Hepatic Artery Infusion Via Percutaneously Implanted Arterial Port-A-Cath In Elderly Patients

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Citation

Abstract
Background: Up to now no definitive data on hepatic artery infusion for colorectal liver metastases in elderly patients are available. Percutaneous implantation of an arterial Port a Cath was considered for the treatment of 39 elderly patients suffered for colorectal liver metastases non eligible for surgery.

Methodology: The distal left subclavian artery was punctured under the clavicle and an angiographic study of the hepatic district was performed. Gastroduodenal artery or anomalous hepatic arteries were embolised with Gianturco coils. Then a polyurethane catheter was inserted distally into the hepatic artery and connected to the reservoir through a 3-4 cm subcutaneous tunnel. All patients underwent regional chemotherapy with FUDR 0.3 mg/kg/die + desamethasone 2 mg/die + Leucovorin 15 mg/m2 in continuous infusion.

Results: We noticed 5 dislocations of the catheter and 2 hepatic artery thrombosis. Only one patient definitively suspended the treatment for complications related to the technique. Drugs toxicity occurred in 30.8% of patients. We found neither cholecystitis nor sclerosing cholangitis. 47% of objective clinical responses was noticed.

Conclusions: Preliminary results suggest that hepatic artery infusion could be indicated in the treatment for elderly patients with inoperable colorectal liver metastases.

INTRODUCTION
Age is one of the most important cancer-related risk factor, while colorectal carcinoma is one of the most important causes of death for cancer disease (1).

Nevertheless the indications of chemotherapy for elderly patients is still a controversy. To our knowledge no data are available on regional chemotherapy in the treatment of elderly patients affected with colorectal liver metastases non-eligible for surgery.

At the time of the initial diagnosis of colorectal cancer 20% of patients have liver metastases and in one half of them liver is the only site of metastasis (2). 60% among all the patients who die for colorectal cancer will develop liver metastases during the course of their disease (3). Both the treatment for hepatic metastases and the surgical resection of the primitive lesion play their part in the prognosis of these patients (4). About 10% of patients suffering for colorectal liver metastases are eligible for surgery with an overall five years survival of about 30% (5). For patients whose liver metastases are considered non-eligible for surgery the development of efficacious alternative treatments is needed.

Liver metastases depends on the hepatic artery for most of their blood supply, whereas normal liver parenchyma gets blood supply mainly from the portal vein (6). Hepatic artery infusion (HAI) of chemotherapeutic drugs has been used in the treatment of colorectal liver metastases since 40 years ago. Randomised trials about regional chemotherapy with continuous infusion demonstrated high number of hepatic responses (40-60%), while no definitive data about survival are available (7,8,9,10,11,12).
A meta-analysis study found that HAI with FUdR produced a 10% (P=0.041) and 6% (P=0.124) survival advantage at 1 and 2 years (13).

In our centre we have developed a technique for hepatic arterial Port-a-cath implantation in local anaesthesia with the aid of fluoroscopy (14). The aim of the study was the retrospective evaluation of the technique of implantation and regional chemotherapy for colorectal liver metastases in elderly patients, in terms of feasibility, complications, toxicity, response rate and survival time.

**METHODODOLOGY**

**PATIENTS**

From April 1996 to September 1999, 39 patients aged over 65 (range 65-83) and suffering for colorectal liver metastases underwent the placement of an arterial hepatic port a cath by a transcutaneous access to perform regional chemotherapy.

Eligibility criteria to enter the study were:

- Age > 65 years.
- Colorectal liver metastases not eligible for surgical liver resection.
- Primary colorectal cancer radically resected without evidence of regional relapse of disease.
- No evidence of extra-hepatic disease.
- No evidence of hepatic failure

Median and mean age of patients were respectively 72.3 and 72 years (SD ± 3.22). Cholecystectomy had been previously performed in 4 patients.

Patients' performance status according to ECOG criteria was: 6 P.S.0, 13 P.S.1, 12 P.S.2 and 8 P.S. 3.

