Efficacy and tolerability of corticosteroids in pediatric cancer chemotherapy patients

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ABSTRACT
Efficacy and tolerability in the treatment of pediatric cancer was studied in the present investigation. Prednisone, Hydrocortisone, Dexamethasone, Prednisolone and Methyl prednisolone were used in the treatment. The pediatric patients were divided into six groups. Each group was given one corticosteroid along with their regular chemotherapy. The efficacy of chemotherapy was satisfactory in groups when compared with groups received only chemotherapy.

1. INTRODUCTION
Corticosteroids (CS), also called glucocorticoids or steroids, are the hormones produced by the adrenal cortex, part of the adrenal glands.
 Cortisone was first identified by the American chemists Edward Calvin Kendall and Harold L. Mason while researching at the Mayo Clinic. Kendall was awarded the 1950 Nobel Prize for Physiology or Medicine along with Philip S. Hench and Tadeus Reichstein for the discovery of adrenal cortex hormones, their structures, and their functions. These hormones affect almost all body organs and are extremely important in maintaining homeostasis when secreted in normal amounts. Disease results from inadequate or excessive secretion.
 Corticosteroids have been used as anticancer agents since the 1940s, with activity reported in a wide variety of solid tumors, including breast and prostate cancer, and the lymphoid hematologic malignancies. They are commonly found in regimens for acute lymphocytic leukemia, Hodgkin’s and non-Hodgkin’s lymphoma, myeloma, and chronic lymphocytic leukemia.
 Corticosteroids are used as drugs in a variety of disorders. Corticosteroids are secreted directly into the bloodstream. Cortisol is approximately 90% bound to plasma proteins (80% to an alpha globulin called transcortin or cortisol-binding globulin and 10% to albumin). This high degree of protein binding slows cortisol movement out of the plasma, so that it has a relatively long plasma half-life of 60 to 90 minutes. The remaining 10% is unbound and biologically active. In contrast, aldosterone is only 60% bound to plasma proteins and has a short half-life of 20 minutes. In general, protein binding functions as a storage area from which the hormones are released as needed. This promotes more consistent blood levels and more uniform distribution to the tissues.
 CS is an important class of naturally occurring and synthetic steroid hormones that affect virtually every aspect of human physiology. CS therapy affects endogenous CS production and has a suppressive effect on hypothalamic-pituitary-adrenal (HPA) axis.
 Mechanism of action: The pharmacological actions of steroids are generally an extension of their physiological effects. Adrenal corticosteroids exert effects on almost every organ in the body. In normal physiological concentrations, they are proceeds from 17- hydroxyprogesterone and 1-deoxycortisol to yield cortisol.

Thus, steroid intermediates are converted to steroid end products by sequential 17-21-, and 11-hydroxylation reactions. 11-Hydroxylation is essential for glucocorticoid and mineralocorticoid activity of a steroid. The steroid hydroxylase system has the characteristics of a mixed-function oxidase, since two substrates, steroid and NADPH, are oxidized. All hydroxylases seem to be associated with a specific cytochrome P450.

The 17- and 21-hydroxylase enzymes are associated with microsomes, whereas the 11-hydroxylase has a mitochondrial origin. Since the last-named enzyme is not detectable in other steroid-producing tissues, the term 11-oxygenated steroids are
considered synonymous with adrenal steroids. Aldosterone synthesis involves an essential 18-hydroxylation step catalyzed by P450c18 with corticosterone as the precursor; this reaction also takes place within the mitochondria.

Cortisol diffuse into target cells & binds to a cytoplasmic glucocorticoid, thyroid & retinoid receptors. The activated receptor – glucocorticoid complex enters the nucleus & binds to steroid response elements on target DNA molecules. This either induces the synthesis of specific mRNA or represses genes by inhibiting transcription factors. Eg; NFKB.

