Neoadjuvant chemotherapy in patients with locally advanced gallbladder cancer


ABSTRACT

Aim: Surgery is the only curative option for patients with gallbladder cancer (GBC). This study looks at the outcome of patients treated with neoadjuvant chemotherapy (NACT).

Patients & methods: This is retrospective analysis of the prospectively maintained database of patients with locally advanced GBC treated between February 2009 and September 2013 with NACT. Patients received gemcitabine-platinum based regimen.

Results: A total of 37 patients (median age: 54 years, 64.9% females) received NACT. Overall response rate was 67.5%. In total, 17 patients (46%) underwent R0 resection. Median overall survival/progression-free survival of the whole group was 13.4/8.1 months, respectively. Patients who underwent surgery had a significantly better overall survival (median not reached vs 9.5 months) and progression-free survival (25.8 vs 5.6 months), respectively.

Conclusion: NACT increases resectability and survival in patients with locally advanced GBC.

Gallbladder cancer (GBC) is a common cancer in the Ganges belt of northern India with an age-adjusted incidence of 9–14 per 100,000 women annually [1]. Most of the data on GBC is from the western literature where cholangiocarcinoma is more common compared with GBC, hence these are clubbed together for most clinical trials [2–4]. Most cases of GBC present at an advanced stage, precluding surgery [5]. Postoperative recurrences following curative resection for GBC are usually distant, hence the use of adjuvant therapy can improve survival after curative resection especially in node positive patients as has been shown in some studies but definitive data from BILCAP study is pending [6–8]. Given that surgery remains the only curative option available to patients, if patients with locally advanced or borderline resectable disease can be downstaged and offered resection, this may change the outcome of this group of patients [9,10]. ABC-02 trial has established the use of gemcitabine-platinum as the standard of care in patients with advanced GBC [2]. We present here the data on patients with locally advanced GBC who were treated with curative intent with neoadjuvant chemotherapy within a multidisciplinary team.

Patients & methods

• Patients

Patients with histologically or cytologically confirmed locally advanced GBC from a prospectively maintained database were included in the analysis. Patients diagnosed between February 2009 and September 2013 were treated at Tata Memorial Centre. The criteria to commence chemotherapy were ability to give signed informed consent to treatment, ECOG performance
status of 0–1, adequate renal function tests and liver function tests not more than two-times normal. Patients with serious uncontrolled concomitant illness were not considered eligible to receive therapy.

All patients underwent a staging workup which included a contrast-enhanced computed tomography (CT) scan of abdomen and chest or a PET-CT scan and tumor markers (CEA and CA19.9). The patients were categorized as locally advanced if they had: gallbladder mass invading more than 2 cm of the liver parenchyma, adherent to duodenum and/or hepatic flexure of colon without porta hepatis or vascular invasion, had coeliac, gastrohepatic, portocaval or peripancreatic lymphadenopathy and port site metastases. There is no accepted definition of borderline resectable GBC. We, at our center believe that GBC should be treated with systemic chemotherapy in cases with imaging features of loco-regional advanced disease as defined. These may be reclassified as borderline resectable GBC in the future. All patients were discussed within a multidisciplinary joint clinic and labelled as being treated with curative intent. Patients not considered operable by the surgical team but not fulfilling these criteria were taken as early GBC for the purpose of this analysis. Indications for chemotherapy in these patients included a collection in the subhepatic space after previous cholecystectomy suspicious of intraoperative spillage, a soft tissue mass in the GB (gall bladder) fossa in close proximity to common bile duct and a soft tissue thickening in

Figure 1. Consort diagram for the 37 patients treated with neoadjuvant chemotherapy.
CR: Complete response; NACT: Neoadjuvant chemotherapy; OS: Overall survival; PD: Progressive disease; PFS: Progression-free survival; PR: Partial response; SD: Stable disease.
the gallbladder neck on imaging in two patients respectively who underwent a previous surgery. The thinking behind giving chemotherapy in these last patients was that the primary surgeon would have unknowingly dissected through the tumor, which could have resulted in tumor dissemination. Chemotherapy in all these patients was administered to know the tumor biology and whether any definitive features of inoperability developed in the interim.

