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EDITORIAL

NOTCH mutations as prognostic markers in T-ALL

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Risk stratification plays a fundamental role in the treatment of acute lymphoblastic leukemia (ALL). Thus, patients harboring clinical features, immunophenotypic markers, cytogenetic or molecular abnormalities that are associated with increased risk of relapse are treated with intensified chemotherapy protocols, while patients classified as low risk are spared from the additional toxicity associated with these treatments.

This strategy has been overly successful in B-precursor ALL, leading to substantial improvements in outcome for specific subsets of high-risk patients. Moreover, in the case of Philadelphia chromosome-positive ALL, combination therapies including BCR–ABL1 tyrosine kinase inhibitors provide a molecularly tailored treatment for this subset of high-risk patients.[1] For T-ALL in various Berlin–Frankfurt–Munster (BFM)-like treatment protocols, patient stratification has been based primarily on patient response to a glucocorticoid-based prophase therapy as well as minimal residual disease (MRD) analysis.

The recent identification of activating mutations in *NOTCH1* and *FBXW7* resulting in constitutively active NOTCH1 signaling in about 60% of T-ALL patients opened the question of the prognostic implications of these molecular alterations.[2–5] Moreover, anti-NOTCH1 therapies hold the promise of providing a molecularly tailored treatment for this disease.[2,6] Early studies on the prognostic significance of NOTCH activation in T-ALL showed that *NOTCH1* mutations are not associated with poor outcome and suggested that in fact they could be associated with good prognosis. Thus, an original study comprising 157 pediatric T-ALL patients from the pediatric ALL-BFM 2000 study found that *NOTCH1* mutations were associated with low levels of MRD and improved relapse-free survival.[7] However, analysis of a series of 72 pediatric T-ALL patients treated in the Dutch Childhood Oncology Group (DCOG) protocols ALL-7/8 or ALL-9 failed to demonstrate an improved outcome for patients harboring *NOTCH1* mutations.[8] Similarly discrepant results were obtained in adult T-ALL. Thus, analysis of 141 T-ALLs treated in the Lymphoblastic Acute Leukemia in Adults (LALA)-94 ($n=87$) and the GRAALL-2003 ($n=54$) trials showed positive prognosis for patients with *NOTCH1* and/or *FBXW7* mutations.[9] Yet, these results could not be validated in a series of 88 patients treated in the MRC UKALLXII/ECOGE2993 protocol.[10] Overall these studies suggested that *NOTCH1* mutations could be associated with improved outcome in some series, but that the prognostic impact of *NOTCH1* mutations in T-ALL could be influenced by differences in therapy. However, a definitive answer was somehow concealed by methodological differences and the limited sample size of these studies.

Three different studies in this issue of *Leukemia* revisit the question of the prognosis significance of *NOTCH1* and *FBXW7* mutations in T-ALL to bring a more conclusive answer to this question. First, a study by Kox and coworkers for an extended series of 301 T-ALL patients treated in the ALL-BFM 2000 study demonstrates that activating mutations in the NOTCH signaling pathway are associated with improved responses to prophase therapy with glucocorticoids and methotrexate and lower levels of MRD. However, in those patients classified as high risk based on response to prophase therapy and/or MRD, the presence of activating mutations in the NOTCH pathway does not have a positive impact in prognosis.

Next, Clapier *et al*. report the analysis of 134 patients treated in the EORTC-CLG 58881 and 58951 studies. In this series, *NOTCH1* and *FBXW7* mutations are associated with improved therapy response and decreased MRD levels. However, this increased response to therapy did not translate to improved outcome. Moreover, in the group of high MRD levels the presence of genetic alterations in the NOTCH pathway seemed to be associated with worse outcome.

Finally, Zuurbier and coworkers report the study of 72 patient samples from the DCOG ALL7/8 and ALL9 studies and 74 cases treated in the COAL97 clinical trial. The analysis of activated NOTCH1 protein levels in primary patient samples and microarray expression analysis of NOTCH target genes demonstrate that indeed *NOTCH1* and *FBXW7* mutations correlate with increased NOTCH signaling. This study confirms that NOTCH-activating mutations are associated with good prednisone response. However, as in the case of the EORTC-CLG series, this higher sensitivity to chemotherapy did not translate into improved survival.

The association of NOTCH mutations with increased response to glucocorticoids is indeed a surprising result given that activated NOTCH1 can protect normal thymocytes from glucocorticoid-induced cell death[11] and that inhibition of NOTCH signaling with γ-secretase inhibitors can reverse glucocorticoid resistance in some T-ALL patient samples and cell lines.[12,13]

Overall, these three studies show that NOTCH activation is associated with improved early therapeutic response. However, this early benefit translates into improved overall survival only in some series, most probably as a result of differences in therapy. In addition, *NOTCH1* and *FBXW7* mutations fail to predict prognosis among high-risk patients, which is consistent with the presence of *NOTCH1* activating mutations in a significant fraction of patients at relapse. As a result, analysis of *NOTCH1* and *FBXW7* mutations does not seem to improve our current risk-stratification strategies. In this regard, a recent study identifying the absence of biallelic deletion in the *TCRγ* locus as a prognostic marker associated with primary refractory and early-relapse leukemia may provide a better avenue toward developing a molecular risk-stratification approach in T-ALL.[14]

Conflict of interest

The author declares no conflict of interest.

A Ferrando[1,2,3]
[1]*Institute for Cancer Genetics, Columbia University Medical Center, New York, NY, USA;*
[2]*Department of Pediatrics, Columbia University Medical Center, New York, NY, USA and*
[3]*Department of Pathology, Columbia University Medical Center, New York, NY,USA*
E-mail: af2196@columbia.edu

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