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REVIEW ARTICLE

AN INSIGHT ON ACUTE MYELOID LEUKEMIA: PEDIATRIC PERSPECTIVE

***Emmanuel Ifeanyi Obeagu[1] and Keerthana Gnanavel[2]**
[1]Department of Medical Laboratory Science, Kampala International University, Western Campus, Ishaka, Uganda. https://orcid.org/0000-0002-4538-0161
[2]Biotechnology, MGR College, Hosur-635130, Tamil Nadu, India.

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Abstract

Acute leukemia is the most common childhood malignancy, accounting for nearly 35% of all childhood cancers. Acute myeloid leukemia (AML) accounts for 15-20% of childhood acute leukemias. The majority of AML cases are de novo, but a minority may present as secondary malignancies. AML is a highly heterogeneous disease, the diagnosis of which involves morphology, immunophenotyping, cytochemistry, and diagnostic analyzes involving leukemic blasts derived from peripheral blood or bone marrow exhibiting cytogenic and molecular characteristics. Includes combinations. By identifying recurrent genetic mutations, it is now possible to improve individual prognosis and guide treatment management. Pediatric acute myeloid leukemia (AML) is a heterogeneous disease that requires a multifaceted therapeutic approach. Although the outcomes of low-risk AML have improved significantly over the past decades, high-risk AML continues to be associated with poor prognosis. Recent advances in molecular diagnostics, risk stratification, and supportive care have helped improve outcomes in childhood AML.

****Corresponding Author:-*** **Emmanuel Ifeanyi Obeagu;** Department of Medical Laboratory Science, Kampala International University, Western Campus, Ishaka, Uganda. https://orcid.org/0000-0002-4538-0161

Introduction

Leukemia accounts for approximately 30% of all childhood malignancies, of which 15-20% are acute myeloid leukemias (Rasche et al., 2018). Acute leukemia is the most common childhood malignancy, accounting for nearly 35% of all childhood cancers, with acute lymphoblastic

leukemia (ALL) and acute myeloid leukemia (AML) accounting for 80% of all acute leukemias can be divided into two main subtypes. Accounting for 15-20% of acute leukemias in pediatric patients, the incidence of AML is highest in infants at 1.5 per 100,000 per year and decreases to 0.4 per 100,000 at ages 5-9 years (De Rooij et al. 2015). AML is a highly heterogeneous disease in terms of its morphology, immunophenotyping, and clinical manifestations often associated with leukocytosis, anemia, and thrombocytopenia (de Rooij et al., 2015). Morphological examination is performed using blood and bone marrow smears with May-Grunwald-Giemsa or Wright-Giemsa staining (Dohner H et al., 2009; Obeagu et al., 2020; Obeagu et al., 2022; Obeagu und Babar, 2021; Obeagu, 2022). Although the majority of AML cases arise as de novo malignancies in previously healthy individuals, cases have been reported in which AML arises as a secondary malignancy. It has been seen in individuals with underlying hematologic and genetic disorders such as Fanconi anemia, Bloom syndrome, ataxia-telangiectasia, Schwackman-Diamond syndrome, Noonan syndrome, and dyskeratosiscongenita. Trisomy 21 is the most common genetic factor for the development of AML (Puumala S et al., 2013). AML pathogenesis involves aberrant proliferation and differentiation of clonal populations of bone marrow stem cells (De Kouchkovsky and Abdul, 2016). The first classification system used to distinguish between the various subtypes of AML was the French-American-British (FAB) classification system introduced in 1976. We identify eight subtypes of AML (M0–M7) based on the morphological and cytochemical features of leukemia cells (Obeagu and Obeagu, 2018; Obeagu et al., 2021; Obeagu et al., 2022). The FAB classification was superseded by WHO in 2001 and subsequently revised in 2008 and late 2016 with morphology, immunophenotype, clinical manifestations, and recurrent genetic abnormalities such as myeloid sarcoma and myeloproliferation associated with Down syndrome (Arber et al., 2016) and (Vardiman et al., 2008).

In pediatric patients, specifically under the age of 2, it is important to search for translocations that are specific for pediatric AML, as WHO classification does not represent them as new disease categories due to their rarity. These translocations, mentioned above, include t(7;12) (q36;p13) and t(11;12)(p15;p13) (de Rooij*et al*., 2015 and Arber *et al*., 2016).