### Treatment

All patients received gemcitabine-based chemotherapy. Neoadjuvant chemotherapy comprised of Gem–Cis (gemcitabine 1000 mg/m\(^2\) as a 30-min infusion on day 1, 8 and cisplatin 25 mg/m\(^2\) on day 1 and 8 of a 21-day cycle) or Gem–Ox (gemcitabine 1000 mg/m\(^2\) on day 1 as a 100-min infusion and oxaliplatin 100 mg/m\(^2\) on day 2 over 2 h every 14 days).

### Toxicity assessment

Toxicity was graded using the National Cancer Institute Common Terminology Criteria version 3 grading system and only grade 3 and 4 toxicities were recorded with regularity in the clinical notes [11].

### Assessment of response

Tumor responses were assessed radiographically after three (Gem–Cis) or four (Gem–Ox) cycles after completion of chemotherapy. Designations of response were based on the standardized response definitions established by the WHO [12]. Complete response (CR) was defined as the disappearance of all known disease for at least 4 weeks. Partial response (PR) was defined as greater than or equal to 50% decrease in the sum of the products of the tumor’s longest dimension and its widest perpendicular measurement for at least 4 weeks, without the appearance of new metastases.

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**Table 1. Demographic features of patients.**

<table>
<thead>
<tr>
<th></th>
<th>Subjected to curative resection (n = 18)</th>
<th>Not subjected to curative resection (n = 19)</th>
<th>Total (n = 37)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female:male</td>
<td>11:7</td>
<td>13:6</td>
<td>24:13</td>
<td>0.64</td>
</tr>
<tr>
<td>Median age (range), years</td>
<td>53 (30–71)</td>
<td>54.5 (31–73)</td>
<td>54 (30–73)</td>
<td>0.43</td>
</tr>
<tr>
<td>ECOG score:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>– 0</td>
<td>6</td>
<td>6</td>
<td>12</td>
<td>0.91</td>
</tr>
<tr>
<td>– 1</td>
<td>12</td>
<td>13</td>
<td>25</td>
<td></td>
</tr>
<tr>
<td>Median baseline CA 19-9 (range), IU/ml(^†)</td>
<td>30.4 (2–74,605)</td>
<td>76.9 (1–7498)</td>
<td>22.5 (1–74,605)</td>
<td>0.72</td>
</tr>
<tr>
<td>Median baseline CEA (range), ng/ml(^‡)</td>
<td>3.8 (1.2–463)</td>
<td>5.29 (0.8–186.9)</td>
<td>3.88 (0.8–463)</td>
<td>0.57</td>
</tr>
<tr>
<td>Median albumin (range), g/dl</td>
<td>4.2 (2.9–4.9)</td>
<td>3.9 (3.2–4.5)</td>
<td>4.1 (2.9–4.9)</td>
<td>0.22</td>
</tr>
<tr>
<td>Status of disease:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>– Early</td>
<td>3</td>
<td>0</td>
<td>3</td>
<td>0.1</td>
</tr>
<tr>
<td>– Locally advanced</td>
<td>15</td>
<td>19</td>
<td>34</td>
<td></td>
</tr>
<tr>
<td>Site of disease:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>– Liver</td>
<td>12</td>
<td>12</td>
<td>24</td>
<td>0.82</td>
</tr>
<tr>
<td>– Nodal</td>
<td>6</td>
<td>9</td>
<td>15</td>
<td>0.39</td>
</tr>
<tr>
<td>– Adjacent organ</td>
<td>6</td>
<td>7</td>
<td>13</td>
<td>0.82</td>
</tr>
<tr>
<td>– Others</td>
<td>1</td>
<td>4</td>
<td>5</td>
<td>0.34</td>
</tr>
<tr>
<td>Pathological differentiation:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>– MDAC</td>
<td>8</td>
<td>2</td>
<td>10 (27%)</td>
<td>0.12</td>
</tr>
<tr>
<td>– PDAC</td>
<td>4</td>
<td>3</td>
<td>7 (18.9%)</td>
<td></td>
</tr>
<tr>
<td>– SRCA</td>
<td>1</td>
<td>1</td>
<td>2 (5.4%)</td>
<td></td>
</tr>
<tr>
<td>– AC (not graded)</td>
<td>4</td>
<td>11</td>
<td>15 (40.5%)</td>
<td></td>
</tr>
<tr>
<td>– Others</td>
<td>1</td>
<td>2</td>
<td>3 (8.1%)</td>
<td></td>
</tr>
<tr>
<td>Regimen used:</td>
<td></td>
<td></td>
<td></td>
<td>0.09</td>
</tr>
<tr>
<td>– Gem–Ox</td>
<td>13</td>
<td>18</td>
<td>31 (83.8%)</td>
<td></td>
</tr>
<tr>
<td>– Gem–Cis</td>
<td>5</td>
<td>1</td>
<td>6 (16.2%)</td>
<td></td>
</tr>
<tr>
<td>Previous gallbladder surgery</td>
<td>6/18 (33.3%)</td>
<td>7/19 (36.8%)</td>
<td>13/37 (35.1%)</td>
<td>0.82</td>
</tr>
</tbody>
</table>

\(^†\) Not available in 1.
\(^‡\) Not available in 6.

