Abstract. Background: In patients locally progressing after two lines of chemotherapy, some locoregional approaches showed encouraging results in terms of local control of disease. The aim of our study was to evaluate toxicity, clinical response and quality of life in 48 patients with unresectable colorectal liver metastases submitted to selective internal radiotherapy (SIRT). Materials and Methods: Up to now 35 patients with unresectable colorectal liver metastases, refractory to two lines of chemotherapy, underwent intra-arterial infusion of resin microspheres with yttrium-90 (SIR-spheres). Pre-treatment evaluation included a CT scan, blood tests, a PET scan and arteriography of celiac trunk, hepatic and superior mesenteric artery; extrahepatic uptakes and pulmonary shunts more than 10% were excluded by a Scinti-scan. The gastroduodenal artery was embolized before the SIR-spheres injection. Other exclusion criteria were liver dysfunction and anatomical vascular anomalies. The clinical response was evaluated by CT-scan following the RECIST criteria. Median follow-up was 4 months. Results: Median number of metastases was 4 (range, 1-15), 38% of cases presenting hepatic involvement <25%. The median SIRT dose delivered was 1.7 GBq. Median pulmonary shunt was 6%. No operative mortality occurred; early toxicity (within 48 hours) was 20.6%, shown as fever, acute pain and leucocytosis. The late toxicity was 24.1% with chronic pain, jaundice and nausea being the most frequent. All the toxic events were graded 2 or 3 according to the WHO scale. Preliminary results were available in terms of clinical response after 6 weeks: 12.5% had a partial response, 75% a stable disease, while progression of disease, was observed in 12.5% of the patients. Conclusion: SIRT is a safe treatment in terms of acute and late toxicity. Intra-arterial microspheres could represent a good therapeutic option for patients with progressing liver metastases only, after two lines of systemic chemotherapy.

In 2005 about 150,000 new cases of colorectal cancer were diagnosed in the United States (1). About 20% of them had liver metastases at diagnosis while a further 30% developed a hepatic relapse during the follow-up (2).

Surgical resection is the only chance of curative treatment, 5-year overall survival ranging from 25%- 60% in carefully selected patients (3-5). Unfortunately, only 5% to 17% of patients affected by liver metastases can benefit from radical surgery (6). For the unresectable patients, regimens of systemic chemotherapy based on oxaliplatin and irinotecan as first- and second-line showed satisfactory results in terms of downstaging, downsizing and survival rate (7).

In patients with liver metastases only, locoregional chemical, thermal and radiation treatments showed encouraging results in terms of control of disease. In view of this, several studies on radioembolization started in the 1990's in Australia (8-11) and then in the United States (12-16). The rationale of radioembolization is the injection of embolic particles (microspheres) loaded with radionuclide beta emitting isotope Y-90 directly into the site of the disease.
The aim of our multicentric prospective clinical trial was to evaluate the clinical hepatic response, time to liver progression and quality of life in patients with colorectal liver metastases not responding to the two previous lines of i.v. chemotherapy and submitted to intra-arterial injection of SIR-spheres with yttrium-90, with the liver being the only site of disease, eventually combined with minimal extrahepatic disease.

Materials and Methods

From June 2005, four centers (Regina Elena Cancer Institute of Rome, Policlinico S. Orsola Malpighi of Bologna, G. Pascale Cancer Institute of Naples and University of Udine), all members of the Italian Society of Locoregional Therapies in Oncology, enrolled 35 patients with colorectal liver metastases (not responding to i.v. chemotherapy based on oxaliplatin and/or irinotecan) in a multicentric prospective clinical trial of intra-arterial injection of SIR-spheres with yttrium 90. Forty-eight patients was a sample size needed to guarantee a power of 80% at a significance level of 5%, if a response rate of 30% was observed, and 15% not acceptable. Inclusion criteria were: histologically proven hepatic metastases, primary resected, performance status ≤2 (WHO), age between 18 and 75, life expectancy >6 months, hepatic involvement <50%, bilirubin ≤1.5 g/dl and written consent. Exclusion criteria were hepatic cirrhosis, ascitis, pulmonary shunt >10%, major anatomical vascular anomalies and portal and/or arterial thrombosis.

All the patients were evaluated before inclusion by CT scan to identify the "target lesions" and to evaluate the liver and nodule volumetry. The lesions were considered as target when measurable. For each target lesion, the largest diameter was utilized to establish the objective response. Response was evaluated by RECIST criteria: complete response, in case of disappearance of lesions; partial response, when a reduction of target lesions was ≥30% in maximum diameter; when an increase ≥20% or new lesions appeared, a progression of disease was defined; all the other events were considered as stable disease. A CT-guided biopsy of the healthy and metastatic liver was performed to determine the objective response. Response was evaluated by RECIST criteria: complete response, in case of disappearance of lesions; partial response, when a reduction of target lesions was ≥30% in maximum diameter; when an increase ≥20% or new lesions appeared, a progression of disease was defined; all the other events were considered as stable disease. A CT-guided biopsy of the healthy and metastatic liver was performed to determine the objective individual biological profile. A PET-scan studied the lesion uptake.

Angiography of the celiac trunk, selective hepatic circle and superior mesenteric artery was performed to evaluate arterial hepatic and gastroduodenal-pancreatic anatomy. Moreover, during this first procedure, Albumin macroaggregated (with behavior similar to microspheres) were injected into the hepatic artery and a further Scinti-scan evaluated distribution in both the metastatic and healthy liver and pulmonary shunt as well. Dose was calculated considering the patient and metastases characteristics using the following parameters: GBq = (BSA-0.2) + (% Tumor involvement/ 100), tumor involvement being the ratio of the volume of liver metastases to the total volume of liver plus nodules.

