**Leukemia**

**Finding:** Late-recurring T-ALL can be a second leukemia.

**Significance:** First evidence suggesting genetic predisposition.

**Impact:** Second T-ALL might respond to first-line therapy.

---

**RELAPSING T-ALL CAN BE SECOND DISEASE**

T-cell acute lymphoblastic leukemia (T-ALL) is a childhood disease that has an approximately 75% rate of 5-year event-free survival. However, relapse often occurs on or just after treatment, and prognosis for these patients is very poor. In a recent article, Szczepanski and colleagues examined 22 patients with T-ALL that relapsed more than 2.5 years after diagnosis to determine whether these disease recurrences represented a second, independent disease.

The authors found clonal T-cell receptor (TCR) rearrangements in 20 of the 22 patients. In 12 of these 20 patients, identical TCR rearrangements were seen at diagnosis and in the relapsed cancer. Strikingly, however, in the other 8 patients, the clonal TCR rearrangements seen at diagnosis were absent in the second disease. Comparative genomic hybridization array analysis showed that 7 of these 8 patients had completely different patterns of copy number variation between first and second disease. In the other patient, a well-known somatic microdeletion was observed. Finally, the authors were unable to detect any genetic markers of the second disease in samples of the original disease. These data suggest that a significant percentage of late relapsing T-ALL may in fact represent new disease, and it is possible that these patients have a genetic predisposition to T-ALL development.


---

**Breast Cancer**

**Finding:** SRC activation is a common step in both de novo and acquired trastuzumab resistance.

**Significance:** Treatment with SRC inhibitor sensitizes trastuzumab-resistant cells.

**Impact:** Combination therapy may improve clinical outcome.

---

**SRC INHIBITION OVERCOMES TRASTUZUMAB RESISTANCE IN HER2-OVEREXPRESSING BREAST CANCERS**

Overexpression of human epidermal growth factor receptor-2 (HER2 or ERBB2) is associated with poor clinical prognosis and survival in breast cancer. Treatment with trastuzumab, a humanized antibody that targets HER2, in patients with HER2-positive breast cancer shows clinical benefit; however, many patients do not respond to treatment due to either de novo or acquired resistance. Because of the heterogeneity of trastuzumab resistance, management of patients with HER2-positive breast cancer remains clinically challenging.

In a recent article, Zhang and colleagues identify activation of the nonreceptor tyrosine kinase SRC to be the key node common to both the de novo and acquired mechanisms of trastuzumab resistance. Using trastuzumab-resistant, HER2-overexpressing breast cancer cells, the authors first show that SRC activation, mediated by increased phosphorylation at Tyr416, occurs downstream of multiple receptor tyrosine kinase pathways and plays a critical role in acquired trastuzumab resistance. SRC is also shown to interact directly with the protein phosphatase PTEN, and PTEN loss in breast cancer cells results in SRC phosphorylation and development of de novo trastuzumab resistance. Importantly, in both in vitro and in vivo models, treatment with saracatinib, an orally available small molecule inhibitor of SRC, sensitized trastuzumab-resistant cells and tumors to trastuzumab treatment. A retrospective analysis of primary breast tumors further correlated relative increases in SRC activity with clinical resistance to trastuzumab. Overall, the results suggest that combined treatment with both trastuzumab and SRC inhibitor can overcome resistance and provide more effective therapy for patients with HER2-overexpressing breast cancer.


---

**Note:** Research Watch is written by Cancer Discovery Editors. Readers are encouraged to consult the articles referred to in each item for full details on the findings described.
SRC Inhibition Overcomes Trastuzumab Resistance in HER2-Overexpressing Breast Cancers

Cancer Discovery 2011;1:11.

Updated version  Access the most recent version of this article at: http://cancerdiscovery.aacrjournals.org/content/1/1/11.2

E-mail alerts  Sign up to receive free email-alerts related to this article or journal.
Reprints and Subscriptions  To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at pubs@aacr.org.
Permissions  To request permission to re-use all or part of this article, contact the AACR Publications Department at permissions@aacr.org.