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Perspectives for yttrium-90 radioembolization as therapeutic option for hepatocellular carcinoma

Marta Burrel[1], Patricia Bermúdez[1], and Alejandro Forner-González[2]

[1]Angioradiology Section. Radiology Department, and [2]Liver Unit. Hospital Clínic de Barcelona. Barcelona, Spain

Correspondence: Marta Burrel
e-mail: MBURREL@clinic.cat

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The therapeutic management of hepatocellular carcinoma (HCC) has achieved great advances in the past few years (1). Before the publication of the SHARP clinical trial, which showed the effectiveness of sorafenib in patients with advanced HCC (2), no effective systemic therapy was available and only transarterial chemoembolization (TACE) had shown an impact on survival in clinical trials (3,4). TACE takes advantage of HCC's unique, almost exclusive arterial vascularization (as opposed to the liver parenchyma, which is supplied by both arterial and portal vessels), a fact that allows selective drug delivery and embolization of the tumor's blood supply. While TACE is the treatment of choice for patients with intermediate-stage HCC (5), not all patients in such stage are good candidates for TACE (6). Specifically, absence of preserved portal flow (e.g., because of portal thrombosis) represents an absolute contraindication to TACE given a high risk of ischemic hepatitis development. Transarterial radioembolization (TARE) is a form of brachytherapy where yttrium-90 (Y-90)-laden microspheres are injected into an artery as a source of internal radiation. The small size of Y-90-laden microspheres, together with the low penetrance of this

beta-ray emitter, allows delivery of high-dose radiation to the tumor, while preserving the adjacent liver parenchyma, with hardly any embolization effect. This absence of embolization effect determined the feasibility of TARE in patients with portal thrombosis and/or inadequate portal flow. TARE was initially evaluated in patients with HCC where other approaches had failed or were unfeasible, usually including patients with extensive tumors, modestly impaired liver function, and/or portal thrombosis. In early studies TARE proved to be a safe, well-tolerated therapy, effective in terms of radiographic response but with highly variable reported survival rates reflecting the inclusion of patients with highly variable clinical features regarding tumor stage, liver function, selectivity (lobar, bilobar, or selective therapy), and sequence (first-line or after prior treatment failure) (7-12). These promising results reported by various retrospective studies justified performing clinical trials to confirm TARE benefits in terms of survival versus systemic therapy with sorafenib in patients with locally advanced HCC. Unfortunately, two clinical trials designed to demonstrate TARE superiority over sorafenib therapy, one in France and one in Southeast Asia, obtained negative results (13,14): TARE failed to to show greater survival when compared to sorafenib despite significantly superior tumor responses. These two clinical trials had important methodological limitations that are worth highlighting. First, both studies were carried out in centers with little experience in this procedure. Furthermore, patients were included with excessive tumor load and/or borderline liver function. Finally, absence of tailored dosimetry, which was not recognized as an effective strategy to improve TARE results when both studies were designed, may have partly contributed to the poor results obtained in the TARE arm. Associating TARE with sorafenib also failed to demonstrate any survival increases versus sorafenib alone (15), and we are now expecting the final results of the STOP-HCC (NCT01556490) study, where patients with irresectable HCC are randomized to receive sorafenib versus TARE followed by sorafenib within 2 to 6 weeks post-TARE (16). Based on these studies, the clinical practice guidelines issued by the European Association for the Study of the Liver and by the Spanish scientific societies involved in the management of HCC established there was enough evidence to not recommend using TARE in patients with advanced-stage HCC, and no recommendations could be offered for intermediate-

stage HCC since only uncontrolled cohort studies were available (5,17).

Management with TARE follows the same radiobiological rules of external radiation therapy: absorbed doses must reach a threshold for effects to be observed (deterministic), and the higher the absorbed dose, the greater the effect will be. According to manufacturer instructions, Y-90 activity is estimated based on body surface area when resin microspheres are used, or liver-absorbed dose (80-150 Gy) for glass microspheres, totally ignoring tumor-absorbed dose. However, the tumor-absorbed dose may be easily, accurately established with SPECT/CT with albumin macroaggregates using multicompartmental models (18). Multicompartmental models allow an estimation of absorbed doses in tumors and perfused non-tumoral liver, as well as in total liver tissue. Using this personalized dosimetry the Y-90 activity needed to reach or overcome a tumor-absorbed dose threshold while limiting the dose absorbed by the non-tumoral liver (to prevent liver toxicity) may be established. The concept of tailored dosimetry was assessed in the DOSISPHERE-01 multicenter clinical trial, where personalized dosimetry aimed at delivering > 205 Gy to the index lesion was shown to be superior to standard dosimetry in an interim analysis (19). The index lesion's objective response rate was significantly higher in the personalized dosimetry arm (71 % *vs.* 36 %, p = 0.0074), with a median survival of 26.5 months versus 10.7 months in the standard dosimetry arm (p = 0.0096). Serious adverse events did not increase in the personalized dosimetry arm, mostly due to the inclusion of patients with adequate liver reserve and unilobar treatment in most cases (19). Similarly, superselective TARE, which allows delivery of high energy doses to the tumorous liver segment (known as radical segmentectomy), has shown in various retrospective studies, in patients with single tumors not amenable to surgical resection or ablation, a high rate of long-lasting objective responses and survival comparable to that reported with ablation/surgical resection (20,21). Furthermore, pathology analysis has shown complete necrosis in 30 of 45 (67 %) patients treated with TARE who subsequently underwent liver resection or transplantation (22). Finally, the potential usefulness of TARE combined with immune therapy is being explored, based on TARE's ability to increase the amount of tumor antigens released thus stimulating T-cell activation, which might improve immune response against the tumor, as suggested by the clinical

observation of tumor responses far from the irradiated area, a phenomenon known as abscopal effect (23). The results of the NASIR-HCC (NCT03380130) phase-2 study have been reported, which included patients with irresectable HCC, predominantly with single-lobe involvement, who were treated with TARE and then received nivolumab. A total of 42 patients were included, no synergistic toxicity was observed, an objective response was seen in 38 % of cases (11.9 % with a complete response), and median survival was 20.6 (95 % CI: 17.3-24.0) months (24).

Clinical experience with TARE for HCC started with advanced HCC but was then gradually extended to intermediate and early stages. Clinical trials available to date advise against its use in advanced stages, and the dramatic spread of systemic therapy hinders TARE options in this scenario. The most promising results were achieved in patients in early stages where TARE, using tailored dosimetry and superselective approaches allowing selective delivery of high-dose radiation to the tumor, has obtained high radiographic response and long-term survival rates comparable to those shown with other curative-intent options such as surgery and ablation. Ideally, TARE effectiveness in early stages should be assessed in randomized clinical trials comparing this option with alternatives such as percutaneous ablation or TACE. TARE might thus become indisputably recognized as a therapeutic option in this setting. However, the design and conduct of such clinical trials is complex, which in part accounts for their absence. Prospective cohort studies will never be a substitute for the scientific evidence provided by clinical trials, but those properly designed, including appropriately selected patients according to well-defined inclusion and exclusion criteria, where the procedure is carried out in a regulated, protocolized manner, will offer valuable information and facilitate the positioning of TARE as a useful therapeutic tool for the management of HCC.

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