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Pediatric Acute Myeloid Leukemia with KMT2A rearrangement – can Partner Gene Help Determine Need for Hematopoietic Stem Cell Transplant?

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Abstract

Objective: Pediatric acute myeloid leukemia (AML) with KMT2A rearrangement is seen in 15-20% of patients. KMT2A has been shown to rearrange with more than 80 distinct partner genes. In this study we examined the pattern of the various KMT2A rearrangements and their treatment outcomes in our patient population. Methods: We retrospectively analyzed pediatric AML patients with KMT2A rearrangement seen in our institution between January 2005 and December 2015. Results: There were 18 evaluable patients with equal genders. The median age was 4.12 years (range 0-13.5). FAB classification M5 was the most common morphology. Common translocation partner was KMT2A/MLLT3. Ten patients were treated with chemotherapy only and 8 with hematopoietic stem cell transplantation (HSCT). There were 50% patients alive in each group. Conclusion: KMT2A patients can be treated with both chemotherapy and HSCT. The different fusion partners can lead to heterogeneous outcomes in children with KMT2A rearranged AML. Further prospective studies are needed to delineate the high-risk sub-sets in KMT2A rearranged AML that will benefit from HSCT.

Introduction

Pediatric acute myeloid leukemia's (AMLs) are a heterogeneous group of diseases that can be categorized according to their morphology, lineage, and cytogenetics. Current improvements in outcome of pediatric AML reflect the use of intensive chemotherapy, accessibility to hematopoietic stem cell transplantation (HSCT) as well as advancements in both supportive care and treatment of infections in these children. Most centers around the world manage to achieve complete remission (CR) rates of about 80–90%, relapse rates of 30–40%, event-free survival (EFS) rates of 50% and overall survival (OS) rates of nearly 70%.[1]

Modern-day technology has enabled the identification of relevant cytogenetic abnormalities that can be used in clinical practice for disease risk stratification.[2-4] In the study by Song et al., patients with adverse cytogenetics showed significantly poorer outcomes than those with favorable cytogenetics.[5] Hence the prognostication of AML with various cytogenetic abnormalities is particularly essential for determining the optimal treatment approach for these patients.

Cytogenetic abnormalities found on chromosome 11q23 that involves the Lysine (K)-specific MethylTransferase 2A (KMT2A), previously known as mixed-lineage leukemia (MLL) gene rearrangements, have been

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seen in about 5-11% of adult and 15-20% of pediatric AML patients.[6-8] KMT2A has been shown to rearrange with more than 80 distinct partner genes and this promiscuity of the oncogene leads to the heterogeneous presentation and prognosis of the disease.[9]

To study the clinical significance of the various KMT2A rearrangements and its impact on patient treatment outcomes we ought to analyze the various partner genes, additional chromosomal abnormalities, time to remission induction, treatment related mortality, types of donor and conditioning if stem cell transplant is done and so on. Herein, we retrospectively examined outcomes of two pediatric cohorts with AML and KMT2A rearrangements who were treated with either chemotherapy alone or allogeneic HSCT.

Methods

We collected clinical data on all patients under the age of 14 years with a diagnosis of KMT2A-rearranged AML treated by Pediatric Hematology / Oncology Department at the King Faisal Specialist Hospital and Research Centre in Riyadh, Saudi Arabia from January 2005 till December 2015. Data pertaining to the patient demographics, disease, transplant-related parameters and outcome was collected on a case report form. Final dataset and analysis was performed in IBM-SPSS for Windows after data cleaning and quality check.

Statistical considerations

Data set was prepared using IBM-SPSS for Windows (Version 20) and descriptive statistics were performed. Outcome analysis was done in the light of the identified risk factors. Overall Survival was calculated using Kaplan-Meier Survival analysis. Survival benefits were compared using appropriate test statistics depending upon the distribution of the observations.

Ethical consideration

The data from the patient's medical records was collected and maintained at the Department of Pediatric Hematology/Oncology in accordance with institutional policy on data confidentiality, security and safety. The study was a retrospective review; hence no consent/assent was taken from patients/parents. A waiver of informed consent/assent was granted by the Institutional Review Board of the hospital.

Results

Twenty-one (10.4%) AML patients (n=201) were identified to have the KMT2A rearrangement. Three of these died within a few weeks of diagnosis and were thus excluded from the analysis. The characteristics of the remaining 18 patients are described in Table 1. The age ranged from 0-13.5 years (median 4.12 years; average 4.6 years). There was no difference seen in gender predisposition. Morphologically, FAB classification M5 was most frequently seen. Common translocation partners seen in our patients are shown in Figures 1B. The most common translocation seen was KMT2A/MLLT3.

