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EDITORIAL COMMENTARY

The dosimetric importance of the number of ^{90}Y microspheres in liver transarterial radioembolization (TARE)

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Transarterial radioembolization (TARE) with ^{90}Y microspheres is a very promising treatment modality in inoperable primary liver malignancies (mainly hepatocellular carcinoma, HCC), as well as in secondary liver lesions (mainly colorectal metastases), with some interesting results in other less diffused malignancies such as intrahepatic cholangiocarcinoma and neuroendocrine metastases. However, TARE is not yet included in liver management guidelines, since it has been introduced into clinical practice only recently, randomized studies demonstrating better outcomes with respect to consolidated standard of care have not yet been performed. Two kinds of ^{90}Y-loaded microspheres are available, as we discuss in detail in the following sections.

The guidelines published by the European Association for the Study of the Liver (EASL) [1] recommend the use of transarterial chemoembolization (TACE) in patients with intermediate stage HCC (multinodular, stage B according to the Barcelona Clinic Liver Cancer, BCLC, classification system) [2], while the administration of a biological pharmaceutical (sorafenib, a multikinase inhibitor) is recommended in patients with advanced stage disease (BCLC stage C; that is, patients with symptomatic tumours and/or an invasive tumoral pattern, i.e. vascular invasion/extrahepatic spread) [3, 4]. Many studies below the highest level of evidence in which patients with intermediate and advanced HCC were treated with ^{90}Y microspheres have already suggested the outcomes following TARE compare favourably with those following conventional treatments [5–10].

Several phase III randomized trials studies are recruiting or have just been activated to provide the highest level of evidence of the outcome improvement after TARE in these two class of patients [11].

Two worldwide trials are planned with ^{90}Y glass microspheres. STOP-HCC (http://clinicaltrials.gov/ct2/show/NCT01556490?term=NCT01556490&rank=1) will compare the safety and effectiveness of microspheres in patients with advanced unresectable hepatocellular carcinoma in whom treatment with standard-of-care is planned. All patients will receive the standard-of-care sorafenib with or without the addition of microspheres. Patients with portal vein thrombosis are excluded from this study, since they will be specifically under study in the YES-P trial (http://clinicaltrials.gov/show/NCT01887717), in which the outcomes after treatment with sorafenib alone and with microspheres alone will be compared.

^{90}Y resin microspheres in HCC are also under investigation. The study SIRVENIB has as its primary objective to compare overall survival between TARE and sorafenib. Patients with intermediate stage (BCLC stage B) or advanced stage (BCLC stage C) without extrahepatic disease (only with branch portal vein thrombosis) can be enrolled in this study (http://clinicaltrials.gov/ct2/show/NCT01135056?term=SIRspheres&rank=16). The SARAH study is enrolling only patients with advanced HCC (BCLC stage C) with or without portal vein thrombosis. The comparison will be between sorafenib alone and TARE alone (http://clinicaltrials.gov/ct2/show/NCT01482442?term=SIRspheres&rank=18). The SORAMIC study (http://www.clinicaltrials.gov/ct2/show/NCT01126645?term=soramic&rank=1) will compare the TARE + sorafenib and sorafenib alone in the palliative treatment group. Regarding metastases, because of

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heterogeneity among studies on colorectal carcinoma (CRC) secondary lesions, the role of TARE has not been defined [12]. Only two completed phase III trials have demonstrated an improvement in tumour response, progression-free survival [13] and time to progression [14] following the addition of TARE to chemotherapy alone. Future research should lead to better definition of the role of ^{90}Y radioembolization in association with chemotherapy in the therapeutic strategy in these patients. The following studies were designed with this goal.

The EPOCH trial (http://clinicaltrials.gov/ct2/show/NCT01483027?term=NCT01483027&rank=1) will compare standard-of-care chemotherapy with or without the addition of glass microspheres in patients who have failed first-line chemotherapy.

