 7–36% (24-27). A retrospective phase II study from Tsavaris *et al.* in 2004 examined the efficacy of single agent gemcitabine (800 mg/m^2 of body surface area, weekly) in 14 first line gallbladder cancer patients (24). They showed that 5/14 (35.7%) of patients had a partial response (PR), disease control rate (DCR) was 78.6% (11/14), median time to progression (TTP) was 6.4 months (95% CI, 5.8–7.1) and median OS 17.1 months (95% CI, 15.8–18.5) (24). Gallardo's phase II study from Chile of single agent gemcitabine at a slightly higher dose but reduced frequency (1,000 mg/m^2 weekly for 3 weeks on and 1 week off) showed a PR of 36% (95% CI, 17.1–57.9) (9/25), DCR of 60% (15/25), median duration of response of 5.2 months and median OS of 7.5 months (25). The RRs were lower in two retrospective case series from Japan (26,27). For example, Suzuki *et al.* reported in 2010, 45 consecutive patients treated in a single hospital achieving an overall RR of 8.8% (4/45) and DCR was 57.8% (26/45) (26).

Non-gemcitabine

Non-gemcitabine regimens may be better suited to patients with reduced biliary drainage. Such alternative regimens include S1 alone, an oral fluoropyrimidine containing three agents to increase circulating fluoropyrimidine levels and reduce bowel toxicity, or other agents such as irinotecan or 5-fluorouracil. The multicentre phase II study from Furuse *et al.* showed a partial RR of 45.0% (9/20) and a median OS of 8.1 months in first line gallbladder cancer adenocarcinoma patients (28). In an American Phase II study, single agent irinotecan (CPT-11) showed low level activity in 23 GBC patients with a 4% (1/23) complete response rate (CR), 4% (1/23) PR rate, 57% DCR, median PFS of 2.7 months (95% CI, 1.7–3.3) and median OS 7.0 months (95% CI, 5.7–8.4) (29). 5-fluorouracil (5-FU) with folinic acid showed a 5% (1/20) partial RR and 55% DCR in a single centre study from Pakistan (30). Single agent regimens of capecitabine and leucovorin-modulated 5-FU have been reported but included small populations of gallbladder cancer patients and cannot be relied on for drawing conclusions regarding their activity in gallbladder cancer (31-33).

Clinical data: non-randomised studies of combination chemotherapy

Doublet therapy

Gemcitabine-containing doublet therapy

Doublet chemotherapy with gemcitabine and cisplatin in gallbladder cancer has been shown to achieve overall RRs between 22.7–36.7% (34-36). For example, in 2004, Doval *et al.* indicated early activity with gemcitabine and cisplatin in a gallbladder cancer adenocarcinoma cohort (n=30); the CR rate was 13.3% (4/30), RR was 36.7% (11/30), DCR was 56.7% (18/30), median TTP was 18 weeks (95% CI, 14–24 weeks) and median OS was 20 weeks (95% CI, 14–31 weeks) (36). Lee *et al.*'s phase II study of combination gemcitabine with cisplatin, published in 2007, described a population of 14 patients diagnosed with gallbladder cancer; the RR was 28.6% (95% CI, 4.9–52.2%) (4/14) and DCR was 42.9% (6/14) (35). In a multicentre phase II study of gemcitabine with cisplatin conducted in Australia and New Zealand, Goldstein *et al.* reported a partial RR of 22.7% (5/22) for gallbladder patients (34).

Woo *et al.* examined gallbladder cancer patients who received 2 weekly cycles of gemcitabine (1,000 mg/m^2) and oxaliplatin (100 mg/m^2) and showed a RR of 36% (12/33) with an impressive disease stabilisation rate of 88%, a median TTP of 5.3 months (95% CI, 3.7–6.9) and median OS of 6.8 months (95% CI, 6.1–7.5) (37). Similar results with gemcitabine oxaliplatin (GEMOX) were shown by Harder *et al.* in 2006 and led a PR rate of 40%, DCR of 70% and median OS 11.1 months with 10 patients who were all <76 years old and either PS 0 or 1 (38). Sharma *et al.* studied a 3-weekly regimen of gemcitabine and oxaliplatin in a single centre prospective open label phase II study in India in 48 gallbladder tumour patients and report a complete RR of 6.2%, a lower objective RR of 21.2%, DCR of 56.6%, median PFS of 3 months (95% CI, 2.2–3.8) and median OS of 7.5 months (95% CI, 5.6–8.4) (39). A far lower RR was recorded however in André *et al.*'s international phase II study of gemcitabine and oxaliplatin; the RR was 4.3% (1/23) and the median PFS was 2.5 months (95% CI, 1.6–4.3 months), despite using the same regimen as the other, more effective studies (40).

