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POST CHEMOTHERAPEUTIC TREATMENT IMPACT ON PEDIATRIC PATIENTS WITH ACUTE LYMPHOBLASTIC LEUKEMIA

by

ROAA ALFARSHOOTI

THESIS

Submitted to the Graduate School of Wayne State University, Detroit, Michigan in partial fulfillment of the requirements for the degree of

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Dr. Mohammad Ramzi November 27, 2020

Advisor Date
DEDICATION

I dedicate this humble thesis to my amazing family who believed in me and my abilities. I am grateful for my parents who overwhelmed me with their day and night prayers and who instilled in me the love of learning and supported me to be a physician and continue my graduate education. There are not enough words to describe my love and appreciation for my dear husband, Jasim, who supported me throughout the journey. I am also grateful for my beloved son, Mohammed, who was so patient with me for being too busy in my studies and not providing him with all the care he deserves. I am thankful to have my baby girl, Monai, in my womb throughout the journey of preparing and writing my thesis and who has recently come into this world and made my life even brighter. I am fortunate to have you all in my life.
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I gratefully acknowledge the scholarship funding I received from the Saudi government and Ministry of Health towards my master’s degree. Finally, I would like to express my deep gratitude and appreciation for the generous and genuine support and guidance I have received from everyone throughout my academic years. God praise you all and provide you with happiness and a fruitful future.
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CHAPTER 1 INTRODUCTION

Acute lymphoblastic leukemia (ALL) is the most acute malignant blood disease affecting children. This disease represents about 80% of acute types of leukemia and the most common cause for children’s death under twenty years of age [1]. It was estimated that in the United States, 2500-3500 new pediatric patients were diagnosed with ALL yearly with an incidence rate of 3.4 in 100,000 cases [2]. In Northern America, the incidence rates of ALL among male children are more than 10 in 100,000 and among female children are more than 7 in 100,000 [3]. This type of leukemia is characterized by a malignant proliferation and mutation of immature lymphoid cells residing in the blood, bone marrow, and other organs. Although most of the cases are de novo ALL in a formerly healthy pediatric population, a small number of cases are attributable to predisposing factors including genetic syndromes such as Down syndrome, ataxia-telangiectasia, Fanconi anemia, exposure to some viruses such as HIV and EBV, and ionizing radiation. ALL in pediatric patients develop in the T & B lymphoblasts of the bone marrow [4]. Pediatric ALL patients experience signs of bone marrow failure such as thrombocytopenia, anemia, and leukopenia, in addition to some agonizing symptoms such as pain, fever, fatigue, bleeding, and bruising. ALL is diagnosed when at least 20% lymphoblasts are detected in bone marrow or peripheral blood [4]. Aggressive chemotherapy regimens commonly used in the treatment of pediatric patients with ALL manifest high response rates; however, they contribute to a variety of complications and adverse events.

CHAPTER 2 LITERATURE REVIEW

The incidence of ALL has increased in the United States and globally. This increase is attributed to the advancement in diagnostic techniques and improved access to health care. The stages of ALL can be identified by examining the B and T cells for chromosomal or genetic
variations and classified into abnormalities such as hypodiploidy and hyper-diploidy, amplification, a translocation between different chromosomes, and other unspecified abnormalities. Prognostic predictors of ALL depend on using risk-based stratification and the response to the initial therapy [1]. When prognostication of ALL is accomplished, patients can be assigned to different treatment protocols. Incremental advances in treatment protocols have led to the survival of approximately 80% of the pediatric cases with 5-year event-free survival [5]. However, ALL survivors have to be closely monitored for risks and complications associated with ALL treatment.

**Risk Stratification for Newly Diagnosed ALL Patients**

The paradigm of pediatric ALL treatment depends mainly on risk-based stratification at initial diagnosis. Based on the patient’s features impacting prognosis and risk of therapy failure, cases can be categorized to receive different treatment regimens. High-risk cases usually receive more aggressive and toxic treatment than standard risk cases. Also, the categorization of children with ALL is influenced by another set of risk criteria including age and leukocytes, referred to as the National Cancer Institute (NCI) criteria. Infants and children older than ten years are prone to higher risks of the disease than those children between the ages of 1-10 years old who are at standard risk. Higher levels of leukocytes (>50,000/µL) contribute to greater risk in infants and children older than ten years, while children between the ages of 1-10 years old with lower levels of leukocytes (<50,000/ µL) are considered at standard risk [1].

Another high-risk factor at initial diagnosis is the involvement of the sanctuary sites, which are extramedullary anatomic locations that resist the penetration of systemic chemotherapy and prevent it from reaching the leukemia cells. At diagnosis, studies show that nearly 3% of pediatric patients are likely to display CNS disease interpreted as diagnostic lumbar puncture associated
with the existence of more than five leukocytes/µL and leukemic blasts on cytospin or the presence of other CNS diseases such as the cranial nerve palsy [1]. Moreover, an initial diagnosis in nearly 2% of boys will demonstrate testicular involvement such as enlarged, nonpainful testes. Furthermore, the patients will be at higher risk if they have used corticosteroids before being diagnosed with ALL as this might diminish the number of leukocytes and the presence of sanctuary sites [6].