SIR-spheres are under study in three trials. In the SIR-step trial, investigators propose to evaluate a maintenance strategy comparing TARE plus continuing simplified chemotherapy with/without bevacizumab and chemotherapy with/without bevacizumab alone in patients with dominant or exclusive and unresectable liver metastases from CRC controlled after 3 months of chemotherapy induction (http://clinicaltrials.gov/ct2/show/NCT01895257?term=SIR-STEP&rank=1). The SIRFLOX study will investigate the efficacy and safety of TARE plus a standard chemotherapy regimen of FOLFOX6m in comparison with FOLFOX6m alone as first-line therapy in patients with nonresectable liver metastases from primary CRC. Treatment with the biological agent bevacizumab, if part of the standard of care at participating institutions, is allowed in this study at the discretion of the Investigator (http://clinicaltrials.gov/ct2/show/NCT01721954?term=SIRspheres&rank=11, which links to SIR-step). The FOXFIRE study is an open-label randomized phase III trial of 5-fluorouracil, oxaliplatin and folinic acid with or without interventional radioembolization as first-line treatment in patients with unresectable liver-only or liver-predominant metastatic CRC (http://www.octo-oxford.org.uk/alltrials/trials/FOXFIRE).

Clinical importance of the difference in the number of microspheres

As is well known, two kinds of medical device have been approved by the FDA and EMA, and are commercially available: resin microspheres (http://www.sirtex.com) and glass microspheres (http://www.therasphere.com). Apart from different constituent materials and ^{90}Y distributions (isotope on the surface for resin and internally for glass), the difference which affects their clinical use is the activity per microsphere: 50 Bq per resin sphere and 2,500 Bq per glass sphere at the reference time. The same ratio of 50 is obviously found in the number of injected particle per unit activity: 1 GBq/50 Bq=20 million resin microspheres per gigabecquerel, versus the minimum number of 1 GBq/2,500 Bq=400,000 glass microspheres per gigabecquerel at the reference time. This large numerical difference has important implications. The extremely high number of particles is the most probable cause of flow stasis during resin microspheres administration, which makes the injection of the whole planned activity impossible in up to 35 % of procedures [15]. Stasis has never been reported with glass microspheres [16].

The most important clinical difference arises in relation to dosimetry. Consider the well-known macroscopic formula for the calculation of absorbed dose D: D (grays)=50 A (gigabecquerels)/M (kilograms) [17], where A is the microsphere activity in a bulky liver region and M is its mass.

This formula says that a fixed activity in a fixed region gives a fixed absorbed dose, macroscopically averaged on the perfused volume, no matter the number of particles.

This does not necessarily means that, using different number of particles, the same mean absorbed dose gives the same biological effect.

Consider that 50 Gy in 1 kg are given by resin particles at a density of 20 million per kilogram, i.e. 20 microspheres per cubic millimetre, but by glass spheres at a fifty times lower density of 0.4 per cubic millimetre.

A large difference in dosimetric behaviour at the microscopic level has recently been demonstrated mathematically by Walrand et al. [18]. This is a direct consequence of the different numbers of particles, and of the asymmetric probability in the direction they take at each microcapillary bifurcation. The authors calculated that the same absorbed dose distribution to the portal triads, i.e. to the critical portion of the liver lobule with this kind of treatment, is obtained with a remarkably different mean parenchyma absorbed doses of 40 Gy and 120 Gy for resin and glass microspheres, respectively. Crudely speaking, the lower number of glass spheres gives a less uniform irradiation, which is associated with reduced toxicity, which makes tolerable a three times higher mean parenchyma absorbed dose. This argument and calculation explains why clinical studies have shown that higher mean absorbed doses can be tolerated with glass microspheres than with resin microspheres (70 Gy averaged over the whole non tumoral liver in Child A HCC patients for glass microspheres [19], versus about 40 Gy for resin microspheres [20–23]).

