Abstract

Introduction: Fanconi anemia (FA) is an autosomal recessive syndrome characterized by genomic instability. It is associated with an increased susceptibility to develop leukemias, especially acute myeloid leukemia (AML). The usual period of development of AML is the late teenage years or young adulthood. AML in the setting of FA is associated with a grave prognosis.

Case report: In an eight-year-old boy who was diagnosed with FA seven months back, blast cells in peripheral blood were detected following a respiratory illness. Physical examination revealed polydactyly, hyperpigmentation of the tongue, café au lait macules and hepatosplenomegaly. Bone marrow morphology and flow cytometry were performed, which suggested the diagnosis of AML M4. After providing initial supportive measures, induction chemotherapy was started with Daunorubicin and Cytarabine. After induction, febrile neutropenia ensued, which was treated with multiple antibiotics and supportive measures. Despite these efforts, the child succumbed one month after starting chemotherapy.

Discussion: AML in the setting of FA is associated with an increased susceptibility to toxicity caused by chemotherapeutic agents due to their inherent DNA instability. Consequently, significant toxicity and prolonged periods of aplasia can develop following chemotherapy, resulting in a dismal outcome in these patients. Literature reviews show that newer and personalized treatment modalities like sequential chemotherapy followed by Hematopoietic Stem Cell Transplant can be attempted in these patients, which offer better outcomes. Our case report is unique since it depicts an early age of AML occurrence in the setting of FA and a short interval between their diagnoses.

Keywords: Fanconi Anemia; Acute Myeloid Leukemia; Chemotherapy; Hematopoietic Stem Cell Transplant

Abbreviations: FA: Fanconi Anemia; AML: Acute Myeloid Leukemia; MDS: Myelo Dysplastic Syndrome; HSCT: Hematopoietic Stem Cell Transplantation; RIC: Reduced Intensity Conditioning

Introduction

Fanconi anemia (FA) is a genomic instability syndrome with autosomal recessive inheritance [1]. It is the most common genetic cause of bone marrow failure. More than 18 FA genes have been identified, with FANCA, FANCC, FANCG and FANCD2 being the most frequently involved genes in patients with FA [2-5]. It is associated with congenital anomalies, progressive pancytopenia and a predisposition to malignancies, among which Acute Myeloid Leukemia (AML) is the commonest. Studies conducted on FA patients and mice models support the view that DNA damage and cell stress trigger senescence and cell death in proliferative hematopoietic progenitor cells, with compensatory or inflammation-related mobilization and the eventual attrition of hematopoietic stem cells [1,6-9]. The resulting stem and progenitor cell deficiency, FA intrinsic genetic instability and possibly chronic inflammation are thought to create a strong pressure toward clonal evolution in the bone marrow of FA patients [9-11]. AML in this setting is associated with significant treatment-related mortality and a poor outcome [12-14]. The cumulative incidence of AML ranges from 10% to 37% by 50 years of age and the most common period of development of leukemia is the teenage years or young adulthood [15-18]. Here, we report the case of an eight-year-old boy diagnosed with FA who developed AML seven months later, which is a rarity.

Case Description

An eight-year-old boy was a known case of FA which was diagnosed in December 2015 by Mitomycin-induced chromosomal breakage analysis and was placed on supportive treatment including blood component transfusion (Figure 1). He consulted his pediatrician with a five-day history of fever and cough in August 2016 and a hemogram that was done showed blast cells. He was then referred to our institute for further evaluation and management. On examination, his vitals were...
stable and ECOG performance score was 3. There was pre-axial polydactyly in the right hand, hyper-pigmentation of tongue and multiple small-sized cafe-au-lait macules on his back (Figure 2). Cervical and axillary lymph nodes were found to be significantly enlarged. Further, splenomegaly of 10 cm and hepatomegaly (of 12 cm span) were present.

