Five Must-Read Interventional Oncology Publications From the Last Year

BY SUVRANU "SHOEY" GANGULI, MD

SIRFLOX: Randomized Phase III Trial Comparing First-Line mFOLFOX6 (Plus or Minus Bevacizumab) Versus mFOLFOX6 (Plus or Minus Bevacizumab) Plus Selective Internal Radiation Therapy in Patients With Metastatic Colorectal Cancer

van Hazel GA, Heinemann V, Sharma NK, et al. J Clin Oncol. 2016;34:1723–1731.

SUMMARY/TAKE-AWAY POINTS

This multicenter international study randomized patients with metastatic colorectal cancer (mCRC) between first-line systemic chemotherapy alone and first-line systemic chemotherapy combined with yttrium-90 (Y-90) resin microspheres. Eligible patients with nonresectable liver-only or liver-dominant mCRC and no prior systemic chemotherapy were randomized 1:1 between both arms.

The control arm consisted of mFOLFOX6 (leucovorin calcium [folinic acid], fluorouracil, and oxaliplatin) plus/minus bevacizumab (investigator's discretion), and the treatment arm consisted of the same regimen with a single, whole-liver dose of SIR-Sphere Y-90 resin microspheres (Sirtex Medical Inc.) administered on day 3 or 4 of either cycle 1 or 2.

Five hundred thirty patients were randomized, and the results showed no statistically significant difference in progression-free survival at any site between the two arms (median, 10.2 vs 10.7 months; $P = .43$). However, with the addition of Y-90 microspheres, there was a statistically significant 7.9-month improvement in median progression-free survival in the liver (12.6 vs 20.5 months; $P = .002$).

Objective response rates (complete + partial response) were not statistically significantly different at any site but were statistically significantly improved in the liver (68.8% vs 78.7%; $P = .042$). Grade 3 or higher adverse events slightly increased in the mFOLFOX plus Y-90 arm, including a 3.7% incidence of gastric or duodenal ulcers.

WHY THIS ARTICLE IS IMPORTANT

This is the first large, phase 3, randomized controlled trial evaluating a liver-directed therapy. Liver metastases are the dominant site of disease and dominant cause of death in mCRC. In this study, using Y-90 in addition to standard first-line chemotherapy in patients with liver-dominant metastases improved median progression-free survival in the liver.

The addition of Y-90 had no negative impact on the duration of systemic chemotherapy, and toxicities were acceptable and predicted. This study continues to validate Y-90 as a viable treatment option for mCRC patients and supports its use earlier in the treatment algorithm, away from its traditional use in heavily pretreated patients and/or in the salvage setting.

Questions related to the overall impact on survival cannot be answered by the results of this study alone, and the data from this trial will be combined with two other trials (FOXFIRE and FOXFIRE Global), which have already finished, providing an aggregate of more than 1,100 patients. With this large aggregate number of patients, the power to determine statistical differences in overall survival will hopefully be identified. We are eagerly expecting these data to be analyzed and reported in 2017.

Randomized Trial of Hepatic Artery Embolization for Hepatocellular Carcinoma Using Doxorubicin-Eluting Microspheres Compared With Embolization With Microspheres Alone

Brown KT, Do RK, Gonen M, et al. J Clin Oncol. 2016;34:2046–2053.

SUMMARY/TAKE-AWAY POINTS

This single-center, prospective study randomized patients with hepatocellular carcinoma (HCC) between bland embolization (Bead Block, Biocompatibles UK Ltd.) and transarterial chemoembolization (TACE) with drug-eluting beads (DEB-TACE; LC Bead, Biocompatibles UK Ltd.). Patients had a diagnosis of locally advanced HCC and a bilirubin level < 3 mg/dL. Portal vein invasion at any level was permitted as long as liver function was preserved. Patients could also have limited extrahepatic disease.

Both treatment arms consisted of embolization with 100- to 300-µm particles, and if stasis was not achieved after the particles were administered, increasingly larger sizes of particles were administered until stasis was achieved in the target vessel. Doxorubicin 150 mg was used for the microspheres in the DEB-TACE arm. Of 101 randomized patients, 92 patients underwent a total of 209 embolizations during the entire study (median, 2).

Postembolization syndrome was common in both arms (88% of bland embolization and 84% of DEB-TACE patients), and adverse events were similar in both groups. There was no difference in response rate or progression-free survival between the two groups. Median overall survival was 19.6 months for bland embolization and 20.8 months for DEB-TACE ($P = .64$).

WHY THIS ARTICLE IS IMPORTANT

Conventional TACE has been accepted as the standard of care for locally advanced HCC embolization based on two randomized studies from 2002, in which TACE with doxorubicin was evaluated against best supportive care, each with a relative small number of patients. Although there was a bland embolization arm in one of the studies, the study was not powered to determine the effectiveness of bland embolization when compared to best supportive care. This study questions the long-standing assumption that the chemotherapy has an added benefit to the embolization component of TACE and that bland embolization is inferior to conventional TACE or DEB-TACE.

