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Oxaliplatin Hepatic Arterial Infusion Chemotherapy for Hepatic Metastases from Colorectal Cancer: A Phase I-II Clinical Study

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Abstract. *Oxaliplatin is a new drug active in the treatment of advanced colorectal cancer. Hepatic arterial infusion chemotherapy is under evaluation because of the high target dose and low general toxicity. Twelve patients with liver metastases from colorectal cancer were enrolled, all pretreated with evidence of progressive disease: three after a partial remission induced by oxaliplatin, folinic acid and 5-FU, three patients after a partial remission induced by irinotecan, folinic acid and 5-FU and six patients after failing a 5-FU and folinic acid regimen. They received hepatic arterial infusion chemotherapy with oxaliplatin as 30-min infusion on an out-patient basis every 3 weeks. Dose-limiting toxicity was observed at 175 mg/m^2/cycle and consisted of obliteration of the hepatic artery in one patient, abdominal pain requiring morphine in one patient and severe hypotension requiring plasma expander in a third. Following phase I, all patients received 150 mg/m^2 for six cycles. We reported four cases of partial remission (33%) lasting 24, 15, 12 and 10+ weeks, respectively, 2 stabilisation of disease (17%) lasting more than 12 weeks and six progressions (50%). Six patients (50%) presented CEA reduction of >30% and five patients (41%) showed an increase of > 8% of body weight. The median survival was 13 months (range 6-19). Oxaliplatin did not present significant toxicity for liver parenchyma and biliary tree. We advise that further studies be undertaken with oxaliplatin 150 mg/m^2.*

Hepatic arterial infusion chemotherapy (HAIC) is a recent tool to control liver metastases from colorectal cancer (CRC), but up to now only a few drugs such as 5-FU, fluorodeoxyuridine and mitomycin-C have been found effective and easy to handle (1-6). However, it is still unclear which patients may benefit most from HAIC (7). In HAIC, liver toxicity is frequently the limiting factor for hepatic infusion, thus new anticancer drugs with lower hepatic, biliary and arterial toxicity are needed (8,9). Oxaliplatin and CPT-11 are new drugs, widely adopted in the treatment of advanced colorectal cancer, which could be considered for HAIC (10-15). Specifically, data on the efficacy and feasibility of HAIC using oxaliplatin are limited.

Kern, in a phase I pharmacokinetic study of oxaliplatin infused as HAIC in combination with folinic acid and 5-FU given intravenously, found a recommended dose for phase II studies of 125 mg/m^2. The dose-limiting toxicity (DLT) consisted of leucopenia, obliteration of the hepatic artery and acute pancreatitis (16).

During the course of oxaliplatin clinical trials, the adverse events most often cited were haematological toxicity, gastrointestinal tract toxicity and a neuropathy, unlike that observed with other platinum derivatives. Grade 3/4 neutropenia occurred in 41.7% of the patients in a phase III clinical trial that used the combination of oxaliplatin, 5-FU and folinic acid. Thrombocytopenia is a rare event, sometimes observed after multiple cycles of combined regimen therapy. Nausea and vomiting is usually mild to moderate and readily controlled with standard antiemetics. Grade 1-2 diarrhoea may occur but studies have shown that 5-fluorouracil contributes significantly more to gastrointestinal toxicity than single agent oxaliplatin does. Neurotoxicity consists of a rapid onset of acute sensory neuropathy and a late onset of cumulative sensory neuropathy that occurs after several cycles of therapy. In about three out of four patients, neurotoxicity is reversible with a median time to recovery of 13 weeks after treatment discontinuation (17). According to Kern's experience (16, 24),

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it seems that oxaliplatin is not toxic for liver parenchyma and biliary tree and, thus, it appears eligible for HIAC.

These data concerning oxaliplatin prompted us to plan a phase I-II clinical study in order to better determine the feasibility and the evidence of activity of this drug in liver metastases from CRC.