**TECHNIQUE**

Patients underwent percutaneous implantation of an indwelling arterial hepatic catheter connected with an infusion reservoir (Port-a-cath) for hepatic artery infusion (HAI). Local anaesthesia was performed by injection of Lidocain 20 ml. The distal left subclavian artery was punctured by Seldinger technique under the clavicle, 2 cm laterally to the insertion of the first rib. Colour Doppler Ultrasound allowed to avoid the puncture of the subclavian vein or damages of the artery. The celiac trunk and the superior mesenteric artery were catheterised and preliminary angiographic study of local arterial flow was performed. Congenital anomalous hepatic arteries and gastroduodenal artery were embolized with Gianturco coils (Cook, Bloomington, Illinois).

Then an angiographic guide wire was inserted distally into the hepatic artery and a 5.8 F radiopaque soft polyurethane catheter, 75 cm long (Deltec Sims, St. Paul, Minn., USA) was inserted into the hepatic artery. Infusion of highly concentrated heparin solution (2000 IU) prevented occlusion and fluoroscopic control of catheter position was performed. A subcutaneous subclavear pocket was prepared 3-4 cm under the puncture site and the port was connected to the catheter by a tunnel through the subcutaneous tissue to prevent catheter dislodgement. The whole procedure took about 30-45 minutes.

Patients could be discharged after two hours with prescription of subcutaneous low weight molecular heparin at prophylactic doses until the removal of the catheter.

All patients gave their conscious written consent for the study, which was performed according to the ethical guidelines of the 1975 Helsinki Declaration.

The daily treatment schedule was Fluorodesoxiuridin (FUDR) 0.3 mg/kg/die + Dexamethasone 2 mg/die + Leucovorin 15 mg/m² in continuous infusion through the arterial Port-A-Cath device for 14 days, every 21. All patients received ranitidine 300 mg orally during HAI.

Toxicity was evaluated according to WHO criteria and responses were assessed on CT scan after 3 cycles of HAI. A complete response required the disappearance of all the disease as assessed by CT scan and CEA; an over 50% reduction of the disease was considered a partial response (PR). Survival curves were estimated by the Kaplan-Meier method.
Figure 1
Figure 1: radiological and anatomic demonstration of our hepatic placement of percutaneous arterial port

Figure 2
Figures 2 and 3: Catheter implanted into the hypogastric artery for a loco-regional pelvic chemotherapy for advanced pelvic neoplasm

Figure 3
T.A.P. median time of permanence
- 6 months
- Removed (progression disease, efficacy of the loco-regional treatment, malfunction) in ambulatory setting
- No difference in elderly and patients with a bad Performance Status
- Loco-regional chemotherapy performed in 96% of our patients

RESULTS
The mean number of regional chemotherapy cycles for each patient was 4.9 (SD 2.19). The mean time of permanence of patent arterial catheter was 6.24 months.

We observed 2 cases of hepatic artery thrombosis, one of which was successfully treated with arterial thrombolysis, and 5 dislodgements of catheter, which was always moved again into the hepatic artery with the aid of fluoroscopy. No complications related to gastroduodenal artery embolization occurred. Only one patient (2.6%) definitively suspended the regional treatment for complications related to the technique.

All patients were evaluable for toxicity. We registered 8 cases of diarrhoea of 3rd or 4th degree and 3 cases of recurrent gastritis and 1 of gastroduodenal ulcers (30.8% of toxicity related to intra-arterial drug). We found neither cholecystitis nor sclerosing cholangitis probably because of the sparing of the hepatoduodenal ligament dissection usually performed in the surgical implantation technique, which causes ischemic damages of bile ducts. Temporary suspension of the treatment was needed in 5 patients for toxicity due to drug infusion. Three patients were admitted to hospital. We also found that toxicity related to intra-arterial drug infusion often occurred in patients who had a non-complete occlusion of the gastroduodenal artery. Other embolization of the gastroduodenal artery by Gianturco coils prevented or at least minimised further gastrointestinal toxicity.

Thirty-four patients underwent at least 3 cycles of regional treatment and were valuable for responses. One patient interrupted the treatment for the occurrence of hepatic artery thrombosis, one patient, who was P.S. 3, for toxicity due to...
HAI, one patient died for causes not related to tumoral disease and two refused to continue the therapy without having experienced toxicity. We registered 4 complete responses, 12 partial responses, 7 stable diseases and 11 progressions of disease. The clinical objective response rate was 47% and 2 patients, not eligible for surgery before the treatment, underwent radical surgical resection of residual liver disease after a regional infusion.

