TACE-Based Treatment Combinations Effective Against Intermediate-Stage Liver Cancer

People treated with transarterial chemoembolization plus two drug combination lived longer without cancer progression.

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How doctors treat a form of liver cancer called intermediate-stage hepatocellular carcinoma (HCC) is likely to change, based on updated findings from two large clinical trials. Both trials tested a procedure called TACE in combination with immunotherapy drugs and treatments called angiogenesis inhibitors. TACE, or transarterial chemoembolization, involves using a catheter to deliver chemotherapy directly to the liver.

TACE has long been the standard treatment for intermediate-stage HCC, which is when the cancer hasn't spread beyond the liver but can't be removed surgically because of issues like cirrhosis or the size or location of the tumors.

One trial, called LEAP-012, tested TACE in combination with the immunotherapy drug pembrolizumab (Keytruda) and the angiogenesis inhibitor lenvatinib (Lenvima). The other trial, called EMERALD-1, tested TACE plus the immunotherapy drug durvalumab (Imfinzi) and the angiogenesis inhibitor bevacizumab.

Both studies had similar results: Patients treated with TACE plus the two-drug combination lived longer without their cancer coming back or getting worse, a measure called progression-free survival, than those treated only with TACE. In LEAP-012, the median progression free survival was 14.6 months versus 10 months, respectively, and in EMERALD-1 it was 15 months versus 8.2 months.

Findings from both studies were published on January 18 in The Lancet.

The trials had some key differences, explained NCI's Tim Greten, M.D., who studies new treatments for liver cancer but wasn't involved in either study. In EMERALD-01, for instance, TACE could be performed up to four times, but in LEAP-012 it could only be performed twice.

In addition, Dr. Greten noted, patients in both studies haven't been followed long enough to determine if the combination treatments helped them live longer overall. Nevertheless, he said he

expects that oncologists will begin offering more people with intermediate-stage HCC one of these options.

From a patient perspective, “the improvement in progression-free survival is meaningful,” Dr. Greten said.

Treatment of intermediate-stage HCC in a rut

Hepatocellular carcinoma is the most common form of liver cancer. When diagnosed early, it can be successfully treated with surgery or, in the small percentage of patients who are eligible, a liver transplant. About 70% of patients diagnosed with early-stage HCC are still alive after 5 years, and many are thought to be cured.

And there’s been marked progress in treating HCC that has spread, or metastasized, to other parts of the body. Until recently, people diagnosed with metastatic HCC were likely to live for only a few months. Now, due in large part to treatment approaches that combine immune checkpoint inhibitors and angiogenesis inhibitors, survival can be around 2 years and sometimes longer, Dr. Greten said.

But it’s been a different story for intermediate-stage HCC, where there has been little in the way of meaningful advances since TACE was introduced in the early 2000s, explained Josep Llovet, M.D., of the Icahn School of Medicine, the lead investigator on the LEAP-012 trial.

TACE involves inserting a catheter into an artery in the groin and, with guidance from imaging, carefully snaking it up until it reaches the hepatic artery. From there, the catheter is inserted into the liver, and the chemotherapy is delivered. The artery is then blocked for a period to keep the chemotherapy within the liver.

In most people, TACE keeps the cancer in check for less than a year, and the median time people live overall following the treatment is about 2 to 2.5 years, Dr. Llovet said while presenting the trial’s results in September 2024, at the annual meeting of the European Society for Medical Oncology (ESMO).

Despite many attempts, researchers haven’t been able to improve the outcomes of patients with intermediate-stage HCC, explained Angela Lamarca, M.D., Ph.D., a liver cancer researcher at Fundacion Jimenez Diaz University Hospital in Spain.

“We … know that this is an area of unmet need,” Dr. Lamarca said at the ESMO meeting.

Increased progression-free survival with TACE and drug combinations

The LEAP-012 trial enrolled 480 patients and was funded by Merck, which manufactures pembrolizumab and lenvatinib. Patients were randomly assigned to receive TACE alone or TACE

with pembrolizumab and lenvatinib. In the latter group, patients started those treatments up to a month before undergoing their first TACE treatment.

Along with the improvement in progression-free survival seen with TACE and the two-drug combination, there was also an improvement in the percentage of people still alive 2 years after starting treatment: 75% versus 69%.

Nearly all patients who received the drug combination along with TACE had clinically significant side effects, including liver problems and high blood pressure, the research team reported. About 8% of patients in the pembrolizumab–lenvatinib group stopped using both drugs because of side effects, while a somewhat higher proportion stopped only one of the drugs because of side effects.

The EMERALD-1 trial, which enrolled 618 patients, had three treatment groups: TACE alone, TACE combined with the immunotherapy drug durvalumab, and TACE combined with durvalumab and the angiogenesis inhibitor bevacizumab. The trial was funded by AstraZeneca, durvalumab's manufacturer.

Durvalumab was given one week after the first TACE procedure, whereas bevacizumab was not given until 2 weeks after the last TACE treatment. The trial researchers chose that timing because in an earlier study bevacizumab caused serious side effects when used at the same time as TACE, they explained.

TACE combined with durvalumab and bevacizumab improved progression-free survival compared with TACE alone and compared with TACE and durvalumab: 15 months versus 10 months. The findings, the study team wrote, indicate that combining the two drugs "appears to be important" when used with TACE.

Two years after entering the trial, 32% of people in the TACE–durvalumab–bevacizumab group were alive without their cancer getting worse, compared with 25% in the TACE-alone group.

Nearly all patients in the trial had some side effects from treatment, with about 28% stopping treatment at some point because of side effects. In the durvalumab–bevacizumab group, the most common serious side effects were high blood pressure and anemia.

Dr. Lamarca said it was "very, very good news" to have two clinical trials showing improvements in progression-free survival and that the combination approach was something she will likely use in her patients with intermediate-stage HCC. However, she noted that the results "seem to be more robust" for the combination of pembrolizumab and lenvatinib used in the LEAP-012 trial.

Further refining treatment for intermediate-stage HCC

There are still many unknowns about the optimal treatment of intermediate-stage HCC, Dr. Lamarca said. That includes when to perform additional TACE procedures, she continued, a decision "that is very challenging and that [varies] from one institution to another."

There’s also the question of the best timing for using the drug combinations along with TACE, wrote Florian Reiter, M.D., and Andreas Geier, M.D., both of the University Hospital Wurzburg in Germany, in an accompanying editorial in The Lancet.

Some trials are testing giving these drug combinations “well before TACE,” Drs. Reiter and Geier wrote, “reserving the use of TACE only for patients” whose cancer starts to progress after completing treatment with both drugs.

Although TACE is the standard treatment for intermediate-stage HCC at most hospitals, at some large cancer centers, Dr. Greten explained, a similar catheter-based treatment called TARE is often used. With TARE, beads filled with a radioactive compound instead of chemotherapy drugs are delivered directly into the tumor.

The procedure is usually reserved for people who have small tumors, he cautioned, and there’s no evidence that it helps patients live longer than those treated with TACE.

Ongoing clinical trials are testing TACE and TARE in combination with other immunotherapy drugs and targeted therapies. AstraZeneca, for example, is conducting a trial called EMERALD-Y90 that is testing TARE using a radioactive compound called Yttrium 90 combined with durvalumab and bevacizumab.

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