Patients and Methods

Definitions. We adopted the following definition as reported by Eisenhauer *et al.* (18). Dose-limiting toxicity (DLT) is grade 3 or 4 toxicity or symptomatic grade 2 toxicity, necessitating dose suspension or reduction and grade 2 biochemical toxicity lasting more than 7 days. The maximum tolerated dose (MTD) is the dose at which 2 patients experienced dose-limiting toxicity. The recommended dose for phase II studies is lower than the MTD or the dose reached in plasma levels in studies on preclinical activity in animal models.

Patients. From December 1st 2001 we started this monocentric study at the Oncology Department, San Giuseppe General Hospital, Empoli, Florence, Italy. Eligibility criteria for the study were: histological or cytological proof of unresectable liver metastases from CRC, resistant to any previous treatment, or the presence of other tumors for which no therapy is available; the presence of assessable or measurable disease; an ECOG performance status of 0,1 or 2; a life expectancy of at least 3 months; age 45-75 years; adequate haematological, renal, hepatic and cardiac functions; normal blood pressure; and negative heart history. No prior chemotherapy was allowed within the preceding four weeks. Patients with extra-hepatic metastases and those with concurrent or previous malignancies within the previous 5 years, except for adequately treated *in situ* carcinoma of the cervix or squamous cell carcinoma of the skin, were excluded. We enrolled 12 patients, 8 males and 4 females, with a median age of 57 years (range, 47-68) and an ECOG performance status of 0 (n=8) or 1 (n=4). All cases had liver metastases from CRC and the median involvement of the liver was 30% (range 20-50%).The patients had already been treated with evidence of progressive disease: three after a partial remission induced by oxaliplatin, folinic acid and 5-FU, three patients by irinotecan, folinic acid and 5-FU and six patients progressed after 5-FU and folinic acid regimen.

Treatment. All the patients had, surgically or angiographically, a port placed (6/6) in the hepatic artery. The functioning of the device was checked before every cycle of treatment by directed angiography. Ranitidine, 300 mg tablet, was administered in the evening . A low dose of warfarin to achieve an INR (International Normalized Ratio) of 1.5-2.0 was administered once a day to reduce catheter-related arterial thrombosis during the treatment. Flushes of heparin solution were administered before and after HAIC. The starting dose of total oxaliplatin per cycle was 25 mg/m^2 diluted in 100 ml of glucose 5% solution, 30-min short infusion, every 21 days. It was increased by 25mg/m^2 steps per cycle upon the observation of no or only one case of toxicity grade 3-4 or symptomatic grade 2 toxicity among three patients treated. Chemotherapy cycles were repeated every 3 weeks. Supportive therapy included a 5-HT3-antagonist *i.v.* and dexamethasone 8 mg *i.v.* prior to the application of oxaliplatin.

After the determination of DLT and MTD, our patients received further HAIC with the previous step dose of oxaliplatin for six cycles on an outpatient basis in order to complete the phase II clinical study.

Haematological and non-haematological toxicity was assessed according to NCI Common Toxicity Criteria. Response to therapy was assessed according to WHO criteria by sonographic and CT scan imaging (19). The degree of liver involvement and its re-evaluation after the treatment was determined by the same group of radiologists. All the patients had confirmation of response by CT or MNR completed.

Study conduct. Before starting therapy, all the patients gave their informed consent to participate in the evaluation after being informed about the purpose and investigational nature of the study as well as about its potential risks. The study design adhered to the declaration of Helsinki and was approved by the ethics committees of the participating institutions prior to its initiation.