Prednisone and dexamethasone are corticosteroids. They have profound effects on metabolism, immune response, inflammatory response, and many other body systems and processes. In the treatment of cancer, they are often given to patients to alleviate symptoms caused by chemotherapy, or to treat the hypercalcemia associated with some cancers. They are used for the palliative management of acute leukemias and lymphomas. Their mechanism of action on these cancers is not well understood. These drugs may be given by mouth or by injection.

![Diagram of Pharmacological Drug Classification of corticosteroids](image1)

![Diagram of Immunosuppression action of corticosteroids](image2)

2. MATERIALS AND METHODS

New treatment approaches for the childhood Hemato malignancies: Researchers are now studying the causes, diagnosis, and treatment of leukemia at many medical centers, university hospitals, and other institutions.

Genetics: Scientists are making progress in understanding how changes in the DNA inside bone marrow stem cells can cause them to develop into leukemia cells. Understanding these gene changes (such as translocations or extra chromosomes) can help explain why these cells may grow out of control, and why they don’t develop into normal, mature cells.
Doctors are now looking to use these changes to help them determine a child’s outlook and whether they should receive more or less intensive treatment.

This progress has already led to vastly improved and very sensitive tests for detecting leukemia cells in blood or bone marrow samples, polymerase chain reaction (PCR) test.

For example: It can identify very small numbers of leukemia cells based on their chromosome translocations or other rearrangements. This test is useful in determining how completely the leukemia has been destroyed by treatment, and whether a relapse will occur if further treatment is not given.

Clinical trials: Most children with leukemia are treated at major medical centers, where treatment often means taking part in clinical trials to get the most up-to-date care. Several important questions are now being studied in clinical trials, among them are:

- Why do some children with acute lymphocytic leukemia (ALL) relapse after treatment, and how can this be prevented?
- Are there other prognostic factors that will help identify which children need more or less intensive treatment?
- Can chemotherapy drug resistance in acute myelogenous leukemia (AML) be reversed?
- Are there better drugs or combinations of drugs for treating the different types of childhood leukemia?
- When exactly should a stem cell transplant be used to treat leukemia?
- How effective are stem cell transplants in children who don’t have a brother or sister who is a good tissue type match?
- Can a second stem cell transplant help children who relapse after a first stem cell transplant?
- What are the best treatment approaches for children with less common forms of leukemia, such as juvenile myelo-monocytic leukemia (JMML) and chronic myeloid leukemia (CML)?

Immunotherapy to treat childhood leukemia: Are treatments that boost a child’s own immune system to help fight leukemia. Some types of immunotherapy have shown a lot of promise in treating ALL, even when other treatments are no longer working.

Chimeric antigen receptor (CAR) T-cell therapy: In this treatment, immune cells called T cells are removed from the child’s blood and genetically altered in the lab to have specific receptors (called Chimeric antigen receptors, or CARs) on their surface. These receptors can attach to proteins on the surface of leukemia cells. The T cells are then multiplied in the lab and given back into the child’s blood, where they can seek out the leukemia cells and launch a precise immune attack against them.

This technique has shown very encouraging results in early clinical trials against some advanced, hard-to-treat cases of ALL. In many children the leukemia could no longer be detected after treatment, although it’s not yet clear if these children have been cured.

Some children have had serious side effects from this treatment, including very high fevers and dangerously low blood pressure in the days after it’s given. Doctors are learning how to manage these side effects are still improving how they make the T cells and are learning the best ways to use them. CAR T-cell therapy is only available in clinical trials at a handful of major medical centers at this time.

Monoclonal antibody therapy: Antibodies are proteins made by the body’s immune system to help fight infections. Man-made versions, called monoclonal antibodies, can be designed to attack a specific target, such as a protein on the surface of leukemia cells.