The first clinical indication of this effect from the efficacy point of view (same efficacy with different absorbed doses from different numbers of particles) was reported by Rhee et al. [24]. A higher median absorbed dose was delivered to each lobe using glass microspheres (right lobe 117 Gy, left lobe 108 Gy) than using resin microspheres (right 50.8 Gy, left 44.5 Gy; $p<0.01$). According to RECIST response criteria, the disease control rate was the same 6 months after treatment (92 % with glass and 94 % with resin

particles). The lower number of spheres achieved the same success rate with higher absorbed doses. In this work, however, the lobe absorbed dose was evaluated, and not the tumour absorbed dose.

An equivalent but differently phrased statement is that a comparable or even a lower absorbed dose delivered by a higher number of microspheres should give a higher biological effect (both toxicity and efficacy). This was actually reported by Chiesa et al. [25] who compared the results of two studies of the use of TARE in patients with HCC [9, 20]. The study by Strigari et al. [20] had a high liver failure rate of 63 % with a whole-liver median dose of 36 Gy (range 6 – 78 Gy) after BSA-based activity prescription, while the study by our group [9] had about half of that toxicity rate (36.5 %) with almost twice the median liver absorbed dose averaged over the whole organ (65 Gy, range 19 – 148 Gy, following the prescription of 120 Gy to the lobe). Some possible bias imposes caution in this interpretation, since the proportion of whole liver administrations was 48 % in the study by Strigari et al., but negligible in our cohort (6 %), and the toxicity endpoint definitions were different. No bias, however, was present on the efficacy side: we delivered a much higher lesion median mean absorbed dose (387 Gy vs. 97 Gy) obtaining a lower objective response rate (40.4 % vs 77 %) and a lower disease control rate (78.8 % vs 97 %) according to EASL criteria.

Clinical importance of varying the number of glass microspheres by physical decay

There is another important technological difference between the two devices. The resin sphere shelf-life is 1 day, therefore forcing users to inject always substantially the same number of 20 million particles per gigabecquerel. A maximum allowed decay time of 24 h increases by 30 % this already large number. The glass microsphere shelf-life is 12 days. This is a very interesting additional degree of freedom for the user, since the number of particles per gigabecquerel can be augmented simply by physical decay, i.e. waiting longer between the reference date and the day of administration. This number and the particle density per fixed mean absorbed dose in tissue increase with the ^{90}Y physical half-life (64 h, 2.66 days), while the activity per microspheres correspondingly decreases. We can therefore choose a proportionally higher activity at the reference date in order to deliver a fixed lobe absorbed dose of, for instance, 120 Gy, with an increase of the initial activity and of the number of spheres by a factor of 2.2 (111 %) after each period of 3 days, up to a maximum of 2 elevated to the power of (12 days/2.66 days), i.e. 22.6 times the value at reference time. For a fixed mean absorbed dose, glass microspheres can be delivered at a density with respect to resin spheres which spans from 50 times less (at the reference date) to 2.2 times less after 12 days.

This is the basis of the clinical paper by the basis of the clinical paper by the Chicago group we are presenting (Lewandowski et al. [26]). A low particle density in tumour tissues might be suboptimal, especially when treating large tumours, as often encountered in HCC. A higher density could provide a better coverage of the target in terms of uniformity of dose deposition. Therefore, the prescription of 120 Gy to the injected lobe can be implemented by waiting 1 week after the reference time, the so-called “second week” or “extended shelf-life” administration technique. The paper presented in a recent issue of EJNMMI [26] is actually the second report of the group's experience in this area, with a longer follow-up and higher numbers of patients, after a pilot study with fewer patients [27]. In their first reported study, 50 patients with extensive tumour burden and/or markedly hypervascular tumours (13 hepatocellular carcinomas, and 37 liver metastases) underwent radioembolization with extended shelf-life microspheres with a mean lobe radiation dose of 126 Gy. The mean increase in number of particles per gigabecquerel was 111 % obtained through a shift in the administration time of about 3 days, from Friday of the first week to Monday of the second week. Lesion objective responses, assessed by WHO and EASL criteria, were 51 % and 69 %, respectively, with a 27 % EASL complete response rate. The authors concluded that the procedure provided “a safe and effective methodology with promising response rate”.

