Radionuclide therapy for hepatocellular carcinoma

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Abstract

Aim : **Several techniques for radionuclide therapy of hepatocellular carcinoma (HCC) have been developed. In this overview the available radionuclide treatment modalities for HCC are presented, with an emphasis on Yttrium-90 (^{90}Y) microspheres.**

Methods : **We comment on the commercially available products and describe the practical aspects of these treatment modalities. Medical literature was screened for clinical data on these therapies in patients suffering from HCC. The most relevant studies are summarized, focusing on patient selection, safety and outcome.**

Discussion : **Randomized trials are still ongoing or recently initialized. These trials will elucidate the role of ^{90}Y-microspheres in relation to biotherapy and chemoembolization for palliative use in patients not amenable to surgery.**

Conclusion : **Large retrospective or cohort studies proof the safety of ^{90}Y-microspheres for palliative use in HCC patients suffering Child-Pugh A or B7 cirrhosis. Future research will yield more information on its efficacy when compared to chemoembolization or sorafenib. Several groups have reported on the use of selective internal radiation therapy (SIRT) for downstaging patients to surgical curative treatment.** (Acta gastroenterol. belg., **2010**, 73, **484-488**).

Key words : hepatocellular carcinoma or HCC or hepatoma, lipiodol, microspheres, Yttrium-90, Iodine-131, radionuclide therapy, angiography.

Introduction

Hepatocellular carcinoma (HCC) is the most prevalent type of primary liver cancer, representing over 85% of the cases. Based on the GLOBOCAN and WHO databases, it ranks third among the cancer killers in men and sixth among women (1). The major risk factor for HCC is cirrhosis, and the risk of carcinogenesis depends on the underlying cause of cirrhosis. The incidence of HCC is particularly high in case of hepatitis C (HCV), haemochromatosis and hepatitis B (HBV). Alcoholic liver disease represents a lower risk, however still significantly higher compared to for instance biliary cirrhosis. In African and Asian countries facing endemic HBV, education and vaccination programs are needed to fight HCC. In the Western world prevention of obesity and diabetes mellitus type II might affect the incidence of HCC, since new insights warn us for these 'new' risk factors (2).

When analysed on a worldwide basis the mortality of HCC almost equals its incidence, reflecting the low number of patients that can be directed towards curative treatment options. Surgery, being partial hepatectomy or liver transplantation, is the mainstay of curative treatment. Partial hepatectomy results in a 5 year overall survival rate between 32-74%, the best outcomes occurring in patients with no or minimal cirrhosis (Child-Pugh A with bilirubin levels within normal range), without signs of portal hypertension and limited tumour burden (3). For liver transplantation, candidates with a single tumour ≤ 5 cm or a maximum of three nodules ≤ 3 cm have a 5 year survival rate exceeding 70% in most centers (4,5). Based on an intention-to-treat analysis these numbers tend to decrease, due to drop-out on the waiting list (3).

Local ablative therapies such as Radio Frequency Ablation (RFA) should be offered to patients with small tumours that are not amenable to surgery. According to the Barcelona treatment algorithm, patients with intermediate HCC should be directed towards chemoembolization (TACE). The best candidates are patients with preserved liver function and asymptomatic multinodular tumors without vascular invasion or extrahepatic spread.

For advanced HCC oral treatment with the multikinase inhibitor sorafenib (Nexavar®, Bayer) showed in a randomised phase III double-blind placebo-controlled trial a survival benefit of 3 months (6).

In this overview we comment on the use of radionuclide therapy for HCC. Radiolabelled Lipiodol challenged the use of TACE in palliative treatment of HCC and was proposed as an adjuvant therapy following resection. More recently radiolabelled microspheres for intra-arterial use were introduced. The practical aspects of such a 'Selective Internal Radiation Treatment' (SIRT) will be described as well as literature data on patient selection, safety and outcome.

Iodine-131 lipiodol

Lipiodol is a mixture of iodized ethyl esters of the fatty acids of poppyseed oil. It has been used as a contrast material for the detection of HCC because it results in a selective and prolonged retention within the tumour (7). So far, most clinical research was performed using ^{131}I-labelled Lipiodol, which was commercially available as Lipiocis® (CIS Bio International, Gif sur

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Table 1. — **Physical characteristics of radionuclides applied for treatment of hepatocellular carcinoma**

	Iodine-131	Yttrium-90
Eγ (abundance)	364 keV (81.7%)	–
Eβ max (abundance)	606 keV (89.9%)	2280 keV (100%)
physical half life	8.01 days	2.7 days
main production mode	fission product	neutron irradiation

Yvette, France). Recently, this radiopharmaceutical was withdrawn from the market.