Gem–Cis: Gemcitabine–cisplatin; Gem–Ox: Gemcitabine–oxaliplatin; MDAC: Moderately differentiated adenocarcinoma; PDAC: Poorly differentiated adenocarcinoma; SRCA: Signet ring cell adenocarcinoma.
lesions or progression of any one lesion. Stable disease (SD) was defined as less than 50% decrease or less than 25% increase in the size of the measurable disease, without the appearance of new lesions or progression of any lesion greater than 25%, for at least 4 weeks. Progressive disease (PD) was defined as greater than 25% increase in one or more of the measurable lesions or the appearance of a new lesion(s). All patients with a CR, PR or SD were considered for surgery after at least 4 weeks of completion of neoadjuvant therapy.

**Statistical analysis**

All follow-up data are current as of April 2014. The $\chi^2$ test and Fisher’s exact test was used to compare categoric variables and the Mann–Whitney test was used to compare continuous variables. Probabilities of progression-free survival (PFS) and overall survival (OS) were estimated by the Kaplan–Meier method, and compared using the log-rank test. Other outcomes looked for in the study were the response rates (clinical benefit rate was defined as sum of CR + PR + SD) and toxicity of the neoadjuvant chemotherapy.

**Results**

**Patients & treatment**

A total of 37 patients underwent neoadjuvant chemotherapy with curative intent. Figure 1 shows the treatment flowchart for these 37 patients. There were 24 females and 13 males with a median age of 54 years (range: 30–71 years). Based on imaging criteria, the disease was locally advanced in 34 and early in three patients. Baseline demography is shown in Table 1. Thirteen patients had an abnormal CEA (normal range: 0.3–2.7 ng/ml), 18 patients had an abnormal CA 19–9 level (normal range, 0–37 U/ml) and nine patients had both abnormal CA 19-9 and CEA levels. A total of 13 (35%) patients had undergone previous surgery. In total, 31 patients received Gem–Ox and six received Gem–Cis and the median number of cycles administered were four (range: 2–12); all patients completed the prescribed chemotherapy.

**Toxicity**

Data regarding toxicity was available for 36 patients who received neoadjuvant chemotherapy. Of these, 24 (66.7%) did not have any toxicity, seven patients had grade 3 or 4 toxicity and five had grade 1 or 2 toxicity. The grade 3 and 4 toxicities included grade 4 thrombocytopenia in three, grade 3 thrombocytopenia, grade 3 diarrhea, grade 3 neutropenia and grade 4 neutropenia in one patient each. Postoperative bile leak developed in 1/18 (5.5%) patient.
• Activity endpoints
Data on response is shown in Table 2. The clinical benefit rate was 81% and the overall response rate was 67.5% (5 CR and 20 PR). No difference in response rates was seen between Gem–Ox (CR: 5, PR: 14, SD: 5, PD: 7) and Gem–Cis chemotherapy (PR: 6; p = 0.1). The median follow-up was 11.9 months (range: 6.64–58.2). The median OS and PFS for the whole group were 13.4 months (range: 10.8–16) and 8.1 months (range: 5.8–10.4), respectively (Figure 2). The mean OS for the patients who underwent surgical resection was 40.9 months (median survival not yet reached) versus a median survival of 9.5 months for those who did not undergo surgical resection (p = 0.001). Median PFS was 25.8 months for patients who underwent surgical resections, 5.6 months for those who did not undergo surgery (p < 0.0001) (Figure 3).

• Surgical treatment
Surgical resection with a curative intent was undertaken in 18 patients and of these R0 resection was achieved in 17 patients. Surgery was not performed in patients due to various reasons which included PD in eight, SD in five, inoperable disease on staging laparoscopy or initial laparotomy in three, disease progression while awaiting surgery in two and refusal for surgery in one (Figure 1). The intraoperative findings during surgical exploration in 18 patients are detailed in Table 2. The surgical procedures included radical cholecystectomies in 15 and revision cholecystectomy in three patients.

