Letters to the Editor

Intra-arterial hepatic chemotherapy combined with continuous infusion of 5-fluorouracil in patients with metastatic cholangiocarcinoma

Cholangiocarcinoma refers to primary cancer of intrahepatic bile ducts. Resection is the most effective treatment, with a median survival of 36 months and a 5-year survival rate of 50%; however, unresectable tumors have a very poor prognosis with a median survival of 11 months and a 3-year survival rate of 21% [1, 2]. No good chemotherapy regimen is currently available, but 5-fluorouracil (5-FU), doxorubicin and mitomycin-C have been reported to produce transient partial remission in a small proportion of patients [3].

The use of epirubicin, cisplatin and 5-FU as a continuous 24-h infusion (ECF) was investigated in 25 patients with a 40% partial response (PR) and a median response duration of 10 months [4].

The rationale for the use of intra-arterial hepatic chemotherapy (IAHC) for the treatment of biliary tract cancer is related to: (i) the natural history of the tumor, with a growth through a local extension rather than distant metastases; (ii) the high hepatic extraction upon the first pass of some drugs that reach the bile canaliculi at high concentrations; and (iii) the fact that the blood supply of the upper biliary tree and gall-bladder derives from the hepatic artery [5]. While some studies have yielded promising results, with response rates ranging from 40% to 78% [6, 7], it is not possible to judge whether there is an advantage over systemic chemotherapy.

In our opinion, an interesting method of investigation is to combine systemic and intra-arterial approaches: in this pilot study we have evaluated the combination of IAHC and 5-FU continuous infusion according to the ECF regimen described previously by Ellis et al. [4].

From January 2000 to December 2001, 10 patients were enrolled into this trial (six females, four males; median age 61 years, range 52–70 years). Performance status, according to World Health Organization (WHO) criteria, was one in six patients and two in four patients. Nine out of 10 patients had histologically confirmed cholangiocarcinoma with liver involvement (seven >50% and two <25%), three had peritoneal involvement and one had nodal recurrence. All patients have no previous chemotherapeutic treatment and only one was radically resected 24 months before nodal recurrence.

Epirubicin and cisplatin were administered as an infused bolus by angiographic catheter introduced into the proper hepatic artery using the Seldinger technique, at a dosage of 50 mg/m² and 60 mg/m², respectively, every 3 weeks. Patients received standard intravenous hydration after cisplatin. 5-FU was infused over 14 days by continuous infusion at a dosage of 200 mg/m² through a central venous catheter. Response was evaluated according to WHO criteria and toxicity was graded according to National Cancer Institute common toxicity criteria.

Forty-one treatment cycles were administered, and no side effects related to angiographic procedure were observed. Three cases of deep venous thrombosis related to the central venous catheter were observed. One case of reversible acute pancreatitis occurred. Mild hematological and gastrointestinal toxicity was observed, as was one case of grade 3 leukopenia, one case of grade 3 mucositis and two cases of grade 3 alopecia.

The overall response rate, including complete response (CR), PR and stable disease (SD), was seven out of 10: CR, using positron emission tomography (PET) evaluation, was seen in one patient out of 10, and PR and SD according to CT scan were seen in three patients each. Three out of 10 patients showed disease progression.

After a median follow-up of 6.9 months (range 2–24 months) median survival was not reached, and 1- and 2-year survival was 55%. Time to treatment failure was 10 months. Currently, seven patients are alive and three patients have not shown any disease progression. This combined regimen appears to be feasible and safe, and has an interesting response rate and survival. The major technical problem is related to the management of the central venous catheter, which needs standardized guidelines.

Further studies are warranted to verify these preliminary results.

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