Transarterial chemoembolization using drug eluting microspheres in refractory colorectal liver metastases with 18F-FDG PET/CT follow-up to assess therapeutic response

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ABSTRACT
Purpose: The purpose of this study was to evaluate the efficiency of transarterial chemoembolization using drug eluting microspheres loaded with irinotecan in the treatment of the colorectal liver metastases after failure of chemotherapy.

Patients and methods: This prospective study was conducted from March 2014 to June 2016. The patients including 16 men and 6 women (mean age, 55 years) with metastatic colorectal carcinoma to the liver underwent transarterial chemoembolization using drug eluting microspheres as a salvage therapy after failure of systemic chemotherapy. Each patient underwent 18F-FDG PET/CT study before the procedure as well as 2 and 4 months after it to assess the response to therapy.

Results: Favorable response was seen in 13 patients (59.1% of patients), progression of the disease occurred in 3 patients (13.6% of patients) while stationary disease was seen in 5 patients (22.7% of patients) and one patient died from brain metastases before the 2 months follow-up.

Conclusion: Transarterial chemoembolization using drug-eluting microspheres loaded with irinotecan is a safe and effective salvage treatment of liver metastases from colorectal carcinoma not responding to systemic chemotherapy.

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1. Introduction

Advanced colorectal carcinoma with development of hepatic metastases leads to poor prognosis unless lesion resection is possible. Unfortunately, about 80% of patients with hepatic metastases are unsuitable candidates for radical resection and liver metastatic disease is considered as life limiting for the majority of patients. Systemic chemotherapy can cause regression of activity, size and number of hepatic metastases; yet, local therapy could be used in non responding cases and may be helpful for long-term survival. Transarterial chemoembolization (TACE) was introduced several years ago (as a local therapy) in order to provide high concentration of the chemotherapeutic agent within the lesion. This technique leads to stable disease or partial response in 60–75% of patients with liver metastases [1–3].

Chemoembolization using drug eluting microspheres (DEM TACE) was developed to prolong the release of chemotherapeutic agent within the tumor in a prolonged and slow manner. Microspheres (HepaSphere™ Microspheres) 30–60 µm are able to absorb chemotherapeutic
agent (Irinotecan). After being mixed with contrast media, microspheres get larger size to 100–200 μm and slowly release the cytotoxic drug. The advantage of DEM TACE is to increase the concentration of chemotherapeutic agent within the tumor, with decreased systemic side effects and toxicity [4,5]. Additionally, the arterial supply of the tumor is embolized by the spheres inducing ischemic effect [6,7].

PET/CT using 18F-FDG can reveal the metabolic information of tumor tissues at the molecular level and can be used to diagnose malignancy with high sensitivity and specificity. Because changes in tissue metabolism always precede changes in tissue structure, PET/CT can be used to assess the early response after TACE treatment and to show residual, recurring and metastasized lesions by quantitatively analyzing the changes in the standardized uptake value (SUV) of the lesions before and after TACE treatment [8–13].

The aim of this study was to evaluate safety and efficacy of DEM TACE loaded with irinotecan in treatment of patients with unresectable colorectal liver metastases after failure of systemic chemotherapy, using 18F-FDG PET/CT study as a method to assess the therapeutic response.

2. Patients and methods

2.1. Patients

From March 2014 to June 2016, a total of 22 patients (16 males and 6 females) ranging in age from 43 to 65 years (mean age, 55 years) with colorectal hepatic metastases, after unfavorable response to systemic chemotherapy were subjected to transcatheter arterial chemoembolization (TACE) using drug-eluting microspheres with irinotecan. The number and size of lesions are shown in Table 1. The exclusion criteria were as follows: Child-Pugh class B and C patients, poor bleeding profile, main portal vein thrombosis and renal impairment. Each patient underwent 18F-FDG PET/CT study before the procedure as well as 2 and 4 months after it, to assess the response to therapy.

### Table 1

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The patients were asked to fast for 6–8 h before the study and their blood glucose value was kept less than 160 mg/dl at the time of the tracer injection. The time of uptake from 18F-FDG injection to onset of emission scan was about 60 min.

A PET emission scan was performed over several bed positions (5–7), each with an axial field of view of approximately 15 cm per bed position with an in-plane spatial resolution of 4 mm. The acquisition time of emission data was 2 min per bed position in time range between 13 and 17 min.

A 128 integrated multi-slice CT machine was used to do the diagnostic contrast-enhanced CT images immediately after PET scanning, covering the identical transverse field of view. Iodinated non ionic contrast agent (Omnipaque 350) was administrated IV (100 ml) using an injector, with an injection flow of 5 ml/s just before the beginning of the scan. The parameters of the diagnostic CT scan were as follows: 120 mA, 130 kV, 0.5 s tube rotation time, slice thickness 5 mm, 8-mm table feed and 3 mm incremental reconstruction. All PET, CT and PET/CT images were reconstructed and viewed on Philips workstation, which provided multi-planar reformatted PET, CT and fused PET/CT images with linked cursors as well as 3D maximum intensity projection (MIP) images and PET images in video mode.

2.4. Image analysis

A combined team, including one nuclear medicine physician and one radiologist, interpreted the PET, CT and fused PET/CT images. They were aware of each patient’s history and clinical data. They recorded the number, size and activity of the hepatic metastatic lesions before and after DEM TACE. The activity of the lesions was detected qualitatively as well as quantitatively using the Standardized Uptake Value to assess the response to therapy.

