KMT2A Rearrangements in Pediatric Intermediate-Risk Acute Myeloid Leukemia: Fusion Partner Impact and Prognostic Insights. A Comprehensive Survival Analysis

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Introduction

Chromosomal rearrangements involving KMT2A (KMT2A-r), located at chromosome band 11q23, occur in 20%-25% of children with acute myeloid leukemia (AML). Previous studies have reported that the impact varies depending on the specific fusion partner. However, definitive consensus is lacking on risk stratification for patients harboring KMT2A-r.

Aim

The current study aimed to report the outcome of pediatric patients with KMT2A-r Intermediate Risk AML (IR-AML) and the impact of specific fusion partner.

Methods

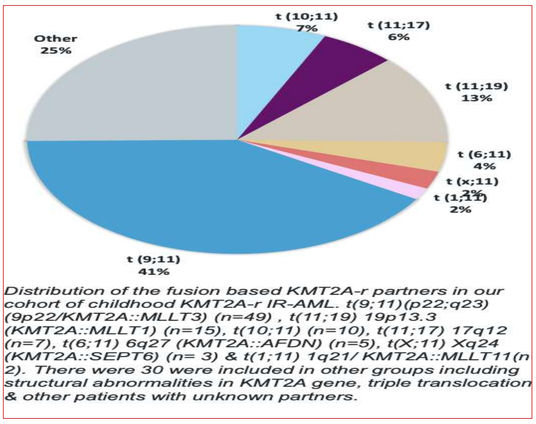
We retrospectively analyzed 610 IR-AML pediatric patients diagnosed at the Children Cancer Hospital Egypt 57357 from January 2008 to December 2021.Patients were assigned to 7 different groups according to fusion partner. Patients who had triple-way translocations, unknown KMT2A fusion partners, or other structural abnormalities in the KMT2A gene, were assigned to KMT2A-r "other".

Additional cytogenetics abnormalities (ACA) were defined as any chromosomal aberrations in addition to KMT2A-r.

Complex karyotype was defined as > 3 cytogenetic abnormalities, whether structural or numerical.

Results

Of the 610 patients diagnosed with IR-AML, 150 (24.6%) had KMT2A rearrangements. KMT2A-r was significantly associated with hyperleukocytosis (P=0.029), CNS disease (P=0.003), monocytic differentiation (P=0.001), ACA (P=0.04), and complex karyotype (P=0.001).



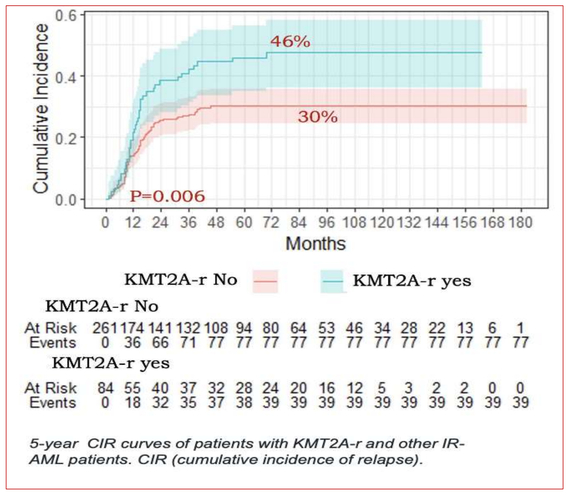
Distribution of the fusion based KMT2A-r partners in our cohort of childhood KMT2A-r IR-AML. t(9;11)(p22;q23) (9p22/KMT2A::MLLT3) (n=49) , t(11;19) 19p13.3 (KMT2A::MLLT1) (n=15), t(10;11) (n=10), t(11;17) 17q12 (n=7), t(6;11) 6q27 (KMT2A::AFDN) (n=5), t(X;11) Xq24 (KMT2A::SEPT6) (n= 3) & t(1;11) 1q21/ KMT2A::MLLT11(n 2). There were 30 were included in other groups including structural abnormalities in KMT2A gene, triple translocation & other patients with unknown partners.

Among the identified fusion partners, t(9;11) (p22;q23) (9p22/KMT2A::MLLT3 fusion) was the most prevalent, accounting for 40.8%. Conversely, t(X;11)Xq24 (KMT2A::SEPT6)(n= 3, 2.5%) & t(1;11)1q21/ KMT2A::MLLT11(n= 2, 1.7%) were the least common.

Results

After excluding patients who died before the end of induction 1 evaluation, 520 were eligible for survival analysis, of whom 121 (23.2%) had KMT2Ar.

Overall Survival (OS) and Event Survival (EFS) of KMT2A-r patients were 46.1%- 95% CI (36.9-55.3) and 39.3%- 95% CI (30.4-48.2), respectively. KMT2A-r was an independent predictor of relapse with a cumulative incidence of relapse (CIR) of 46% versus 30% in the KMT2A negative group (P=0.006). Within the KMT2A-r group, ACA and complex karyotype adversely affected the outcome with 5-year OS of 34.1% (P=0.024) and 26.3% (P= 0.003), respectively.



5-year CIR curves of patients with KMT2A-r and other IR-AML patients. CIR (cumulative incidence of relapse).

There was heterogeneity in outcome depending on the fusion partner. EFS ranged from 16.7% to 57%,while OS from 20% to 68.6%, and relapse-free survival (RFS) from 19.3% to 66.7%. Patients with t (9;11) 9p22 (KMT2A::MLLT3) demonstrated better outcomes, with 5-year OS, EFS, and RFS rates of 52%, 48.4%, and 51.7%, respectively. In contrast, t (6;11) 6q27 (KMT2A::AFDN) and t (11;19) 19p13.3 (KMT2A::MLLT1) were associated with the worst outcomes, with 5-year OS of 20% and 26%, RFS of 20% and 19.3%, and EFS of 20% and 16.7%, respectively.

Summary

KMT2A-r -is an independent prognostic factor for relapse in pediatric IR-AML patients. The presence of ACA and a complex karyotype in KMT2A-r patients is associated with poorer outcomes, emphasizing the need for aggressive treatment and innovative therapeutic strategies for these groups .

References

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