Studies of gemcitabine with capecitabine show RRs similar to gemcitabine with cisplatin (41-44). For example, Cho *et al.* described a phase II combination trial of gemcitabine and high dose capecitabine which gave a 33% (8/24) PR rate, 75% (18/24) DCR, median TTP of 6 months (95% CI, 3.8–8.1) and median OS of 16 months (95% CI, 13.8–18.3) (42). In Riechelmann's phase II trial of gemcitabine and capecitabine in unresectable gallbladder cancer patients, 1/27 patients had complete responses (4%), 9/27 had PRs (33%), DCR was 64% (15/27), median PFS and median OS were 4.4 months (95% CI, 0.1–9.4 months) and 7.7 months (95% CI, 4.6 months–not reached) (44). Alberts *et al.*'s phase II study, reported in 2007, combined gemcitabine with pemetrexed which, in 16 gallbladder cancer patients, showed a complete RR of 6.3% and overall RR of 12.5% (45).

Non-gemcitabine doublet chemotherapy

Of the non-gemcitabine containing regimens, a phase II study of doublet therapy with capecitabine and cisplatin in gallbladder cancer adenocarcinoma showed a high partial RR of 53.3% (8/15), along with the same DCR (scans were performed every 6 weeks) and a survival rate at 1 year of 66% (46). The RR of capecitabine and cisplatin was lower in another phase II study; the RR was 32% (6/19) (47). It was also far lower in Woo *et al.*'s retrospective gallbladder cancer case series of 59 patients; the RR was 14.2%, DCR was 65.2%, median TTP and overall survival of 4.2 and 7.2 months respectively (48).

5-FU and cisplatin showed good activity in a Japanese phase II which reported a partial RR of 46.7% (4/15) and DCR of 66.7% (10/15), however the median time to treatment failure was 85 days and median OS 150 days (4.9 months) (49). Ducreux *et al.* used a similar cisplatin and 5-FU combination, and showed a partial RR of 36% (4/11) in the first line gallbladder cancer adenocarcinoma patients (50). Unfortunately, there is only one study which reported RRs for gallbladder cancer in an S1-containing regimen: Kim *et al.*'s 2011 single centre phase II doublet regimen of oxaliplatin and S1 showed RRs of 40% PR in 10 first-line patients with gallbladder cancer (51). Oxaliplatin and capecitabine showed good activity in a German prospective multicentre phase II trial reported in 2008 by Nehls *et al.* (52); they reported a complete response in 1/27 patients (4%), an overall RR of 30% (8/27), DCR of 63% (17/27), median TTP of 4.7 months (95% CI, 4.3–11.7) and overall survival of 8.0 months (95% CI, 4.3–11.7) (52). Low RRs (<10%) are reported in studies of uracil-tegafur combined with intravenous doxorubicin (53,54).

Triple therapies

A recent open-label, single-arm phase II trial of gemcitabine, cisplatin and nab-paclitaxel triple therapy reported by

Shroff *et al.* from two American centres (n=60, intention to treat population) has shown impressive data across BTCs; the RR was 45%, median PFS was 11.8 months (95% CI, 6.0–15.6) and median OS was 19.2 months (95% CI, 13.2 months to not estimable) (55). Gallbladder cancer specific survival data was reported (n=13), but not RRs; the PFS was 4.1 months (95% CI, 2.1–14.9) and median OS was 15.7 months (95% CI, 3.8 months to non-reached) (55). This study is being expanded into a phase III and may change the standard treatment of all or certain biliary tract cancers (intrahepatic cholangiocarcinoma was the histological primary with the best survival data in this study) (55). Sohn *et al.* reported a trial of triple therapy of 5-FU added to gemcitabine and cisplatin, and showed a RR of 40% (6/15) with 1 (6.7%) complete response, which was slighter higher than reported for gemcitabine cisplatin doublet therapy, however with a high burden of toxicity (for example, 71.4% patients developed Grade 4 neutropenia) (56). Gemcitabine and 5-FU with oxaliplatin has been reported to lead to a 23% (8/35) partial RR, a 69% (24/35) DCR with a median TTP of 5.7 (95% CI, 3.1–8.1) months and median OS of 9.9 months (95% CI, 7.5–12.2) (57). Gemcitabine, leucovorin and 5-FU led to 3/14 (21.4%) PRs, with a median PFS of 5.2 months (95% CI, 1.7–9.1) and median OS of 7.2 months (95% CI, 3.6–11.7) in first line gallbladder cancer patients in the US (58).