^{131}I-Lipiodol is always applied intra-arterially, often administered in the *A. hepatica propria* or *communis*, or in case of limited disease more selectively. Treatment is carried out without a pretherapeutic arteriographic assessment using a scout dose. Activities between 40 and 60 mCi are generally prescribed. To protect the radiologist and hot lab personnel, a heavy lead shield is fixed around the syringe containing the radioactivity. Besides emitting electrons, ^{131}I is also a gamma emitter (Table 1), hence strict radioprotection guidelines are mandatory. Following administration the patient is hospitalized in a dedicated radionuclide therapy ward for about 7 days, to comply with the Belgian radioprotection legislation.

Most reports using ^{131}I-Lipiodol agree on its good tolerance. Undesirable effects that are observed fairly frequently consist of moderate and temporary fever (29%), moderate and temporary disturbances of the biological liver tests (20%) and pain on injection (12.5%). Moderate and reversible leukopenia (7%) and serious diffuse infiltrative pneumopathies (2%) are observed more rarely. These diffuse infiltrative pneumopathies appear about 1 month after the injection of Lipiocis®, most frequently after the second injection. They are clinically manifested by the appearance of dyspnea that is sometimes associated with dry cough and bilateral crepitations.

Clinical trials with ^{131}I-Lipidol focused on its use in palliative patients, with or without portal vein thrombosis, as well as applications in patients awaiting liver transplantation and in an adjuvant setting, to prevent recurrent disease in patients who underwent liver resection.

Palliative treatment with ^{131}I-Lipiodol (n = 65 patients) was compared to TACE (n = 64 patients) in a prospective, randomised trial. No statistical difference in survival was recorded (8). Importantly, treatment tolerance was much better in the ^{131}I-Lipiodol arm with only 3 reported serious side-effects versus 29 in the TACE arm ($p < 0.01$).

In a study from Hong Kong patients undergoing curative resection for HCC were randomly assigned a single 50 mCi administration of ^{131}I-Lipiodol (n = 21) or no further treatment (n = 22) (9). An interim analysis suggested a survival benefit for the group patients treated with ^{131}I-Lipiodol following resection. In an update on the 5 and 10 year survival no long term survival benefit could be proven, despite a clear advantage in disease free survival (10).

Yttrium-90 Microspheres

Practical aspects

Microspheres for radionuclide therapy are designed (20-40 μm) to get trapped in the arteriolary vessels following intra-arterial injection. Two types of radiolabelled microspheres are currently commercially available for treatment of inoperable liver tumours. Both are loaded with the pure beta emitter Yttrium-90 (^{90}Y, see also Table 1). TheraSphere® (MDS Nordion, Canada) consist of glass and SIR-Spheres are resin microspheres (Sirtex™, Sirtex Medical Ltd, Australia). ^{90}Y has a half life of 64h. Since it is a pure electron emitter, radioprotection guidelines are less stringent because there is no need for patient isolation. Syringes and vials containing the ^{90}Y-microspheres are easily shielded by the use of plastic. However, patient work up is more elaborative compared to treatment with radiolabeled lipiodol. First, an arteriography of the liver is performed to plan and simulate the actual treatment, often scheduled 2 weeks later. During this first arteriography, all tumours and their feeding vessels are mapped and the interventional radiologist looks actively for collateral vessels from the liver vasculature to the gastro-intestinal tract, pancreas, abdominal wall... . If necessary these collateral vessels are coil-embolized. Subsequently a radiopharmaceutical (Technetium-99m macroaggregated albumin (^{99m}Tc-MAA) is administered to simulate the distribution of the microspheres in case of treatment with ^{90}Y. The distribution can be imaged by use of a scintigraphy (Fig. 1). The MAA scintigraphy is used for ruling out excessive shunting of microspheres to the lungs, to rule out deposition of extrahepatic activity in the abdomen in case of transport of via collateral arteries and to verify adequate targeting of the tumour lesions within the liver. This first angiography and MAA scintigraphy takes about 2-4 hours. No general anaesthesia is required.

If this preparatory procedure is successful, treatment is scheduled about 2 weeks later. This delay is mainly related to the fact that both kinds of microspheres need to be imported in Europe. Because no anatomical mapping or often no additional coiling is required for administering the radiolabelled microspheres, this arteriographic procedure is less time consuming. Infusion with SIR-Spheres can cause some pain on infusion but this is manageable with analgetics, without the need for general anaesthesia. Subsequently, a post therapy scintigraphy is acquired to verify the distribution of the microspheres (Fig. 2). In our hospital, the patient stays hospitalized for 24 h following treatment. In the USA it is often performed in a day clinic setting. According to the Belgian legislation, no specific radioprotective restrictions are required. However, it seems wise to avoid close contact for prolonged time with small children or pregnant women in the first 48 h and to maintain good hygiene to avoid urinary contamination in the first 48 h (11).

