Small molecule inhibitor shows promise in trastuzumab-resistant metastatic breast cancer

May 28 2009

Fox Chase Cancer Center researchers report that a combination of trastuzumab and neratinib (HKI-272) a novel small molecule inhibitor of the HER2 receptor (ErbB2) appears active in women with HER2-positive metastatic breast cancer who have progressed on previous trastuzumab based therapies. More than one-quarter of the women in a phase I/II trial had their tumors shrink on the combination therapy.

"I think this is very promising. Neratinib induces clinically meaningful responses," says Ramona Swaby, M.D., a medical oncologist and attending physician at Fox Chase. Swaby will present the study results on Monday, June 1, at the annual meeting of the American Society of Clinical Oncology.

Trastuzumab is standard therapy for women with HER2-positive metastatic breast cancer and the majority of women respond to the treatment. However, over time some women will develop resistance to the drug and their tumors will start to grow again. For these women, alternative therapies are needed.

Both trastuzumab and neratinib inhibit the HER2 receptor expressed on the surface of HER2-positive breast cancer cells. Trastuzumab blocks the extracellular portion of the receptor, while neratinib blocks the intracellular portion. Researchers think that the combination may

provide the one-two punch necessary to knock out the tumor cells.

Forty-five women with trastuzumab-resistant breast cancer enrolled in the trial. In the phase I portion of the trial, women received either 160 mg or 240 mg neratinib daily plus trastuzumab 4 mg/kg IV loading dose followed by 2 mg/kg weekly. None of the patients experienced dose limiting toxicities. The most common grade 3/4 adverse events included diarrhea (13%), nausea (4%) and vomiting (4%). The researchers saw no evidence of cardiac toxicity with the combination.

Of the 33 patients in the phase II portion of the trial who are evaluable for response, nine (27%) had an objective response to the combination therapy. Additionally, 47% were progression-free at 16 weeks, which was the primary endpoint of the trail, and the median progression-free survival was 19 weeks. Seven women continue on therapy at this time. (Updated results will be presented at the meeting.)

"Trastuzumab has certainly made a difference in patient care, but there is still room for improvement," Swaby says. "For example because trastuzumab is an antibody it does not cross the blood-brain barrier so is not effective at treating or preventing brain metastases. It is incredibly heartbreaking to think you are out of the woods and then to have brain metastases occur. Neratinib, a small molecule drug that can cross the blood-brain barrier, potentially may treat brain metastases. More studies are needed"

"The phase II data are snapshots of what this drug is capable of," Swaby says. "Phase III trials are underway, which I think is the right next step for this medicine. My patients in the study did well."

Source: Fox Chase Cancer Center (news : web)