Discussion
This is the first published study of the use of neoadjuvant chemotherapy in patients with locally advanced GBC. Majority of patients with GBC present with advanced disseminated disease but there is a small group of patients who present with loco-regionally advanced disease and these should be considered for treatment with a radical intent based on the findings of our study. However, this still needs to be validated in a prospective trial. Neoadjuvant chemotherapy downstaged 48.6% of the patients in our study for them to undergo potentially curative surgery and the locally advanced cases in our series, would have required major resections in the form of major liver resections and additional organ resections as per imaging.

Our data is consistent with another study published in patients with locally advanced biliary tract cancer in 22 patients treated with
Figure 3. Survival curves comparing patients who underwent surgical resection versus those who did not.
Cum: Cumulative; OS: Overall survival; PFS: Progression-free survival.

Gemcitabine alone which showed that patients who are able to undergo surgery after downstaging have a longer OS [13]. Patients who were able to undergo surgery in our study had a significantly better OS and PFS.

Two studies explored the role of preoperative therapy in the form of chemoradiotherapy but in the setting of incidentally detected GBC [14,15]. The prospective Phase II study by de Aretxabala et al. was the first to test the role of preoperative chemoradiotherapy. A total of 18 patients with an incidentally detected GBC were treated with preoperative radiation (4500 cGy; 180 cGy/fraction, 5 days/week) concurrent with a continuous infusion of 5-fluorouracil [14]. Out of the 15 patients who were subjected to resection, 13 could be resected. In another retrospective study from the same center, 14/23 patients underwent surgical resection after preoperative chemoradiotherapy [15]. In our study, all patients were able to complete the course of CT and 48.6% (18/37) patients were able to undergo surgery with curative intent.

Table 3. Response rates compared with other studies for advanced biliary tract cancer treated with gemcitabine-based combination chemotherapy.

<table>
<thead>
<tr>
<th>Response</th>
<th>Our study† (n = 37)</th>
<th>ABC-02‡ (n = 61) [2]</th>
<th>BT22§ (n = 41) [16]</th>
<th>Andre 2004¶ (n = 33) [17]</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>5 (13.5%)</td>
<td>0%</td>
<td>0%</td>
<td>NA</td>
</tr>
<tr>
<td>PR</td>
<td>20 (54%)</td>
<td>37.7%</td>
<td>19.5%</td>
<td>NA</td>
</tr>
<tr>
<td>SD</td>
<td>5 (13.5%)</td>
<td>47.5%</td>
<td>48.8%</td>
<td>26%</td>
</tr>
<tr>
<td>PD</td>
<td>7 (19%)</td>
<td>14.8%</td>
<td>22%</td>
<td>39%</td>
</tr>
<tr>
<td>Clinical benefit rate (CR + PR + SD)</td>
<td>30/37 (81%)</td>
<td>85.2%</td>
<td>68.3%</td>
<td>62%</td>
</tr>
</tbody>
</table>

†One patient died while on treatment and response could not be assessed radiologically but there was biochemical progression.
‡Response rates with Gem–Cis in gallbladder cancer patients.
§Response rates with Gem–Cis in biliary tract cancer patients.
¶Response rates with Gem–Ox in biliary tract cancer patients.
The clinical benefit rate (CR + PR + SD) of 81% in our study was similar to that seen with gemcitabine-based combination chemotherapy for advanced gallbladder and biliary tract cancers in published series (Table 3) [2,16–17]. As shown, the CR+PR rate in our study is higher compared with other studies which could be a reflection of earlier stage disease in our study. It is also possible that the biology of Indian patients is different compared with other studies as has been shown from our metastatic data set where the clinical benefit rate with gemcitabine-platinum regimen is only 40% compared with 60–85% in metastatic studies [2,17–18].