Patient outcomes in relation to the KMT2A translocation are provided in Table 2. In the eight children with the KMT2A/MLLT3 translocation 3 (37.5%) were treated with HSCT and 5 (62.5%) patients with chemotherapy alone. In general, three patients with KMT2A/MLLT3 needed 2nd line chemotherapy for remission induction, amongst which two (66.7%) went into disease remission while one failed to get into remission.

We had four (22.2%) patients with KMT2A/MLLT1 who presented with high white blood counts (WBCs) and despite achieving induction early did poorly because of disease relapse. They were all treated with chemotherapy except for one with HSCT. The only surviving patient in this set had chemotherapy. Another equally common (n=4, 22.2%) translocation seen was KMT2A/MLLT11 with most of the patients being infants with age range of 0.54-1 year and having a balanced sex ratio (2-boys and 2-girls). Both the girls were in the HSCT group and survived while the boys were in the chemotherapy alone set and succumbed to their disease.

Among the total of 18 patients 10 were treated with chemotherapy alone while eight got HSCT. For those

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who continued with chemotherapy alone 7 (70%) were in remission after 2-cycles of induction and 9 (90%) were in remission after completing 4-cycles of chemotherapy. In the HSCT cohort three (37.5%) patients were in remission after 2-induction cycles and of the remaining five patients four had to be switched to 2nd line chemotherapy in order to achieve remission. All of the eight patients were in morphological remission prior to transplant.

The donor source for our HSCT patients was mostly (87.5%) matched related donor except for one patient who got an umbilical cord blood transplant. All the patients got myeloablative conditioning with Busulfan and Cyclophosphamide. Patients got a median of 4-courses before proceeding to transplant. Except for one patient where engraftment testing was not available all the rest of the seven patients had more than 96% myeloid chimerism at Day+100. Four patients relapsed post-transplant and three of these included those who had been moved to 2nd line chemotherapy regimens. All of the four relapsed patients died.

Cumulative probability of overall survival (OS) at 5-year of KMT2A rearranged AML was 50.0±11.8%; 50.0%±15.8% in chemotherapy alone compared to 50.0%±17.7% in HSCT group (P-Value: 0.639, Fig. 2). Five (50%) out of the 10 patients treated with chemotherapy alone died where four were due to progressive disease while one (1) death was secondary to treatment-related-toxicity (TRT). All of the mortality (n=4, 50%) in the HSCT group was also due to progressive disease. None of our patients in the transplant group had problems with acute graft-versus-host disease (GvHD), chronic GvHD, hemorrhagic cystitis or viral infections such as cytomegalovirus (CMV).

Discussion

This study aimed to examine the outcomes of pediatric AML with KMT2A rearrangements at our institution that were treated both by chemotherapy alone as well as HSCT. Our numbers were limited in this retrospective analysis for identifying significant prognostic factors when looking at outcomes. In our qualitative analysis the outcome for patients with KMT2A rearrangements undergoing chemotherapy versus HSCT was equal (50%).

Studies have identified that residual disease is an important prognostic factor when discussing outcomes of transplant in patients.[10-12] Aiming for negative measurable residual disease (MRD) is essential given its impact on outcomes of relapse and survival seen in adults patients with AML undergoing HSCT.[13] We had no data on deeper remission with MRD in our patient cohort and we might have missed patients with lower levels of MRD going to HSCT. Despite this possibility of having taken some of our patients with MRD to HSCT, they did manage to have relatively better outcomes when taking into account their myeloablative conditioning and its treatment related mortality (TRM). There are reports underscoring the significance of cytogenetics in AML patients undergoing HSCT. All of the KMT2A rearrangements seen in our study fall in the intermediate group classification except for the KMT2A/MLLT4 or t(6;11).[14,15] We had only patient with t(6;11) who expired despite being in morphological remission prior to HSCT. Among the rest KMT2A/MLLT3 or t(9;11) translocations were associated with better prognosis.[4] In our patients, KMT2A/MLLT3 translocations were frequently encountered and had a good prognosis (alive=4; 50%) when compared to other KMT2A rearrangements.

