

Five Must-Read Interventional Oncology Publications From the Last Year

BY SUVRANU "SHOEY" GANGULI, MD, FSIR

Y90 Radioembolization Significantly Prolongs Time to Progression Compared With Chemoembolization in Patients With Hepatocellular Carcinoma

Salem R, Gordon AC, Mouli S, et al. *Gastroenterology*. 2016;151:1155–1163.e2.

SUMMARY/TAKE-AWAY POINTS

This article reports the results of an investigator-initiated, open-label, single-center, phase 2, prospective, randomized study evaluating conventional transarterial chemoembolization (cTACE) and transarterial radioembolization (TARE) with yttrium-90 (Y-90) for hepatocellular carcinoma (HCC). cTACE was performed with 75 mg/m² (maximum, 150 mg/m²) of doxorubicin, with the drug/Lipiodol (Guerbet LLC) combination followed by embolic microspheres (Embospheres, Merit Medical Systems, Inc.). TARE was performed with glass microspheres (TheraSphere, BTG International) using a 120-Gy dose to the treated area. Over 7 years, 45 patients were randomized (24 patients to TARE and 21 patients to cTACE). The study was halted because of slow accrual and competing studies. The study evaluated time to progression (TTP), evaluated by intention-to-treat analysis. Secondary outcomes included safety, rate of response, and Kaplan-Meier survival time.

Patients in the TARE group had significantly longer median TTP than patients in the cTACE group

(> 26 vs 6.8 months, respectively; $P = .0012$) (hazard ratio [HR], 0.122; 95% confidence interval [CI], 0.027–0.557; $P = .007$). A significantly greater proportion of patients in the cTACE group developed diarrhea or hypoalbuminemia than those in the TARE group (21% vs 0%; $P = .031$ and 58% vs 4%; $P < .001$; respectively). There was a trend for more fatigue with TARE ($P = .08$). Toxicities and complications were otherwise similar. Response to therapy was similar in each group ($P = .433$). Median survival time (censored to liver transplantation) was 17.7 months for the cTACE group as compared with 18.6 months for the TARE group ($P = .99$).

WHY THIS ARTICLE IS IMPORTANT

There are no randomized studies between TACE and TARE for HCC, and this study strives for respectable level 1 evidence on the topic, with interesting results. The significant difference in TTP between the TARE (> 26 months) and the cTACE (6.8 months) groups is striking, with apparently less overall side effects. This lends credence to the idea that a single TARE proce-

ture may provide the same local treatment effect as required by multiple TACE procedures, which becomes more important in cost-conscious medicine. Also interesting is that longer TTP did not translate to increased overall survival (OS), suggesting that local control (as an isolated variable) is insufficient for survival improvement, something that appears to be borne out in other interventional oncology (IO), liver-directed randomized studies. There are multiple, apparent limitations of this study, including the small number of patients in each

arm followed over a long period of time, the halting of the study due to slow accrual at a single-center institution, and the fact that cTACE was utilized rather than drug-eluting bead TACE. However, TARE is not currently listed in staging/treatment classifications for HCC, such as the Barcelona Clinical Liver Cancer staging classification, given the lack of randomized data. This phase 2 study lays the groundwork for a phase 3 study and possibly signals the beginning of a shift from TACE to TARE as the default treatment for unresectable HCC.

Tremelimumab in Combination With Ablation in Patients With Advanced Hepatocellular Carcinoma

Duffy AG, Ulahannan SV, Makorova-Rusher O, et al. *J Hepatol.* 2017;66:545–551.

