Palliative chemotherapy with gemcitabine and weekly high-dose 5-fluorouracil as 24-h infusion in metastatic biliary tract and gall bladder adenocarcinomas

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At present, systemic treatment is not generally recommended for advanced biliary tract and gall bladder carcinomas. In particular cases, however, it may be justified to consider systemic chemotherapy treatment. In four cases we investigated the efficacy of palliative systemic treatment in metastatic biliary tract and gall bladder adenocarcinomas. Similar to the proceedings in a phase II study for metastatic pancreas adenocarcinomas, four patients with advanced biliary tract and gall bladder adenocarcinomas received a combination treatment of gemcitabine (GEM) and weekly high-dose 5-fluorouracil (5-FU) as a 24-h infusion. Altogether, the four patients received 96 chemotherapy applications. The palliative chemotherapy was tolerated well. In one patient, leukocytopenia (toxicity grade III) and thrombocytopenia (toxicity grade III) occurred. In three patients, the palliative systemic treatment led to stable disease, partly with a significant decrease of the CA 19-9 tumor marker, and in one patient to partial remission (PR). The survival times in these four patients were 6, 10, 17 and 26 months. Even in the case of PR, a curative hemihepatectomy right could be achieved after 'downsizing'. We conclude that in the four case studies, the applied palliative combination treatment based on GEM and 5-FU proved to be effective. However, future multicenter studies will be necessary to determine the significance of palliative chemotherapy in biliary tract and gall bladder carcinomas. *Anti-Cancer Drugs* 14:87–90 © 2003 Lippincott Williams & Wilkins.

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Introduction

Every year, 21 700 new cases of metastatic biliary tract and gall bladder carcinomas are registered in the US. In Germany, the new cases number approximately 6000 each year [1–3]. Due to uncharacteristic early symptoms, biliary tract and gall bladder carcinomas are frequently diagnosed in an advanced stage, and thus discovered too late for curative resection [2,3].

The median survival time for patients with advanced metastatic biliary tract and gall bladder carcinomas is between 4 and 8 months [2,3]. At present, no chemotherapy regimen is generally established for palliative treatment. In 1996, Glimelius *et al.* showed in a subgroup analysis of 37 patients with biliary tract carcinomas that a systemic treatment based on 5-fluorouracil (5-FU) as bolus application versus best supportive care may lead to an improvement in survival time (6.5 versus 2.5 months) and in quality of life (EORTC-QLQ-C30) [4]. Due to positive results with gemcitabine (GEM) monotherapy in metastatic pancreas carcinoma [5], GEM monotherapy was also applied for biliary tract and gall bladder carcinoma, and first experiences were collected [6–11]. In the following, we report on the combination chemotherapy treatment with GEM and weekly high-dose 5-FU as a 24-h infusion in four patients with metastatic biliary tract and gall bladder carcinoma.

Patients

Case report 1

From December 1998 to August 1999, a 73-year-old female patient suffering from a histologically confirmed adenocarcinoma of the gall bladder with liver metastases and duodenal infiltration received a palliative chemotherapy treatment consisting of GEM (1000 mg/m^2 i.v. as a 0.5-h infusion; day 1, 8, 15, q.d. 29) and weekly high-dose 5-FU (2000 mg/m^2 i.v.; day 1, 8, 15, q.d. 29) as a 24-h infusion. For antiemetic reasons 50 mg i.v. of Alizaprid was administered. During the treatment period, the following toxicities were observed: hypokalemia (grade II), hyponatremia (grade I), nausea (grade I), diarrhea (grade I), loss of appetite (grade I), increase of temperature (grade II), chills (grade I) and anemia (grade II). In the monthly

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follow-up, computed tomography of the abdomen revealed a stable disease (SD) status. During therapy, CA 19-9 decreased from 673 to 276 U/ml, while weight and ECOG index remained stable. The administration of Metamizol p.o. and Tramadol p.o. maintained the pain level in the right abdominal area unchanged. The therapy was subjectively well tolerated by the patient. The palliative chemotherapy treatment was finished after 8 cycles in August 1999 due to progressive disease (PD). Because of an increasing duodenal tumor infiltration, a laparoscopic gastroenterostomy was carried out, followed by an intensified supportive treatment. The patient died on the 28 September 1999. The survival time, counted from the beginning of palliative therapy, was 10 months.