The survival curve estimated by Kaplan Meier method is reported in table 1. Cumulative Proportion Surviving was 50% at 13 months and 20% at 24 respectively. 30 out of 39 patients had body-weight increase >10% and 25 out of 39 had reduction in supportive treatments for at least 9 months.

**DISCUSSION**

In Western countries, the rapid increase of the elderly population will inevitably lead to a remarkable growth of the number of new cancer cases (15). Up to now, about 60% of all cancers are diagnosed in patients aged 65 years (16). This is probably due to the prolonged exposure to cancerogenetic substances with an increasing of the overall dose and the risk of realising a cancerogenesis process during life time, a decreasing of the immunologic apparatus and deficiency of “DNA repair” system.

The management of elderly patients in current oncologic practise is still a controversy. No definitive data are available on the treatment tolerance, the oncologic results and sequelae. Moreover elderly patients are often treated inadequately and the advanced disease is due to the fact that they are less frequently screened (17,18).

Ninety % of the patients, aged over 70 years and affected with cancer, suffer from at least another chronic disease, which needs a medical treatment (19). Moreover the influence of drugs complications is increased in elderly people. This higher rate of toxicity has been demonstrated both for haematological, gastrointestinal (mucositis, nausea, vomiting and gastroduodenal ulcers) (20), cardiovascular (21), respiratory (22) and neurological (23) complications. Nevertheless, thanks to the progress in the treatment of comorbidities and drugs complications in elderly people, chemotherapy has become more frequently used.

Recent studies highlighted that age is not a reason to exclude patients from optimal treatment with surgery, radiotherapy or chemotherapy (24). On the other hand the feasibility and the outcome of hepatic artery infusion for the treatment of elderly patients with unresectable colorectal liver metastases has been poorly documented.

The rationale of HAI approach is based on favourable pharmacokinetics, which allow the delivery of higher doses of drugs to the liver when given by the intra-arterial route (25). Potential theoretical advantages of percutaneous implantation of indwelling arterial catheters to perform regional chemotherapy are the saving of laparotomy, the performance of the procedure on an outpatient basis, the beginning of drug infusion immediately after the implantation, the avoidance of post-operative immune-depression. Moreover the percutaneous approach allows us to occlude not targeted arteries by embolising the same to prevent or minimise gastroduodenal complications. In the
case of uncompleted occlusion of the gastroduodenal artery or collateral vessels, they can be embolized again.

Catheter dislodged can be replaced. Costs and invasiveness are lower (26) and regional treatment could be performed in a higher number of patients because of the fewer cases of untreatable complications.

According to our experience the response rate of HAI infusion in elderly patients for colorectal liver metastases is similar to the results obtained by the same treatment in younger people (1). Toxicity seems to be a little higher but it could be prevented through a more strict evaluation of hepatic arterial flow setting before every cycle. In fact we have noticed that arteries embolised with Gianturco coils are frequently patent again after few months. The injection of marked albumin from the arterial port is useful to establish the drug perfusion and non-targeted arteries can be embolised again.

The main advantage of the technique of implantation used in our centre is the possibility to move again the dislodged catheters into the hepatic artery. Furthermore only one patient could not perform regional chemotherapy for untreatable complications due to the technique.

The comprehensive cost of the implantation of an arterial catheter by our technique is estimated about 2000$ that is considerably less than one half the minimum previously estimated for a surgical implantation (26).

Up to now surgery is the best treatment of colorectal liver metastases. HAI allowed to make two elderly patients eligible for radical surgical resection.

CONCLUSIONS

In conclusion HAI by a percutaneous implantation of arterial port-a-cath is a promising therapy for elderly patients with colorectal liver metastases not eligible for surgery. Our experience suggests that elderly patients should not be exclude from such treatment. Nevertheless more data are needed to confirm our results and more attention has to be paid to avoid extra-hepatic infusion of drugs in order to increase the tolerance of the therapy.

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References

17. Ganz PA, Does (or should) chronologic age influence the choice of cancer treatment? Oncology (Huntingt) 1993; 6:45-49.
25. Ensminger WD; Rosowsky A; Raso V; Levin DC; Glode M; Come S; Steele G; Frei E. A clinical pharmacological evaluation of hepatic arterial infusions of 5-fluoro-2'-deoxyuridine and 5-fluorouracil. Cancer Res 1978; 38: 3784-3792
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