Checkpoint Combination May Slow Liver and Biliary Tract Cancer

Seventy percent of liver cancer patients had either a partial response or stable disease.

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A combination of two immune checkpoint inhibitors, Imfinzi (durvalumab) and tremelimumab, appeared to slow progression of advanced liver and biliary tract cancer in a small study, researchers reported at the 2019 Gastrointestinal Cancers Symposium this month in San Francisco. However—as seen in other studies of immunotherapy for these cancers—the overall response rates are low.

Over years or decades, chronic hepatitis B or C, heavy alcohol use, fatty liver disease and other causes of liver injury can lead to the development of hepatocellular carcinoma (HCC), the most common type of primary liver cancer. HCC is often detected late and is hard to treat. Liver cancer does not respond well to traditional chemotherapy. Targeted therapy—including the standard first-line therapy, Nexavar (sorafenib)—and immunotherapy show some promise, but a majority of patients do not respond and mortality remains high. Biliary tract cancer, involving the gallbladder or bile ducts, is even more difficult to treat.

Charalampos Floudas, MD, and colleagues from the National Cancer Institute evaluated a combination of two immune checkpoint inhibitors in people with advanced liver or biliary tract cancers.

Imfinzi is a monoclonal antibody that blocks the PD-L1 protein on cancer cells. PD-1 is an immune checkpoint on T cells that helps regulate immune function. Some tumors can hijack PD-1 to turn off immune responses against them. Drugs that block the interaction between PD-1 and PD-L1, its binding partner, can release the brakes and restore T-cell activity. Tremelimumab, which is not yet approved by the Food and Drug Administration, blocks CTLA-4, a different immune checkpoint that suppresses T-cell multiplication. It is in the same drug class as the approved medication Yervoy (ipilimumab).

This study included 10 people with HCC and 12 with biliary tract cancers that could not be surgically removed or treated locally. Most were men and the median age was about 63. Seven of the liver cancer patients had hepatitis C; one had hepatitis B. Most had compensated liver disease, or well-preserved liver function. A quarter had cancer that had metastasized, or spread beyond the liver or biliary tract. They had previously tried, or been offered and refused, at least one prior

therapy.

Participants were treated with Imfinzi plus tremelimumab for four monthly cycles, followed by Imfinzi alone once monthly until disease progression or unacceptable side effects occurred. They received CT scans every eight weeks to monitor tumor response or progression.

Two people with liver cancer (20.0 percent) and one person with biliary tract cancer (8.3 percent) achieved partial responses; there were no complete responses. In addition, five HCC patients (50.0 percent) and five biliary tract cancer patients (41.7 percent) had stable disease. Adding these numbers, the researchers reported disease control rates of 70.0 percent for HCC and 50.0 percent for biliary tract cancer. These rates reflect the number of people who did not progress, but there's no way to know whether an individual with stable disease was helped by the treatment or would not have progressed anyway.

For the liver cancer group, the median progression-free survival (PFS)—meaning patients were still alive without worsening of disease—was 7.8 months and the median overall survival (OS) was 15.9 months. This is similar to the median OS in the CheckMate 040 study of the PD-1 checkpoint inhibitor Opdivo (nivolumab) and slightly longer than the median OS of 12 to 14 months in a study comparing the first-line targeted therapies Nexavar and Lenvima (lenvatinib). The biliary tract cancer group did not fare as well, with a median PFS of 3.1 months and median OS of only 5.45 months.

Treatment was safe and generally well tolerated. Three people (13.6 percent) had severe (grade 3 or higher) adverse events.

Based on these findings, the researchers concluded, "Combined immune checkpoint inhibition with Imfinzi and tremelimumab is well tolerated and demonstrates promising activity in patients with advanced HCC and biliary tract cancer."

In addition to its small size, a limitation of this study is that it did not include a comparison group that used Imfinzi alone, so it is unclear how much tremelimumab contributed to efficacy. This question is being studied in the Phase III HIMALAYA trial, in which people with previous untreated inoperable liver cancer will be randomly assigned to receive Imfinzi alone, Nexavar alone or one of two regimens combining Imfinzi and tremelimumab.

Click here to read the study abstract.

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