Case report 2

In a 69-year-old patient, an adenocarcinoma of the left liver lobe infiltrating the pancreatic head was histologically confirmed in August 1999. The tumor could be immunohistochemically determined as biliary tract carcinoma. An explorative laparatomy histologically confirmed mesenterial lymph node metastases and a peritoneal carcinosis. From September to October 1999, the patient received a palliative chemotherapy treatment consisting of GEM (1000 mg/m^2 i.v. as a 0.5-h infusion; day 1, 8, 15, q.d. 29) and weekly high-dose 5-FU (2000 mg/m^2 i.v.; day 1, 8, 15, q.d. 29) as a 24-h infusion. For antiemetic reasons 50 mg of Alizaprid i.v. was administered. During the treatment period, the following toxicities were observed: fatigue (grade I), loss of appetite (grade I), flatulence (grade I), loss of weight (grade I), leukocytopenia (grade II), GOT increase (grade I), nausea (grade I) and exanthema (grade I). In the monthly follow-up, CT of the abdomen revealed a SD status. CA 19-9 was initially 103 824 U/ml and remained unchanged during therapy with a level of 99 055 U/ml. The ECOG index was constant. The administration of Tramadol p.o. maintained the pain effectively under control during the entire treatment period. At the request of the patient, the palliative chemotherapy treatment was finished after 2 cycles in October 1999. The patient died on 9 February 2000. The survival time, counted from the beginning of palliative therapy, was 6 months.

Case report 3

In 1994, a central hepatic resection with hepaticojejunostomy histologically confirmed an adenocarcinoma of the left hepatic duct (pT1b, pN0, cM0, G1–2, R0) in a 66-year-old female patient. In March 1999, multiple liver metastases were detected by MRT of the abdomen and histologically confirmed as adenocarcinoma. From April 1999 to March 2000, the patient received a palliative chemotherapy treatment consisting of GEM (1000 mg/m^2 i.v. as a 0.5-h infusion; day 1, 8, 15, q.d. 29) and weekly high-dose 5-FU (2000 mg/m^2 i.v.; day 1, 8, 15, q.d. 29) as a 24-h infusion. For antiemetic reasons 50 mg i.v. of Alizaprid was administered. During the palliative chemotherapy treatment, the following toxicities were observed: leukocytopenia (grade I), nausea (grade I), hand-and-foot-syndrome (grade I), fatigue (grade I), diarrhea (grade I), alopecia (grade I), conjunctivitis (grade I), GOT increase (grade I), GPT increase (grade II) and hyperglycemia (grade II). In the monthly follow-up, MRT of the abdomen revealed a partial remission of the liver metastases. During therapy, CA 19-9 decreased from 1170 to 34 U/ml, while weight and ECOG index remained stable. The therapy was subjectively well tolerated by the patient. The mild abdominal pain was regressive under therapy. In April 2000, after 12 treatment cycles, a curative hemihepatectomy right could be performed in the Department of Surgery of Erlangen University. Unfortunately, 5 months after the surgical intervention, a recurrence of liver metastases was detected, but the patient refrained from undergoing new systemic treatment. The patient died on 14 May 2001. The survival time, counted from the beginning of palliative treatment, was 26 months.

Case report 4

In 1992, a 62-year-old patient with a histologically (ED 1992) confirmed adenocarcinoma of the papilla vateri underwent curative papillectomy (pT2, N0, M0, G1, R0) and biliodigestive anastomosis. In November 1998, liver metastases were detected. The biopsy of a liver metastasis histologically confirmed an infiltration of a scarcely differentiated adenocarcinoma, equated with a metastasis of the papilla carcinoma. From January 1999 to February 2000, the patient received a palliative chemotherapy treatment consisting of GEM (1000 mg/m^2 i.v. as a 0.5-h infusion; day 1, 8, 15, q.d. 29) and weekly high-dose 5-FU (2000 mg/m^2 i.v.; day 1, 8, 15, q.d. 29) as a 24-h infusion. For antiemetic reasons 50 mg i.v. of Alizaprid was administered. During palliative therapy, the following toxicities were observed: leukocytopenia (grade III), alcalic phosphatase increase (grade I), anemia (grade II), thrombocytopenia (grade III), hyperglycemia (grade II), hypokalcemia (grade I), GOT increase (grade I), GPT increase (grade I), diarrhea (grade I), conjunctivitis (grade I), alopecia (grade I) and fatigue (grade I). Due to leukocytopenia (grade III) and thrombocytopenia (grade III), the GEM dose was reduced by 25% during the first cycle (day 15) and the 5-FU dose by 25% during the second cycle (day 8). In the monthly follow-up, CT of the abdomen revealed a SD status. The initial CA 19-9 value was 20 U/ml and remained stable under therapy. The ECOG index was constant and the therapy subjectively well tolerated by the patient. The pain in the upper abdominal area was regressive under therapy. Due to tumor progression, the systemic palliative treatment was finished after 10 cycles in March 2000. The patient died on 5 September 2000. The survival time, counted from the beginning of palliative treatment, was 17 months.

