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Commentary

COMMENTARY

Transarterial radioembolization with Yttrium-90: current status and future prospects

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In recent years, transarterial radioembolization (TARE) with Yttrium-90 (Y90) has emerged as a technique for treating malignant neoplasms in the liver. Compared with other locoregional therapies, such as transarterial chemoembolization (TACE), patients who underwent TARE with Y90 have higher tumor response rates and better outcomes. Moreover, no significant treatment-related complications or treatment-related deaths have been reported [1]. We here review the clinical application of TARE and its associated issues.

TARE is most frequently used to treat hepatocellular carcinoma (HCC). Salem *et al.* [2] performed a study to compare the effects of TACE and TARE in 179 patients with Barcelona Clinic Liver Cancer (BCLC) stages A or B HCC. They found similar tumor response rates in the two groups (74% in the TACE group vs 87% in the TARE group) ($P = 0.433$). However, patients in the TARE group had a significantly longer median time to progression (>26 months) than those in the TACE group (6.8 months) ($P < 0.001$). Furthermore, the occurrence rate of complications was lower in the TARE group. The most recent study by Salem *et al.* [3] presented overall survival (OS) outcomes in a 1,000-patient cohort acquired over a 15-year period. On the basis of these data, they decided to adopt TARE as the first-line transarterial locoregional therapy for patients with HCC. The only treatment recommended by the BCLC system for patients with advanced HCC and portal vein tumor thrombus (PVTT) or hepatic vein tumor thrombus is Sorafenib [4]. However, the management of advanced HCC is complex and still controversial. Recently, two phase III clinical trials compared TARE and Sorafenib and concluded that the results of TARE are not better than those of Sorafenib in terms of survival benefits [5]. However, this does not mean that TARE should not be used to treat advanced HCC. In fact, the difficulties and potential biases undermining trials that compare an interventional procedure (TARE) with a drug (Sorafenib) should be carefully analysed. Spreafico *et al.* [6] performed a single-center retrospective study that included 120 patients with advanced HCC and PVTT. These patients were all treated with TARE. Median OS was 14.1 months (95% confidence interval, 10.7–17.5) and 1-year and 3-year OS rates were 53.2% and 18.5%, respectively. These survival results seem to be better than those achieved by Sorafenib. The researchers further developed a prognostic score model to predict response to TARE for patients with HCC and PVTT. They identified three prognostic categories: favorable, intermediate, and dismal prognoses. Median OS in these three categories was 32.2, 14.9, and 7.8 months, respectively ($P < 0.001$) [6]. This model may help doctors to better identify patients who are suitable for TARE treatment.

Liver transplantation (LT) is a curative therapy option for patients with HCC who meet the Milan criteria. However, there is usually a 6-month to 1-year wait for an appropriate donor liver. During this period, interventional procedures are usually required to prevent tumor progression. In addition, the tumor stage of patients with HCC that does not meet the Milan criteria can be reduced by interventional therapy to the point of meeting these criteria. Interventional specialists may prefer TARE because of its better disease-free survival and OS and lower toxicity than with TACE. Ettorre *et al.* [7] performed TARE before LT in 22 patients with HCC, including 3 who met the Milan criteria prior to treatment with TARE and 19 who did not. Downstaging was observed in 78.9% of cases and bridging was achieved in

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100% of cases. Liver resection (LR) is another important procedure for treating HCC. However, many patients with advanced HCC do not meet the criteria for radical resection on presentation. TARE with Y90 can serve as a safe bridge to LR by treating tumors and promoting hypertrophy of the future liver remnant.

A recent study has identified the immune effects of TARE in patients with HCC. This immunological impact can elicit a sustained therapeutic response characterized by regression of locally advanced HCC and delaying of disease progression. Chew *et al.* [8] detected immune activation in the local microenvironment of tumors treated with TARE. They identified potential biomarkers associated with positive clinical response and built a prediction model to identify sustained responders prior to TARE treatment. This model provides a new means of studying the relationship between Y90 and immune responses. A combination of Y90–TARE and immunotherapy may improve the clinical outcomes of patients with liver cancer.

TARE can be used to treat not only HCC, but also intrahepatic cholangiocarcinoma and colorectal cancer, neuroendocrine tumor, and breast-cancer liver metastases. The safety and efficacy of TARE in the treatment of these liver tumors have been confirmed previously [9].

Although the adverse effects of TARE are not significantly greater than those of TACE, they should not be ignored. The high-dose beta-radiation emitted in TARE penetrates only 2.5 mm from the source, thus limiting its effects to the site of delivery. However, the off-target diversion of Y90 microspheres to tissues other than the tumor may lead to complications; the most prominent of these complications are radiation gastritis and gastrointestinal ulcers, cholecystitis, radiation pneumonitis, and radioembolization-induced liver disease. Experts recommend that the TARE procedure be performed in accordance with appropriate quality-assurance standards and radiation doses be calculated strictly according to the manufacturer's recommendations. Patients who are sensitive to radiation damage or have reduced liver functional reserve are at high risk of significant tissue damage. Physicians should adopt the most appropriate strategies for the prevention, early diagnosis, and management of potential radiation injury to the liver and other organs [10].

In conclusion, TARE is an excellent treatment of patients with advanced hepatobiliary cancer who are not eligible for surgery. However, prospective randomized–controlled trials are still required to further demonstrate the role of TARE with Y90. With further study of the immunological effects of Y90, the authors believe that the combined application of Y90 and immunotherapy will show great power in the treatment of cancer.

Authors' contributions

Y.L.M. proposed the study and revised the manuscript. H.Y.Y. and B.J. drafted the first manuscript. G.X., L.J.S., and S.D.D. made a writing suggestion and revised the first draft. All authors contributed to the design and interpretation of the study and to further drafts. Y.L.M. is the guarantor. All authors read and confirmed the final version of this paper.

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Conflicts of interest

None declared.

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