Regimens without gemcitabine can lead to reasonable RRs such as 5-FU, high dose levofolinic acid and oral hydroxyurea on a weekly schedule which showed a 9/30 (30%) PR rate, DCR of 57% and median OS of 8 months (59). In addition, less common combination regimens have been studied and some could be effective. For example, triplet chemotherapy with gemcitabine, oxaliplatin and huachansu (a traditional Chinese medicine from the skin of the Bufo toad) showed a partial RR of 34.8%, DCR of 65.2%, median PFS 5.8 months and median OS 10.5 months in a cohort of 23 patients of which 86% were first line (60). Finally, a multicentre phase II from Germany reported by Feisthammel *et al.* examined triplet chemotherapy with irinotecan, folinic acid and 5-FU and showed a low partial RR of 15% (2/12), DCR of 31% (4/13), an estimated median PFS of 5.3 months (159 days) and OS of 9.1 months (273 days) (61).

Quadruple therapy

A prospective case series was reported by Cereda *et al.* examining a quartet chemotherapy regimen of gemcitabine, cisplatin, epirubicin and 5-fluorouracil; they report a RR of 33.3% (4/12) gallbladder adenocarcinoma patients and a median OS of 9.6 months (62). Quadruple chemotherapy with 5-FU, cisplatin, doxorubicin and interferon alpha 2b was studied in 2001 with 17 evaluable first line, GBC adenocarcinoma patients who had a complete RR of 5.9%, PR of 35.3%, DCR of 64.7% and median OS of 11.5 months (95% CI, 5.4–17.6), but with notable toxicity such as 41% grade 3/4 neutropenia across the whole study cohort of 41 GBC and cholangiocarcinoma patients (63).

Randomised phase II studies

A summary of the randomised studies is provided in Table 1

The first phase II randomised trial exploring the role of the cisplatin and gemcitabine combination in advanced biliary tract cancer was the UK phase II ABC-01 clinical trial. This study was later on converted into a phase III study (ABC-02) and will therefore be discussed later on. Okusaka *et al.* reported a randomised phase II study (BT22) comparing gemcitabine alone against gemcitabine and cisplatin which suggests a survival advantage for patients treated with gemcitabine and cisplatin over gemcitabine alone of 9.1 months (95% CI, 6.9–11.6) against 6.7 months [(95% CI, 4.2–11.0); P=0.675] (65). The BT22 clinical trial confirmed the previous findings from the ABC-02 study and suggested benefit from combination chemotherapy in an Asian population. However, it did not separately report the GBC response/outcome data (65,69).

The BINGO trial from Malka *et al.* was conducted across 18 hospitals in Greece and France and reported 11 GBC patients who were treated with GEMOX and 11 gallbladder cancer patients who were treated with GEMOX plus cetuximab (67). The objective RR was 45% (5/11) for the GEMOX cohort and in the intention to treat GEMOX plus cetuximab group of 18% (2/11) (67).

Morizane *et al.* compared the RRs and median OS of S1 monotherapy against doublet therapy of gemcitabine and S1 in 2013 (66). Gallbladder cancer patients treated with S1 alone had a 16.7% (3/18) RR and gemcitabine and S1 was 12.5% (2/16); the median OS was 6.5 months (95% CI, 3.6–8.0) with S1 alone and 11.7 months (95% CI, 6.3–13.9) in the combination arm (66). Due to the low toxicity of the combination regimen a higher dosage was taken forward into the phase III trial, which has been reported in abstract form and is discussed in the next section.