Pediatric AML has been described since the 1900s with a formal classification was established in adults in 1976 by the French-American-British (FAB)-Classification (Rasche, *et al.*, 2019) and there are already six subtypes of AML that have been established and described by regular introduction of immunophenotyping modified this morphology and cytochemistry-based classification during the 1990s (Bennett *et al.*, 1976,1985, and 1991., Bloomfield and Brunning., 1985).
In the WHO classification in 2001, a shift from morphology to a primarily genetically-based classification has been released and continuously extended. In Europe, the prognosis of children with AML shows an unacceptable level of inequality of survival rates, ranging from less than 50% to 80% whereas, in the 1980s, almost all children suffering from AML died, today, up to 75% of the children survive. However, this is only feasible in a well-structured setting of comprehensive diagnostics, intensive therapy, and effective supportive care (Bonaventure *et al.*, 1995-2009).

Except for acute promyeloblastic leukemia (APL), improved survival has been achieved by using long-known conventional drugs, mainly cytarabine and anthracyclines. Scheduling risk group

stratification, modifications of allogeneic stem cell transplant (alloHSCT), and management of complications allowed for curing most children (Plana *et al.*, 2021 and Zwaan*et al.*, 2015).

Treatment-related toxicity remains relatively high at 2% to 4% in pediatric AML based on intensive chemotherapy and alloHSCT when indicated (Lehrnbecher et al., 2004). Despite the greatly improved chances of survival, this therapy has serious acute and long-term side effects, and new and innovative therapies are needed without jeopardizing the results achieved. It should be a more targeted treatment, perhaps with fewer side effects.Another aspect is that healing is paramount. Adults with a peak age of 70 years and older may benefit from achieving disease control over several years, whereas in children, cure should remain the primary goal (Bhatt et al. 2021, Molgaard et al., 2011, and Stefanski et al., 2021). Regarding more precise treatment options, differential therapy with all-trans retinoic acid (ATRA) and arsenic trioxide (ATO) is already used in APL. This makes it possible for the first time to cure without chemotherapy with significantly reduced side effects (Creutzig et al., 2018). Recent improvements in the molecular genetics and etiology of AML have been implemented in the new World Health Organization (WHO) classification of AML (Swerdlow et al., 2008). As reported by Dohner et al., these changes, along with the definition of new diagnostic and prognostic markers and associated targeted therapies, replace previous recommendations by an international group commissioned by the European LeukemiaNet for her AML in adults updated reported in 2010.

Acute Myeloid leukameia in Paediatrics

The incidence of invasive fungal infections is up to 15% in children with AML, which is similar to that in adults commonly caused by Candida and Aspergillus species (Rubnitz J, 2012). And therefore prophylaxis should be administered to all children with agents such as voriconazole, itraconazole, micafungin, or caspofungin due to drug interactions (e.g., itraconazole and voriconazole) and variable pharmacokinetics, voriconazole should be held during courses of chemotherapy and levels should be monitored periodically (Lehrnbecher T, Groll A, 2011).

Bacterial infections occur in up to 70% of children during AML therapy (Sung et al., 2007). The estimated incidence in children with high-risk AML of severe bacterial infections is 50–60% and the estimated incidence of invasive fungal infections is 7.0–12.5% (Kaya et al., 2009 and Kobayashi et al., 2008). A retrospective study from St. Jude Children's Research Hospital (SJCRH) in patients with AML found that the use of intravenous cefepime or vancomycin in conjunction with oral ciprofloxacin or a cephalosporin significantly reduced the incidence of bacterial infection and sepsis compared with patients receiving only oral or no antibiotic prophylaxis (Kurt et al., 2008).

Hematopoietic stem cell transplantation (HSCT) is used as consolidation therapy after remission. Allogeneic HSCT (allo-HSCT) has been found to be more useful than autologous HSCT (auto-HSCT). Several studies have found no benefit of autologous HSCT compared with non-myeloablative chemotherapy during initial complete remission (Stevens et al., 1998; Oliansky et al., 2007; Woods et al., 2007; et al., 2001, Ravindranath et al., 1996 and Alonzo et al., 2005).

In a preclinical study, atovaquone induced apoptosis in her AML cells, inhibited the mechanistic targets of rapamycin, inhibited oxidative phosphorylation (oxphos), and prolonged survival in a patient-derived xenograft model. (Stevens et al., 2019).

Conclusion

AML diagnosis and treatment have improved significantly over the past decades. Risk stratification allowed for more targeted and specific treatment while avoiding overtreatment for low-risk patients and allowing more intensive treatment for other patients.

Childhood's treatment of her AML, even if the economic impact is modest, should not be considered exclusively as a "waste product" of adult medicine, and is entitled to individual child-specific therapy development should this applies both to research into pediatric therapies and to the timely establishment of therapies successfully used in her AML in adults.

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