Discussion

At present, systemic treatment is not generally established in locally advanced or metastatic biliary tract and gall bladder carcinoma. However, in particular cases it is certainly justified to consider chemotherapy treatment. In several phase II studies, response rates ranging from 8 to 37% could be achieved due to GEM monotherapy (1000–1200 mg/m^2) in advanced biliary tract and gall bladder carcinomas [8–12]. In these studies, the median survival time ranged from 6.5 to 10 months [9–12]. To date, most publications abstain from differentiating the therapeutic results in biliary tract and gall bladder carcinomas [8,9,11,12]. The efficacy assessment of systemic treatment in phase II studies is somehow limited, because the spontaneous course of disease can vary considerably in advanced biliary tract and gall bladder carcinomas. Until now, particularly the following combination chemotherapy schedules comprising 5-FU (bolus), folinic acid + mitomycin C, 5-FU (24-h infusion), folinic acid + oxaliplatin, 5-FU ('de Gramont' schedule), folinic acid + cisplatin, GEM + cisplatin and GEM + docetaxel, respectively, have been the focus of attention and have been thoroughly investigated [12–17].

Based on the first results of a randomized EORTC phase II study, it could be shown that in biliary tract and gall bladder carcinomas, the response rate improved from 7 to 19% and the median survival time from 5.3 to 7.8 months due to combination chemotherapy treatment (weekly high-dose 5-FU as 24-h infusion, folinic acid + biweekly cisplatin) versus monotherapy treatment (weekly high-dose 5-FU as 24-h infusion) [18].

Similar to the proceedings of a phase II study for metastatic pancreas adenocarcinoma [19], we applied the GEM combination chemotherapy treatment and weekly high-dose 5-FU as a 24-h infusion in four patients with advanced biliary tract and gall bladder carcinomas. The 96 chemotherapy treatment applications were tolerated well by the four patients. Only in the case of one patient did a higher-grade toxicity occur as leukocytopenia (grade III) and thrombocytopenia (grade III). Due to palliative systemic treatment, SD, in some cases accompanied by a significant decrease of the CA 19-9 tumor marker, could be achieved in three cases. In one female patient with PR (case report 3), a curative hemihepatectomy right (R0) could be carried out after 'downsizing' by systemic chemotherapy treatment, which is comparable to the proceedings in metastatic colorectal carcinomas [20]. The survival times were 6, 10, 17 and 26 months.

The significance of systemic treatment in locally advanced or metastatic carcinomas of the biliary tract and the gall bladder should be investigated in even more detail within the framework of comprehensive multicenter phase III studies.