SUMMARY/TAKE-AWAY POINTS

This study evaluated whether the immune checkpoint inhibitor tremelimumab, a fully human monoclonal antibody that binds to cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) on the surface of activated T lymphocytes, could be combined safely and feasibly with ablation or chemoembolization for advanced HCC. Ablative therapies are known to induce a peripheral immune response, which may enhance the effect of anti-CTLA-4 treatment. Patients were given tremelimumab at two dose levels (3.5 and 10 mg/kg) every 4 weeks for six doses, followed by three monthly infusions until off-treatment criteria were met. On day 36, patients underwent subtotal ablation or chemoembolization. Staging was assessed by contrast-enhanced CT or MRI every 8 weeks. The primary objective was feasibility, and secondary objectives included a variety of immunologic parameters to determine if there was an immune response to treatment and to assess safety, toxicity, and preliminarily efficacy.

Thirty-two patients with HCC were enrolled. No dose-limiting toxicities were encountered, and the most common toxicity was pruritus. Nineteen patients were considered evaluable (as they had lesions outside of the areas treated with ablation or TACE), and of these, a confirmed partial response was achieved in five patients (26.3%; 95% CI, 9.1%–51.2%). Twelve of 14 patients with quantifiable hepatitis C virus experienced a marked reduction in viral load. All study patients with evaluable material (n = 12) showed immune cell infiltration within the tumors. For this refractory HCC population, the probability of tumor progression-free

survival (PFS) at 6 and 12 months was 57.1% and 33.1%, respectively, and median time to tumor progression was 7.4 months (95% CI, 4.7–19.4 months). Median OS was 12.3 months (95% CI, 9.3–15.4 months).

WHY THIS ARTICLE IS IMPORTANT

This article is the first published study combining immune checkpoint inhibition (immunotherapy) with IO techniques, an area that will grow in interest and data tremendously in the near future. Previous studies have shown that IO techniques can result in immune system activation. The immune system can potentially recognize and kill cancer cells that are left behind after IO therapies, as well as cancer cells remote to the treatment area. Immune checkpoint inhibitors can enhance this effect. This pilot study combined immune checkpoint inhibition with subtotal ablation or TACE in patients with advanced HCC, demonstrating intriguing clinical activity. Positive activity was seen with reduction in hepatitis C virus viral load and accumulation of intratumoral CD8+ T cells. Objective tumor responses were also identified outside of the ablated or embolized zone, with durable responses observed (partial responses lasted 7, 8, 9, 9, and 19 months). The combination was also well tolerated overall. The question remains of whether the IO procedure contributed to the efficacy seen. Is the immune system further activated due to the cellular disruption and necrosis from IO therapies, which in turn increases the treatment response; or is the immune checkpoint inhibition alone sufficient for clinical benefit? A randomized study will be needed to answer this question.

Ablation of Locally Advanced Pancreatic Cancer With Percutaneous Irreversible Electroporation: Results of the Phase I/II PANFIRE Study

Scheffer HJ, Vroomen LG, de Jong MC, et al. Radiology. 2017;282:585–597.

SUMMARY/TAKE-AWAY POINTS

This phase 1/2 prospective study from the Netherlands investigated the safety of percutaneous irreversible electroporation (IRE) for locally advanced pancreatic cancer. Thermal ablative techniques have been limited in pancreatic cancer given the high morbidity and mortality associated with thermal damage to bile ducts and vessels. IRE is based on the pulsatile application of electric energy delivered between two electrodes. The electric pulses change the existing cellular membrane potential, resulting in nanoscale defects in the lipid bilayer of the membrane, which disrupts cellular homeostasis and leads to apoptosis. Theoretically, IRE destroys all cells within the ablation zone but—owing to the primarily nonthermal mechanism—leaves supporting extracellular matrix structures unaffected.

Safety, quality of life (QOL), pain perception, and efficacy in terms of time to local progression, event-free survival, and OS were evaluated. Pain perception and QOL were evaluated using specific questionnaires. Twenty-five patients with histologically proven locally advanced pancreatic cancer (≤ 5 cm) were prospectively included to undergo percutaneous IRE using CT guidance. The median largest tumor diameter was 4 cm (range, 3.3–5 cm). After a median follow-up of 12 months, median event-

free survival after IRE was 8 months, and the median time to local progression after IRE was 12 months. Median OS was 11 months from IRE and 17 months from diagnosis. There were 12 minor complications and 11 major complications in 10 patients. There were no deaths within 90 days after IRE.

