Feasibility of Intrahepatic Arterial Paclitaxel in Two Patients

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Citation

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Abstract

Objective: To demonstrated the feasibility of organ perfusion with paclitaxel in the hepatic artery of patients with refractory liver metastases.

Design: Case report study

Patients: Two patients with advanced liver metastases from gynecological cancers.

Results: Intrahepatic arterial infusion of paclitaxel is feasible. Toxic effects include local pain, and systemic effects similar to the ones observed after i.v. infusion.

Conclusions: Clinical trials should be performed to better define the use of paclitaxel infused in the intrahepatic arterial circulation for the treatment of extensive liver metastases. Given the activity of paclitaxel in a wide range of cancers, this modality may be useful in specific situations.

INTRODUCTION

The natural history of intraparenchymal liver metastases from various malignant neoplasms is usually similar. The mean survival of patients with untreated liver metastases is approximately 6 months. More than 50% of the patients who die of cancer have liver metastases at autopsy.[1] Because of the ominous prognosis of liver metastases, therapeutic approaches have focused on controlling liver disease, surgically if feasible, or by direct infusion of chemotherapeutic agents into the hepatic artery or the portal vein.[2] Seventy-five percent of the liver blood flow is supplied by the portal vein, and 25% by the hepatic artery. However, most malignant liver tumors derive their blood supply from the hepatic artery.[3,4] Theoretical advantages for locoregional intrahepatic arterial therapy include the delivery of a high concentration of drug to the tumor, and possibly a decrease of systemic toxicity. The chemotherapy drug commonly used for liver infusion is floxuridine.

Paclitaxel, a taxane derived initially from the bark of the pacific yew tree Taxus brevifolia stabilizes microtubules by preventing their depolymerization[5] and thus blocking the cell cycle in the G_2/M phase. Paclitaxel has demonstrated significant activity against both platinum-sensitive and platinum-refractory ovarian cancers,[6,7,8] and against breast[9] and lung cancers.[10] Because the drug?s cytotoxic activity is correlated with its concentration8 and area under the plasma concentration-time curve, locoregional delivery at high concentrations could be of potential benefit. Paclitaxel has already been used for locoregional chemotherapy, such as peritoneal administration.[11] Walton reported one other case of intrahepatic arterial infusion of paclitaxel,[12] and Japanese authors have published treatment with hepatic intraarterial docetaxel.[13]

We report the cases of two patients with chemotherapy-refractory liver metastases, one from ovarian cancer and the other one from choriocarcinoma, who received intrahepatic arterial paclitaxel as a single agent or in combination with other chemotherapy for palliation.[14]

CASE REPORTS

CASE 1

A 53-year-old woman who presented with a pelvic mass (18x17cm) underwent total abdominal hysterectomy and bilateral salpingo-oophorectomy with optimal debulking. The pelvic mass was multicystic with solid components arising from the right adnexa. There were no peritoneal

adhesions or seeding. The liver was unremarkable on direct examination. Peritoneal washings were negative for malignant cells, and lymph node samples showed no involvement with tumor. She was diagnosed as having stage IC endometrioid ovarian carcinoma. The pathological examination also revealed foci of undifferentiated anaplastic spindle cells in the ovary. She was subsequently started on combination chemotherapy with carboplatin and cyclophosphamide. However, after two cycles of chemotherapy rapidly progressive liver metastases developed in the patient. Fine-needle aspiration of the liver lesions showed an undifferentiated anaplastic carcinoma. Initial physical examination demonstrated a sick patient with an enlarged liver (9 cm below the right coastal margin) and a 2x2-cm mass in the right vaginal wall.

A computerized tomography (CT) scan of the abdomen showed numerous low density lesions scattered throughout both lobes of the liver. Paclitaxel was delivered by continuous arterial infusion at a dose of 175 mg/m2 (total dose 300 mg) over 24 hours, and followed by granulocyte colony-stimulating factor (G-CSF, 5µg/kg/day). Pain in the right upper quadrant required an infusion of morphine sulfate. A transient ileus developed and a chest x-ray showed a right-sided atelectasis. These complications were treated with intravenous fluids, broad-spectrum antibiotics, and steroids and improved rapidly during the following 48 hours. The granulocyte nadir (1000 cells/µl) was noted on the sixth day and lasted 4 days. The platelet nadir (38,000 cells/µl) was reached on day 7.

The patient was discharged from the hospital 2 weeks after paclitaxel administration in good general condition. At the time of discharge, the liver was 7 cm below the costal margin. However, the patient was thought to be a poor candidate for further therapy because of the rapid progression of disease in the untreated left lobe of the liver and she died 1 month later of progressive disease.