Fig. 1. — Anterior view of whole body ^{99m}Tc-macroaggrgated albumin scan following intra-arterial injection, showing selective uptake of the tracer in the liver without lung shunting.

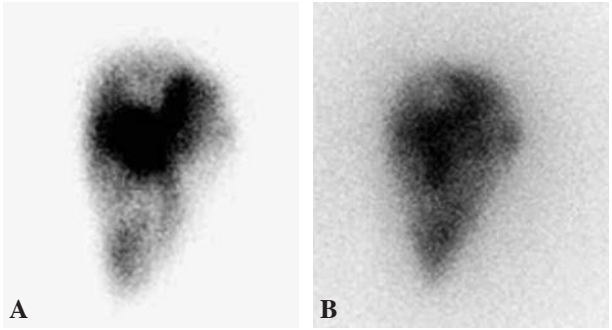

Fig. 2. — A : Anterior planar view of the liver following intra-arterial injection of ^{99m}Tc-macroaggregated albumin (right lobe) ; B : Anterior planar view of the liver following injection in the right lobe of ^{90}Y-microspheres showing adequate targeting of the known tumour lesions, as predicted on the macroaggregated albumin-scan (Brehmsstrahlung scan).

Patient selection

According both product approvals, ^{90}Y-microspheres can be used for inoperable liver tumours. However, in practice, patients for ^{90}Y-microsphere treatment are mainly referred for treating chemorefractory colorectal liver metastasis, HCC or neuro-endocrine liver metastasis. These indications represent the bulk of literature reports. To a minor extend, other types of tumours are treated, such as chemorefractory breast cancer, ocular melanoma and cholangiocarcinoma. Theoretically, all liver malignancies with sufficient arterial blood supply can be treated with this modality. However, to date supportive scientific evidence for doing so is scarce except for colorectal liver metastasis and HCC. In these disease settings, patients who are no candidates for surgical strategies or otherwise possible curative treatment modalities such as RFA, might be considered for SIRT. However, patients with substantial extrahepatic disease should not be referred for liver-directed treatments. Exclusion criteria are summarized in Table 2.

Literature data on safety and efficacy

At present no randomized trials were available for proving the efficacy of SIRT for HCC. This is in contrast with SIRT for colorectal liver metastasis where some small randomized trials supporting its use were reported (12-14). For HCC, several large retrospective datasets were described in detail, for TheraSphere® as well as for SIR-Spheres. Also some cohort studies and comparative studies with historical controls are available. In this review we will summarize the safety and efficacy data of the largest reported patient populations for both kind of microspheres and highlight some studies that focused on particular patient groups.

The largest monocentric prospective cohort study to date involves the use of glass microspheres (TheraSphere®) in 526 infusions in 292 HCC patients (15).

This patient group treated in Chicago had a mean diameter of the largest lesion of 7 cm. About one out of two patients had a Child-Pugh B status and/or Barcelona Clinic Liver Cancer (BCLC) C disease stage. Toxicities mainly consisted of fatigue (57%), pain (23%), and nausea/vomiting (20%). A rise in bilirubin was less common. The 30-day mortality rate was 3%. No cases of gastro-intestinal ulcerations were encountered. Response rates were 42% and 57% based on World Health Organization (WHO) and European Association for the Study of the Liver (EASL) criteria, taking into account changes in contrast enhancement on imaging), respectively. Response on imaging was predictive of survival. Changes in tumour dimensions were often occurring about 6 months following treatment, whereas changes in the contrast enhancement pattern of the tumour were preceding tumour shrinkage with several months. Survival depended on the degree of underlying cirrhosis. Patients without portal vein thrombosis and with Child-Pugh A disease had a survival of 22 months, versus 15 months for Child-Pugh B patients. In patients with portal vein thrombosis survival was limited to 6 months.

In a cohort study from Essen, Germany, TheraSphere® treatment was applied in 108 patients suffering from HCC not amenable to selective TACE : multifocal (> 4) or large (> 10 cm) HCC, or HCC involving the portal vein or recurrent HCC. Seventy six percent was Child-Pugh A and 22% had a score B7 (16). Again transient fatigue and abdominal discomfort were frequently reported. One case of cholecystitis, requiring cholecystectomy was recorded. No ulcerations of the stomach or duodenum were suspected. A single case of dissection of the proper hepatic artery was encountered but this dissection remained without clinical consequences. In patients with normal baseline bilirubin values mild elevation was detected in 30%, whereas only 3% developed a grade III elevation. However patients who presented with elevated bilirubin levels prior to therapy, 17% had grade mild elevations of bilirubin and in 20% it involved a grade III/IV rise in bilirubin. The overall median survival was 17 months, again strongly dependent on the Child-Pugh status and portal vein patency.