In the more comprehensive paper [26], the number of patients was increased to 134. The objective response was still high, though with a slight decrease (48 % and 57 % by WHO and EASL criteria, respectively), but with an impressive 97 % WHO disease control rate, and a 21 % EASL complete response rate. The treated pathology was again heterogeneous, and the toxicity was compared to a range of published data. Therefore the definitive highest level of evidence of the superiority of the extended shelf-life approach with glass microspheres has still to be pursued by more rigorous, possibly randomized studies. However, the idea of having a device numerically intermediate between the really embolic resin spheres and the “first-week” glass microspheres, is new, interesting, and extremely appealing. Maybe it is not by chance that the third emerging kind of microsphere for radioembolization, loaded with ^{166}Ho, have an initial activity per particle of 450 Bq [28] which is intermediate between 50 Bq and 2,500 Bq of the two existing products.

The paper by Lewandowski et al. also mentions the embolic role of an augmented number of microspheres, although previous results are controversial in this respect: a trend toward improved survival of patients with the stasis phenomenon [29], in contrast to only mild inflammation of animal tissues embolized with nonradioactive resin microspheres [30].

Some caveats should be raised about the new idea. First, as we would expect from theory [25], and as we reported above for the two kinds of spheres, increasing the number of particles keeping the same 120 Gy paradigm should be accompanied by an increase in both aspects of biological effectiveness, i.e. efficacy but also toxicity. The latter should therefore be carefully investigated with dosimetry-based studies. Not by chance has our group published a safety-based treatment planning criterion for glass microspheres [26] valid only with a decay interval of 3.75 days, i.e. the fixed interval before administration that we applied to all patients in our retrospective dosimetry study. Second, the use of glass microspheres after 12 days decay, with a number per gigabecquerel just half that of resin spheres, could lead to the same stasis phenomenon as the use of the latter device. Third, since all the above reported calculations and clinical results are in agreement emphasizing the importance of the number of microspheres per gigabecquerel, this should be considered a crucial variable in clinical trials. It should therefore at least be reported, and ideally fixed within each trial, to avoid bias derived from an uncontrollable variable. In other words, in the near future, writing about generic "radioembolization" with glass spheres could be improved by more rigorous scientific radioembolization reporting specifying the day of administration. Indeed, two glass sphere treatments with administrations 1 week apart should be considered completely different.

A third practical note is about the fact that the use of glass microspheres with the second week technique will require more often than now shipment of activity higher than the maximum available for a single vial (20 GBq). More than one vial will be more often purchased per patient. This does not increase the cost of the treatment, since the price is fixed per treatment, not per vial.

In conclusion, the theoretical considerations of Walrand et al. [18] discussed above, as well as all the clinical results discussed above, are in agreement both comparing different types of spheres and different numbers of glass spheres. They all give the same indication. For a fixed mean absorbed dose, the higher is the number of particles per gigabecquerel (up to the stasis limit), the higher is the biological effect. Nonuniformity of absorbed dose deposition is a key factor making the biological effect of 1 Gy in nuclear medicine therapy different from 1 Gy delivered by an external beam. The implications of this fact apply not only to microspheres therapy, but for instance could explain the different renal toxicity after ^{90}Y-DOTATOC and ^{177}Lu-DOTATOC therapy. The other key factor, already established, is the dose rate, which required the introduction of the biologically effective dose (BED) for proper interpretation of renal toxicity after ^{90}Y-DOTATOC therapy of neuroendocrine tumours [31]. In both aspects, dosimetry is essential to understand the underlying mechanism.

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