Case Report

Role of steroids in the treatment of Acute Myeloid Leukemia in Children

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Abstract

The use of steroids in the management of Acute Myeloid Leukemia (AML) along with chemotherapy has been questionable and is not a part of any standard regimen. Various studies have claimed diverse opinions about the role of steroid in AML, many of them suggesting it may cause reduction in tumor load by causing blast apoptosis. In this case series of two children with AML, we have tried to show how steroids (Prednisolone and Dexamethasone) in a case of AML-M7 with RAM phenotype led to blastic transformation whilst causing cytoreduction and tumor lysis in the second case of non-promyelocytic AML who presented with hyperleukocytosis.

We hereby present two such cases with contrasting findings to determine the role of steroids in AML.

Keywords: Acute myeloid leukemia, steroids, apoptosis, leukocytosis, tumor lysis syndrome

INTRODUCTION

Acute Myeloid Leukemia is characterized by clonal proliferation of myeloid, erythroid and/or megakaryocytic lineage, leading to pancytopenia, bleeding, and infection. Approximately 20% of patients present with high white blood cell (WBC) counts (i.e., >50×109/L) at diagnosis. (1) Considerable progress has been made in understanding the molecular alterations and epigenetics in AML leukemogenesis like the role of inflammation in the disease progression or failure in remission, chemoresistance, and myelosuppression. (2) This reliably points towards the advantage of using anti-inflammatory drugs such as steroids in AML especially with hyperleukocytosis. (3)

Based on the case reports of two children with AML, it can be shown how on one hand steroid may lead to leukocytosis unmasking the disease, while on the other, may lead to apoptosis and tumor lysis. Our first patient was diagnosed with AML-M7 with RAM phenotype (high risk) after blasts became evident with steroid-induced leukocytosis and disease progression. The other was a case of non-promyelocytic AML with high baseline leucocyte counts in tumor lysis syndrome which worsened with steroids, suggesting its apoptotic role in AML. Role of steroids in AML leukemogenesis, especially in the cases associated with intrinsic chemo-resistance and hyperleukocytosis needs to be discussed.

