Ann Surg Oncol (2022) 29:5357–5358
https://doi.org/10.1245/s10434-022-11970-x

Annals of
SURGICAL ONCOLOGY
OFFICIAL JOURNAL OF THE SOCIETY OF SURGICAL ONCOLOGY

EDITORIAL – HEPATOBILIARY TUMORS

Another Signal from DEBIRI

Michael C. Soulen, MD[1], and Sarah B. White, MD, MSc[2]

[1]Department of Radiology, Abramson Cancer Center, University of Pennsylvania, Philadelphia, PA; [2]Medical College of Wisconsin, Milwaukee, WI

In this issue of *Annals of Surgical Oncology*, Dr. Martin and colleagues report an open label, phase II, randomized trial of standard-of-care first-line systemic chemotherapy for unresectable intrahepatic cholangiocarcinoma with or without chemoembolization using irinotecan-loaded microspheres (DEBIRI).[1] The study addresses an important goal of improving outcomes in this disease. Standard chemotherapy during this study period was gemcitabine/cisplatin based on ABC-02, which reported overall survival (OS) of 11.7 months and progression-free survival (PFS) of 8.0 months.[2] Current systemic therapies based on gemcitabine backbones with platinum ± nab-paclitaxel provide a median OS of 19.2 and PFS of 11.2 months.[3] Liver-directed therapies such as transarterial chemoembolization (TACE) or radioembolization (TARE) provide improved response rates, PFS, and OS in systematic analyses of largely retrospective data, with the best outcomes reported for patients also receiving systemic therapy, but prospective studies intentionally integrating liver-directed and systemic therapies are limited.[4,5]

In the current study, 24 subjects received per-protocol therapy in the DEBIRI arm and 22 in the control group. Two subjects allocated to each arm did not receive per-protocol therapy for reasons unrelated to feasibility. Importantly, treated subjects received similar intensity and duration of chemotherapy in both arms, with a similar incidence of dose reduction or interruption, and a similar profile of grade 3 or higher toxicities. Total chemotherapy exposure in this report was consistent with contemporary trials of systemic therapy. Based on these results, the combination of DEBIRI with gemcitabine-based chemotherapy regimens for intrahepatic cholangiocarcinoma is feasible and safe.

The primary efficacy outcome measure was the response rate. Three different response assessment systems were used: mRECIST, RECIST 1.1, and Choi. It is not clearly stated which response criterion was the primary endpoint, but mRECIST appears likely, which would be a self-fulfilling prophecy. mRECIST measures the longest diameter of enhancing tumor. Since the tumors in the experimental arm were embolized, substantial reduction in enhancement is expected. Furthermore, central review of response was performed by the principal investigator, which is methodologically flawed due to unavoidable bias. Nonetheless, a blinded independent review was conducted using the more treatment-agnostic RECIST system. Results using RECIST 1.1 were significantly better in the DEBIRI arm. Although response rates are a weak surrogate endpoint in oncology, this is a signal that the addition of liver-directed therapy (LDT) could lead to oncologic benefit and is worthy of further study.

An important consequence of the improved morphologic response in the DEBIRI arm was the increase in the conversion rate to curative-intent resection or ablation from 8% to 25%. These curative-intent procedures can lead to substantial gains in PFS and OS. Colorectal liver metastases treated with DEBIRI have shown similar rates of downstaging.[6] The current study does not state if these subjects were censored in the survival analysis at the time of surgery or ablation. If not, the survival outcomes reported are skewed by the subsequent curative interventions.

Estimates of survival are imprecise from such an underpowered sample size. PFS and OS in both arms had overlapping 95% confidence intervals measured in years.

First Received: 18 May 2022
Accepted: 20 May 2022
Published Online: 12 June 2022

M. C. Soulen, MD
e-mail: Michael.soulen@pennmedicine.upenn.edu

No conclusion of superiority is justified, but the data provide a basis for powering a larger study to better estimate efficacy.