Sharma *et al.* randomised patients diagnosed with

Table 1 Table detailing the regimens, response rates and survival data for gallbladder cancer patients within randomised phase II and III studies which have been published as complete manuscripts

Author, year (ref.)	Histology	Regimen	n	Assessment of response	Complete response rate (%)	Overall response rate (%)	Disease control rate (%)	Progressive disease (%)	Median PFS (95% CI) (months)	Median OS (95% CI) (months)
Randomised Phase II										
Falkson, 1984 (64)	Not specified	A: 5-FU 600 mg/m^2/day, days 1–5 every 5 weeks; B: 5-FU as in (A) with streptozotocin 500 mg/m^2/day intravenously for the first 5 days of cycle 1 only; C: 5-FU 500 mg/m^2/day orally for first 5 days which repeats every 5 weeks and given a single dose of Methyl-CCN 150 mg/m^2 on cycle 1 day 1 only	A: 18; B: 16; C: 19	Not reported	Not reported	A: 11.1; B: 12.5; C: 5.3	Not reported	Not reported	Not reported	Not reported
Sharma, 2010 (21)	Adenocarcinoma	A: Best supportive care; B: 5-FU 425 mg/m^2 and folinic acid 20 mg/m^2 weekly for 30 weeks; C: Gemcitabine 900 mg/m^2 and oxaliplatin 80 mg/m^2 on days 1 and 8 every 3 weeks	A: 27; B: 28; C: 27	RECIST, not otherwise specified	A: 0; B: 0; C: 7.7	A: 0; B: 14.3; C: 30.7	A: 3.7; B:21.4; C:68.7	A: 92.3; B: 78; C: 31	A: 2.8; B: 3.5; C: 8.5	A: 4.5; B: 4.6; C: 9.5
Okusaka, 2010 (65)	Not specific	G-arm: single-agent gemcitabine at dose of 1,000 mg/m^2 on days 1, 8 and 15 of a 28-day cycle; GC-arm: cisplatin 25 mg/m^2 plus gemcitabine 1,000 mg/m^2 on days 1, 8 of a 21-day cycle	G-arm =17; GC-arm =15	RECIST, not otherwise specified	Not reported	Not reported	Not reported	Not reported	Not reported	G-arm =6.7 (4.2–11.0); GC-arm =9.1 (6.9–11.6)
Morizane, 2013 (66)	Carcinoma, not otherwise specified	A: S1 monotherapy was given orally twice daily for 4 weeks, followed by a 2-week gap in therapy. Cycle is 6 weeks long; B: Gemcitabine + S1 1,000 mg/m^2 gemcitabine was infused on days 1 and 8, and S-1 was given orally twice daily from days 1 to 14. Three-week cycle	A: 18; B: 16	RECIST version 1.0	Not reported	A: 16.7; B: 12.5	Not reported	Not reported	Not reported	A: 6.5 (3.6–8.0); B: 11.7 (6.3–13.9)

Table 1 (*continued*)

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Author, year (ref.)	Histology	Regimen	n	Assessment of response	Complete response rate (%)	Overall response rate (%)	Disease control rate (%)	Progressive disease (%)	Median PFS (95% CI) (months)	Median OS (95% CI) (months)
Malka, 2014 (67)	Not reported	A: Gemcitabine 1,000 mg/m^2 was administered as a fixed dose rate, 100 min intravenous infusion (10 mg/m^2 per min) on day 1, and oxaliplatin 100 mg/m^2 was given as a 2 h infusion on day 2 as part of a 2-week cycle; B: Same regimen with cetuximab 500 mg/m^2 infusion on days 1 or 2	A: 11; B: 11 (intention to treat)	RECIST version 1.0	Not reported	A: 45; B: 18	Not reported	Not reported	Not reported	Not reported
Randomised phase III										
Valle, 2010 (68)	Not reported	A: Gemcitabine-only group - dose of 1,000 mg per square meter on days 1, 8, and 15 every 4 weeks; B: Cisplatin (25 mg per square meter of body-surface area) followed by gemcitabine (1,000 mg per square meter), on days 1 and 8 every 3 weeks	A: 56; B: 61	RECIST version 1.0	A: 0; B:0	A: 21.4; B: 37.7	A: 76.8; B:85.2	A: 23.2; B: 14.8	Not reported	Not reported

