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"Risk Factors for Development of Chronic Myeloid Leukemia-like Disease in Philadelphia Chromosome-Positive Acute Lymphoblastic Leukemia Patients"

Philadelphia chromosome-positive (Ph+) Acute Lymphoblastic Leukemia (ALL) is a rare subtype of ALL that historically has been associated with worse outcomes and can present either as *de novo* Ph+ ALL or as the lymphoid blast crisis phase of Chronic Myeloid Leukemia (CML). A small percentage of Ph+ ALL patients relapse with a CML-like picture. The risk factors, characteristics, and outcomes of this population have not been well characterized.

We conducted a retrospective study of pediatric patients with Ph+ ALL treated at St. Jude Children's Research Hospital between 2000 and 2023. A total of 43 children with newly diagnosed Ph+ ALL were identified, among which 8 (18.6%) relapsed with CML-like disease. Baseline characteristics, early adverse events, tyrosine kinase inhibitor (TKI) use, minimal residual disease (MRD) results, and survival data were reviewed. Based on treatment outcome, patients were divided into three groups: those who remained in remission (Remission), those who had refractory disease or relapse (Refractory/Relapse), and those who developed CML-like disease (CML-like). CML-like disease was defined as the presence of *BCR::ABL1* above 10^{-3} by flow cytometry MRD in the absence of Ph+ ALL relapse after completion of ALL therapy or as Ph+ ALL occurring in the background of CML (considered to be the CML blast crisis phase).

The CML-like group had a significantly higher white blood cell (WBC) count at diagnosis than the refractory/relapse and remission groups ($p = 0.002$) as well as than the combined non-CML-like group, which included all patients in the remission and refractory/relapse groups ($p = 0.006$). The CML-like group had a significantly greater highest WBC count when compared to the refractory/relapse and remission groups ($p=0.002$) and when compared to the non-CML-like group ($p = 0.003$). Moreover, patients who developed a CML-like picture were more likely to present at diagnosis as status 2 central nervous system involvement (CNS2), while patients without CML-like disease were more likely to present as CNS1 ($p = 0.007$). Patients with CML-like disease were more likely to have the p210 BCR/ABL1 breakpoint ($p = 0.011$) and to show a discrepancy between same-day negative flow cytometry yet positive polymerase chain reaction (PCR) results compared to the remaining Ph+ ALL cases ($p = 0.015$). Moreover, patients with CML-like disease tended to remain on TKIs for longer compared to the remaining groups ($p = 0.060$). There was no difference between MRD results during induction among the three different groups. 5-year overall survival rates were not significantly different between groups.

Higher WBC at diagnosis, CNS status 2 or higher, and p210 BCR/ABL1 breakpoint may be helpful in predicting which Ph+ ALL patients are at higher risk for developing CML-like disease. Awareness of the CML-like subtype may benefit clinicians in early decision-making regarding course of treatment.