Hepatic artery infusion using oxaliplatin in combination with 5-fluorouracil, folinic acid and mitomycin C: oxaliplatin pharmacokinetics and feasibility.

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BACKGROUND: Several studies have demonstrated the efficacy of systemic oxaliplatin (Oxa) in combination with 5-fluorouracil (5-FU) and folinic acid (FA) for the treatment of colorectal liver metastases (CRLM). However, nothing is presently known about the pharmacokinetics of Oxa administered via the hepatic artery and only very little about the feasibility and toxicity of Oxa used for hepatic artery infusion (HAI). PATIENTS AND METHODS: We designed a phase II trial using Oxa in combination with 5-FU/FA and mitomycin C (MMC) for HAI treatment of patients with isolated non-resectable CRLM. Oxa (130 mg/m²) was delivered on day (d) 1 as a 120-min infusion followed by FA (140 mg/m²) for 10 min and 5-FU (480 mg/m²) for 120 min from d1 to d5 and MMC (7 mg/m²) for 30 min on d5 every 35 days. For Oxa pharmacokinetics, peripheral venous blood was collected before, during and after arterial infusion. Oxaliplatin was determined by liquid chromatography with post-column derivatization in blood ultra filtrate. RESULTS: A total of 33 HAI cycles were administered to 5 patients with tolerable toxicity, which mainly consisted of grade I and II nausea, vomiting, leucopenia, thrombopenia and abdominal pain. During 4 cycles nausea/vomiting III degree occurred, during 3 cycles diarrhoea and abdominal pain III degree. No neurotoxicity > or = II degree and no catheter occlusion was observed. Staging showed 4 PR and 1 PD. Pharmacokinetic analysis revealed an AUC value of 85.3 micrograms x min/ml after HAI. Recalculating these values with the previously reported AUC value for systemic administration (161 micrograms x min/ml) revealed a liver extraction ratio of 0.47 for Oxa. CONCLUSION: We conclude from our results that Oxa in combination with 5-FU/FA and MMC may be a feasible protocol for HAI treatment without major toxicity, especially avoiding higher grade neurotoxicity. This is probably attributable to the low systemic bioavailability of Oxa.

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