Molecular pathology selected abstracts

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Use of a 21-gene assay to inform chemotherapy benefit in node-positive breast cancer

February 2022—The Oncotype DX assay, from Exact Sciences, measures the expression of 16 cancer-related genes and five reference genes in breast cancer biopsy or resection specimens to determine risk of recurrence. The clinical utility of the assay was originally demonstrated in the landmark TAILORx (Trial Assigning Individualized Options for Treatment) study. The study showed that in hormone receptor-positive, HER2-negative, axillary lymph node-negative breast cancer, patients with a low risk score (0–25) could be treated effectively with endocrine therapy alone, while those with a high-risk score (26–100) benefited significantly from chemotherapy. Consequently, the assay is used routinely to guide oncologists in making treatment decisions. However, one-third of breast cancer patients have lymph node metastases at the time of diagnosis, and the clinical utility of the Oncotype DX assay in this patient population is less clear. In the recent RxPONDER (A Clinical Trial Rx for Positive Node, Endocrine Responsive Breast Cancer) study, more than 5,000 patients from 632 trial sites across nine countries were randomized to receive endocrine therapy alone or chemotherapy followed by endocrine therapy. All patients had hormone receptor-positive, HER2-negative, nodal stage N1 breast cancer and had an Oncotype DX recurrence score of 25 or less. The plan was to follow these patients for 15 years after randomization to compare invasive disease-free survival. However, after a median patient follow-up of 5.3 years, the study authors determined that the results were significant enough to report. They found that the benefit of chemotherapy was associated with menopausal status in the patient population with low Oncotype DX recurrence scores. In premenopausal women, chemotherapy improved invasive disease-free survival across all subgroups. However, in postmenopausal women, chemotherapy provided no significant benefit, and the survival curves of the two treatment groups essentially overlapped. Subgrouping the postmenopausal women by age, grade, tumor size, number of positive lymph nodes, and stratification of recurrence score also showed no benefit with regard to chemotherapy in any of the subgroups. Overall, the authors concluded that postmenopausal women with N1 breast cancer and an Oncotype DX recurrence score of 25 or less could be safely treated with endocrine therapy alone, whereas premenopausal women with nodal disease benefitted from adjuvant chemotherapy.

Kalinsky K, Barlow WE, Gralow JR, et al. 21-gene assay to inform chemotherapy benefit in node-positive breast cancer. *N Engl J Med*. 2021. doi:10.1056/NEJMoa2108873

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Benefits of gene therapy to treat beta-thalassemia

Beta-thalassemia is a hereditary disease caused by any one of a number of mutations in the *HBB* gene that encodes the β-globin subunit of hemoglobin, the oxygen-carrying component of red blood cells. These mutations vary in severity and reduce or abrogate β-globin production, causing ineffective hemoglobin synthesis, impaired red blood cell production, and anemia. The anemia associated with β-thalassemia is often severe and leads to patients undergoing blood transfusions throughout their life. While allogeneic hematopoietic stem cell transplantation potentially can be a curative therapy, it is associated with a high risk of graft failure, graft-versus-host disease, and other complications. Betibeglogene autotemcel (beti-cel) is a gene therapy developed for transfusion-dependent β-thalassemia. It involves harvesting and modifying a patient's hematopoietic stem cells

using a lentiviral vector encoding a functional β-globin gene that also has an amino acid substitution at position 87 (p.T87Q). This substitution was included because it inhibits polymerization of sickle hemoglobin in patients with sickle cell anemia. However, it has the added benefit of being able to distinguish the hemoglobin derived from beti-cel therapy from a patient's endogenous hemoglobin. The patient then undergoes myeloablation with busulfan, followed by reinfusion of the modified stem cells. In this phase three study, the authors evaluated the efficacy and safety of this gene therapy in 23 β-thalassemia patients, including eight patients younger than 12 years of age. Neutrophil engraftment occurred at a median of 23 days after beti-cel infusion, and platelet engraftment occurred at a median of 46 days after the infusion. Patients were hospitalized for a median of 45 days for the procedure. Twenty of 22 (91 percent) patients achieved transfusion independence, receiving their last red blood cell transfusion 0.5 to 2.4 months (median, 0.9 months) after beti-cel therapy. One patient could not be evaluated for the primary end point. In the patients that achieved transfusion independence, the average hemoglobin level was 11.7 g/dL, with the endogenous hemoglobin comprising an average of 3.0 g/dL and the hemoglobin with the p.T87Q substitution comprising an average of 8.7 g/dL. The authors also found improved red blood cell production in patients' bone marrow. In many of the patients that achieved transfusion independence, iron studies showed reduced liver iron concentration, allowing the patients to discontinue iron chelation therapy. And many of the adverse events that were observed could be attributed to conditioning and myeloablation. This study demonstrates the efficacy and safety of beti-cel gene therapy for treating β-thalassemia. Many of the patients who received the therapy achieved hemoglobin levels close to the normal range and were able to discontinue red blood cell transfusions.

Locatelli F, Thompson AA, Kwiatkowski JL, et al. Betibeglogene autotemcel gene therapy for non-β^0/β^0 genotype β-thalassemia. *N Engl J Med*. 2021. doi:10.1056/NEJMoa2113206

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