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NOS inhibitor plus taxane promising for resistant triple negative breast cancer
By Marilynn Larkin

NEW YORK (Reuters Health) - In patients with local or metastatic chemoresistant triple-negative breast cancer (TNBC), the novel nitric oxide synthase (NOS) inhibitor L-NMMA (NG-monomethyl-L-arginine) combined with a taxane induced responses in a phase 1/2 trial.

"We identified the inducible nitric oxide pathway as a potential target several years ago by sequencing the residual cancers from breast cancer patients who did not respond to chemotherapy," Dr. Andrew Chung of Houston Methodist told Reuters Health by email. "Through a series of experiments in small animals, we established the mechanism of action and combination, and took this novel first-in-class molecule to completion of the phase 2 study."

"While we expected changes in immune cells in circulation and on the immune microenvironment, it was still surprising and gratifying to see that the drug worked like what we (saw) in animal experiments," he said.

Phase 3 trials are expected to launch in mid-2022, he added.

As reported in Science Translational Medicine, the team tested the docetaxel/L-NMMA combination in 35 patients (median age, 59) with chemoresistant metastatic TNBC: 15 in the phase 1 dose-finding trial and 24 in the phase 2 efficacy trial (including four recommended phase 2 dose patients from the phase 1 trial).

Of the 15 patients in the phase 1 portion of the trial, 87% had metastatic disease and 13% had LABC that was refractory to anthracycline-based chemotherapy. All LABC patients had doxorubicin plus cyclophosphamide as their first drug regimen.

Of the 24 patients in phase 2, 54% had metastatic disease with a median of five prior chemotherapy regimens, and 46% had anthracycline-chemorefractory LABC.

The overall response rate was 45.8% (11 of 24). Responses were seen in 9 of 11 patients with LABC (81.8%) and 2 of 13 patients with metastatic TNBC (15.4%).

Three patient with LABC (27.3%) had a pathological complete response at surgery.

Grade 3 or greater toxicities occurred in 21% of patients, but no adverse events were attributed to L-NMMA.

Further investigation showed that responders had an increase in CD15+ neutrophils and a decrease in arginase (a marker of protumor N2 neutrophils) at the end of treatment. In contrast,

nonresponders showed greater expression of markers associated with M2 macrophage polarization and increased concentrations of circulating IL-6 and IL-10 cytokines.

Dr. Chang said he expects that L-NMMA might be effective in other resistant cancers as well, particularly those of the liver and pancreas.

Three experts commented on the study in separate emails to Reuters Health. Dr. Michael Simon, co-leader, Breast Cancer Multidisciplinary Team at the Karmanos Cancer Institute in Detroit, said, "This is a potentially hopeful treatment combination that may move the needle forward. I found it impressive that they looked at biological correlates. (Also), the study drug had few side effects."

"I am not sure what percent of the patients with metastatic disease already had a taxane, which could reduce the likelihood of response," he noted. "This (approach) might be better suited for patients that have not had a taxane previously either for locally advanced disease or in the metastatic setting."

Dr. Dhvani Thakker, Director, Women''s Medical Oncology at Mount Sinai South Nassau in Oceanside, New York, noted, "There is a concern for thrombosis on this treatment since patients with active cancer are at a high risk of thrombosis. Additionally, the majority of patients with TNBC had received treatment with (doxorubicin) in the past. There remains a concern for cardiotoxicity specifically in this patient population."

Dr. Victor Guardiola, a medical oncologist and hematologist at Baptist Health''s Miami Cancer Institute, added. "We should take these results with caution at this time, as positive results in early phases of investigation cannot always be duplicated in phase 3 clinical trials."

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