CASE SYNOPSIS

CASE 1

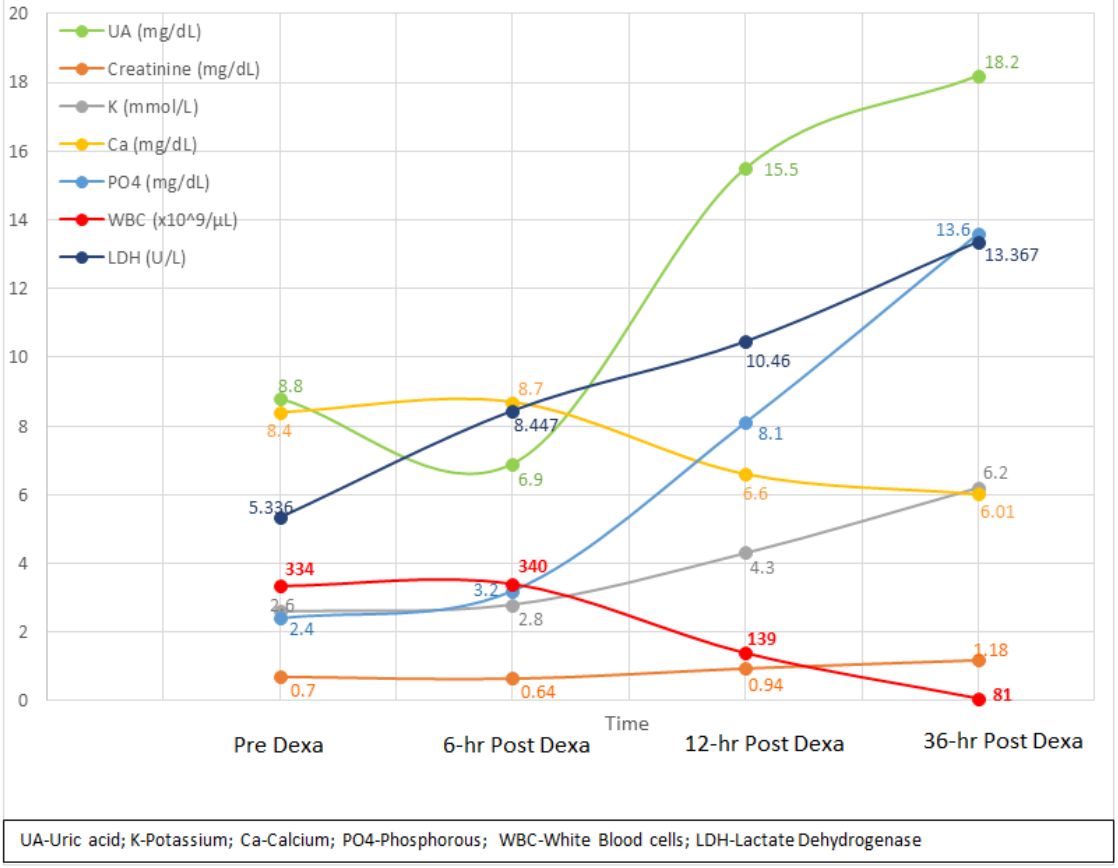
A 14-month-old female presented with reduced appetite, abdominal distension, and fever for 3 months. On examination, the patient had pallor, bilateral pitting oedema, hepatosplenomegaly (liver 4 cm and spleen 9 cm below costal margin) and ascites. Complete blood count and peripheral smear revealed bicytopenia (Hemoglobin 6.3 gm%; WBC 7.4x109 per microL; platelet count 20x109/microL) with lymphocytosis (77%) and reduced reticulocyte count (0.07%) without any abnormal cells. Biochemical investigations ruled out any evidence of tumor lysis syndrome. While ascertaining infective causes in the diagnostic workup, the patient's serology was found to be positive for Toxoplasmosis IgG and IgM. Bone marrow aspiration and biopsy at that time was normocellular with the shift to left in the myeloid series and no abnormal cells. Parameters for hemophagocytic histiocytosis (ferritin, fibrinogen, fasting triglyceride) were negative. Lymphocyte subset analysis and immunological workup were negative for autoimmune lymphoproliferation/ cytopenia. Due to clinical deterioration in the absence of any obvious infective, or malignant etiology, the child was empirically started on oral steroid (Prednisolone @2mg/kg/day) suspecting underlying immune-mediated cytopenia. After 4 days, she developed leukocytosis, and peripheral smear demonstrated the presence of blasts. Repeat bone marrow aspiration now demonstrated hyperproliferative marrow with a blast cell population of 73%. Flow cytometry revealed bright expression of CD56, CD33 and negative CD2, CD3, CD4, CD5, CD10, CD19, CD20, CD34, CD38, HLA-DR and MPO s/o AML-M7 with RAM phenotype. Conventional karyotyping from previous bone marrow showed hyper diploidy (49,XX,+3,+7,+21[14] / 46XX). Polymerase chain reaction (PCR) for AML was negative. CSF analysis was negative for blasts. The treatment regimen of the patient included 4 cycles of chemotherapy (2 cycles of induction with Cytarabine 100mg/m2 and Daunorubicin 50mg/m2 and 2 cycles of high-dose Cytarabine 18g/m2). She responded well after first cycle of induction and minimal residual disease was negative. Unfortunately, she relapsed after 6 months and died of disease while on palliation.