gallbladder cancer to three groups (21). The first arm was described previously in this review and was managed with best supportive care (21). The second arm received gemcitabine with oxaliplatin and showed 7.7% (2/27) complete responses, 23% (6/27) PRs (23%) and 38% (10/27) incidences of stable disease leading to a marked increase of median PFS [8.5 months (95% CI, 5.7–11.3)] and median OS [9.5 months (95% CI, 5–14)] (21). FU and folinic acid (n=28) was the third gallbladder cancer arm and Sharma *et al.* suggests that is weakly active regimen with negligible effect on median OS (4.5 to 4.6 months), although 4 (14.3%) PRs and 2 (7.1%) incidences of stable disease were recorded (21). Several regimens were used in Falkson's 1984 study which showed for patients with untreated gallbladder cancer that the objective RR for 5-FU oral alone was 11.1% (2/18), for 5-FU with streptozotocin was 12.5% (2/16) and for 5-FU and Methyl-CCNU it was 5.3% (1/19) (64).

Randomised phase III

The ABC-02 trial reported in 2010 was a multi-centre phase III trial conducted across the UK which compared gemcitabine against gemcitabine with cisplatin in advanced/metastatic biliary tract cancers (68). Gemcitabine alone was administered at a dose of 1,000 mg/m^2 on days 1, 8, and 15 every 4 weeks. When the whole population was analysed, the doublet chemotherapy showed a benefit in PFS (median PFS in the gemcitabine group was 5.0 and 8.0 months in the gemcitabine cisplatin group) and in OS (median OS was 8.1 months in the gemcitabine group and 11.7 months in the gemcitabine cisplatin group). In patients with gallbladder tumours, the gemcitabine alone arm showed a partial RR of 21.4% (12/56), DCR of 76.8% (43/56) and progressive disease of 23.2% (13/56) (68). The doublet chemotherapy arm administered cisplatin (25 mg/m^2) and gemcitabine (1,000 mg/m^2) on days 1 and 8 every 3 weeks and, in the subgroup of GBC, the trial reported a partial RR of 37.7% (23/61), DCR of 85.2% (52/61) and progressive disease in 14.8% (9/61) (68). The median PFS and OS survival for gallbladder was not specifically reported however there was improved median OS in terms of the hazard ratio (HR) =0.61; (95% CI, 0.42–0.89) in favour of the doublet chemotherapy when the subgroup with gallbladder cancer was analysed (68). When these results are compared to the data from other biliary tract cancer in the same clinic trial [partial RR 18.0% for the cisplatin gemcitabine group, rate of progression as best response 21% for the cisplatin gemcitabine group and OS HR 0.57 (95% CI, 0.34–0.94) for intrahepatic cholangiocarcinoma, 0.73 (95% CI, 0.43–1.23) for extrahepatic cholangiocarcinoma, 0.59 (95% CI, 0.32–0.90) for hilar cholangiocarcinoma and 0.62 (95% CI, 0.21–1.82) for ampullary tumours)], there seems to be a towards increased objective RR in the gallbladder cancer group (compared to other biliary tract cancer). However, the impact on differences on OS benefit seemed marginal, with all subgroups presenting a similar HR. Whether this is increased partial RR reflects an easier assessment of the radiological response assessment is unclear (70).

There are two, additional relevant phase III trials which have been presented in abstract form and compare gemcitabine and cisplatin with alternative gemcitabine-containing doublet therapies. JCOG1113/ FUGA-BT, has been conducted in Japan with contained a total of 354 patients with biliary tract cancer who were randomised to be treated with either gemcitabine plus cisplatin or gemcitabine plus S1. A preliminary report was presented at the American Society of Clinical Oncology (ASCO) 2018 meeting which showed non-inferiority in terms of the primary endpoint of median OS; gemcitabine-cisplatin led to a median OS of 13.4 months and gemcitabine with S1 led to a median OS of 15.1 months [HR =0.945; (95% CI, 0.777–1.149), P=0.00459] and comparable, if not slightly better secondary endpoints in median PFS, clinically significant AEs and SAEs, planned dose delivery and convenience (since gemcitabine with S1 does not require the pre-hydration needed to administer cisplatin), although the RR was slightly better with gemcitabine with cisplatin (32.4% *vs.* 29.8%) (71). However, the gallbladder data has not been published yet for this trial.