All the patients were admitted the day before the procedure and evaluated for quality of life by the EORTC (QLQ-C30; CR-38; QLQ-LMC-21; QLQ-SAT 32; HADs) questionary; all of them were discharged one or two days later. On the day of intra-arterial microsphere infusion, the gastro-duodenal artery and other hepatic collateral branches were embolized with micro-coils. Yttrium-90 resin SIR-spheres (resin with bound yttrium) infusion was delivered into the common hepatic artery with an endovascular microcatheter (2.7 Fr. size). Blood, clinical examinations and chest X-ray were carried out on days 1, 8 and 30 after the microsphere infusion. Six weeks after the procedure, the patients underwent a CT-scan to evaluate the response. After 12 weeks another CT-scan was repeated with a guided biopsy to observe liver structure and any possible changes of the metastases profile. A PET-scan also evaluated modifications of lesion uptake.

The median follow-up was 4 months up to date.

Results

The median number of metastases was 4 ranging from 1 to 15, median diameter of nodules was 47 mm (range, 20-97) with hepatic involvement <25% in 38% of cases, and between 25% to 50% in the remaining patients. The median dose administered was 1.7 GBq (range: 0.9-2.2 GBq) and the median pulmonary shunt was 6% (maximum 9%). None of the patients studied for pulmonary shunt were excluded from treatment. All the patients were evaluable for operative mortality, complication and toxicity. No mortality was observed, while 7 out of 35 (20.6%) patients showed toxic events within 48 hours from microsphere injection (fever: 4, leucocytosis: 2, acute pain: 1); all toxic responses were controlled with medical treatment. Late events (after 48 hours) were observed in 8 patients (24.1%), with chronic pain, transient elevation of liver enzymes ≥2 fold of normal values, jaundice and nausea being the most frequent. All events were grade 2-3 (WHO).

After 6 weeks from treatment, a partial response, stable disease and progression were observed in 12.5%, 75% and 12.5%; respectively.

Modifications of radiological morphology of metastatic lesions was often observed, being better defined in comparison with normal liver parenchyma, showing a decreased attenuation representative of edema and microinfarction. Morphological changes, such as attenuated metabolic activity were observed by PET-scan in case of response.

The short follow-up and the small number of patients evaluable after 6 weeks from treatment did not allow any survival analysis.

Selective internal radiotherapy (SIRT) did not worse the quality of life in the functional and symptomatic areas except than the global quality of life. Patients did not show high levels of distress.

Discussion

The concept of SIRT arose in the 1950's, but only in the second half of the 1980's did studies take place in Australia first and then United States (8-16). In recent trials the SIRT application showed high rates of response in patients affected with colorectal liver metastases. Gray et al. published results obtained from 29 unresectable colorectal liver metastases
patients treated by SIRT. In 12 of them systemic chemotherapy with 5-FU was administered; the response rate was more than 45%, with a stabilization of disease in 40% and progression in only 18% of the cases (8). Subsequently, the same authors published data concerning toxicity and activity of combination of SIR-spheres and intra-arterial infusion of Fluoxuridine (FUDR): 71 patients were enrolled, the response rate was 86% and the median survival observed in patients with only liver disease was 18.5 months vs. 17.3 months in cases of extrahepatic disease (17). Toxicity was acceptable with only one death from fulminant hepatitis (17). Seventy-four patients with colorectal metastases as the only site of disease were randomized in a phase III clinical trial on intra-arterial administration of FUDR with or without SIR-spheres (18). The patients submitted to combined treatment showed high response rates in comparison to those with intra-arterial FUDR alone (44% vs. 18%); only in 8.3% of cases treated with a combined regimen was a progression of disease observed vs. 23.5% with FUDR alone (18). The survival analysis did not show any statistically significant difference between the two groups, but time to liver progression was significantly longer in the patients submitted to combined therapy, while toxicity was similar. In a phase II study, the SIR-spheres were utilized also in combination with i.v. 5-FU and leucovorin, but, unfortunately, the low number of patients enrolled did not permit evaluation of the response rate; however, the toxicity was low (19).

Recently, in a multicentric US retrospective clinical review, Kennedy et al. collected data about toxicity, response rates and median survival of colorectal liver metastases patients refractory to conventional chemotherapy and treated by SIRT alone (20). More than two thirds responded to treatment despite previous regimens of chemotherapy, while median survival was more than double compared to non-responders and no grade 4-5 toxic events were observed (20).

Our multicentric prospective phase II study started with the primary end-point to identify the role of SIRT as a locoregional treatment in patients with unresectable colorectal liver metastases as the only site of disease. As the first Italian multicentric clinical study, very satisfactory results were observed in terms of toxicity and compliance with treatment. All toxic events were controlled by medical treatment. Therapy with microspheres as third-line could favourably affect quality of life (18, 21-22).

In conclusion, SIRT is a safe treatment for patients with unresectable colorectal liver metastases not responding to conventional systemic chemotherapy, with acceptable acute and chronic toxicity, and a good therapeutic option after systemic chemotherapy when the liver is the only site of disease. Studies on homogeneous series with colorectal liver metastases and different combinations to deliver SIRT are not yet available, therefore, its impact on the prognosis needs further investigation.

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References


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