Example: Blinatumomab (Blincyto), a special kind of monoclonal antibody that can attach to 2 different proteins at the same time. One part of blinatumomab attaches to a protein found on B cells (the cells that become leukemia cells in most cases of ALL). Another part of the antibody attaches to a protein on immune cells called T cells. By binding to both of these proteins, this drug brings the leukemia cells and immune cells together, which is thought to cause the immune system to attack the cancer cells. Early results with this drug against B-cell ALL have been promising, although so far it has been studied more in adults than in children.

Study design: Institutional Ethics Committee forms all of the participating sites approved the protocol for this prospective, parallel – group, 6 months study. Before any study – specific procedure was performed, each patient’s parent or guardian were provided written, informed consent and patient assent was obtained when age appropriate (typically of patients age ≤ 12years).

The study procedures were conducted in accordance with the ethical principles of the Declaration of Helsinki and its amendments and with the Central Drug Standards Control Organization recommendations, Indian Council for Medical Research, and Good Clinical Practice guidelines.

Patient selection & Procedures: The 150 pediatric patients of age ≤ 12years receiving corticosteroids with chemotherapy were enrolled in this study between January to June 2016. 130 patients were met the inclusion criteria with the following conditions: Acute lymphoblastic leukemia (ALL), Acute myeloid leukemia (AML), Acute pro–myeloid leukemia (APML), Idiopathic thrombocytopenia (ITP), Evans syndrome, Hemophagocytic Lymphohistiocytosis (HLH). Exclusion criteria included 20 patients with co-morbid conditions and morbidity. Parents or guardians provided written informed consent. Patients underwent physical examination and blood collection for determination of disease condition.

Disease state: The diagnosis of the disease was based on the clinical presentation. The 130 pediatric leukemia
patients who met inclusion criterion were ALL – 47(61%), AML – 5(6.5%), APML – 13(16.9%), ITP – 12(15.6%), Evans syndrome – 22(28.6%), HLH – 31(40.3%).

The total average percentage number of pediatric leukemia patients was divided into 6 groups based on their age and with respective disease conditions.

**Treatment:** The treatment is categorized into three phases they are:
- Induction phase (IP).
- Consolidation phase (CP).
- Maintenance phase (MP).

The 130 leukemia pediatric patients are divided into groups with respect to disease conditions in this study. Based on the disease condition treatment is initiated.

**Induction Phase:** In the initial phase of this study patients were prospectively randomized into 6 programs.

**Group 1:** ALL patients received Doxorubicin 30mg/m², Vincristine 1.4mg/m², Prednisone 40mg/m², Asparginase 5000IU/m². The median time of observation from patient entry was 4 weeks.

**Group 2:** AML patients received Cytarabine 3000mg/m², Daunorubicin 60mg/m², Etoposide 50mg/m². The median time of observation from patient entry was 2 months.

**Group 3:** APML patients received Cytarabine 3000mg/m², Daunorubicin 60mg/m², Etoposide 50mg/m². The median time of observation from patient entry was 3 months.

**Group 4:** ITP patients received Prednisolone 40mg/m², IvIg 0.8mg/m². The median time of observation from patient entry was 2 weeks.

**Group 5:** Evans syndrome patients received Prednisolone 1mg/kg/day, Etoposide 50mg/m², Cyclophosphamide 650mg/m². The median time of observation from patient entry was 4 months.

**Group 6:** HLH patients received Dexamethasone 0.6mg/kg. The median time of observation from patient entry was 4 weeks.

**Consolidation phase:**
- **Group 1:** ALL patients received Cytarabine 3000mg/m², Etoposide 100mg/kg, Methotrexate 12.5mg, methyl prednisolone 32mg/m². The median time of observation from patient entry was 2 months.
- **Group 2:** AML patients received Cytarabine 3000mg/m², Etoposide 100mg/m².
- **Group 3:** APML patients received Cytarabine 3000mg/m², Etoposide 100mg/m².
- **Group 4:** ITP patients received Rituximab 350mg/m². The median time of observation from patient entry was 4–6 weeks.
- **Group 5:** Evans syndrome patients received IvIg (Intravenous Immunoglobulin) 2gms/kg/day, prednisolone 40mg/m². The median time of observation from patient entry was 4 weeks.
- **Group 6:** HLH patients received IvIg 0.5gms/kg, Etoposide 100mg/m². The median time of observation from patient entry was 2 weeks.