A few relevant inconsistencies and details are missing in this report. The manuscript is described as multicenter, with four institutions represented in the authorship, but, in the Methods, patient selection is attributed to a single tumor board. The distribution of subjects among institutions should be reported to assure generalizability of the results. DEBIRI was not standardized in the protocol. Two drug-eluting embolic products were used, with different kinetics of irinotecan delivery and toxicity profiles, but only one is described in the Methods. Furthermore, the number of subjects treated and the outcome with each device are not reported. Microsphere size was not standardized and no methods are described for size selection. Additionally, the authors describe treating in a lobar fashion, instead of tailoring treatment to the site of disease. Prior studies in colorectal liver metastases treated with DEBIRI demonstrated statistically significant improvement in survival, both with smaller beads and when beads were delivered selectively.[7] Two patients did not receive the target DEBIRI dose due to vascular changes induced by bevacizumab; however, there is no mention of bevacizumab in the protocol, indicating that the systemic therapy was also not standardized.

Adding TACE to systemic chemotherapy may provide incremental benefit but there is no expectation of synergy. In contrast, radioembolization could benefit from the potent radiosensitizing properties of gemcitabine and platinum compounds. The multicenter phase II MISPHEC trial of gemcitabine-based chemotherapy plus radioembolization had an objective response rate by RECIST of 41%, median PFS of 14 months, and OS of 22 months [8]. Nine of 41 subjects (22%) were downstaged to surgery, with eight achieving R0 resection. These data are promising but no randomized trials of chemotherapy ± TARE have been reported as yet.

The authors are to be congratulated for executing this trial. It is difficult to accrue to trials of this design when the experimental therapy is available off-study. The SIRCCA trial of chemotherapy ± TARE failed for this reason. LDT trials in first-line are also challenged by intense competition from new systemic drug regimens. We believe that the appropriate conclusion of this study is that the addition of LDT does not compromise standard-of-care first-line systemic therapy in this disease. We look forward to a subsequent report validating the efficacy of integrating DEBIRI in the first line for intrahepatic cholangiocarcinoma.

DISCLOSURE Michael Soulen has received research support from Guerbet, Sirtex, and Pfizer, and has acted as a consultant for Guerbet, Genetech, and Astra Zeneca. Sarah White has undertaken a consulting role for Guerbet, Cook, and BD; is a member of the speaker's bureau for Penumbra; is a member of the Advisory board for Astra Zeneca and Guerbet; and has received research support from Guerbet, Insightec.

REFERENCES

1. Martin RCG II, Simo KA, Hansen P et al. Drug-Eluting Bead, Irinotecan Therapy of Unresectable Intrahepatic Cholangiocarcinoma (DELTIC) with concomitant systemic gemcitabine and cisplatin. *Ann Surg Oncol*. 2022. https://doi.org/10.1245/s10434-022-11932-3
2. Valle J, et al. Cisplatin plus gemcitabine versus gemcitabine for biliary tract cancer. *N Engl J Med*. 2010;362:1273–81.
3. Schroff RF, Javle MM, Xiao L, et al. Gemcitabine, cisplatin and nab-paclitaxel for the treatment of advanced biliary tract cancers: a phase II clinical trial. *JAMA Oncol*. 2019;5(6):824–30.
4. Mosconi C, Solaini L, Vara G, Brandi N, Cappelli A, Modestino F, et al. Transarterial chemoembolization and radioembolization for unresectable intrahepatic cholangiocarcinoma: a systemic review and meta-analysis. *Cardiovasc Intervent Radiol*. 2021;44(5):728–38.
5. Edeline J, Lamarca A, McNamara MG, Jacobs T, Hubner RA, Palmer D, et al. Locoregional therapies in patients with intrahepatic cholangiocarcinoma: a systematic review and pooled analysis. *Cancer Treat Rev*. 2021;99:102258.
6. Martin RCG II, Scoggins CR, Tomlty D, et al. Irinotecan drug-eluting beads in the treatment of chemo-naive unresectable colorectal liver metastasis with concomitant systemic fluorouracil and oxaliplatin: results of pharmacokinetics and phase I trial. *J Gastrointest Surg*. 2012;16:1531–8.
7. Ngo A, von Stempel C, Corbo B, et al. Transarterial chemoembolisation of colorectal liver metastases with irinotecan-loaded beads: a bi-institutional analysis of 125 treatments in 53 patients. *Cardiovasc Intervent Radiol*. 2019;42:979–90.
8. Edeline J, Touchefeu Y, Guiu B, et al. Radioembolization plus chemotherapy for first-line treatment of locally advanced intrahepatic cholangiocarcinoma: a phase 2 clinical trial. *JAMA Oncol*. 2020;6:51–9.