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Gene Expression and Benefit of Chemotherapy in Women With Node - Negative, Estrogen Receptor - Positive Breast Cancer

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The use of adjuvant chemotherapy in the treatment of early-stage node-negative breast cancer has increased greatly in the last decade in the United States. Ideally, the decision to use chemotherapy in addition to hormonal therapy in the treatment of axillary node negative and estrogen receptor (ER) positive breast cancer should be based on not only baseline risk (prognostic information) but also prediction of degree of benefit from chemotherapy. Current treatment guidelines in the United States and Europe recommend consideration of chemotherapy for the vast majority of patients.

A number of biologic and clinical clues have suggested that not all patients derive the same degree of benefit from chemotherapy. An overview of randomized trials suggests that younger women may benefit more from chemotherapy than older women. Diagnostic tests that predict clinical benefit from chemotherapy are not yet available for routine clinical use.

Gene expression analysis in individual tumors is a promising approach for defining responsiveness to chemotherapy. Several small studies have been performed in breast cancer patients treated with neoadjuvant chemotherapy before surgery, and gene expression profiles have been associated with the likelihood of pathologic complete response.

Taking advantage of National Surgical Adjuvant Breast and Bowel Project (NSABP) clinical trials archived paraffin block tissue bank, we have developed and validated a 21-gene assay that is now offered as a commercial reference laboratory test (Oncotype DX, Genomic Health Inc, Redwood City, CA). The 21-gene panel includes genes involved in

tumor cell proliferation and hormonal response, characteristics that have been reported to be associated with chemotherapy response in general. We explored the interaction between Oncotype DX assay and chemotherapy benefit using tissue blocks collected from NSABP trial B20 which tested the worth of adding cyclophosphamide, methotrexate, and fluorouracil (CMF) or methotrexate and fluorouracil (MF) chemotherapy to 5 years of tamoxifen in the treatment of node-negative, ER-positive patients. We sought to determine whether the prespecified 21-gene reverse-transcriptase polymerase chain reaction (RT-PCR) assay predicts the benefit of chemotherapy in the NSABP B20 patients.

Patients with node-negative, ER-positive breast cancer in the NSABP B20 study did not benefit equally from chemotherapy. The prespecified 21-gene RT-PCR assay predicted the magnitude of benefit of either CMF or MF chemotherapy. The likelihood ratio test for interaction between chemotherapy treatment and recurrence score (RS) was statistically significant ($p = .038$). Patients with tumors who had high RSs (≥ 31) experienced a large chemotherapy benefit (relative risk, 0.26; 95% CI, 0.13 to 0.53), with a mean absolute decrease in distant recurrence rate at 10 years of 27.6% (SE, 8.0%). Patients with tumors that had low RSs ($RS < 18$) derived minimal, if any, benefit from chemotherapy treatment (relative risk, 1.31; 95% CI, 0.46 to 3.78), with a mean absolute decrease in distant recurrence rate at 10 years of -1.1% (SE, 2.2%). Patients with tumors that had intermediate RSs ($RS, 18$ to 30) did not appear to receive a substantial benefit, but the uncertainty in the estimate (relative risk, 0.61; 95% CI, 0.24 to 1.59) can not exclude

a clinically important benefit from chemotherapy treatment.

It should be noted that samples from the NSABP B20 tamoxifen-treated patients were used in one of the three studies used to select the 21 genes and to design the RS algorithm. However, samples from the NSABP B20 tamoxifen plus chemotherapy treated patients were not previously analyzed or used in the Oncotype DX development. Moreover, results from analysis of the NSABP B14 tamoxifen-treated patients (also not used in the development of the RS) were very similar to the results from analysis of the NSABP B20 tamoxifen-treated patients.

Few previous studies have examined biomarkers in patient cohorts from randomized trials comparing chemotherapy versus no chemotherapy. Studies that have examined the relationship between the response of tumors to chemotherapy and factors such as histologic grade and DNA ploidy have yielded inconsistent results. However, tumors with characteristics associated with greater aggressiveness (eg, poor histologic grade, high levels of uPA/PA-1, ER negativity, high proliferative index) tended to respond better to chemotherapy. In addition, there were trends for statistical interaction between clinical variables and chemotherapy benefit when all the NSABP B20 patients were examined. The 21-gene RT-PCR assay brings a high degree of precision and standardization to the quantification of important biologic characteristics of individual breast cancers. The RS calculation integrates the contribution of proliferation related genes and hormone receptor pathway genes. The data from this study indicates that greater chemotherapy benefit is observed in patients whose tumors have high RSs.

The clinical implications of these results for patients with low or relatively high RSs are relatively clear. For many women with low RSs, the anticipated benefit of adding chemotherapy to hormonal therapy may not exceed the risks. For many women with high RSs, the anticipated benefit of adding chemotherapy appears to be very favorable when compared with the risks. However, for women with intermediate RSs, it is uncertain that the benefits of chemotherapy exceed the risks. Additional study of the benefits and risks of chemotherapy in this middle range of patients is needed. The National Cancer Institute (NCI; National Institutes of Health, Bethesda, MD) Program for the

Assessment of Clinical Cancer Tests (PACCT) Strategy Group, in collaboration with US Breast Intergroup, including NSABP, is considering a study that will further refine our ability to select patients for chemotherapy with RSs in the middle range. However the results of the planned study will be available only after 2010, and until such time the results of Oncotype DX assay will have to be considered in the context of other clinical parameters in the selection of candidates for chemotherapy.