**Maintenance phase:** Maintenance therapy in patients achieving complete remission consisted of

**Group 1:** ALL patients received Methotrexate 12.5mg, methyl prednisolone 30mg/m².
Group 2: AML patients received Busulfan 50mg/m2, Etoposide 100mg/m2
Group 3: APML patients received Busulfan 50mg/m2, Etoposide 100mg/m2
Group 4: ITP patients received methyl prednisolone 30mg/kg m2, IvIg 2g/kg/day
Group 5: Evans syndrome patients received cyclosporine 5mg/kg/day, Rituximab 375 mg/m2, Vincristine 1.4mg/m2
Group 6: HLH patients received cyclosporine 2mg/kg/day, prednisolone 40mg/kg/m2.

3. RESULTS AND DISCUSSION

Efficacy and Tolerability assessment: The primary efficacy end point in this study was the rate of complete remission (CR). Pediatric leukemia patients were assessed monthly for remission status. A pediatric leukemia patient had to meet the following criteria to be classified as having achieved CR: leukemic blasts absent from peripheral blood; percentage of blasts in the bone marrow 5% or less, as measured by morphologic studies, either bone marrow aspirate or biopsy; peripheral blood counts with hemoglobin level 9 g/dL or greater, absolute neutrophil count 1500/µL or greater, and platelet count 100 000/µL or greater. Deaths occurring within 1 month after discontinuation of study drug were reported as a serious adverse event.

The primary safety assessment was monitoring of adverse events (AE), was defined as any reaction, side effect, or other untoward event, regardless of relationship to study drug, that was not present at baseline and that occurred during the conduct of the clinical trial. An Adverse events also defined as treatment emergent or infusion-related adverse events or any clinically significant abnormal laboratory finding in order to ensure maximum tolerated dose criteria had not been fulfilled before escalating to the next dosage safety findings were thoroughly reviewed and discussed with the protocol. Ongoing adverse events were followed for as long as necessary until the event resolved or stabilized.

Efficacy: This is a prospective study which was conducted between January 2016 and June 2016 at Rainbow Children’s Hospital in Hyderabad. Of the 150 pediatric patients, 130 pediatric patients were randomized in the study.

The 130 leukemia pediatric patients who are enrolled and met the inclusion criterion were differentiated into groups based on leukemia diseases i.e; ALL, AML, APML, ITP, HLH, Evan’s syndrome. In the Leukemia pediatric patients, the diagnosis was made based on the complete blood count. The CBC includes hemoglobin, WBC, RBC, platelet count, packed cell volume, C-reactive protein.

The complete blood count of 130 pediatric patients was monitored with the standard reference range. During the study period, the complete blood count after the initiation of corticosteroidal drugs with cancer chemotherapy leukemia pediatric patients were assessed monthly for remission status; during this process the leukemia blasts showed decrease in count in the peripheral blood which is collected from pediatric leukemia patients. The range or limit of cells in the bone marrow should be 5% or less, hemoglobin level 9g/dL or greater, neutrophil count 1500/µl or >, and platelet count 100000/µl or >, Deaths occurring within 1 month of the study were reported as serious adverse effects.

Treatment: The treatment is categorized into 3 phases Induction phase, Consolidation phase, Maintenance phase. The treatment includes corticosteroids with chemotherapy drugs were initiated in the pediatric leukemia patients. After the initiation of corticosteroidal drugs with cancer chemotherapy treatment in pediatric leukemia patients, the efficacy results of corticosteroidal drugs are depicted in Table.1.