CASE 2

A 33 year old woman, gravida II para II, was diagnosed with WHO high risk metastatic choriocarcinoma. She was treated with one course of methotrexate, actinomycin D, and cyclophosphamide (MAC). After which, she developed a large brain mass (5x3 cm) arising from the epidural space in the right posterior temporal/occipital area. She was then treated with radiotherapy of the whole brain (40 Gy). After completion of radiotherapy, MAC chemotherapy was resumed. Despite an initial response, as demonstrated by decrease in ßHCG, she recurred with an enlarged uterus. Two cycles of etoposide, methotrexate, actinomycin D, cyclophosphamide, and vincristine (EMA-CO) were administered,[15] followed by an abdominal hysterectomy with no improvement. A CT scan of the abdomen and pelvis showed a hepatic mass. Examination of a CT-guided biopsy of the liver revealed a poorly differentiated carcinoma with marked anaplasia and similar features to those seen initially.

Treatment consisted of an intrahepatic arterial infusion of paclitaxel (200 mg/m2) over 24 hours, followed by intravenous bleomycin (20 units), floxuridine (100 mg/m2), and cisplatin (75 mg/m2). G-CSF (5 µg/kg/day) was given for 10 days for bone marrow support after each cycle of chemotherapy. She tolerated a total of four cycles of this chemotherapy without experiencing any major toxic effects, and a partial response was obtained. Before the fifth cycle of therapy, the tumor progressed rapidly, with the development of multiple new metastases in the lungs and the liver. The patient's tumor did not respond to further chemotherapy. She died 4 months later of progressive disease.

DISCUSSION

These two patients treated with intrahepatic arterial paclitaxel for liver metastases from ovarian cancer and choriocarcinoma tolerated the treatment well. A suggestion of antitumor activity was observed in these extremely chemoresistant tumors. Case 2 demonstrated a partial, albeit brief, objective response. Main toxic effects included pain, ileus, right lower lobe atelectasis, grade 2 neutropenia with G-CSF support, and grade 3 thrombocytopenia.

The bulk of clinical experience with intrahepatic arterial therapy has been accumulated in patients with colorectal adenocarcinoma. Intrahepatic arterial therapy has also been used to treat hepatocellular carcinoma[16] and liver metastases of breast cancer.[17] In the early 1960s, Sullivan et al. were the first to use the locoregional delivery of drugs to treat liver metastases of colo-rectal cancer. Responses as high as 60% were observed.[18] By comparison, the best standard systemic therapy available (5-fluorouracil and folinic acid) yields a response rate of 25%, with a median survival of approximately 12 months.[19] Improvement in catheter technology, infusion pumps, and surgical techniques have also reduced morbidity.[20] In clinical trials comparing the use of intrahepatic arterial floxuridine with systemic therapy, response rates have usually been superior with regional therapy (42-62% vs 10-21%), and a trend for longer survival was observed.[21,22] A few patients (< 5%) who received

intrahepatic arterial therapy are long term survivors. There are no long term survivors among patients treated with systemic therapy.[23] Complications associated with the delivery of intrahepatic arterial floxuridine include hepatitis, biliary sclerosis, arterial thrombosis, and peritonitis.2 Failure to respond to systemic chemotherapy is not a contraindication to intrahepatic therapy because the pharmacokinetic characteristics of arterial hepatic infusion are a determinant factor of response.[24] However, the response rate drops to 30%.

The antitumor activity of hepatic arterial infusion is explained by pharmacokinetic factors such as drug metabolism, type of tumor, delivery systems, organ extraction, and drug clearance. The ideal drug is completely extracted from the hepatic blood circulation at the first liver passage, yields a high local concentration with little systemic exposure and has a low toxic profile. Floxuridine is the paradigme of high hepatic extraction.[25]

These pharmacokinetic considerations were reviewed by Collins and summarized in the following formula:[26]

$R_d = 1+ [Cl_{TB} / Q(1-E)]$

where: R_d is a quantitation of the pharmacokinetic advantage of intra-arterial administration, Cl_{TB} is the total body clearance obtained during intravenous infusion, Q is the blood flow through the treated organ, and E is the extraction ratio during a single pass through the treated organ.

Paclitaxel carries some of the characteristics needed for intrahepatic arterial therapy. Distribution studies done in rats 24 hours after intravenous infusion show a high concentration of the drug in the liver, and a liver to plasma ratio of 25:1.[27] In humans, the drug?s elimination curve is triphasic. Half lives $T_{1/2}$a, $T_{1/2}$ß, and $T_{1/2}$? have been estimated to be 0.2, 1.9, and 20.7 h--ours, respectively.[28] Paclitaxel is hydroxylated in the liver by the P-450 cytochrome complex and mainly excreted in the bile. Less than 10% is excreted unchanged in the urine.28 Cancer patients treated with intravenous paclitaxel demonstrate extensive tissue and protein binding (93-98%), but that did not prevent most of the intraarterially administered paclitaxel to be extracted by the liver in the patient described in Walton's study.12 Our experience demonstrates the feasibility of hepatic arterial delivery of paclitaxel either as a single agent or in combination with other active drugs. Pharmacokinetic studies during and after organ infusion with paclitaxel are needed to estimate the exact extraction ratio of the drug, and to determine whether regional infusion confers a pharmacokinetic advantage over systemic infusion. Toxic effects after intrahepatic arterial delivery need to be evaluated in phase I-II settings, but in our limited experience, is comparable to intravenous administration of paclitaxel.

CORRESPONDENCE TO

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