Radioembolisation of hepatocellular carcinoma patients using ^{90}Y -labelled microspheres: towards a diffusion of the technique?

Etienne Garin

Published online: 8 October 2011
© Springer-Verlag 2011

Radioembolisation of patients with liver carcinoma using microspheres labelled with ^{90}Y is increasingly being used with promising results. Although more complex than ^{131}I -Lipiodol therapy, this technique is associated with fewer radioprotection constraints along with a better safety profile, as it is always preceded by diagnostic angiography and hepatic perfusion scintigraphy using $^{99\text{m}}\text{Tc}$ -labelled macroaggregated albumin (MAA). Two different products are currently available: glass and resin microspheres. Glass microspheres, which present a low embolic potential ($25 \pm 10 \mu\text{m}$ in diameter; 2 500 Bq per sphere; available activities of 3, 5, 7, 10, 15 and 20 GBq), were initially developed for treating hepatocellular carcinoma (HCC) patients and can also be used in the case of portal vein thrombosis (TheraSphere, MDS Nordion, Kanata, ON, Canada). In contrast, resin microspheres exhibit a more marked embolic potential ($35 \pm 10 \mu\text{m}$ in diameter; 500 Bq per sphere; available activity of 3 GBq) and were initially developed for treating hepatic metastases (SIR-Spheres, SIRTech Medical Limited, Sydney, Australia), with portal vein thrombosis being a relative contraindication to their use. Due to these differences, the efficacy and toxicity profiles of both products may be different, and it is thus important to analyse separately and compare the results obtained with glass and resin microspheres.

The trial performed by Lambert et al. and published in the current issue of the *European Journal of Nuclear Medicine and Molecular Imaging* [1] is the third European feasibility study on the use of glass microspheres in the setting of HCC, while most of the other studies were conducted by a few North American teams with substantial experience in this research area. Their report confirms that this technique may be utilised by teams with no prior experience in the use of microspheres, without major complications and with comparable efficacy results. In fact, while taking into account tumour necrosis, Lambert et al. reported an objective response rate of 50%, in line with previous results published by Salem et al. [2] (57% in a series involving 291 patients) and Hilgard et al. [3] (40% in a series involving 108 patients).

Although no study has compared ^{90}Y -labelled microspheres and ^{131}I -Lipiodol therapies, glass microspheres are likely to display improved efficacy. Due to the absence of major radioprotection constraints, significant ^{90}Y activities can be delivered ($>10 \text{ GBq}$), while the injected activity for the glass microspheres is adapted on a case-by-case basis depending on the injected liver (IL) volume (with ^{131}I -Lipiodol therapy, a standard activity of 2.2 GBq was used). The activity of ^{90}Y -labelled microspheres to be injected is calculated based on the following formula derived from Medical Internal Radiation Dose (MIRD) formalism and simplified due to the lack of microsphere metabolism following implantation:

$$\text{ILD}_{(\text{Gy})} = \text{IA}_{(\text{GBq})} \cdot (1 - S) \cdot 50 / W_{(\text{Kg})} \quad (1)$$

where IA represents the activity to be injected, S the percentage of pulmonary shunting as measured by MAA liver perfusion scan and W the mass of the liver volume to be treated, with the ultimate goal to achieve an IL dose of $120 \pm 20 \text{ Gy}$.

E. Garin (✉)
Department of Nuclear Medicine,
Comprehensive Cancer Institute Eugène Marquis,
CS 44229,
35042 Rennes, France
e-mail: e.garin@rennes.unicancer.fr

E. Garin
INSERM, U-991, Liver Metabolisms and Cancer,
F-35033 Rennes, France

Several cases of portal vein thromboses associated with partial or complete regression were reported after using glass microspheres, which was never observed following ^{131}I -Lipiodol therapy [4]. Furthermore, ^{131}I -Lipiodol therapy did not exhibit any efficacy in liver metastasis patients, whereas both glass and resin microspheres [5] were shown to be efficacious in this indication.

The toxicity profile of glass microspheres was shown to be acceptable in the Lambert et al. study, in line with previously published reports [2–4]. The risk of pulmonary toxicity is effectively detected by MAA scintigraphy, and patients presenting pulmonary risks are systematically excluded from therapy. The risk of developing gastrointestinal ulcers, which was estimated to range from 2.9 to 4.8% in a recent meta-analysis [6], is limited due to coil embolisation. It should be noted that for ^{131}I -Lipiodol therapy, there were no predictive factors allowing for the identification of at-risk patients.

In the publication by Lambert et al., the authors discussed the concept of a learning curve, which has been scarcely mentioned in the scientific literature. However, this notion is key to radiolabelled microsphere therapy, because of the technological knowledge required for full arterial mapping that enables the operator to correctly choose the best catheter position for optimal tumour targeting and identify the arterial branches vascularising the gastroduodenal area in order to conduct coil embolisation. This learning curve may directly impact objective response rates, toxicity profiles, as well as patients being excluded from treatments. The relatively high rate of patients considered ineligible for treatment in the Lambert et al. study (i.e. 19 versus only 7.5% for Hilgard et al. [3]) is likely to be accounted for by the learning curve. Therefore, when comparing the results of different studies, it is essential to consider the experience of the respective teams.