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References

1 Landis SH, Murray T, Bolden S, Wingo PA. Cancer statistics, 1999. *CA Cancer J Clin* 1999; **49**:8–31.
2 Becker HD, Kreis M. Tumoren der extrahepatischen Gallenwege. In: Becker HD, Hohenberger W, Junginger T, Schlag PM (editors): *Chirugische Onkologie.* Stuttgart: Thieme-Verlag; 2002, pp. 345–353.
3 Becker HD, Pinoy J. Gallenblasentumoren. In: Becker HD, Hohenberger W, Junginger T, Schlag PM (editors): *Chirugische Onkologie.* Stuttgart: Thieme-Verlag; 2002, pp. 337–344.
4 Glimelius B, Hoffmann K, Sjöden PO, Jacobsson G, Sellstrom H, Erlander LK, *et al.* Chemotherapy improves survival and quality of life in advanced pancreatic and biliary cancer. *Ann Oncol* 1996; **7**:593–600.
5 Burris HA, Moore MJ, Andersen J, Green MR, Rothenberg ML, Modiano MR, *et al.* Improvements in survival and clinical benefit with gemcitabine as first-line therapy for patients with advanced pancreas cancer: a randomized trial. *J Clin Oncol* 1997; **15**:2403–2413.
6 Castro MP. Efficacy of gemcitabine in the treatment of patients with gall bladder carcinoma: a case report. *Cancer* 1998; **82**:639–641.
7 Teufel A, Lehnert T, Stremmel W, Rudi J. Chemotherapy with gemcitabine in patients with advanced gallbladder carcinoma. *Z Gastroenterol* 2000; **38**:909–912.
8 Mezger J, Sauerbruch T, Ko Y, Wolter H, Funk C, Glasmacher A. Phase II study with gemcitabine in gallbladder and biliary tract carcinomas. *Onkologie* 1998; **21**:232–234.
9 Arroyo G, Gallardo J, Rubio B, Orlandi L, Yanez M, Gamargo C, *et al.* Gemcitabine (GEM) in advanced biliary tract cancer (ABTC). Experience from Chile and Argentina in phase II trials. *Proc Am Soc Clin Oncol* 2001; **20**:626.
10 Gallardo JO, Rubio B, Fodor M, Orlandi L, Yanez M, Gamargo C, *et al.* A phase II study of gemcitabine in gallbladder carcinoma. *Ann Oncol* 2001; **12**:1403–1406.
11 Valencak J, Kornek GV, Raderer M, Ulrich-Pur H, Krauss G, Greul R, *et al.* Gemcitabine for the treatment of advanced biliary tract carcinomas: evaluation of two different dose regimens. *Onkologie* 1999; **22**: 498–501.
12 Raderer M, Hejna MHL, Valencak JB, Kornek GV, Weinlander GS, Bareck E, *et al.* Two consecutive phase II studies of 5-fluorouracil/leucovorin/mitomycin C and of gemcitabine in patients with advanced biliary cancer. *Oncology* 1999; **56**:177–180.
13 Gebbia V, Majello E, Testa A, Pezella G, Giuseppe S, Giotta F, *et al.* Treatment of advanced adenocarcinomas of the exocrine pancreas and the gallbladder with 5-fluorouracil, high dose levofolinic acid and oral hydroxyurea on a weekly schedule. Results of a multicenter study of the Southern Italy Oncology Group (GOIM). *Cancer* 1996; **78**: 1300–1307.
14 Kuhn R, Ridwelski K, Rudolph S, Schmidt C, Fahlke J, Lippert H, *et al.* Phase II study of weekly gemcitabine and docetaxel in advanced or metastatic gallbladder carcinomas. *J Cancer Res Clin Oncol* 2002; **78**:397.
15 Arkenau H-T, Nehls O, Klump B, Hass HG, Greschniok A, Gregor M, *et al.* Palliative therapy for advanced biliary tract carcinoma with oxaliplatin (OXA), 5-fluorouracil (5-FU) and leucovorin (LV). *J Cancer Res Clin Oncol* 2002; **87**:P440.
16 Taieb J, Mitry E, Boige V, Artru P, Ezenfis J, Lecomte T, *et al.* Optimization of 5-fluorouracil (5-FU)/cisplatin combination chemotherapy with a new schedule of leucovorin, 5-FU and cisplatin (LV5FU2-P regimen) in patients with biliary tract carcinoma. *Ann Oncol* 2002; **13**:1192–1196.
17 Doval DC, Sekhon JS, Fuloria J, Gupta SK, Vaid AK, Gupta S, *et al.* Gemcitabine and cisplatin in chemotherapy-naive, unresectable gallbladder cancer: a large multicenter, phase II study. *Proc Am Soc Clin Oncol* 2001; **20**:622.
18 Mitry E, Van Cutsem E, Van Laethem JL, Gress T, Jeziorski K, Wagener T, *et al.* A randomised phase II trial of weekly high dose 5FU (HD-FU) with and without folinic acid (AC) and cisplatin (P) in patients (pts) with advanced biliary tract carcinoma: the EORTC 40955 Trial. *Proc Am Soc Clin Oncol* 2002; **21**:696.

19 Wein A, Wehler M, Fischer B, Happich K, Schirner I, Boxberger F, *et al.* Phase II study with 24-h infusion of high-dose 5-Fluorouracil (5-FU) and Gemcitabine (GEM) in metastatic pancreas cancer. *Proc Am Soc Clin Oncol* 2002; **21**:620.

20 Wein A, Riedel C, Köckerling F, Martus P, Baum U, Brueckl WM, *et al.* Impact of surgery on survival in palliative patients with metastatic colorectal cancer after first line treatment with weekly 24-hour infusion of high-dose 5-fluorouracil and folinic acid. *Ann Oncol* 2001; **12**:1721–1727.