Weekly gemcitabine for the treatment of biliary tract and gallbladder cancer

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Summary

Objectives: To evaluate the efficacy and safety of weekly administration of gemcitabine treatment in chemotherapy-naïve patients with advanced biliary tract and gallbladder cancer. Patients and methods: Gemcitabine at a dose of 800 mg/m\(^2\) was administered weekly as a 30-min infusion to patients with previously operated, histologically confirmed, metastatic, or unresectable locally advanced cholangiocarcinoma. Treatment was continued until unacceptable toxicity or disease progression. Results: A total of 30 patients (median age 66 years; range 54–72 years) were included in the study. A median of 14 (range, 4–33) weekly doses was administered. Out of 30 patients evaluable for response, nine partial responses were observed (30.0%), while a further 11 patients demonstrated stable disease (36.7%). The median time to disease progression was 7 months (range, 5–34). Overall response rate was superior in patients with cancer of the gallbladder (ORR = 35.7%) compared with those patients with biliary duct cancer (ORR = 27.3%). This correlated to a significantly longer time to progression of 6.4 months (95% confidence interval (CI), 5.6–7.1 months) versus 3.6 months (95% CI, 2.9–4.3 months; \(p = 0.03\)) and a significantly better overall survival of 17.1 months (95% CI, 15.8–18.5 months) versus 11.4 months (95% CI, 10.2–12.6 months, \(p = 0.021\)). Toxicities were generally mild with only one case of grade 3 neutropenia. There were no cases of febrile neutropenia and no treatment-related deaths. Conclusions: Weekly administration of gemcitabine provides a safe, well-tolerated, and effective treatment for chemotherapy naïve patients with advanced cholangiocarcinoma, particularly with a gallbladder origin.

Introduction

Biliary tract cancers, adenocarcinoma of the gallbladder and bile ducts are fairly uncommon tumors. For the majority of patients presenting with gallbladder and cholangiocarcinoma the prognosis is poor [1]. Even following radical surgery, which is the only current potentially curative treatment for patients with resectable tumors, the median survival is limited to a few months and the 5-year survival rates are between 5–10% [2]. This is not only related to the chemo-resistance of these tumors and their unknown etiology, but also to the fact that the majority of patients present with inoperable advanced disease due to the lack of early symptoms. Surgery continues to be the only potentially curative treatment. Median
survival in patients with inoperable tumors ranges from 5 to 8 months, thus patients with advanced cholangiocarcinoma have a dismal prognosis. The role of chemotherapy remains largely palliative. A variety of chemotherapeutic regimens have been investigated, however, both single-agent and combination therapies demonstrate meager response rates of 5–30%, with an approximate median duration lasting 8.5 months [3–7].

Therefore, studies incorporating small numbers and the poor therapeutic results so far provide only little evidence with regards to potentially active chemotherapeutic regimens in patients with advanced and unresectable disease. The role of chemotherapy in these patients is negligible, and particularly in those with cholangiocarcinoma, the toxicity of chemotherapy might outweigh the palliative effect. Gemcitabine is a nucleoside analogue that inhibits the synthesis of DNA by interfering with cytidine triphosphate production and inhibits the activity of ribonuclease reductase. It demonstrates a mild toxicity profile, is an effective single agent in lung, breast, and bladder cancer; and has proven superior as a single agent in patients with advanced pancreatic cancer when compared to 5-Fluorouracil [8].

A limited number of reports have examined the efficacy of gemcitabine in cholangiocarcinomas, however, these early reports are encouraging with response rates reaching 36% [7–12]. We have, therefore, conducted a phase II trial to investigate the efficacy and safety of single agent gemcitabine, administered in a weekly schedule, in chemotherapy na"ıve patients with histologically confirmed metastatic or unresectable locally advanced cholangiocarcinoma.

Patients and methods

Inclusion criteria and patient selection

Eligible patients had histologically confirmed advanced cholangiocarcinoma of the gallbladder or biliary tree with evidence of metastatic disease or unresectable local recurrence and no previous chemotherapy. Patients had to have bidimensionally measurable disease on a computed tomography (CT) scan or magnetic resonance imaging (MRI), to have a Karnofsky performance status of greater than 50% and age <75 years. Additional inclusion criteria were adequate renal, liver (total serum bilirubin <3 g% and transaminases less than two times the upper normal limit), and bone marrow function (WBC > 3.5 × 10⁹/L, platelets > 100 × 10⁹/L). Patients with diabetes, cardiac insufficiency, psychotic disorders, or those that had undergone any prior palliative chemotherapy were excluded. Patients with other serious or uncontrolled illnesses, other malignancy, or central nervous metastasis were not eligible for treatment.

The study was performed according to Good Clinical Practice (GCP) guidelines and the Declaration of Helsinki. Approval was obtained from all local ethical boards, and written informed consent was obtained from all patients.

Pre-treatment, follow-up and response evaluation

Patients received gemcitabine (800 mg/m²) as a 30-min intravenous (i.v.) infusion weekly, nonstop, until the appearance of severe toxicity, disease progression, or patient refusal. Pre-treatment evaluations included a complete medical history and physical examination; tumor measurements were performed by both physical examination and CT documentation of disease prior to treatment. All patients received an initial CT evaluation of the chest and abdomen, and bone scan. Additional imaging was conducted with CT, MRI, abdominal ultrasound, and X-ray for confirmation of suspicious lesions in the liver, lymph nodes, or other sites.

In addition to clinical examination, full blood counts, differential counts, and complete biochemical profiles including liver function parameters, ECG, appropriate serum tumor marker measurements (CEA and CA19-9), and a chest X-ray were performed prior to chemotherapy and then at two monthly intervals. Blood counts and differential counts were performed prior to each course of chemotherapy. CT imaging of the chest and abdomen were performed every 2 months, unless signs of recurrence were present. Toxicity was evaluated according to the WHO criteria [13].

Evaluation of response was performed following every eight weekly courses of chemotherapy, unless signs of progression were evident. Patients experiencing toxic death despite objective responses at measurable sites were categorized as treatment failures. Complete response (CR) was defined as the disappearance of all signs and symptoms of disease for at least four consecutive weeks, including documented disappearance of all known lesions by physical examination, X-rays, CT, and bone scan; and the