



New insights into benefits of combination treatment with yttrium-90 and gemcitabine in patients with intrahepatic cholangiocarcinoma

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The treatment of patients with irresectable hepatic metastases of pancreatic cancer (PC) and intrahepatic cholangiocarcinoma (ICC) remains challenging despite growing therapeutic options and providing adequate palliative care always includes the decision between quality of life and most effective oncologic results. Gemcitabine is a relatively well tolerated substance but median overall survival of patients with PC or ICC with metastases treated with gemcitabine monotherapy was reported 5.7 (1) and 8.1 (2), respectively.

Selective internal radiation therapy (SIRT) or transarterial radioembolization (TARE) has emerged as a treatment option for patients with primary or secondary hepatic malignancies that are usually not eligible for surgical treatment (3,4). Microspheres loaded with yttrium-90 (⁹⁰Y) are applied in the hepatic artery after radiologically guided selective catheterization allowing for a more precise radiation of tumor tissue while only mildly affecting liver tissue.

Still, SIRT with or without synchronous chemotherapy is not widely evaluated in hepatic metastases of PC and ICC and most studies only have small number of cases rarely exceeding 20 treated patients. Intraarterial therapy (including two patients treated with TARE) for multifocal ICC was compared to surgical resection in a collective of 116 patients with no statistically significant difference in overall survival, support the effect of local therapies in the liver (5). A single center study for PC patients with hepatic metastases reported partial response or stable disease in 9 of

13 patients and median overall survival of 12 months after TARE (6) and another publication in a similar collective with 16 patients could show an objective response in 47% and a median survival of 9 (range, 0.9–53.0) months after previous gemcitabine-based chemotherapy (3). Thirty-three patients with metastatic PC that had progressed under systemic chemotherapy and other oncologic treatments underwent TARE at one of three institutions with partial response or stable disease in 79% (7).

In an article now published in the *Journal of Gastrointestinal Oncology* by Nezami and colleagues 8 patients (three with PC and 5 with ICC) that had not received prior systemic therapy for advanced stage disease underwent TARE with ⁹⁰Y and concomitant gemcitabine within an open-label phase Ib clinical trial. Patients with unilobar disease (n=4) received one treatment with TARE at day 2 after first gemcitabine therapy and patients with bilobar disease (n=4) received a second treatment at day 37. All patients had a tumor burden of >50% of total liver. Majority of patients were female, and the mean age was 69.4±6.9. Due to an early death of one patient 1.2 months after ⁹⁰Y TARE, seven patients were eligible for tumor response evaluation. Response was evaluated using positron emission tomography/computed tomography (PET/CT) scan. Overall, there was a treatment response rate of 62.5% at 3 months. There was a statistically significant better objective response in ICC patients. The median hepatic progression free survival (HPFS) for PC was 4.4 (1.2–4.9) as compared to 16.3 (2.7–22.5) months in ICC patients

($P < 0.001$). Median progression free survival of all patients was 6.9 (1.2–22.4) months. The authors report, that there was no non-targeted embolization according to a post- ^{90}Y treatment single-photon emission CT (SPECT)/CT scan (bremsstrahlung). There was one case of full response in a patient with ICC. All patients encountered transient fatigue representing the most common treatment-associated complication. Transient liver toxicity after ^{90}Y -TARE and gemcitabine occurred in 7 (87.5%) patients. None of the toxicities were permanent and also no persistent hepatobiliary toxicity was reported within 90 days.

The results provided by Nezami and colleagues are of great interest and clinically relevant because they show the feasibility of applying systemic chemotherapy and TARE in patients with hepatic metastasis of pancreatobiliary origin and prove that even full response is possible. They showed that a dosage of up to 600 mg/m² gemcitabine could safely be applied in seven of the eight patients with higher grade (grade 2–3) hepatobiliary toxicity being only transient in three patients. PET/CT scan showed a response rate of 62% which is in accordance with other publications in the field (3,7). However, only a small sample size could be included, and enrolment had to be stopped because there were not enough chemotherapy naïve patients. This addresses a common issue of patient selection for local ablative procedures. Even though the authors did not report any significant post ^{90}Y -TARE complications, treatment with radioembolization can lead to post-radioembolization syndrome causing, among others, gastrointestinal ulceration and radiation pneumonitis. Therefore, patient selection and preparation by strict inclusion criteria, as was done here, enrolling only patients with adequate liver function and determination of lung shunting fraction $< 20\%$ before therapy plays a crucial role when planning TARE. All this is a limitation for TARE application because in the clinical reality, many patients with systemic disease and predominant hepatic manifestation have already impaired liver function due to past chemotherapy or the malignancy itself. Also, gemcitabine is not the only available treatment for patients with metastatic PC and ECOG 0–1 as newer studies report (8,9), a fact that should be considered in the interpretation of the data. On the other hand, as toxicity from systemic chemotherapy should be limited when applying ^{90}Y -TARE, and gemcitabine properties of radiosensitization were aimed for in this study, monotherapy with gemcitabine is reasonable even in the context of newly available data. For the 5 ICC patients, ^{90}Y -TARE response was significantly better compared to the PC

patients, as was the HPFS with 4.4 (1.2–4.9) for PC *vs.* 16.3 (2.7–22.5) months for ICC ($P < 0.001$). ICC patients in the palliative setting are treated usually with gemcitabine-based systemic chemotherapy showing only moderate effects on response and survival (10). Especially in the light of more systemic treatment options for PC patients, the benefit of ^{90}Y -TARE might be greater in ICC patients and thus data by Nezami and colleagues provided here is a considerable base to further conduct randomized trials with a focus on ICC patients.

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