The superiority of any one liver-directed therapy for HCC has not been demonstrated in past head-to-head studies. Although a subset analysis in previous studies may have shown better tolerability and response of DEB-TACE versus conventional TACE, overall survival has never been proven superior with any one method. This study was well designed to isolate the effect of doxorubicin, given that the sole difference between the two arms was the addition of doxorubicin to the microspheres. This study adds to the evidence that chemoembolization is not more effective than embolization alone. Early reports of systemic doxorubicin failed to demonstrate efficacy for the treatment of HCC.

It is worth noting that this study did not show that bland embolization was superior to DEB-TACE either, including in postembolization syndrome or adverse events. Therefore, although the argument can be made that adding doxorubicin to bland embolization does not bring any benefits, it also does not appear to have any disadvantages.

Randomized Controlled Trial of Irinotecan Drug-Eluting Beads With Simultaneous FOLFOX and Bevacizumab for Patients With Unresectable Colorectal Liver-Limited Metastasis

Martin RC 2nd, Scoggins CR, Schreeder M, et al. Cancer. 2015;121:3649–3658.

SUMMARY/TAKE-AWAY POINTS

Similar to the previously mentioned SIRFLOX study, this multicenter study was also a randomized controlled trial evaluating patients with mCRC and the combination of a liver-directed therapy with first-line systemic chemotherapy. Patients were eligible if they had unresectable mCRC with no prior systemic chemotherapy and liver-dominant disease (defined as > 80% of the tumor body burden confined to the liver but < 60% of the liver replaced by tumor).

The control arm received mFOLFOX6 and bevacizumab alone, and the treatment arm received mFOLFOX and bevacizumab combined with irinotecan drug-eluting beads (FOLFOX-DEBIRI), which were delivered on days 7 and 21. Treatment was administered via a lobar approach

on the basis of the extent and distribution of the disease. The number of treatments was determined by the physician after reevaluation and imaging after the four cycles of FOLFOX and two DEBIRI treatments, based on the degree of response, tolerance of combination therapy, and quality of life. Irinotecan was loaded into DEBIRI (100–300 µm; LC/DC Bead, Biocompatibles UK Ltd.) at 50 mg/mL for a total dose of 100 mg per vial, with up to one vial administered during each treatment.

After 10 patients were treated with FOLFOX-DEBIRI to assess safety, as mandated by the US Food and Drug Administration, 60 patients were randomized into the two groups. It is worth noting that there was a statistically significant worse overall performance status in the treatment group as compared with the control group (Eastern Cooperative Oncology Group performance status of 1 or 2, 56% vs 32%, respectively; $P = .04$), as well as a greater incidence of patients with liver-dominant disease (ie, the presence of extrahepatic disease) versus liver-only disease (55% vs 31%, respectively; $P = .05$).

Forty patients in the treatment arm underwent a total of 115 DEBIRI treatments, with a median of four DEBIRI treatments. There was a significantly greater incidence of grade 3/4 toxicities in the treatment arm, predominantly because of device-related serious adverse events. After a median follow-up of 19 months, the overall response rate was statistically significant at 2 ($P = .01$), 4 ($P = .03$), and 6 months ($P = .05$) in the treatment arm versus the control arm. There was a statistically significant improvement in liver progression-free survival in the treatment group (median, 17 months [range, 12–23 months]) compared with the control group (median, 12 months [range, 11–24 months]; $P = .05$). Overall extrahepatic progression-free survival was similar in the two groups.

WHY THIS ARTICLE IS IMPORTANT

Although the patient population was not as large as the SIRFLOX trial, this is a well-designed prospective, multicenter, randomized controlled trial evaluating a liver-directed therapy, something the interventional oncology field continues to require. This study showed that using DEBIRI in addition to standard first-line chemotherapy in patients with liver-dominant metastases improved median progression free-survival in the liver, as well as the overall response rate.

This study also showed that a liver-directed therapy, such as DEBIRI, could be given concurrently with systemic chemotherapy, with acceptable toxicities and adverse events. There was no negative impact on the ability to administer systemic chemotherapy with the addition of DEBIRI, as the median number of chemotherapy cycles was similar between both arms. This study helps support using liver-directed therapy earlier in the treatment algorithm for mCRC patients. The authors also established a simplified DEBIRI technique, which does not require specialized centers, but instead can be performed in both community and academic facilities safely and effectively.

Oncogenesis: An "Off-Target" Effect of Radiofrequency Ablation

Rozenblum N, Zeira E, Scaiewicz V, et al. Radiology. 2015;276:426–432.

SUMMARY/TAKE-AWAY POINTS

This study reported a laboratory experiment assessing HCC development after radiofrequency ablation (RFA), partial surgical hepatectomy, and a sham operation in a mouse model. It also assessed ways to inhibit HCC recurrence after RFA. Tumor load, tumor frequency, and survival of MDR2 knockout mice (an inflammation-induced HCC model) were compared between groups that underwent RFA, 35% partial hepatectomy (ie, left lobectomy), or a sham operation (controls). In this model, tumors develop and are scattered throughout the entire liver by 12 months because all the hepatocytes bear the knockout. Tumor load and tumor incidence were also evaluated in mice treated with a c-Met inhibitor after RFA.

