Leukemia

Major finding: *ERG* deregulation by deletion or expression of a dominant-negative transcript drives a subset of B-ALL.

Mechanism: DUX4 upregulation and binding at the *ERG* locus promotes expression of an alternative *ERG* transcript.

Impact: The identification of DUX4/ERG B-ALL may improve patient risk stratification and guide treatment.

DUX4 REARRANGEMENT AND *ERG* DEREGULATION CHARACTERIZE A B-ALL SUBTYPE

The genetic underpinnings of many cases of B-progenitor acute lymphoblastic leukemia (B-ALL) have not been determined. A subset of cases displays a characteristic gene expression profile and frequent deletion of *ERG*, which encodes an ETS-family transcription factor essential for hematopoietic differentiation. To further characterize this and other B-ALL subtypes, Zhang and colleagues performed expression profiling and DNA copy-number analysis on 1,913 patients with B-ALL combined with whole-genome, whole-exome, and RNA sequencing in a subset. A distinct gene expression profile was observed in 141 (7.6%) cases, and 85 (55.6%) of those had focal deletions of *ERG* that were not present in other cases. Further, in all cases with transcriptome data available, the gene encoding the double-homeobox transcription factor DUX4 was upregulated by a chromosomal rearrangement placing *DUX4* under the control of the *IGH* enhancer. Transcriptional deregulation of *ERG* was observed in all *DUX4*-rearranged cases with identification of a noncanonical aberrant *ERG* transcript (*ERG*alt) that lacked the N-terminus and instead was initiated from an alternative exon 6 fused to exon 7 and the downstream exons, resulting in a truncated protein. Analysis of data from the Pediatric Cancer Genome Project showed that expression of aberrant ERG transcripts was rare in other ALL subtypes and other tumor types. DUX4 bound at the alternative exon 6 of *ERG* and promoted expression of *ERG*alt, providing a mechanism by which *DUX4* rearrangement may promote *ERG* deregulation. Functionally, ERGalt retained DNA binding activity and acted as a competitive inhibitor of wild-type ERG, and mice transplanted with cells expressing ERGalt developed pre-B cell leukemia, suggesting that it promotes lymphoid leukemogenesis. The identification and genomic characterization of a B-ALL subtype characterized by *DUX4* rearrangement and *ERG* deregulation may allow for improved risk stratification and guide therapy in patients with B-ALL, as patients with this form of leukemia have an excellent prognosis. ■

Zhang J, McCastlain K, Yoshihara H, Xu B, Chang Y, Churchman ML, et al. Deregulation of DUX4 and ERG in acute lymphoblastic leukemia. Nat Genet 2016 Oct 24 [Epub ahead of print].

Clinical Trials

Major finding: Blinatumomab was active across age and risk groups in patients with relapsed or refractory BCP–ALL.

Clinical relevance: At the determined recommended dose, blinatumomab achieved complete responses in 39% of patients.

Impact: Single-agent blinatumomab therapy warrants further investigation in pediatric patients with BCP–ALL.

BLINATUMOMAB HAS ACTIVITY IN PEDIATRIC PATIENTS WITH ADVANCED BCP–ALL

The bispecific T-cell engager antibody blinatumomab targets CD19 on B-cell lymphoblasts and has demonstrated clinical activity in adult patients with relapsed or refractory B-cell precursor acute lymphoblastic leukemia (BCP–ALL). However, blinatumomab has not been tested in pediatric patients. Von Stackelberg and colleagues investigated the safety and efficacy of blinatumomab in a multicenter, open-label phase I/phase II trial in pediatric patients with relapsed or refractory BCP–ALL. In the dose-escalation phase I study, 49 patients were treated to determine the maximum-tolerated and recommended blinatumomab doses, and 44 patients enrolled in the phase II study received the recommended dose of blinatumomab to determine the complete response rate. Secondary endpoints included the incidence of adverse events, and overall and relapse-free survival. Of the 70 patients in total who received the determined recommended blinatumomab dose, 27 (39%) achieved a complete response within two cycles, including 14 patients who achieved a complete minimal residual disease response. Complete responses were observed in all age groups and across subgroups, including Philadelphia chromosome–positive and *MLL*-translocated tumors. Adverse events were consistent with what had previously been observed with blinatumomab in adults. The primary treatment-related adverse event leading to permanent treatment discontinuation in two patients was grade 3/4 cytokine-release syndrome, which occurred in 4 patients. The median overall survival for all 70 patients who received the recommended dose was 7.5 months, and the median relapse-free survival among patients who achieved a complete response was 4.4 months. In addition to determining the recommended dose of blinatumomab for pediatric patients with BCP–ALL, this study indicates that blinatumomab has antileukemic activity in pediatric patients with relapsed or refractory BCP–ALL across age groups and in patients with unfavorable cytogenetics and supports its further clinical investigation. ■

von Stackelberg A, Locatelli F, Zugmaier G, Handretinger R, Trippett TM, Rizzari C, et al. Phase I/phase II study of blinatumomab in pediatric patients with relapsed/refractory acute lymphoblastic leukemia. J Clin Oncol 2016 Oct 3 [Epub ahead of print].