Editorial

The role of selective internal radiotherapy with Y-90 resin microsphere in first-line therapy for hepatic colorectal metastases

Antonio Costanzo[1], Valentina Rampulla[1], Antonio Varricchio[1], Fausto Petrelli[2]

[1]Surgical Oncology Unit, Surgical Department, [2]Oncology Unit, Medical Sciences Department, ASST Bergamo Ovest, Treviglio, BG, Italy

Correspondence to: Fausto Petrelli, MD. Oncology Unit, Oncology Department, ASST Bergamo Ovest, Piazzale Ospedale 1, 24047 Treviglio, BG, Italy. Email: faupe@libero.it.

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The liver is the primary site of metastases in colorectal cancer (CRC) because the majority of the venous mesenteric drainage enters the hepatic portal venous circulation. More than 50% of patients with CRC will develop hepatic metastases over the course of their life. This ultimately leads to death more than two-thirds of these patients (1).

Surgery is curative in only 20% of patients, and 70% will develop recurrence, even when combined with systemic therapy. Yet it remains the main therapeutic option (2).

When surgery is not possible, e.g., non-resectable disease or patients unfit for it—other ablative methods have been developed in last decades including radiofrequency ablation. The latter can prolong the overall survival, with or without surgery and chemotherapy, in patients with colorectal liver metastases (3).

Although systemic chemotherapy has largely improved outcome with the development of modern chemotherapy agents and biologics, the response rates and overall survival gains remain rather disappointing. For this reason, efforts to seek alternative treatments remain one of the primary aim of research. Furthermore, to reduce the burden of toxicity of chemotherapy and to maximize its therapeutic effects, more targeted and selective locoregional approaches have been developed. Among these are hepatic arterial infusion (HAI) and radiation-based therapy.

HAI therapy is a locoregional treatment based on the delivery of chemotherapeutic agent through the hepatic arterial circulation. This provides high local drug concentrations with the goal of minimizing systemic toxicity. Among the various agents studied, floxuridine is a good candidate for HAI because it has a short half-life (<10 min) and more than 90% hepatic extraction, resulting in a 16-fold higher concentration in liver metastases compared with venous administration.

Some prospective trials have investigated using HAI alone, but other studies showed best survival benefits in multimodality treatment: properly selected patients with CRC liver metastases can achieve a 5-year survival benefit as high as 78% with hepatic resection followed by adjuvant systemic therapy plus HAI. However, treatment with HAI could have side effects that need to be balanced with the survival benefit, particularly, the risk of biliary sclerosis in less than 5% of patients (4-6). As regards radiation-based therapies, external beam radiation has not found a defined place in the management of liver tumours because of high risk of fatal hepatitis based on veno-occlusive mechanism (7).

Selective internal radiotherapy with Yttrium-90 resin microspheres consists of delivering β-emitter microspheres into the arterial supply of the liver under fluoroscopic guidance. The delivery of the resin microspheres into branches of the hepatic artery—which supplies the majority of blood to liver tumours—results in selective targeting by high-dose radiotherapy. This happens because the healthy

liver is supplied predominantly by the portal venous system and therefore relatively spared from radiation exposure (8).

Yttrium-90 is a high-energy, pure β-emitter with a half-life of 64 hours and maximum tissue penetration of 11 mm, which makes it very suitable for treatment of liver tumours. Yttrium-90 is relatively straightforward to use, with limited issues relating to radioprotection for the patient, family or attending staff. The microspheres are approximately 35 μm in diameter, which means they are permanently entrapped at the arteriolar end of the capillary bed.

The technique provides that any arteriovenous shunting through the liver or the tumour is assessed before selective internal radiotherapy (SIRT) is performed. This assessment needs hepatic arteriography and a scan of the chest and abdomen with a gamma camera, after hepatic artery administration of 99mTc-macroaggregated albumin (MAA). The MAA scan is also useful to confirm the area of the liver to be treated and that extrahepatic foregut structures are not being accessed by the delivery system.

Because the MAA aggregates are similar to microspheres size, their distribution after hepatic arterial delivery will be similar to that of administered microspheres. If the shunt exceeds 13% of the vascular tumoral bed, the SIRT should either not be performed, or administered at reduced dose (7).