These data have implications with respect to cancer pathogenesis and metastasis. Adjuvant chemotherapy targets micrometastatic cells present after removal of primary tumor. Success in predicting chemotherapy benefit using analysis of the primary tumor implies that primary tumor and micrometastatic cells share molecular characteristics. Recent studies indicate that, overall, tumor molecular signatures tend to be preserved across different stages of tumor progression. Our published studies with the 21-gene RS as well as other gene expression profiling studies demonstrate that expression profiling of the primary tumor can predict distant disease recurrence. However, eventual tissue tropism of the metastases or survival of tumor cells in specific organ sites might require differential expression of certain genes in only a subset of the original tumor population. Animal model system results from Massague's group suggest that although metastatic cells need to acquire a specific set of genes for organotropic metastasis, their basic driving force is still governed by poor-prognosis genes in the primary tumor. Our results suggest that poor prognosis genes also influence chemotherapy response.

The relevance of this study with CMF chemotherapy to other regimens is under investigation. In a study of 89 patients with locally advanced breast cancer, Gianni et al found that the RS also positively correlated with the probability of a pathologic complete response to neoadjuvant treatment with an anthracycline/taxane regimen. Patients with tumors with low RSs (< 18) rarely had a pathologic complete response. This suggests that relationship between the RS and chemotherapy benefit is not regimen specific. Whether there are specific predictor genes for particular chemotherapeutic drugs or regimens is not yet established. The NSABP trial B40 has been designed to address this question.

In summary, the RS assay not only quantifies the

likelihood of breast cancer recurrence in women with node-negative, ER-positive breast cancer, it also predicts the magnitude of chemotherapy benefit. The results of this and other studies strongly suggest that not all women with breast cancer benefit equally from chemotherapy.

References

1. Mariotto A, Feuer EJ, Harlan LC, et al: Trends in use of adjuvant multi-agent chemotherapy and tamoxifen for breast cancer in the United States: 1975-1999. *J Natl Cancer Inst* 94:1626-1634, 2002
2. Henderson IC, Patek AJ: The relationship between prognostic and predictive factors in the management of breast cancer. *Breast Cancer Res Treat* 52:261-288, 1998
3. Hayes DF, Trock B, Harris AL: Assessing the clinical impact of prognostic factors: When is "statistically significant" clinically useful? *Breast Cancer Res Treat* 52:305-319, 1998
4. Bast RC Jr, Ravdin P, Hayes DF, et al: 2000 update of recommendations for the use of tumor markers in breast and colorectal cancer: Clinical practice guidelines of the American Society of Clinical Oncology. *J Clin Oncol* 19:1865-1878, 2001
5. Eifel P, Axelson JA, Costa J, et al: National Institutes of Health Consensus Development Conference Statement: Adjuvant therapy for breast cancer, November 1-3, 2000. *J Natl Cancer Inst* 93:979-989, 2001
6. Carlson RW, Edge SB, Theriault RL: NCCN: Breast cancer. *Cancer Control* 8:54-61, 2001 (suppl 2)
7. Goldhirsch A, Wood WC, Gelber RD, et al: Meeting highlights: Updated international expert consensus on the primary therapy of early breast cancer. *J Clin Oncol* 21:3357-3365, 2003
8. Fisher B, Jeong JH, Bryant J, et al: Treatment of lymph-node-negative, oestrogen-receptor-positive breast cancer: Long-term findings from National Surgical Adjuvant Breast and Bowel Project randomised clinical trials. *Lancet* 364:858-868, 2004
9. Early Breast Cancer Trialists' Collaborative Group (EBCTCG): Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: An overview of the randomised trials. *Lancet* 365:1687-1717, 2005
10. Buchholz TA, Stivers DN, Stec J, et al: Global gene expression changes during neoadjuvant chemotherapy for human breast cancer. *Cancer J* 8:461-468, 2002
11. Ayers M, Symmans WF, Stec J, et al: Gene expression profiles predict complete pathologic response to neoadjuvant paclitaxel and fluorouracil, doxorubicin, and cyclophosphamide chemotherapy in breast cancer. *J Clin Oncol* 22:2284-2293, 2004
12. Chang JC, Wooten EC, Tsimelzon A, et al: Gene expression profiling for the prediction of therapeutic response to docetaxel in patients with breast cancer. *Lancet* 362:362-369, 2003
13. Gianni L, Zambetti M, Clark K, et al: Gene expression profiles in paraffin-embedded core biopsy tissue predict response to chemotherapy in women with locally advanced breast cancer. *J Clin Oncol* 23:7265-7277, 2005
14. Cronin M, Pho M, Dutta D, et al: Measurement of gene expression in archival paraffin-embedded tissues: Development and performance of a 92-gene reverse transcriptase-polymerase chain reaction assay. *Am J Pathol* 164:35-42, 2004
15. Paik S, Shak S, Tang G, et al: A multigene assay to predict recurrence of tamoxifen-treated, node-negative breast cancer. *N Engl J Med* 351:2817-2826, 2004