The overall median OS and PFS in our study was 13.4 and 8.1 months, respectively. The OS and PFS for the patients not subjected to curative resection in our study were 9.5 and 5.6 months respectively which is similar to the survival in the studies which have used gemcitabine-based chemotherapy in advanced setting [19–22]. The median OS and PFS in these studies have ranged from 6.8 to 9.1 months and 3.4–6.3 months respectively [19–22]. The survival outcomes for surgical resection in our study were far superior to those of the nonsurgical group; thus emphasizing the importance and need for such an approach in this patient population (Figure 3). Our results when compared with other surgical series where aggressive surgery for GBC was performed without neoadjuvant chemotherapy, reveals that these series had lower R0 resection rates (Table 4) [23,24]. This is probably due to the fact that chemotherapy allowed us to choose those who were likely candidates for a curative resection.

There are limitations to our data. Our study is a retrospective analysis, which explores the option of neoadjuvant chemotherapy in locally advanced GBC. Though the study numbers are small for patients who received chemotherapy, this is hypothesis generating and could form the basis of future randomized studies in neoadjuvant setting so as to generate high-quality evidence.

**Conclusion**

Patients with locally advanced GBC should be considered for neoadjuvant chemotherapy so that some patients may be downstaged and surgical option may be considered in these patients. This needs to be confirmed in prospective randomized trials.

**Future perspective**

This paper will hopefully change the thinking of oncologists and surgeons so that each patient at diagnosis is classified into locally advanced or borderline resectable GBCs. The definition of borderline resectable GBC needs to be agreed upon. Surgery as an option may be considered in these patients after downstaging with preoperative therapy. A randomized trial looking into neoadjuvant chemotherapy and chemoradiotherapy will help define which is the better option for these patients. Markers of drug resistance for platinum (ERCC1) and those for gemcitabine (hENT1 and MMP7) will help better select patients for neoadjuvant chemotherapy.

**Table 4. Comparison of R0 resection rates with other series where an aggressive resection for gallbladder cancer was carried out.**

<table>
<thead>
<tr>
<th>Study (year)</th>
<th>Number of patients</th>
<th>R0 resection</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rossi (2012)</td>
<td>16</td>
<td>6/16 (37.5%)</td>
<td>[23]</td>
</tr>
<tr>
<td>Dixon (2005)*</td>
<td>99</td>
<td>33/99 (33%)</td>
<td>[24]</td>
</tr>
<tr>
<td>Our series</td>
<td>21</td>
<td>17/37 (46%)</td>
<td></td>
</tr>
</tbody>
</table>

*This series compared two time periods.*

**EXECUTIVE SUMMARY**

**Background**

- This is the largest series evaluating the role of neoadjuvant chemotherapy in patients with gallbladder cancer.

**Results**

- Out of 37 patients who received neoadjuvant chemotherapy, the clinical benefit rate was 81% and the overall response rate (complete response + partial response) was 67.5%, and 18/37 patients were able to undergo surgery for gallbladder cancer and of these 17 patients had an R0 resection. Patients who underwent surgery had a significantly better overall survival (median not reached vs 9.5 months) and progression-free survival (25.8 vs 5.6 months), respectively, compared with those who did not.

**Conclusion**

- The study thus paves way to evaluate the role of neoadjuvant treatment in future prospective trials.
Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.

References

Papers of special note have been highlighted as:
- of interest; •• of considerable interest


- Published in 2013 gives an up-to-date information on the incidence of gallbladder cancer in India.


- Landmark paper that established the use of gemcitabine-platinum in patients with gallbladder cancer. This was the pivotal Phase III trial that has established the use of gemcitabine-platinum as standard of care in biliary tract cancers.


- This was the first randomized study to show benefit of adjuvant chemotherapy in patients with gallbladder cancer.


- The results of this study will define the role of adjuvant chemotherapy in patients with biliary tract cancers.


- This study looked at role of neoadjuvant chemotherapy in patients with locally advanced biliary tract cancer with good outcome for those who underwent surgery.

14. de Aretxabala X, Roa I, Burgos L et al. Neoadjuvant chemoradiotherapy in incidentally detected gallbladder cancer. This could also be extrapolated for use in patients with locally advanced gallbladder cancer.


- Retrospective study showed that postchemoradiotherapy, 14/23 patients could undergo resection.


- This study showed that the use of doublet gemcitabine–cisplatin leads to better outcome compared with gemcitabine alone in Japanese patients.


- This group published the initial data and follow-up data for use of gemcitabine and oxaliplatin in advanced biliary tract cancers. Oxaliplatin is better tolerated and requires less infusion time than cisplatin.


Neoadjuvant chemotherapy in gallbladder cancer

- This study confirms that being able to proceed to curative resection is the only chance for long-term survival.

