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EDITORIAL

# SIRT and chemotherapy in unresectable iCCA: Ready to take off



In this issue, Edeline et al compared the results of standard systemic chemotherapy (gemcitabine and cisplatin or gemcitabine and oxaliplatin) versus the combination of selective internal radiation therapy (SIRT) and chemotherapy, as first-line treatment in patients with liver-only intrahepatic cholangiocarcinoma (iCCA).[1] By collecting individual patients data from 5 large prospective clinical trials of systemic therapy alone and 1 trial of systemic therapy plus SIRT (MISPHEC) and applying the emulated target trial paradigm as a statistical method, the authors showed that the combination of SIRT and chemotherapy is able to improve both overall survival (OS) and progression-free survival.[1] The inverse probability treatment weighting using a propensity score was also implemented to balance confounding factors between groups. Although prospective randomized trials are still desirable to confirm these findings, these results, derived from a solid statistical method, represent a step forward to better delineate the role of SIRT in the treatment algorithm of iCCA. Moreover, the absolute gain of about 6 months in both OS and progression-free survival is also relevant from a clinical point of view in a population of unresectable, liver-only iCCA. The low rate of secondary resections (8% vs. 3% after adjustment) further highlights the challenging patient population analyzed.

Numerous publications reported the safety and efficacy of SIRT both in first-line and at disease progression or recurrence, with a median OS of ~14 months, consistent across the different studies.[2,3] The longer median OS (21.7 mo) reported by Edeline et al in the combination arm may be the result of multiple factors.[1,4] The MISPHEC trial included only treatment-naïve patients with liver-only disease or very limited extrahepatic disease.[4] Moreover, the trial investigated a combined approach in which SIRT was to be performed at predefined time points (days 3–21 of cycles 1 and 3 in patients with unilobar and bilobar disease, respectively), with no delays in chemotherapy.[4] The rational of this combination and the potential synergistic effects between chemotherapy and SIRT are not yet fully understood, although it is acknowledged that the radiation damage induced by SIRT may enhance the susceptibility of cancer cells to chemotherapy. Finally, the dosimetric approach proposed by the MISPHEC trial was different compared with previous studies. Together with the standard dosimetry adopted with glass microspheres (administered activity of 120 Gy to the target liver volume), the protocol allowed to use the intensified personalized dosimetry derived from the experience gained treating HCC (at least 205 Gy to the tumor and 150 Gy to the target liver), and authors reported 120 Gy median absorbed dose to the target liver and 317 Gy to the tumor, much higher compared with other studies.[2] Dosimetry data on iCCA are still lacking. However, preliminary observations suggested that a mean tumor absorbed dose of at least 75 Gy with resin microspheres and 150 Gy using glass spheres are needed to significantly improve survival,[5] in line with what is reported in the MISPHEC study.[4] However, achieving higher tumor absorbed doses without harming the nontarget liver volume requires some specific anatomical features. The tumors should be confined, possibly to 1 hemiliver or contiguous segments, and should display a sufficient arterial vascularization as to allow selective intratumoral uptake of the microparticles. In this scenario, naïve patients represent the ideal candidates, devoid of the risk of vascular impairments caused by previous loco-regional or systemic treatments. Finally, as suggested for HCC,[6] the preliminary diagnostic work-up with the prevision of the expected tumor absorbed dose should represent the main driver to select iCCA patients for SIRT and should become part of the inclusion criteria in future clinical studies.

The study showed that SIRT has an effect on controlling tumor progression, as demonstrated by the longer progression-free survival in the combination treatment arm.[1] Moreover, in the unadjusted population, the rate of secondary resections was higher in patients treated with SIRT, possibly determined by the tumor downsizing and stimulation of contralateral liver

**Abbreviations:** iCCA, intrahepatic cholangiocarcinoma; OS, overall survival; SIRT, selective internal radiation therapy.

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hypertrophy.[7] Indeed, the MISPHEC trial pointed out that a more intensive regimen aiming to convert patients to resection could be justified in patients with unilobar disease and no cirrhosis, who are initially considered unresectable due to close proximity to major vessels and/or insufficient liver remnant.[4]

As pointed out by the authors, the study included only patients treated with standard chemotherapy, not considering the more recent introduction of durvalumab in the first line following the positive results of the phase 3 TOPAZ-1 trial.[8] Also, considering the positive results of the KEYNOTE-966 phase 3 trial[9] further supporting the role of chemoimmunotherapy as the standard of care in the first-line setting, future studies are needed to understand if and to what extent the addition of SIRT may further enhance the benefits of immunotherapy.

Furthermore, any future investigation will have to take into account the tumor molecular profiling, assessing how SIRT could be integrated into the rapidly evolving scenario of iCCA treatments.

The natural conclusion of the presented findings is that there is a need for further prospective and, possibly, randomized trials. However, previous experiences (such as the SIRCCA trial) have shown that randomized controlled trials are difficult to be completed in the setting of a highly selected population, such as the one suggested by this analysis (ie, with unresectable, liver-only disease, in which high selective tumor absorbed dose should be achieved). There is a need to exploit and verify alternative, more realistic and less resource-consuming models that can produce high-quality scientific evidence that may impact guidelines, recommendations, and clinical practice. The debate is open, but in the present study, Edeline et al are showing how to build evidence creating a sort of "scientific consortium," sharing data collected from previous prospective trials and analyzing these data through solid statistical analysis. The study is based on the emulated target trial paradigm that aims to overcome the challenges and limitations of randomized controlled trials by simulating the randomization process and evaluating the treatment effects in a hypothetical cohort of patients.[10] To mitigate the well-known limitations of this paradigm and strengthen the robustness of their findings, the authors combined multiple data sources and several statistical methods. The obtained results are convincing and provide valuable clinical information, useful as a starting point for future investigations.

In conclusion, the study by Edeline et al deserves attention since it sets the basis for a better definition of the role of SIRT in combination with systemic therapy as first-line approach for patients with liver-only unresectable iCCA. Future studies are warranted to investigate how results may be affected by the tumor molecular profile, to improve the personalized dosimetry approach, and to test newer combinations of SIRT with chemoimmunotherapy, in the rapidly evolving field of iCCA. Efforts are needed in the scientific community to conceive newer strategies to produce solid scientific evidence in a realistic, sustainable, and ethical way.

## CONFLICTS OF INTEREST

Irene Bargellini consults, advises, and is on the speakers' bureau for Boston Scientific and Terumo. She consults and is on the speakers' bureau for Eisai, Roche, and Sirtex. She received grants and has other interests with AstraZeneca. She advises Microbot Medical. She is on the speakers' bureau for Bayer, GE Healthcare, Guerbet, and MSD. Lorenza Rimassa consults, advises, and is one of the speakers' bureau and received grants from AstraZeneca, Eisai, Incyte, Ipsen, and Roche. She consults, advises, and is on the speakers' bureau for Bayer, Exelixis, Eli Lilly, MSD, and Nerviano Medical Sciences. She consults, advises, and received grants from Zymeworks. She consults and advises Basilea, Bristol Myers Squibb, Genenta, Hengrui, IQVIA, Jazz Pharmaceuticals, Servier, and Taiho Oncology. She is on the speakers' bureau for Gilead, Merck Serono, and Sanofi. She received grants from Agios, BeiGene, and Fibrogen. Gianluca Masi consults, advises, and received grants from AstraZeneca, Bayer, Eisai, MSD, Roche, Servier, and Sirtex. He received grants from Terumo.

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