A hemogram revealed 9 gm% Hb, WBC counts above 1 lakh with 80% blasts and a platelet count of 60,000. LDH was found to be five times higher than the standard value and serum albumin was low. Bone marrow aspiration study and flow cytometry suggested Acute Myeloid Leukemia (AML) M4 (Figure 3). Conventional cytogenetics was found to be normal. After the patient was stabilized using supportive measures, induction with Daunorubicin (45 mg/m² for 3 days) and Cytosine arabinoside (100 mg/m² for 7 days) (3+7 protocol) was started on September 8, 2016. Following induction, febrile neutropenia developed and he was started on parenteral Ceftazidime and Amikacin. The blood culture was sterile and a chest X-ray showed right middle lobe consolidation. Antibiotics were upgraded to Meropenem and later, Tigecycline since the symptoms persisted. Amphotericin-B was added, as well. Generalized edema developed and serum biochemistry revealed severe hypoalbuminemia, hypoproteinemia, hypokalemia and hypocalcemia. Along with blood components therapy, the correction of electrolytes and albumin was done. In spite of all these efforts, his condition worsened and he succumbed on October 3, 2016.
Discussion

In the setting of FA, both Myelo Dysplastic Syndrome (MDS) and AML are often preceded by a Bone marrow failure phase. Although AML can be diagnosed de novo, it more often develops from an MDS phase with the proportion of blast cells increasing over months or years. A retrospective analysis of 145 cases of FA by Rosenberg et al. [16] which was published in 2003, observed 9 cases of AML, 14 cases of solid tumors and 23 cases of MDS. By the age of 17 years, 12% of patients had died from hematological complications or the development of cancer. Similarly, 10% of cases developed AML by the age of 24 years, following which the incidence remained constant [16]. Talbot et al. reported the outcome of five FA cases with AML, treated using sequential chemotherapy followed by hematopoietic stem cell transplantation (HSCT) from 2006 to 2011. After a median follow-up of 28 months, all patients remained in complete remission [19]. In 2008, Ayas et al. [20] reported on 11 patients with FA having MDS and/or clonal abnormalities, including 1 patient with clear AML, who were transplanted using cyclophosphamide and total body irradiation (TBI; 450 cGy) [20]. Among them, 10 patients were reported to be alive with no evidence of disease with a median follow up of approximately 4 years. The overall excellent results illustrate the possibility of long-term survival after HSCT in this context. More recently, Mitchell et al. reported on 21 FA patients who were transplanted due to AML (n=12), ALL (n=1) and advanced MDS (n=8). They had a median FU of approximately 10 years, with a 5-year overall survival rate of 33%, illustrating again that long-term remission could be achieved after HSCT in patients even in the case of overt leukemia [14].

FA patients who develop MDS and/or leukemia are not easy to manage because sensitivity to DNA-damaging agents limits the therapy that they can tolerate [21]. In such patients, chemotherapy is regularly associated with significant toxicity and, possibly, prolonged aplasia, with certain complications that may eventually contraindicate HSCT. One possibility is the use of sequential chemotherapy, which has been described in non-FA patients who are not in remission and has achieved acceptable results [22]. Today, many centers recommend sequential chemotherapy followed by HSCT in the setting of FA with AML. It comprises pre-transplant chemotherapy with fludarabine (30 mg/m² per day for 5 days) and cytarabine (1 g/m² twice per day for 5 days) with granulocyte colony-stimulating factor injections (FLAG), which are followed 3 weeks later by a reduced intensity conditioning (RIC) regimen (4 days of cyclophosphamide, 10 mg/kg; 4 days of fludarabine, 30 mg/m²; and TBI 2 Gy) that is delivered during chemotherapy-induced aplasia. Again, anti-thymocyte globulin is used in total doses of 5 mg/kg in the case of matching unrelated donors alone [1,23].

Conclusion

Usually, AML in FA develops during the late teenage years or in young adulthood. Thus, our case report is unique since it reports an early age of occurrence of AML and a short interval between the diagnoses of FA and AML. Lifelong follow-up is imperative for children with FA, as they have high risk of developing secondary leukemias. Children with AML in the setting of FA are more prone to the development of toxicity to chemotherapy agents and are associated with dismal outcomes. Hence, individualized and advanced treatment modalities including sequential chemotherapy followed by HSCT would offer better survival advantage to these patients.

References