Results

Toxicity. The DLT and MTD were observed at dose level 7, *i.e.*, at 175 mg/m^2/cycle, and comprised diarrhoea, leukopenia grade 3 in two patients, obliteration of the hepatic artery in one patient, abdominal pain requiring morphine in one patient and severe hypotension requiring plasma expander in another. Accordingly, the dose for further phase II studies was determined to be 150 mg/m^2/cycle. DLT and MTD consisted of obliteration of the hepatic artery in one patient, abdominal pain grade 4 in one requiring morphine, severe hypotension requiring plasma expander, fluids and steroids in one. Overall, toxicity grade 1-2 mainly consisted of nausea/vomiting (5 out of 12 patients), anaemia (4 out of 12), upper abdominal pain (3 out of 12), thrombocytopenia (3 out of 12) and sensory neuropathy (5 out of 12).

Antitumor efficacy. The twelve patients entered in the phase II study were evaluable for response. They received 72 cycles of HAIC. No cycles were postponed because of toxicity. We reported four cases of partial remission (33%) lasting 24, 15, 12 and 10+ weeks, 2 stabilisation of disease (17%) lasting at least more than 12 weeks and six progressions (50%). Two responders had experienced a previous PR linked to the oxaliplatin, 5-FU and folinic acid combination, while 2 had had PR due to the irinotecn, 5-FU and folinic acid combination. Six patients (50%) presented CEA reduction of >30%. Five patients, 4 with PR and 1 with SD, showed a clear clinical improvement with an increase of > 8% of body weight. These patients did not present ascites or hypoalbuminea. Eight patients showed reduction of biochemical liver parameters > 20%, owing to metastases. Two non-responders stopped analgesics for 8 weeks. The median survival was 13 months (range, 6-19 months). The median time to failure was 14 weeks (range, 10-24 weeks). Five patients received a third

line of chemotherapy without any response: they died of liver progression. Seven patients died because of liver and extra-target progression.

Conclusion

Liver resection is the first choice in patients with metastases from CRC (20,21). For unresectable situations, systemic chemotherapy seems to prolong the survival (22,23). HAIC is a valuable therapeutic option for patients with hepatic metastases from CRC not suitable for resection as well as for following complete resection, perhaps being more active than systemic chemotherapy alone (1-5).

As the addition of irinotecan and oxaliplatin to standard chemotherapy combination schedules of 5-FU and folinic acid has been shown to increase the antitumor efficacy when administered systematically (11-14), the results of these new agents during HAIC has been recently studied and determined (10,16,24). They may increase the response rate and long-term results during this treatment modality and additional analyses are needed to better define their optimal schedule and therapeutic potential.

Our study evaluated the side-effects of oxaliplatin applied as HAIC as a single agent. The toxicity was substantially similar to the one observed following systemic administration of the same drug with the exception of upper abdominal pain (16, 17). This occurred in 3 out of 12 patients and it is considered to be the result of higher local drug concentrations as compared to intravenous therapy since this observation has been made frequently during various combination of drugs applied as HAIC (1-4,6,9). Mild sensory neuropathy , which is a specific side-effect of oxaliplatin, occurred in 5 out of 12 patients while severe neuropathy was not observed. This corresponds to the 45% incidence observed during intravenous administration of oxaliplatin in combination with folinic acid and 5-FU (11,12). Other frequently observed toxicities included nausea/vomiting and hematotoxicity, which are also both well characterised during systemic application of oxaliplatin (11,12,15-17). Overall, the oxaliplatin given as HAIC was well tolerated. It can be safely administered, especially to good PS patients in which the side-effects may be even less significant. A clinical benefit, as defined by partial response or stable disease, was achieved in six out of twelve evaluable patients (50%).

As reported by Kern (24), short infusion is probably preferable to a prolonged one because of the hepatic metabolism of oxaliplatin.

HAIC seems the best way to induce further responses in patients relapsed or failed to systemic chemotherapy without severe toxicity. Oxaliplatin, at the dose of 150mg/m^2 diluted in 100 ml of glucose 5%, every 21 days on an out-patient basis, seems safe, feasible and well accepted. Oxaliplatin is active as HAIC in liver metastases from colorectal cancer and can rescue patients previously treated with an oxaliplatin- or irinotecan-based regimen, or 5-FU and folinic acid schedules.

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