The exact place of this new therapeutic approach in HCC treatment is still to be confirmed by the results of an ongoing randomised trial, as to date only non-randomised data are available.

Major progress in terms of response rates and safety profile is still to be made. In fact, two studies published in 2011 showed that by using a quantitative analysis of MAA single photon emission computed tomography (SPECT)/CT, dosimetric evaluation of both tumour and non-tumour volumes, and not just the hepatic volume to be treated as currently done, was feasible [4, 7]. These two studies demonstrated that the doses absorbed by the tumour strongly correlated with response rates, with a dose threshold being required in order to achieve an objective response. In addition, one of these studies showed that the overall survival of patients administered an average tumour dose of >205 Gy as calculated using the aforementioned standard formula (Eq. 1) was significantly superior to those

administered <205 Gy (18 vs 9 months, $p=0.0322$ [4]). The ability of MAA SPECT/CT to predict response and survival prior to treatment constitutes a major achievement in this field of research, as it allows for improved patient selection and enables the administration of increased activities to carefully selected patients, as previously reported [4].

In conclusion, the study presented by Lambert et al. in this issue [1] appears to provide key data regarding the feasibility, efficacy and safety of radioembolisation using ^{90}Y -labelled glass microspheres in HCC patients. Although the implementation of this new therapeutic approach is more complex, its safety profile appears superior to that of ^{131}I -Lipiodol, on account of the prior diagnostic angiography performed to identify patients at risk of developing pulmonary or gastroduodenal complications. Regarding glass microsphere therapy, recent results obtained with MAA SPECT/CT-based dosimetry clearly demonstrate the necessity of defining a decisional algorithm based on hepatic tumour and non-tumour volumes, rather than on the dosimetric evaluation of hepatic injected volume alone. Such an algorithm should lead to improved efficacy results in the case of voluminous hepatic tumours, which are difficult to treat, and perhaps to further reduced hepatic toxicity, currently considered to be low [2–4].

Radioembolisation with ^{90}Y -labelled microspheres presents several distinct advantages, notably the absence of major radioprotection constraints, superior efficacy compared to ^{131}I -Lipiodol therapy, as well as the possibility of treating both hepatic metastases and HCC, identifying patients at risk of developing pulmonary or digestive complications and, more recently, predicting responses and survival even prior to treatment. Considering these multiple advantages, this new therapeutic approach should be more widely used than was the case for ^{131}I -Lipiodol.

Conflicts of interest E. Garin is a consultant for Nordion.

References

1. Lambert B, Sturm E, Mertens J, Oltenfreiter R, Smeets P, Troisi R, et al. Intra-arterial treatment with (^{90}Y) microspheres for hepatocellular carcinoma: 4 years experience at the Ghent University Hospital. *Eur J Nucl Med Mol Imaging* 2011. doi:10.1007/s00259-011-1881-2.
2. Salem R, Lewandowski RJ, Mulcahy MF, Riaz A, Ryu RK, Ibrahim S, et al. Radioembolization for hepatocellular carcinoma using yttrium-90 microspheres: a comprehensive report of long-term outcomes. *Gastroenterology* 2010;138(1):52–64.
3. Hilgard P, Hamami M, Fouly AE, Scherag A, Müller S, Ertle J, et al. Radioembolization with yttrium-90 glass microspheres in hepatocellular carcinoma: European experience on safety and long-term survival. *Hepatology* 2010;52(5):1741–9.

4. Garin E, Lenoir L, Rolland Y, Edeline J, Mesbah H, Laffont S, et al. ^{99m}Tc -MAA SPECT/CT based dosimetry accurately predicts tumour response and survival in HCC patients treated with ^{90}Y -loaded glass microspheres: preliminary results. *J Nucl Med* 2011; in press.
5. Sato KT, Lewandowski RJ, Mulcahy MF, Atassi B, Ryu RK, Gates VL, et al. Unresectable chemorefractory liver metastases: radioembolization with ^{90}Y microspheres—safety, efficacy, and survival. *Radiology* 2008;247(2):507–15.
6. Naymagon S, Warner RRP, Patel K, Harpaz N, Machac J, Weintraub JL, et al. Gastroduodenal ulceration associated with radioembolization for the treatment of hepatic tumors: an institutional experience and review of the literature. *Dig Dis Sci* 2010;55:2450–8.
7. Chiesa C, Maccauro M, Romito R, Spreafico C, Pellizzari S, Negri A, et al. Need, feasibility and convenience of dosimetric treatment planning in liver selective internal radiation therapy with (^{90}Y) microspheres: the experience of the National Tumor Institute of Milan. *Q J Nucl Med Mol Imaging* 2011;55(2):168–97.