About the Recently Published Paper on JAMA Oncology “Radioembolization Plus Chemotherapy for First-Line Treatment of Locally Advanced Intrahepatic Cholangiocarcinoma: A Phase 2 Clinical Trial”

Irene Bargellini¹ · Caterina Vivaldi² · Laura Crocetti¹ · Gianluca Masi²

Received: 20 May 2020 / Accepted: 23 June 2020 / Published online: 16 July 2020

© Springer Science+Business Media, LLC, part of Springer Nature and the Cardiovascular and Interventional Radiological Society of Europe (CIRSE) 2020

Introduction

We read with great interest the paper by Edeline et al. published on JAMA Oncology in 2019 [1], prospectively assessing the results of combined radioembolization (selective internal radiation therapy, SIRT) and chemotherapy as first-line treatment option in locally advanced, unresectable intrahepatic cholangiocarcinoma (ICC).

This multicenter study enrolled 41 patients with unresectable ICC and no or limited extrahepatic disease, who received gemcitabine plus cisplatin for at least six cycles and concomitant SIRT during cycle 1 (unilobar disease) or cycles 1 and 3 (bilobar disease).

Authors reported favorable outcomes, with 98% disease control rate at 3 months according to RECIST, up to 93% Choi response rate, median progression-free survival (PFS) of 14 months and median overall survival (OS) of 22 months. These results compare favorably to previous studies, reporting 14–15-month median OS in the general unresectable ICC population treated with SIRT [2, 3].

Toxicity of such treatment protocol could be a matter of concern. Edeline et al. reported 71% of grade 3–4 adverse events and more liver toxic effects in cirrhotic patients, with nine out of 12 cirrhotic patients experiencing liver failure, which was nonreversible in five cases. Of interest, all cases with liver failure received whole-liver SIRT. Thus, intensive combined treatment should be regarded

with caution when dealing with patients with cirrhosis and impaired liver function.

The most interesting finding of the trial is represented by the relatively high percentage of patients who were downstaged to resection ($n = 9$, 22%), with postsurgical 24-month PFS and OS of 66.7% and 88.9%, respectively. These results are consistent with the data reported by the BILCAP trial, using adjuvant capecitabine after resection of biliary tract cancers [4].

These preliminary findings may introduce a new perspective in the treatment management of unresectable ICC. It becomes essential to better delineate the clinical features of those patients, who are excluded from upfront resection, but for whom a more intensive first-line treatment regimen, combining loco-regional treatments with chemotherapy, could open the way to resection and long-term chances of cure. The rationale of this approach is highlighted by recent reports showing that advanced ICC treated with systemic therapy only has a better survival compared to other non-ICC biliary tract cancers [5]. In the paper by Edeline et al., the vast majority of downstaged patients had liver-only disease, with unifocal lesion confined to one hemiliver and no cirrhosis. In this highly selected population, tumor shrinkage combined with the contralateral liver lobe hypertrophy induced by SIRT could overcome the initial unresectability and allow safe R0 resection.

Thus, in the heterogeneous scenario of what is today defined “unresectable ICC,” efforts are needed to identify a subgroup of highly selected patients that could be defined as “potentially resectable” and for whom combination therapies could be the first choice. This could also help in designing future trials investigating modalities and outcomes of ICC downstaging.

✉ Irene Bargellini
irenebargellini@hotmail.com

¹ Department of Interventional Radiology, Pisa University Hospital, Via Paradisa 2, 56126 Pisa, Italy

² Department of Medical Oncology, Pisa University Hospital, Via Roma 55, 56126 Pisa, Italy

In the meantime, targetable biomarkers, such as FGFR (fibroblast growth factor receptors) or IDH (isocitrate dehydrogenase) gene alterations, are being actively investigated, and preliminary data on emerging molecular-targeted therapies and immune checkpoint inhibitors are extremely encouraging [6–8].

Thus, in the next future, clinical data, tumor extension and molecular profiling will be integrated in a multimodal approach, enabling proper definition of subgroups of patients and active integration of systemic therapies, surgery and loco-regional treatments.

Funding This study was not supported by any funding.

Compliance with Ethical Standards

Conflict of interest Irene Bargellini has participated to Advisory Boards and has received speaker honoraria from Sirtex Medical, Terumo Europe and Biocompatibles UK, Ltd. Caterina Vivaldi declares no conflicts of interest. Laura Crocetti has received speaker honoraria from Terumo Europe. Gianluca Masi has participated to Advisory Boards and has received speaker honoraria from Sirtex Medical, Terumo Europe and Biocompatibles UK, Ltd.

Ethical Approval This article does not contain any studies with human participants or animals performed by any of the authors; IRB approval is not required.

Informed Consent For this type of article, informed consent is not required.

Consent for Publication For this type of article, consent for publication is not required.

References

1. Edeline J, Toucheffeu Y, Guiu B, et al. Radioembolization plus chemotherapy for first-line treatment of locally advanced

intrahepatic cholangiocarcinoma: a phase 2 clinical trial. *JAMA Oncol.* 2019;1:1. <https://doi.org/10.1001/jamaoncol.2019.3702> [Epub ahead of print].

2. Zhen Y, Liu B, Chang Z, Ren H, Liu Z, Zheng J. A pooled analysis of transarterial radioembolization with yttrium-90 microspheres for the treatment of unresectable intrahepatic cholangiocarcinoma. *Onco Targets Ther.* 2019;12:4489–98.
3. Bargellini I, Mosconi C, Pizzi G, et al. Yttrium-90 radioembolization in unresectable intrahepatic cholangiocarcinoma: results of a multicenter retrospective study. *Cardiovasc Intervent Radiol.* 2020. <https://doi.org/10.1007/s00270-020-02569-4> [Epub ahead of print].
4. Primrose JN, Fox RP, Palmer DH, BILCAP study group, et al. Capecitabine compared with observation in resected biliary tract cancer (BILCAP): a randomised, controlled, multicentre, phase 3 study. *Lancet Oncol.* 2019;20(5):663–73.
5. Lamarca A, Ross P, Wasan HS, et al. Advanced intrahepatic cholangiocarcinoma: post hoc analysis of the ABC-01, -02, and -03 clinical trials. *J Natl Cancer Inst.* 2020;112(2):200–10. <https://doi.org/10.1093/jnci/djz071>.
6. Lamarca A, Barriuso J, McNamara MG, Valle JW. Molecular targeted therapies: ready for “prime time” in biliary tract cancer. *J Hepatol.* 2020;pii:S0168-8278(20)30165-3. <https://doi.org/10.1016/j.jhep.2020.03.007> [Epub ahead of print].
7. Abou-Alfa GK, Sahai V, Hollebecque A, et al. Pemigatinib for previously treated, locally advanced or metastatic cholangiocarcinoma: a multicentre, open-label, phase 2 study. *Lancet Oncol.* 2020;21(5):671–84.
8. Abou-Alfa GK, Macarulla T, Javle MM, et al. Ivosidenib in IDH1-mutant, chemotherapy-refractory cholangiocarcinoma (ClarIDHy): a multicentre, randomised, double-blind, placebo-controlled, phase 3 study. *Lancet Oncol.* 2020;1:1. [https://doi.org/10.1016/S1470-2045\(20\)30157-1](https://doi.org/10.1016/S1470-2045(20)30157-1) [Epub ahead of print].

Publisher’s Note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.