In ALL treatment corticosteroidal drugs along with chemotherapy showed efficacy of prednisone – 22%, hydrocortisone – 10%, dexamethasone – 20%, prednisolone – 30% and methylprednisolone – 18%. However, remission was short (1 year), and relapse, often coinciding with the appearance of steroid resistance, was inevitable. For these reasons, multiple drug therapy was initiated, which involves combining prednisolone with other cytotoxic agents. With the advent of regimens which contain prednisolone, more than 90% of children and 60 to 80% of adults achieve remission. The inclusion of agents such as daunorubicin, L-asparaginase, cytosine arabinoside, doxorubicin, and cyclophosphamide appears to prolong remission, but whether it increases the rate of remission is unclear. After remission is achieved, a 2 - 3 years program of maintenance therapy follows that involves regular intensive chemotherapy sessions that include corticosteroids.

In refractory cases, or in cases of relapse, which occurs in approximately 20% of children with acute lymphoblastic leukemia, re-induction involves more aggressive combination chemotherapy, again including a corticosteroid. However, overall survival rates after relapse remain fairly low, averaging 35 to 65% in children and less in adults.

In AML corticosteroids showed effectiveness of prednisone – 3%, hydrocortisone – 5%, dexamethasone – 40%, prednisolone – 50%, methylprednisolone – 2%. Prednisolone showed more effective in AML, after prednisolone dexamethasone appeared to have little value in the treatment of acute myeloid leukemia. While they have been included in some combination chemotherapy, their importance in such regimens is unclear.

In ITP prednisolone should remain the drug of choice for the initial management. It showed highest response of 60% than other corticosteroidal drugs. Treatment with corticosteroids may not only reduce the rate of platelet destruction but may also rapidly alter...
endothelial cell integrity to facilitate primary hemostasis & to reduce bleeding and bruising. IvIg has been the second drug of choice after corticosteroids for many years. IvIg is administered for patients who are resistant to corticosteroids.

In Evans syndrome prednisolone is the first line agent and effectively controls acute episodes, though relapses may be frequent when patients are weaned off prednisolone. After prednisolone, prednisone showed more response in pediatric patients.

In HLH the most common treatment is a core combination of prednisolone and Etoposide, as suggested in the international HLH-94 protocol. Patients who are recovering with this therapy are weaned off, while those who are not improving are continued on therapy as a bridge to allogenic hematopoietic cell transplantation (HCT).

Among corticosteroidal drugs, Prednisolone showed major response compared to other corticosteroidal drugs in the pediatric leukemia diseases. The percentage efficacy of prednisolone in ALL – 30%, AML – 50%, APML – 43%, ITP – 41%, Evan’s syndrome – 30%, HLH – 29% respectively.

<table>
<thead>
<tr>
<th>Diseases</th>
<th>Percentage of Corticosteroidal drugs administered in number of pediatric leukemia patients</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Prednison e</td>
</tr>
<tr>
<td>ALL</td>
<td>22%</td>
</tr>
<tr>
<td>AML</td>
<td>3%</td>
</tr>
<tr>
<td>APML</td>
<td>27%</td>
</tr>
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<td>ITP</td>
<td>10%</td>
</tr>
<tr>
<td>Evan’s syndrome</td>
<td>20%</td>
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<tr>
<td>HLH</td>
<td>15%</td>
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4. CONCLUSION

Our study explored efficacy and tolerance of corticosteroids with combination of chemotherapy in pediatric cancer patients. Efficacy is to achieve complete remission with corticosteroids in combination with chemotherapy in pediatric leukemia patients as part of the treatment to destroy cancer cells and make chemotherapy more effective. Our results explored that prednisolone is effective than other corticosteroidal drugs in treatment of leukemia pediatric patients because of its cytotoxic effect and corticosteroids showed preponderance response of complete blood count in combination with cancer chemotherapy. In pediatric leukemia patients, the adverse events observed by administered corticosteroidal drugs are inevitable and manageable.

REFERENCES