Abstract  There is no standard chemotherapy regimen in advanced gastric cancer with poor performance status and hepatic dysfunction. New chemotherapeutical agents and targeted therapy have demonstrated promising results in terms of efficacy and safety in phase II clinical trials. We report the case of a 68-year-old man with stage IV gastric cancer and severe hepatic dysfunction due to liver metastases treated with a combination of oxaliplatin, 5-fluorouracil and cetuximab.

Keywords  Gastric cancer · Oxaliplatin · Cetuximab · Hepatic dysfunction

Introduction

Gastric cancer is the fourth most common neoplasm and the second leading cause of cancer death worldwide [1, 2]. The prognosis for gastric cancer is poor, with a five-year survival of 10–20%, the only curative treatment being surgery. Approximately 60–70% of patients have stage III or IV disease at diagnosis. Systemic chemotherapy can provide symptom palliation, and improve quality of life and survival as compared to best supportive care [3]. There is no standard regimen in advanced gastric cancer, although combination chemotherapy provides higher response rates and modest improvement in survival compared to a single agent. Promising results have been reported with regimens based on oxaliplatin and capecitabine [4] with at least the same efficacy and a better toxic profile, as well as new combinations with targeted therapy with bevacizumab [5] and cetuximab [6]. In the context of severe hepatic dysfunction and poor performance status, the indication of chemotherapy is uncertain.

We present our experience in the treatment of advanced gastric cancer with poor performance status and severe hepatic dysfunction with a new combination regimen with oxaliplatin, 5-fluorouracil and cetuximab.

Case report

A 68-year-old man was diagnosed of advance gastric cancer poorly differentiated of the fundus with lung, liver and abdominal lymph node metastases at presentation. For the previous three months he had referred epigastric abdominal pain, nausea and vomiting and weight loss of 8 kg. The physical examination revealed a 3-cm hepatomegaly and ECOG 2. The biochemical test showed: bilirubin 2.6 mg/dl, GOT 125 UI/l, GPT 89 UI/l, FA 359 U/l, LDH 5.878 UI/l, GGT 1.252 UI/l and the rest of the values were normal. Tumour markers were normal except CA-19.9 279.8 U/ml (range 0–35 U/ml).

Before starting chemotherapy, severe hypercalcaemia developed without bone metastases (normal bone scan), which was controlled with zoledronic acid, corticoids, hydration and diuretics. However bilirubin reached 11.6 mg/dl without dilation of the biliary tract and LDH increased rapidly till 7290 UI/l due to tumour progression. The patient received chemotherapy in a biweekly schedule with oxaliplatin 60 mg/m² day 1, 5-fluorouracil 200 mg/m² in continuous infusion days 1–7 and cetuximab 400 mg/m² loading dose followed by maintenance dose of 250 mg/m² weekly. Dosing adjustment was required because of hepatic dysfunction and poor performance status. After the first cycle diarrhoea and asthenia grade II were observed and the 5-fluorouracil continuous infusion was stopped. Afterwards 5-fluorouracil 400 mg/m² in bolus was administrated in a biweekly schedule. The week after the first dose of chemotherapy the bilirubin
reached 15.4 mg/dl together with a marked decrease in LDH. All symptoms improved markedly and liver disease progression was not observed in the ultrasound scans so it was interpreted as hepatic toxicity or tumour lysis.

The patient received seven cycles of chemotherapy over three months. No grade III–IV toxicity was observed; only grade I mucositis, grade II anaemia and grade I cutaneous toxicity were described. After the seven courses of chemotherapy the CA-19.9, LDH, liver enzymes and bilirubin had normal values. The patient was asymptomatic with ECOG 0 and the physical examination did not reveal pathological findings. After the end of the seventh cycle the CT scan showed a marked partial response [7] in all measurable lesions (Figs. 1 and 2) and the treatment was continued.

Discussion

Epidermal growth factor receptor (EGFR) is a transmembrane glycoprotein that is a member of the tyrosine kinase receptor superfamily. Tumour overexpression of EGFR is associated with a poor prognosis in patients with gastric cancer [8]. Cetuximab is a human-murine chimeric monoclonal antibody directed to the EGFR binding site and has shown antitumoral activity in a great variety of neoplasms such as colorectal or head and neck cancer. In advanced gastric cancer cetuximab has demonstrated efficacy in combination with FOLFIRI in a phase II clinical trial with 38 patients with an overall response rate of 44% and a median time to progression of 8 months [6]. The grade 3–4 toxicity included neutropenia 42.1%, acne-like rash 21.1% and diarrhoea 7.9%.

A number of controlled trials and a meta-analysis provide evidence for the beneficial effect of palliative systemic chemotherapy as compared to supportive care alone for patients with advanced gastric cancer. In a meta-analysis of three trials of systemic chemotherapy vs. best supportive care, patients undergoing combination chemotherapy lived for an average of 6 months longer than those receiving best supportive care [3]. The standard regimens used in advanced gastric cancer have not been tested in severe hepatic dysfunction and the associated toxicity is high. DCF is one of the most active and toxic chemotherapy regimens in gastric cancer. It was not chosen in this clinical case because docetaxel is contraindicated in patients with bilirubin more than 1.5–2 times the upper limit of normal values [9] and patients with abnormal liver function are at significantly higher risk for fatal toxicity. Also, irinotecan combinations and ECF and similar regimens described in the REAL-2 trial [4] were not used because epirubicin and irinotecan are contraindicated in severe hepatic impairment. We considered the toxic profiles of all these combinations were unacceptable in this setting.

The results of the REAL-2 trial show that oxaliplatin could replace cisplatin with comparable efficacy and a more favourable toxic profile. We decided to use oxaliplatin combined with 5-fluorouracil because oxaliplatin in monotherapy has shown very modest activity against gastric or colorectal cancer and all chemotherapy regimens based on oxaliplatin tested in phase II–III clinical trials in gastric cancer have been combined with fluoropyrimidines (oral or intravenous). Oxaliplatin undergoes extensive nonenzymatic conversion to its active cytotoxic species. More than 50% of the drug is cleared through the kidneys and it does not present hepatic metabolism. However, increased AST, ALT and bilirubin grade 3–4 have been reported in 1–5% of patients with oxaliplatin in monotherapy and in all grades up to 13–54% of cases. Postmarketing studies and case reports have shown severe hepatotoxicity in patients with previous hepatic dysfunction and increased liver function test. Because of all these data and the combination with 5-fluorouracil we reduced the dose of oxaliplatin by 30% [10]. In addition, we tried to avoid a long 5-fluorouracil intravenous infusion due to the hepatic dysfunction, so we used a short and low dose of 5-fluorouracil.

Currently, cetuximab is not authorised for gastric cancer; for this reason cetuximab was used with oxaliplatin and 5-fluorouracil as compassionate use.