Gemcitabine, capecitabine and oxaliplatin in advanced biliary tract carcinoma

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To the Editor,

Biliary tract carcinoma includes gallbladder cancer and cholangiocarcinoma. Cholangiocarcinoma can be subdivided into intrahepatic, perihilar (Klatskin) and extrahepatic carcinoma. Biliary tract carcinoma is a relative rare cancer which account for less than 1% of new cancer cases. Only resection is a curative treatment, but unfortunately resection is only possible in approximately 10%, leaving most patients with advanced disease. For patients with advanced disease only palliative treatment is possible. The most active drugs in phase II trials are gemcitabine [1,2], flourpyrimidine/capecitabine [3,4] and cisplatin/oxaliplatin [5–9]. Support for gemcitabine as an anchor drug for the treatment of advanced biliary tract carcinoma comes from a pooled analysis of 104 trials that showed that the subgroup receiving a combination of gemcitabine and platinium-based agent had the greatest benefit [10]. In 2010 Valle published a study with 410 patients where cisplatin and gemcitabine were compared to gemcitabine alone [11]. The patients receiving cisplatin and gemcitabine had a better and impressive median overall survival (OS) of 11.7 months. Cisplatin and gemcitabine were therefore suggested as standard treatment to patients with advanced biliary tract carcinoma. Several phase two trials have replaced cisplatin with oxaliplatin and the combination with gemcitabine and oxaliplatin show similar median OS of approximately 12 months [12,13]. One smaller trial tested the triplet of gemcitabine, oxaliplatin and capecitabine and found it well tolerated with similar median OS [14]. Furthermore, the study showed that the addition of capecitabine allowed a lower oxaliplatin dose than the usual 100 mg/m^2 every second week and subsequently reducing especially neutropenia and neurotoxicity. In the present study we wanted to investigate the efficiency of the triplet gemcitabine, capecitabine and oxaliplatin in daily clinic and compare the results with other similar studies.

Material and methods

From January 2005 to January 2013, 194 patients from two institutions were evaluated retrospective. They were included if they had received a histo- or cytological diagnosis of non-resectable or recurrent biliary tract carcinoma. In cases with indeterminate but malignant histology, imaging should support the diagnosis and other primary tumors should be excluded. Location of the primary tumor could be intrahepatic, perihilar or extrahepatic bile ducts or in the gallbladder. All patients were evaluated non-resectable by liver surgeons. Patients in performance status 0, 1 or 2 were included if they had a bilirubin less than two times the upper limit of the normal range. Two different schedules were used. Capecitabine 650

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mg/m^2 BID continuously with gemcitabine 1000 mg/m^2 and oxaliplatin 50 mg/m^2 day 1 in a two-week schedule (A) or capecitabine 1000 mg/m^2 BID day 1–7, with gemcitabine 1000 mg/m^2 and oxaliplatin 60 mg/m^2 day 1 in a two-week schedule (B). Oxaliplatin and gemcitabine were both given as an infusion over 30 minutes each. The patients continued treatment for at least 6 months or until progression. If treatment was stopped without progression, the patients were followed clinically and with a computed tomography (CT) scan every three months.

Median OS was calculated from the date of first planned treatment until the date of death. Progression free survival (PFS) was calculated from the date of first planned treatment until progression either on CT scan or clinical progression or death. Median OS and PFS were analyzed with the use of Kaplan-Meier curves calculated on IBM SPSS statistics version 19 (SPSS Inc., Chicago, IL, USA). Tumor response was evaluated with CT scan in accordance to the Response Evaluation Criteria in Solid Tumors (RECIST) 1.0 [15]. Only patients who had measurable disease at study entry and had a second CT scan performed were analyzed for objective tumor response. The database was closed for analysis March 2014.