CASE 2

A 6-year-old female child presented with complaints of fever, bilateral neck swellings, abdominal distension, and abdominal pain for a week. On examination, she had pallor, generalized lymphadenopathy, hepatosplenomegaly and moderate ascites. CBC was suggestive of bicytopenia with hyperleukocytosis (Hb-5.5g%/ TLC-334 x109 per microL / PLT-68x109/microL) with 90% blasts demonstrated on peripheral smear. Biochemistry evaluation was suggestive of TLS at presentation (LDH-5336 U/L, uric acid- 11.16mg/dL, creatinine- 0.76mg/dL, potassium-3.39mmol/L, calcium-9.3mg/dL, phosphorous-2.42mg/dL). Coagulation profile was deranged with PT:29.3sec, aPTT:37.5sec, INR:2.57. Immunophenotyping by flow cytometry revealed 88.5% abnormal cells with bright CD33, moderate CD117, CD64, CD11b, CD4, HLA-DR, dim CD36 with negative CD14 and cytoplasmic MPO suggestive of Acute monoblastic leukemia. Cytogenetics by karyotyping showed 47, XX,del(7)(q22q32),del(11)(q23),add(20)(q13.3),+mar(cp20). After 18 hours of admission, the patient started

having altered sensorium, anisocoria and features of increased intracranial pressure. Intracranial bleed was suspected and hence platelets, fresh frozen plasma and packed RBCs were transfused and patient was put on mechanical ventilation. For hyperleukocytosis, the patient was started on Dexamethasone injection 12 hourly. Patient showed transient improvement in TLS parameters after 3 to 7 hours of dexamethasone, however, developed aggressive TLS after 12 hours (Fig. 1). Hence Dexamethasone was withheld and appropriate management was started. However, 1 hour after administering the second dose of Dexamethasone the patient developed cardiac arrest and succumbed.

Figure 1 TLS parameters pre and post Dexamethasone



UA-Uric acid; K-Potassium; Ca-Calcium; PO4-Phosphorous; WBC-White Blood cells; LDH-Lactate Dehydrogenase

DISCUSSION

The curative treatment of AML has been based on a combination of cytarabine and anthracycline as induction chemotherapy followed by intermediate to high- dose consolidation therapy and possibly allogenic stem cell transplantation. So far glucocorticoids have not been a part of the standard protocol for treatment of AML. However, various studies have showed the benefits of using corticosteroids in the treatment of AML. (1,3,5,6) It can be observed that the use of corticosteroids in AML have shown contrasting outcomes in these two cases. While one child had steroid induced leukocytosis which helped in unmasking the disease (Case 1), the other developed steroid induced leukoreduction with worsening TLS (Case 2). These observations are consistent with the findings of a few studies that have demonstrated how steroids can lead to leukocytosis. (4,5,9) The idea of leukocytosis associated with blastic progression by steroids in leukemia is still a novel finding and needs

substantial research. On the contrary, there is enough evidence to suggest how corticosteroids moderate inflammation and leukoreduction in AML thereby increasing chemosensitivity. (2,4,6,9)

A study conducted on using dexamethasone as pre-phase on patients with AML suggested a lower rate of early mortality following induction chemotherapy despite a higher rate of admission to the intensive care unit (ICU). According to the study, dexamethasone, by affecting specific transcriptomic programs and/or by modulating the early inflammatory response which is associated with chemoresistance, might sensitize AML cells to chemotherapy-induced cell death and thereby limit the risk of leukemic growth and relapse.(2) Another study showed that adding dexamethasone to the chemotherapy regimen in AML FAB-M5 with acute respiratory failure from leukemia-related pulmonary involvement significantly diminishes intensive care unit mortality.(7) A case report on myelodysplastic syndrome successfully highlighted the role of high dose methylprednisolone in its treatment.(6) Pretreatment with short course of high dose methylprednisolone (HDMP), before high dose consolidation therapy, reduced duration and severity of neutropenia. In addition, rapid decrease in blast cells in both peripheral blood and bone marrow was also observed with HDMP therapy suggesting GC-induced differentiation. (6,7) A study from a tertiary cancer centre in India concluded how incorporation of steroids in induction regimen of AML could lead to lesser mortality and successful outcomes.(10)

CONCLUSION

The usage of steroids in the treatment regimen of AML has been questionable for quite a long time. Outcomes of different studies and trials have pointed towards different theories, some of them in favour and some against. The two cases in this report showed two contrasting outcomes, but we can comment through our second case that steroids may have a role to play in the management of AML. Further randomized controlled trials are needed to conclude.

CONFLICT OF INTERESTS

None

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