MedicalXpress

Tau protein expression predicts breast cancer survival -- though not as expected

December 14 2008

Expression of the microtubule-binding protein Tau is not a reliable means of selecting breast cancer patients for adjuvant paclitaxel chemotherapy, according to research led by The University of Texas M. D. Anderson Cancer Center.

Presented today, Dec. 13, at the CRTC-AACR San Antonio Breast Cancer Symposium, the researchers found that Tau expression does predict survival, yet in an unexpected way.

In earlier neoadjuvant studies, investigators from M. D. Anderson found that low levels of Tau predicted a good response to pre-operative chemotherapy. In vitro studies had shown that down-regulation of Tau expression increased the sensitivity of breast cancer cell lines to paclitaxel. Other studies suggested that high levels of Tau partially protect microtubules from paclitaxel binding and that low levels of the protein leave microtubules more accessible and vulnerable to the drug.

"If you treat patients who have a low level of Tau protein expression with pre-operative chemotherapy in neo-adjuvant studies, they are very likely to have a good response to the chemotherapy," said Lajos Pusztai, M.D., D. Phil, associate professor of medicine in the Department of Breast Medical Oncology at M. D. Anderson and the study's first author. "We wanted to see if this correlation would hold up in predicting survival in adjuvant studies."

Working with researchers from the National Surgical Adjuvant Breast

and Bowel Project (NSABP), the investigators assessed Tau protein expression in primary breast cancer specimens from 1,942 patients in the NSABP-B28 clinical trial. The goal was to evaluate the prognostic value of Tau in these patients, who were treated with four courses of doxorubicin/cyclophosphamide (AC) or AC followed by four courses of paclitaxel. All hormone receptor-positive patients in the trial also received adjuvant endocrine therapy.

The hypothesis was that patients whose tumors expressed low levels of Tau would preferentially benefit from the addition of paclitaxel to their adjuvant regimen, Pusztai explained. Univariate and multivariate analyses found that both Tau-positive status (high Tau expression) and estrogen receptor (ER) -positive status were associated with better disease-free and overall survival. However, the researchers found no significant correlation between Tau expression and benefit from paclitaxel in the total population or among estrogen receptor (ER) -positive or ER-negative patients.

"We eventually found that Tau is very predictive of survival but in the opposite manner than we initially thought," Pusztai said. "Low Tau expression was actually associated with a relatively poor survival despite a higher sensitivity to chemotherapy."

"On the other hand," he continued, "patients with high levels of Tau-and we knew these patients were not particularly sensitive to chemotherapy-actually did very well. They had a significantly better survival in this large randomized study."

Pusztai noted that survival is determined by baseline prognosis, endocrine sensitivity and sensitivity to chemotherapy-and that Tao is a marker of receptivity for two of these important variables.

"It's receptive to chemotherapy sensitivity but also to endocrine therapy

sensitivity," he added, "and the receptivity is in an opposite manner: Low Tau means higher chemotherapy sensitivity, but it also means lesser sensitivity to endocrine therapy and vice versa. Patients with high Tau expression do very well because they all tend to be ER-positive and very sensitive to endocrine treatment."

This complex interaction between Tau and outcome is not unique, according to Pusztai. It is the same association as with many other biomarkers, including the Oncotype DX breast cancer assay and the proliferation marker Ki-67-an inverse relationship between chemotherapy sensitivity and endocrine sensitivity.

The issues would be far less complicated, Pusztai added, if ER-negative and ER-positive breast cancer were treated as distinct entities. "The most important thing we've learned is that we need to develop prognostic markers, response markers, or any type of biomarker separately for the ER-negative and ER-positive tumors."

Source: University of Texas M. D. Anderson Cancer Center