Twenty-one MDR2 knockout mice were separated into the three groups (seven mice per group). A 6-month survival assay was performed. The RFA group showed increased tumor load ($P = .007$) and reduced survival ($P = .03$) compared to controls. The partial hepatectomy group also showed increased tumor load and decreased survival, with no difference between the RFA group and partial hepatectomy group. There was significant elevation of hepatocyte proliferation after RFA in the distant liver (ablated lobe, $P = .003$; untreated lobe, $P = .02$). A c-Met inhibitor significantly attenuated HCC development in MDR2 knockout mice treated with RFA ($P = .001$).

WHY THIS ARTICLE IS IMPORTANT

In this study, RFA-induced liver regeneration promoted tumorgenesis in a mouse model assessing HCC. This reinforces a phenomenon that is often identified in clinical practice, in which ablation of one focus or multiple foci of HCC or liver metastases causes nontreated and often unidentified foci to blossom, remote to the treated area. There is a potential oncogenic effect to RFA, and this study links HCC recurrence after ablation to the process of liver regenera-

tion that occurs after ablation. The study identifies that untreated HCC foci may respond to cytokines and growth factors that are released during the wound-healing process after ablation.

The study also identified that liver regeneration induced by RFA facilitates c-Met/hepatocyte growth factor axis–dependent HCC tumor formation and that blockage of the c-Met/hepatocyte growth factor axis attenuates HCC recurrence. This raises the possibility for therapeutic intervention to reverse this potentially tumorigenic effect. A combined therapeutic modality of ablation with concurrent administration of a c-Met inhibitor could potentially inhibit HCC recurrence or the growth of untreated distant metastases after thermal ablation treatment.

Radiofrequency Ablation (RFA) Combined With Chemotherapy for Unresectable Colorectal Liver Metastases (CRC LM): Long-Term Survival Results of a Randomized Phase II Study of the EORTC-NCRI CCSG-ALM Intergroup 40004 (CLOCC)

Ruers T, Punt CJ, Coevorden FV, et al. Ann Oncol. 2015;26(suppl 4):iv108–iv116.

SUMMARY/TAKE-AWAY POINTS

This study, which was presented as an abstract at the 2015 American Society of Clinical Oncology meeting and is not yet published, evaluated the benefit of combining systemic chemotherapy with RFA in patients with unresectable mCRC (up to nine hepatic lesions and without extrahepatic disease). Overall survival at 30 months and progression-free survival results were previously reported (*Ann Oncol.* 2012;23:2619–2126), but this study now reports overall survival after a long-term median follow-up of 9.7 years.

Between 2002 and 2007, 119 patients were randomized between first-line systemic chemotherapy (6 months FOLFOX ± bevacizumab) or first-line systemic chemotherapy plus RFA. In the systemic chemotherapy plus RFA arm, subsequent resection was facilitated in 27 (45%) patients. Only six patients in the systemic chemotherapy arm eventually underwent hepatic resection. At 30 months, the overall survival rate was 61.7% for combined treatment and 57.6% for systemic chemotherapy alone. At a median follow-up of 9.7 years, 92 deaths were reported (53 for systemic chemotherapy alone and 39 for systemic chemotherapy plus RFA). There was a significant difference in overall survival in favor of systemic chemotherapy plus RFA ($P = .01$). Observed median overall survival was 45.6 months in the systemic chemotherapy plus RFA arm as compared with 40.5 months in the systemic chemotherapy arm.

WHY THIS ARTICLE IS IMPORTANT

This multicenter study prospectively investigated the efficacy of systemic chemotherapy plus RFA in patients with unresectable mCRC to the liver. The 30-month overall survival was previously reported in 2010, but this study now reports on long-term survival of this well-designed phase 2 study. Overall survival was determined with a strong median follow-up of 9.2 years. It was clear that unresectable liver metastases treated with RFA plus chemotherapy improved long-term overall and progression-free survival by 5.1 months compared with chemotherapy alone in patients with mCRC. This study further demonstrates the utility of liver-directed therapy in unresectable mCRC, warranting further multidisciplinary adjudication for liver-directed and cytoreductive strategies.

This study, along with the previously mentioned two studies evaluating resin Y-90 microspheres and DEBIRI, showed a benefit of combining a liver-directed therapy with first-line systemic chemotherapy for liver-dominant and liver-confined mCRC. This study has the benefit of long-term overall survival, which the other studies do not have. Clearly, adding liver-directed therapies earlier in the treatment regimen of mCRC is showing a benefit with multiple modalities, and this will hopefully change future guidelines and current practice patterns. However, comparing these different approaches will not be easy, and additional factors will need to be considered aside from efficacy and overall survival, including costs, side effects, adverse events, quality of life, and availability. ■

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