Table 2a. — **Contra-indications for ^{90}Y microsphere therapy to be excluded by the clinician**

Patients eligible for curative resection, radiofrequency ablation or liver transplantation on the short term
Pregnancy or breast feeding
Uncontrolled extrahepatic metastatic disease
Karnofsky score < 70%
Bilirubin > 2 mg/dL (unless only a single segment is to be treated)
Child-Pugh score > B7
Previous external beam radiation therapy to the liver (relative)

Table 2b. — **Contra-indications for ^{90}Y microsphere therapy on the basis of subsequent technical investigations**

Unacceptable high lung uptake on macroaggregated albumin (MAA)-scan
Abdominal tracer deposition outside the liver on MAA-scan (consider to repeat the coiling procedure and ^{99m}Tc-MAA injection)
Unfavorable MAA distribution with unacceptable high exposure of the parenchyma and/or lack of accumulation of activity in the tumour(s)

In a European multicentric retrospective study using SIR-Spheres 250 consecutive patients were analysed (17). Toxicity seems to be comparable to what is described for glass microspheres. Overall median survival was estimated to be 14 months, with 16 months for Child-Pugh A patients (n = 203) and 10 months for Child-Pugh B patients (n = 45). In patients without PVT (n = 209) median survival was 15 months versus 16 and 10 months for those patients that presented with branch (n = 25) or main (n = 16) PVT.

There are also some prospective studies on SIR-Spheres available for HCC, from the groups of Lau and coworkers from Hong Kong and Sangro and coworkers from Pamplona (18-20).

An interesting finding from this group is that progressive disease was in almost all cases due to development of new HCC lesions, rather than progression of formerly treated lesions (21).

In a recent report from Pamplona they focussed on the subgroup of elderly patients, treated at their institution over the past years (22). Seventy-three patients were aged over 70 years and this represented 29% over their entire patient population. Complication rates were similar in both age groups, without statistically different results in adverse events. The median overall survival of patients with HCC was similar in elderly and younger groups.

Discussion and Future Research

The above mentioned publications are of value due to the relative large numbers of patients included and the fact that survival data were stratified according to tumour stage and stage of the underlying cirrhosis. However, the favourable toxicity data should be interpreted with care. The participating radiologists were highly skilled in this particular kind of technical procedure. It is generally accepted that for this type of intervention a learning curve exists.

The vast majority of groups setting up intra-arterial liver treatment with radiolabelled microspheres, experience cases of gastroduodenal ulcerations (most often less than 5% risk, but in some reports up to 11%) (23). The possibility of GI bleeding should be communicated to patients and general practitioners when informed on this evolving therapy. Patients should receive guidelines to contact the hospital in case of symptoms possibly related to GI bleeding and follow up visits should be scheduled in all patients. The SIRT-induced ulcers are typically refractory to medical treatment and the extend is underestimated on gastroscopy.

In a recent paper that aims to act as guideline for SIRT in HCC, PVT is considered a contra-indication, and this is in line with the user's manual of both manufacturers. However, in the large experience from Sangro and coworkers as well as Salem *et al*. no scientific basis is found for excluding these patients from SIRT. In our experience SIRT is feasible in case of PVT, however the decision to treat this patients should be based on their general risk profile, taking into account the liver function and overall tumour burden.

At present SIRT is proposed as a palliative therapy for HCC without major extrahepatic spread, when surgery or RFA is not an option. It can also be used for recurrent unresectable HCC. Furthermore, both glass and resine microspheres have been used as a bridging therapy before liver transplantation, or for downstaging patients to surgery (24). At our hospital we do not use SIRT for patients awaiting liver transplantation, unless it is foreseen that the waiting time would exceed 6 months and the patient is presumed to be at risk for dropping out from the list. Recently we were able to achieve a complete response on imaging in a patient with multifocal HCC and she underwent a liver transplantation.

Future research will deal with the role of SIRT in comparison with TACE on one hand and its value compared to or added to so-called biologicals, such as sorafenib. Prospective trials are ongoing and in case of

SIR-Spheres a randomized trial is currently performed to elucidate the additive value of SIRT to sorafenib. In our hospital we plan a randomized study to compare TACE with drug eluting beads versus SIRT. For colorectal liver metastasis a multicenter randomized study is ongoing comparing FOLFOX chemotherapy (5-fluorouracil, oxaliplatin and folinic acid) with or without a single session of SIR-Spheres in first line.

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