WHY THIS ARTICLE IS IMPORTANT

Although IRE is clinically used and sold in practice, high-quality data of this new IO ablation tool from prospective or comparative trials are lacking in the literature. As a result, there are no uniform treatment protocols available or data for proper indications and contraindications for use, so proper patient selection is difficult. This phase 1/2 study begins to answer these questions and in an area IO therapies are not currently standard of care—advanced pancreatic cancer. The investigators concluded that percutaneous IRE for locally advanced pancreatic cancer is generally well tolerated, although major adverse events can occur. The preliminary survival data are encouraging and support the setup of larger phase 2 and 3 clinical trials to assess the efficacy of IRE plus chemotherapy in the neoadjuvant and adjuvant or second-line setting compared with more widely adopted regimens such as chemotherapy and/or radiation therapy.

Irreversible Electroporation Versus Radiofrequency Ablation: A Comparison of Local and Systemic Effects in a Small-Animal Model

Bulvik BE, Rozenblum N, Gourevich S, et al. Radiology. 2016;280:413–424.

SUMMARY/TAKE-AWAY POINTS

This article compared both periablational and systemic effects of thermal radiofrequency ablation and electroporative ablation with IRE in animal models. The goal was to characterize local changes in the ablation and periablation zones, their effects on liver regeneration and cytokine and growth factor production, and their effects on both tumor formation and growth of remote untreated tumors in these animal models. Female C57BL/6 mice ($n = 165$) were randomized to

either radiofrequency or IRE ablation of noncancerous normal liver. The inflammatory response, cell proliferation, interleukin-6 (IL-6) levels, and intactness of vessels in the liver were assessed at 6, 12, and 24 hours and at 3, 7, and 14 days after ablation. Systemic effects were assessed by comparing tumor formation in an MDR2 knockout (KO) mouse model ($n = 15$) and tumor growth in a remote BNL 1ME hepatoma xenograft tumor ($n = 28$). Results were averaged and evaluated by using two-tailed t tests.

Radiofrequency ablation was associated with a well-defined periablational inflammatory rim; however, the infiltrate penetrated the ablation zone for IRE, and this was seen largely along persistently patent vessels. Compared with baseline, peak IL-6 levels for IRE and radiofrequency ablation were 10 and three times higher, respectively ($P < .03$). More tumors formed (≥ 3 mm) in MDR2 KO mice treated with IRE than mice treated with radiofrequency ablation or sham operation. Both radiofrequency ablation and IRE reduced tumor growth in BNL 1ME tumors, but IRE had a greater effect, which was accompanied by more infiltrating lymphocytes compared with sham operation.

Because IRE preserved the patency of the vasculature within the coagulated zone, an increase in infiltrative cells was identified that was associated with a higher serum IL-6 level than radiofrequency ablation. IRE also induced greater systemic effects, including distant tumorigenesis.

WHY THIS ARTICLE IS IMPORTANT

We are still trying to understand what happens on the cellular level after our IO treatments, and we are becom-

ing more aware of potential systemic effects from what have previously been considered focal ablative treatments. Moreover, it is becoming apparent that different energy sources have varied effects beyond the local ablation margin. This article shows that there are distinct cellular differences in the tissue injury pattern between radiofrequency ablation and IRE. IRE resulted in greater cytokine expression, local inflammation, and increased cellular recruitment, with higher systemic release of IL-6, which can lead to increased angiogenesis and subsequent tumorigenesis. IRE also had more distant tumorigenesis in these tumor models. Compared with radiofrequency ablation, hepatic IRE simulated growth of HCC tumors in MDR2 KO mice and led to growth reduction in distant BNL 1ME tumors. The persistent patency of vasculature within the coagulated zone from IRE, something not seen in other thermal ablative technologies, may play a role in the presence of these effects. These findings highlight that differences exist between various ablation modalities already in clinical use. Further understanding of these underlying mechanisms and their impact will be required for proper selection of given ablation tools for specific clinical scenarios.