During the 1980-90's HSCT was widely endorsed for patients with newly diagnosed AML having a matched-sibling donor. Over the decades not only were the intensive chemotherapy regimens optimized along with better supportive care but also reports of low-risk favorable genetics such as t(8;21), inversion (16), myeloid-leukemia of Down syndrome (ML-DS) emerged.[16-18] Hence treating groups moved away from HSCT for low-risk patients. For the other cytogenetic risk-stratifications in myeloid neoplasms the study groups varied in their approach.[19-21] In general there is support for HSCT in patients falling into the high-relapse and unfavorable cytogenetic subsets as well as those with positive MRD after induction cycles.[22]

Apart from the small numbers in this retrospective analysis the other limitations of our study include the lack of MRD data and the analysis of newer mutations such as WT1, NRAS, KRAS, KIT, FLT3-ITD etc. with respect to known KMT2A rearrangements.

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In conclusion, we have shared our experience from a major tertiary care hospital in Saudi Arabia with pediatric KMT2A/MLLT3 and MLLT11 rearranged AML patients doing relatively well with chemotherapy alone. We believe HSCT is a curative option for patients with KMT2A rearrangements and we need to study this prospectively to better delineate those partner-gene subsets that will benefit from HSCT given the high treatment related mortality associated with this approach.

Compliance with Ethical Standards

Funding

This work did not receive any financial support in any form from any funding agency.

Conflict of Interest / Competing Interests

All the authors declare no competing financial interests in the conduct of this study and its publication.

Ethical Approval

This study was submitted to the Institutional Review Board of King Faisal Specialist Hospital and Research Center, Riyadh, Saudi Arabia, and was approved by the Research Advisory Committee through established procedures with Approval Number 2191014 via Reference Number C380/383/40 on 16 January 2019.

Informed Consent/ Assent

Data of interest collected from the patients' medical records were secured as governed by the institutional policies on patient confidentiality and privacy. No informed consents were obtained since this was a retrospective review of data and all data items collected were already documented in medical charts as part of the patients care and disease management documentation.

Acknowledgements

None

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Legends

Table 1 Patient Characteristic

Table 2 Translocation partners in KMT2A rearranged AML

Figure 1(a) Pediatric AML numbers adapted from published data by Meyer et al.

Figure 1 (b) KMT2A fusion partners frequencies in our patients

Figure 2 Overall survival by treatment groups

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Table 1_Peds_KMT2A_01_21JUL2020 PBC.docx available at https://authorea.com/users/355956/articles/479035-pediatric-acute-myeloid-leukemia-with-kmt2a-rearrangement-can-partner-gene-help-determine-need-for-hematopoietic-stem-cell-transplant

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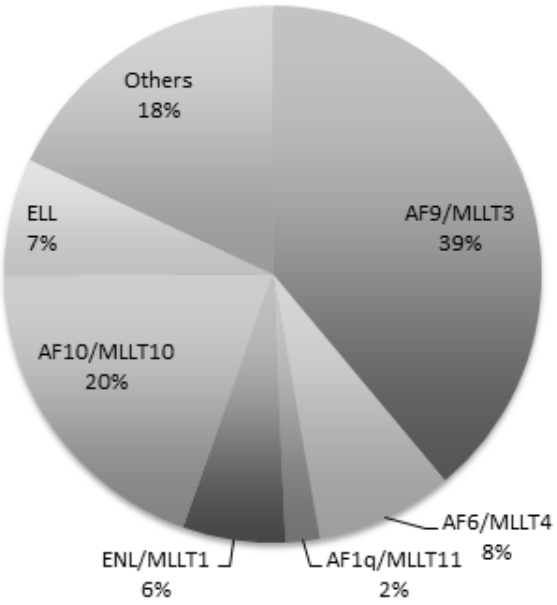
A



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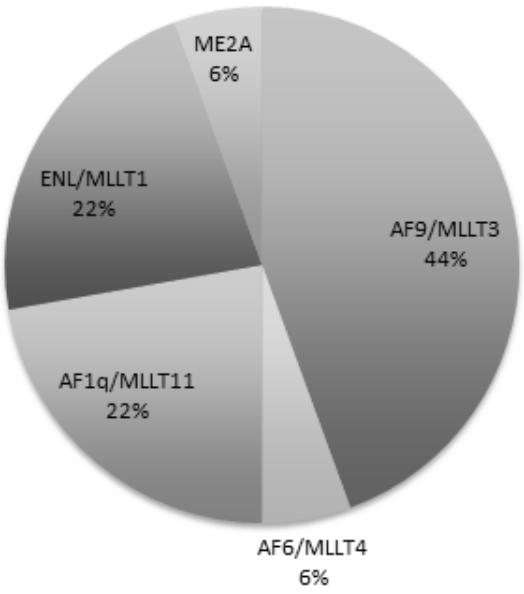

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