

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, Szczepański 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. ■

Szczepański T, van der Velden VH, Waanders E, Kuiper RP, Van Vlierberghe P, Grubm B, et al. Late recurrence of childhood T-cell acute lymphoblastic leukemia frequently represents a second leukemia rather than a relapse: first evidence for genetic predisposition. J Clin Oncol 2011;29:1643–9.

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. ■

Zhang S, Huang WC, Li P, Guo H, Poh SB, Brady SW, et al. Combating trastuzumab resistance by targeting SRC, a common node downstream of multiple resistance pathways. Nat Med 2011;17:461–9.

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.

CANCER DISCOVERY

Relapsing T-ALL Can Be Second Disease

Cancer Discovery 2011;1:11.

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