Overall Survival Analysis of the FOXFIRE Prospective Randomized Studies of First-Line Selective Internal Radiotherapy (SIRT) in Patients With Liver Metastases From Colorectal Cancer

Sharma RA, Singh Wasan H, Van Hazel GA, et al. *J Clin Oncol*. 2017;35(suppl):3507.

SUMMARY/TAKE-AWAY POINTS

The FOXFIRE, SIRFLOX, and FOXFIRE Global (FF-SF-FFG) prospective randomized studies evaluated the efficacy of combining first-line chemotherapy for metastatic colorectal cancer (mCRC) with selective internal radiotherapy (SIRT) using Y-90 resin microspheres in patients with liver metastases. Chemotherapy-naïve mCRC patients with liver metastases not suitable for curative resection/ablation were randomized 1:1 to either oxaliplatin-based chemotherapy (mFOLFOX6/OxMdG) plus/minus an investigator-chosen biologically targeted agent (arm A) or the same systemic therapy (oxaliplatin dose modification) plus a single treatment of SIRT with cycle 1/2 of chemotherapy (arm B). Primary tumor in situ and/or limited extrahepatic metastases were permitted. The primary endpoint was OS, and secondary outcomes included toxicity and safety, PFS, liver-specific PFS, and response rate.

Between 2006 and 2014, 1,103 patients were randomized in 14 countries. Median follow-up was 43.3 months. There was no difference in OS (HR, 1.04; 95% CI, 0.90–1.19; $P = .609$) or PFS (HR, 0.90; 95% CI, 0.79–1.02; $P = .108$). Patients in arm B had significantly more favorable objective response rate ($P = .001$) and liver-specific progression (HR, 0.51, 95% CI 0.43–0.62; $P < .001$), as well as a higher risk of non-liver progression as the first event (HR, 1.98; 95% CI, 1.53–2.58; $P < .001$). Toxicity was higher in arm A, particularly hematologic toxicity. The right-sided primary tumor subset analysis was the only subset analysis that showed a significant treatment effect on OS (HR, 0.67; 95% CI, 0.48–0.92).

WHY THIS ARTICLE IS IMPORTANT

This article represents the largest randomized prospective IO study and builds on the SIRFLOX data that came out 2 years ago, which showed an average 8-month liver PFS benefit when SIRT was added to FOLFOX first-line chemotherapy in patients with liver-only or liver-dominant mCRC. However, despite this significant improvement in liver PFS, the addition of SIRT to FOLFOX first-line chemotherapy in patients with

liver-only or liver-dominant mCRC did not improve OS or PFS at any site. It does validate the local efficacy of radioembolization, as a significant benefit in liver-specific PFS and radiologic response rate was again achieved with the addition of SIRT. One possible explanation for the lack of OS improvement is that patients who received FOLFOX+SIRT were less likely to receive bevacizumab and subsequent postprotocol systemic therapy as compared with the FOLFOX alone group. It is possible that the increased toxicity from adding radioembolization in first-line patients precludes the ability to give as much second-line, third-line, and salvage chemotherapy. It is yet to be determined exactly where radioembolization should be added in the treatment paradigm for mCRC, and these data indicate it might have been ambitious to add it with first-line chemotherapy. The appropriate location is likely after proper patients have been selected after failure on systemic chemotherapy; whether this is after first-, second-, or third-line chemotherapy requires further evaluation. Another interesting finding is that liver metastases from right-sided primary tumors as a subgroup did show an OS benefit when SIRT was added to first-line chemotherapy, which also merits further evaluation. ■

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