The second trial is a single centre phase III randomised study which compared gemcitabine cisplatin (GemCis) against modified gemcitabine and oxaliplatin (mGEMOX) for patients with *GBC* specifically (72). This trial included 108 patients in each arm and reports similar responses rates of 23.5% and 22.6% in mGEMOX and GemCis arms respectively, statistically similar median PFS times of 6 months (95% CI, 4.72–7.27) in mGEMOX arm and 4.5 months in GemCis arm [(95% CI, 3.44–5.55); P=0.123] and statistically similar median OS in the mGEMOX cohort of 9 months (95% CI, 7.77–10.22) and 8 months in GemCis arm [(95% CI, 7.40–8.59); P=0.152] (72).

Maintenance therapy

Whether to continue chemotherapy beyond a fixed period of 6 months or not remains unclear. Following the rationale

of trials such as the PARAMOUNT trial continuation maintenance therapy in non-small cell lung cancer, Ostwal's 2017 retrospective cohort study reported that gallbladder cancers who achieved at least stable disease with 6–8 cycles of gemcitabine-cisplatin had statistically better median PFS and OS if they received continuation chemotherapy rather than second line chemotherapy on progression (73,74). Although the two groups seemed to be well matched, the data needs confirmation in a prospective trial.

Biomarkers

Clinical and biochemical biomarkers for gallbladder cancer prognosis and chemotherapy response prediction are poorly defined. Across BTC there are numerous biomarkers including recurrent *vs.* metastatic disease, number and site of metastases, PS, human equilibrative nucleoside transporter (hENT1) and carbohydrate antigen (CA) 19-9 which seem to affect outcome (6,11,27,68,75-79).

Some studies suggest differential RRs and survival in gallbladder cancer compared to other forms of biliary tract cancer, and future trials may look for robust statistically significant differences (55,67,68). Current opinion is that these differences are likely to be genetically driven. Gallbladder cancer has a greater prevalence of amplifications in human epidermal growth factor receptor 2 (HER2), activatory mutations in KRAS, and their downstream effectors. In contrast, gallbladder cancer is less likely to have isocitrate dehydrogenase (IDH-1) driver mutations and fibroblast growth receptor (FGFR)-2 translocation events in comparison to cholangiocarcinoma (11). However, current pre-clinical data has not addressed how these differences in oncogenes or cell metabolism translate to the aggressiveness of the tumour or susceptibility to standard chemotherapy options. Whether genetic differences lead to differences in prognosis or if these biomarkers are truly predictive remains unclear (11,80).

Neoadjuvant treatment

Most studies show a marked survival benefit for those who are ultimately treated with definitive surgical resection compared to those who could not be treated with surgical resection or received incomplete surgical resection (81-85). For example, Creasy *et al.* reported in a retrospective case series that 10 of 74 patients (14%) with locally advanced or lymph node positive gallbladder cancer who were treated with neoadjuvant, gemcitabine-containing chemotherapy underwent definitive resection; these 10 patients had a median OS of 51 months (95% CI, 11.7–55.3) compared to an 11 month median OS (95% CI, 4.1–23.6) for those who received chemotherapy and underwent surgery but this was not definitive (n=12/74) (P=0.003) (86). Furthermore, a notable proportion of patients included in these studies do proceed to surgery. For example, Gangopadhyay *et al.* report, in a retrospective case series, for locally advanced gallbladder cancer patients having a 3 weekly cisplatin gemcitabine regimen, an overall resection rate of 48.7% (59/121) with 43.0% (52/121) having R0 resections (84). Of 106 gallbladder cancer patients who were treated with single agent gemcitabine in a retrospective case series from Kato *et al.* reported in 2013, 7 received neoadjuvant chemotherapy and all 4 patients with disease control underwent curative surgery (83). Despite cases of increased survival, the overall impact of starting neoadjuvant chemotherapy is unclear and is not robust enough to make recommendation, namely because not all patients can receive curative surgery and there are no studies comparing neoadjuvant chemotherapy with surgery and then adjuvant chemotherapy or palliative surgery and palliative chemotherapy. The difficulty of making comparisons is compounded by the lack of standardised definitions of what is resectable and what is not resectable (85).