3. Results

DEM TACE of the hepatic colorectal metastases was technically successful in all cases with clinical success in about 81.8% of patients. One patient died from brain metastasis 6 weeks after the procedure. Favorable response (decrease in activity, size or number of the hepatic metastases) was present in 13 (59.1%) patients (Figs. 1–3), while stationary disease was seen in 5 (22.7%) patients. However, progression of the disease occurred in 3 (13.6%) patients.

There were no severe complications after the procedure. The main adverse effects were right hypochondrial

Fig. 1. (a) Axial fused PET/CT image of a 60 years old female patient with multiple right hepatic lobe metastases from colonic carcinoma. (b) Right hepatic digital subtraction angiogram shows faint tumoral blushes (arrows); The patient underwent DEM TACE using Hepasphere of size 30–60 μm loaded with 100 mg of irinotecan. (c) Follow-up axial fused PET/CT image after 4 months showing favorable response with reduction of size and activity of the metastatic deposits.
pain (96.6%), fever (46.6%), nausea (66.6%), vomiting (20%), minimal ascites (13%) and anorexia (60%). The developed post procedural ascites was mild and cytological examination of the ascitic fluid revealed absence of malignant cells. The mean time of the procedure was 70 min and all patients were hospitalized for a day after the procedure.

Unfortunately one patient died before the first follow-up (not included in the post procedural response), and two patients died before the second follow-up (70 and 133 days after TACE).

4. Discussion

Although the colorectal liver metastases appear hypovascular in the post contrast cross sectional examinations, that does not indicate that they are not vascularized. A relatively old post-mortem study suggests that liver metastases obtain the majority of their nutrition from the hepatic artery [14]. On the basis of the results of various multicenter trials, it is well known that the regional chemotherapy of liver metastases of colon cancer is much
superior to the systemic chemotherapy and is accepted as an alternative strategy to control tumor progression [15]. However, the proper method of chemotherapeutic drug delivery is still under investigation [1].

Drug eluting microspheres are widely used for hepato-cellular carcinoma which usually has high vascularity from the hepatic arterial branches with significant enhancement in the arterial phase in the triphasic CT examination with satisfactory results [16].

Jarząbek et al., conducted a study on 15 patients with liver metastases from different primaries (colorectal carcinoma, cholangiocarcinoma, gastrinoma, gallbladder and pancreatic carcinoma, GIST, lung, renal, breast and laryngeal carcinoma) using HepaSphere 30–60 μm impregnated with 100 mg of Doxorubicin with follow-up by post contrast MRI. Four patients (26.7%) had partial response, five patients (33.3%) had stable disease and four patients (26.7%) suffered from metastatic progression. Two patients did not report to the follow-up MRI examination. One of the tumors which is well responded to the treatment was colorectal metastasis [1].

Martin RC et al., showed the results of treating unresectable colorectal liver metastases refractory to systemic therapy. This study had evaluated 55 patients with pre-DEBIRI (drug eluting beads loaded with irinotecan) and systemic chemotherapy (FOLFOX + Avastin - 17 patients), (FOLFOX + Avastin and FOLFIRI + Erbitux - 14 patients) and (FOLFOX + Avastin and FOLFIRI + Erbitux and XELOX + Vectibex or other - 24 patients). The median treatment dose of irinotecan was 100 mg (range 100–200 mg). The median number of DEBIRI treatment sessions was 2 (range 1–5). Complete response was noted in 7 (12%), 7 (12%) and 8 (15%) patients 3, 6 and 12 months respectively, partial response in 28 (53%), 21 (38%) and 14 (25%) patients 3, 6 and 12 months respectively, stable disease in 15 (30%), 19 (34%) and 23 (42%) patients 3, 6 and 12 months respectively, progression of disease in 3 (5%), 8 (15%) and 10 (18%) patients 3, 6 and 12 months respectively, death of disease in 0, 5 and 9 patients 3, 6 and 12 months respectively and death of other causes in 2, 0 and 0 patients 3, 6 and 12 months respectively. The authors found that treatment using DEBIRI is safe and effective for patients with metastatic colorectal cancer refractory to multiple lines of systemic therapy [17].

In this study we used the irinotecan, a topoisomerase inhibitor, which is more specific to the colorectal hepatic metastases; also the particles selected to be loaded with irinotecan were drug-eluting microspheres (HepaSphere) with good comparable results with the studies using DEBIRI [18].

Moreover PET/CT, as a follow-up technique, is better than triphasic CT alone or MRI as it has both qualitative and quantitative (SUV) criteria to assess the tumor response to therapy. PET/CT is a hybrid imaging technique, which introduces both anatomical and functional information. This characteristic makes PET/CT the best tool to...
assess the post therapy response. Some hepatic metastases after DEM TACE get larger in size yet appear totally necrotic with diminished activity by PET/CT that may give a false indication of progression (pseudoprogression) in triphasic CT or MRI alone [19].

The difference between HepaSphere and drug eluting beads is that, the HepaSphere particles are present in a dry form in which when hydrated (mixed with the chemotherapeutic agent or contrast media) they get larger size. However both can load the irinotecan and can be used in TACE procedure for colorectal liver metastases [20].

The main limitations of this study are the small number of patients and the relatively limited follow-up sessions which may be attributed to the high cost of PET/CT. However, we demonstrated that DEM TACE is an effective procedure after failure of systemic chemotherapy in patients with hepatic colorectal metastases.

5. Conclusion

Transarterial chemoembolization using drug-eluting microspheres loaded with irinotecan is a safe and effective salvage treatment of liver metastases from colorectal carcinoma not responding to systemic chemotherapy.

Conflict of interest

The authors declared that there is no conflict of interest.

References