Results

One hundred and ninety-four patients were included in the study. The median age was 64.9 years with 57% female. The primary tumor was located in the bile duct in 84% and in the gallbladder in 16%. There were 72 (37%) in ECOG performance status 0, 89 (46%) with PS 1 and 33 (17%) with PS 2. Grade III and IV non-hematological toxicities were rare, less than 5%, but most patients who continued oxaliplatin for more than six months developed neuropathy. We found a PFS of 6.7 months and a median OS of 10.8 months. The patients' performance status at start seems very important for both PFS and OS. Patients with performance status 0, 1 or 2 had a median OS of 15.5, 9.8 and 3.4 months respectively (Table I). The corresponding PFS was 10.2, 6.6 and 1.8 months. If only patients with performance status 0 and 1 had been included the PFS would increase to 7.7 months and the median OS to 12.5 months. Many of the patients in performance status 2 never had a second CT scan due to clinical progression and were not suitable for further treatment. This reflected the patients alive after one year, with 70% alive in patients with performance status 0, 38% with performance status 1 and 3% with performance status 2. The response rate was evaluable in 140 patients (patients were not required to have measurable disease at study entry and some patients, particularly in performance status 2, never had a second CT scan). There were 4% complete response, 26% partial response and 56% stable disease. In subgroup analysis we found no difference in PFS or median OS between the two schedules, sexes, tumor site or in age over or less than 65 years (data not shown).

Discussion

We wanted to evaluate the effectiveness of gemcitabine, oxaliplatin and capecitabine in treating non-resectable biliary tract cancer. PFS was 6.7 months and OS 10.8 months. Most studies with biliary tract carcinoma are relatively small trials which make subgroup analysis speculative. Our study includes 194 patients and we found no difference in subgroups defined by sex, tumor site or age. However, we found that performance status at start of treatment was very prognostic for OS with a median OS at 15.5 months for patients with performance status 0 and only 3.4 months for patients with performance status 2. Only one of the patients with performance status 2 was alive after one year. It is doubtful if these patients benefit from combination chemotherapy at all and this should be discussed with future patients. Most patients with performance status 0 and 1 did well and the schedule was well tolerable due to the relative low oxaliplatin dose. If only patients with performance status 0 and 1 had been included the PFS would had increased to 7.7 months and the median OS to 12.5 months. In the study by Valle where gemcitabine + cisplatin were compared to gemcitabine, they found in a subgroup analysis an advantage in median OS for cisplatin and gemcitabine over gem-

Table I. PFS, median OS and 1-year survival in 194 patients' and response rate in 140 patients' with biliary tract carcinoma in accordance to performance status.

	PFS (months)	m OS (months)	1-year survival (%)	Response rate (%)
PS 0 (n = 72)	10.2 (7.4–13.0)	15.5 (12.2–18.8)	70%	34% (19/56)
PS 1 (n = 89)	6.6 (6.0–7.3)	9.8 (8.5–11.1)	38%	27% (18/66)
PS 2 (n = 33)	1.8 (0.8–2.7)	3.4 (2.0–4.7)	3%	31% (5/16)
PS 0 + 1 + 2 (n = 194)	6.7 (5.7–7.8)	10.8 (9.5–12.0)	43%	30% (42/140)
PS 0 + 1 (n = 161)	7.7 (6.5–8.9)	12.5 (10.9–14.2)	52%	30% (37/122)

citabine for patients in performance status 0 and 1 with a HR of 0.5 (0.33–0.77) and 0.68 (0.51–0.91), respectively, but not for patients in performance status 2 HR 0.90 (0.49–1.66). Caution must be taken when comparing results from different studies, since performance status may be more important than differences between therapeutic regimens.

All patients received oxaliplatin for at least six months and some up to 12 months, except if the disease progressed before the six months or if the patients had an allergic reaction to oxaliplatin. In our report a lower oxaliplatin dose was used compared to other trials with gemcitabine and oxaliplatin. This was done to reduce the risk of neutropenia when adding capecitabine to gemcitabine and oxaliplatin. The lower oxaliplatin dose resulted in very limit problems with nausea and neurotoxicity. It also reflected that patients could continue oxaliplatin for a long period and that dose reduction was rare. The cumulative dose of oxaliplatin may therefore be equal to regiment with higher dose of oxaliplatin.

In conclusion, the combination of gemcitabine, capecitabine and oxaliplatin in daily clinic was well tolerated. The effectiveness in terms of PFS, median OS and response rate was similar to results from clinical trials evaluating gemcitabine and cisplatin/oxaliplatin in patients with biliary tract carcinoma. To establish comparable effectiveness, a randomized trial between cisplatin + gemcitabin and gemcitabine + capecitabine + oxaliplatin is now running.

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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