Second line

There are few studies which examine biliary tract cancers chemotherapy in the second line setting and none which report a best supportive care cohort to compare against (87). Kang *et al.* showed that the median OS for gallbladder patients (n=14) who received various forms of gemcitabine based doublet chemotherapy was 4.4 months (95% CI, 3.2–5.7) in the second-line setting (88). This could be improved by several regimens including folinic acid, 5-FU and oxaliplatin (FOLFOX) which showed encouraging responses as a second line agent in the 2015 prospective case series reported by Dodagoudar *et al.* (89) They reported an impressive RR of 24.2% (16/66) and a DCR of 59.1% (39/66), although the method of cross-sectional imaging response evaluation is not reported (89). The median TTP was 3.9 (95% CI, 3.1–4.7) and median OS 7.6 (95% CI, 6.8–8.2) (89). In Suzuki *et al.*'s 2013 multicentre phase II study 14 2nd line gallbladder cancer patients received S1 after progression on gemcitabine (90). The RR was 7.1% (1/14) with a single PR, DCR was 42.9% (6/14), median PFS was 1.4 months and median OS was 4.7 months (90).

The RR was higher in a previous phase II study reported by Sasaki in 2010; it was 50% (3/6), but no other survival or response data was reported for these patients (91). There are several reported alternative regimens such as irinotecan and capecitabine (XELIRI) or irinotecan monotherapy but many are unsuitable for analysis due to too few gallbladder cancer patients, and poor reporting of gallbladder cancer responses and regimens (78,79,92-100).

Neuroendocrine carcinomas

High grade small cell and large cell neuroendocrine carcinomas of the gallbladder comprise <2% of all gallbladder cancer cases (101). Patients tend to present with advanced disease, and are frequently treated with similar chemotherapy schedules to those used in small cell lung cancer (102). Standard chemotherapy for advanced or metastatic disease is based on a combination of platinum (carboplatin or cisplatin) and etoposide (or infrequently gemcitabine or paclitaxel); there is no standard second line therapy (102-108). First-line systemic therapy recommendations have not been modified for around 30 years, due to the lack of prospective studies (104,107,108).

Conclusions

A variety of systemic chemotherapy regimens have been reported in observational studies and phase II trials suggesting potential effectiveness in gallbladder cancer. Active agents include gemcitabine, platinum compounds and S1. However, reporting bias, inconsistency in the regimens used and variation in patient selection and characteristics, make direct comparisons difficult. The only large phase III trial which has been published and contains accessible gallbladder cancer data is ABC-02 and has established gemcitabine and cisplatin as a standard regimen for both first line biliary tract cancer and gallbladder cancer. However, two new phase III trials have been reported in abstract form and may support the use of gemcitabine combined with oxaliplatin or S1 as the second agent in some first line patients, and a recent non-randomised phase II suggests that the triple therapy of gemcitabine, cisplatin and nab-paclitaxel may prove to extend median overall survival in both biliary tract cancer and gallbladder cancer. No robust data exists comparing the response to chemotherapy between gallbladder and other biliary tract cancer. The ABC-02 clinical trial showed a trend towards increased partial RR in the gallbladder cancer group (compared to other biliary tract cancer), whether this is reflection of an easier radiological response assessment or an actual increased activity of the cisplatin and gemcitabine is unclear, especially in view of similar benefit in terms of OS.

Only three studies report useful data for the second line treatment of gallbladder cancer. Unfortunately, the lack of comparative studies in the second line setting makes it difficult to recommend one of those regimens above others as a salvage therapy after progression to first-line treatment. In addition, whether to treat with neo-adjuvant treatment followed by potential surgery or surgery followed by adjuvant therapy has not been addressed, and the methods and definitions required to examine that question are still lacking.

The prognosis for unresectable and metastatic gallbladder cancer remains poor, and biomarkers for stratifying patients to particular first line therapies are not defined. This could be improved by gallbladder cancer specific analysis and reporting in biliary tract cancer trials or making data available publicly for further analysis. Currently any gallbladder cancer specific signals are being lost within all biliary tract cancers, even though biliary tract cancers are known to have distinct biological and genetic behaviour (13,14). This heterogeneity and data on underlying genetic aberrations also provides an opportunity for combination therapy with targeted or immune-modulatory agents in the first line and on progression which may in carefully designed umbrella trials help us to personalise systemic gallbladder cancer treatment.

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Footnote

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