The evaluation of tumour response after SIRT, or after another kind of treatment, is based on the computed tomography (CT) and/or magnetic resonance imaging (MRI). However, the dimensional criterion only is not enough. When there is a tumour response, serum CEA decreases significantly, and this decrease correlates with metabolic positron emission tomography (PET) response more than CT or MRI (9,10). Moreover, a new generation of blood-based biomarkers is being studied: circulating tumour cells (CTCs), circulating free DNA (cfDNA), micro-RNA (miRNA) and exosomes (6).

The efficacy of SIRT in pretreated metastatic CRC (with liver-dominant disease) has previously been evaluated. A randomised trial showed a significant benefit of chemotherapy (Fluorouracil) plus SIRT versus chemotherapy (Fluorouracil) alone in time to progression. A significant increase in time to liver progression and time to tumor progression, but no significant difference in overall survival between the two arms was observed (11).

Wasan *et al.* conducted a pooled analysis of three multicenter, randomised, phase III trials (FOXFIRE, SIRFLOX and FOXFIRE-Global) on 1,103 patients, recruited between 2006 and 2014 in 14 countries (12). These trials studied the role of the addition of SIRT (single treatment at 1 or 2 cycles of chemotherapy) to first-line FOLFOX chemotherapy (554 patients) for patients with liver-only and -dominant metastatic CRC compared to those treated with FOLFOX alone (549 patients).

The patients were assigned randomly, and the distribution between the two arms is substantially homogeneous with regard to age, sex, WHO performance status, primary tumor site, primary tumor *in situ*, previous adjuvant chemotherapy, metastases at time of diagnosis, extrahepatic metastases status, extent of liver involvement, intention to treat with biological agents (bevacizumab or cetuximab).

In FOXFIRE, chemotherapy consisted in 12 cycles of FOLFOX, and patients could receive anti-VEGF or -EGFR (from cycle 1 in the FOLFOX alone group and cycle 7 onwards in the FOLFOX plus SIRT group). In SIRFLOX and FOXFIRE-Global protocol chemotherapy was continued until disease progression or dose-limiting toxicity, and patients could receive an anti-VEGF (from cycle 1 in the FOLFOX alone group and from cycle 4 in the FOLFOX plus SIRT group).

These three trials showed that the addition of SIRT to first-line oxaliplatin-fluorouracil chemotherapy confers an advantage regarding global disease response—complete and partial—(72% in FOLFOX plus SIRT *vs.* 63% in FOLFOX alone) and hepatic response only. Unfortunately, this effect does not increase the percentage of patients that reach a hepatic resection (17% in FOLFOX plus SIRT *vs.* 16% in FOLFOX alone) nor does it translate into an improvement of overall survival (median 22.6 *vs.* 23.3 months) or progression-free survival (median 11 *vs.* 10.3 months).

Haematological grade 3 or worse adverse events (the most common being neutropenia) were more frequent in the experimental group (46%) than in control group (29%); moreover, SIRT has specific risks such as radiation pneumonitis, hepatitis, gastritis with perforation.

The lack of any overall survival benefit suggests that early use of SIRT in combination with first-line chemotherapy cannot be recommended, except in experimental trials.

The molecular subtypes (according to RAS and BRAF mutations) in these three studies are not currently available, but, based on preliminary data, the authors suggest that patients with CRC liver metastases from right-sided primary tumours could be a clinical subgroup that benefits from SIRT and this could be linked to their molecular

pathway.

CRC is the sum of a heterogeneous group of diseases with molecularly and clinically distinct tumours, based also on the primary site of origin (e.g., colon *vs.* rectal, and right- *vs.* left-sided). Chromosomal instability, deficient mismatch repair (dMMR), aberrant DNA methylation, as well as altered molecular pathways have all been described during the evolution from normal mucosa to adenocarcinoma (6,13). Worst prognosis is associated with right CRC, and, when associated with increased benefit obtained in this subset, this could suggest that intensifying the medical treatment in the right CRC is an intriguing option. Unfortunately, only 54% of patients were planned to receive biological agents in conjunction with chemotherapy. Uncertainty remains as to the best intensification modality in poor prognosis CRC, because a comparison with chemotherapy triplet (FOLFOXIRI + bevacizumab) plus or minus SIRT (or versus FOLFOX + SIRT) for conversion or palliative purposes is not included as a therapeutic option (14).

Ongoing research aims to identify molecular subsets of patients with CRLM to personalise targeted treatments so as to maximise therapeutic interventions, predict treatment response and improve overall survival (6,15).

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None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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