The features of leukemia cells (B versus T lymphocytes) that affect prognosis can be described through the immunophenotype and be used as a sign for differentiating those patients who are at higher risk. Around 80% of pediatric ALL patients have B-precursor immunophenotype which poses a lower risk on those patients [6]. However, ALL patients with T-cell immunophenotype have poor survival rates unless they have received more intensive treatment to increase their cure rate [1]. Those pediatric patients who have early T-precursor (ETP) ALL were found in some studies to be less likely to survive. Furthermore, under 5% of pediatric acute leukemias experience immunophenotypic groups of mixed lineages that cannot be identified as lymphoid or myeloid in origin or experience double lineages that include both lymphoid and myeloid and/or B and T cells origins [6]. These obscure immunophenotypes are linked to unfavorable prognosis [1, 7].

In addition, a molecular classification of risk associated with some markers is recognized with recurrent cytogenetic abnormalities with favorable or unfavorable prognosis. High hyper-diploidy and ETV6/RUNX1 fusion are the most favorable cytogenetic aberrations. It is well-established that in about 30% of B ALL pediatric cases there exist high hyper-diploidy defined as 51–65 chromosomes or DNA index (≥ 1.16) [6, 7]. Children with high hyper-diploidy are likely to have a favorable prognosis and outcome with trisomies of chromosomes 4 & 10. In the same
manner, a favorable prognosis is experienced with about 25% of B ALL cases in children who carry the cytogenetic aberration: ETV6/RUNX1 fusion (due to t [12;21], formerly TEL/AML1) [6, 7]. Except for these two types, other cytogenetic aberrations do not yield any favorable prognosis. One example is hypodiploidy which is characterized by less than 44 chromosomes or DNA index (< 0.81) is related to unfavorable prognosis and outcome [6, 7].

Another example of unfavorable prognosis and outcome is the abnormality of MLL gene rearrangements found in chromosome 11q23. MLL gene rearrangements are noticed in 80% of infants with ALL and 5% of ALL children from age 1-18 years [1]. Because MLL gene rearrangements in infants with ALL are too aggressive, these infants receive more intensive cytotoxic treatment than older children [7]. Furthermore, Philadelphia chromosome-positive (Ph+) ALL observed with BCR-ABL fusion of t (9;22) is another abnormality that results in unfavorable prognosis with standard chemotherapy and is observed in 3% of childhood ALL [6]. Philadelphia chromosome-positive (Ph+) ALL leads to high MRD levels, early relapse, and its treatment outcomes are usually poor [8]. Therefore, patients with (Ph+) ALL are given other alternative therapies such as hematopoietic stem cell transplant and kinase-targeted therapy [7, 8]. A study by Dai et al. confirmed the effectiveness of using the tyrosine kinase inhibitor dasatinib in the treatment of Philadelphia chromosome-positive (Ph+) ALL [8].

**Risk Associated with Response to Initial Therapy for ALL Patients**

In addition to previous risk factors associated with prognosis, another strong prognosis predictor is the reaction to the initial therapy. Commonly, a large number of children with ALL attain complete remission with less than 5% lymphoblasts on microscopic morphology at the end of the induction phase. However, induction failure with more than 5% lymphoblasts is noticed in about 2% of pediatric patients with ALL indicating an unfavorable prognosis with a 33% survival
Induction failure is observed among patients experiencing MLL rearrangement, T-cell immunophenotype, B-precursor immunophenotype (Bp) with high numbers of leukocytes, and Philadelphia chromosome, or observed in older age children [9].

Microscopy examination is challenging, especially in the evaluation of bone marrow and that is why it was replaced with evaluating minimal residual disease (MRD). Evaluating MRD is attained by using flow cytometry or polymerase chain reaction (PCR) that allows detection of leukemic blasts up to 1 in 10,000 – 100,000 cells [10]. The evaluation of MRD is a very powerful means for identifying the patient’s response to early treatment. It is an independent factor for predicting outcome in pediatric patients with ALL, proved to be effective in the peripheral blood as early as day 8 of therapy, and an indication of the level of intensity needed in treatment regimens [7, 10]. Moreover, the risk for relapse is associated with MRD levels at the end of induction of 4-5 weeks and the end of consolidation of 10-12 weeks [7]. Currently, end-induction MRD is normally used for pediatric patients with Bp ALL in risk stratification. However, using MRD for T-cell ALL treatment regimen is developing and hopefully promising. These risk factors are implemented by various oncology groups for pediatric patients, such as the Children’s Oncology Group (COG) and the Berlin-Franklin-Münster (BFM) Group [10].

Treatment of Newly Diagnosed ALL Patients

When it comes to the treatment of newly diagnosed patients, it is significant to prevent incidences of resistance by using four groups of treatment based on multi-drug regimens. There is a variety of chemotherapy regimens with different intensity levels depending on the child at risk. There are four main phases of ALL treatment that include the remission induction, consolidation, maintenance, and therapy directed to the central nervous system (CNS), in addition to the allogeneic hematopoietic stem cell transplant (HSCT) as illustrated in table 1. The phases of
pediatric ALL treatment usually take 2-3 years. The more aggressive the disease, the more intensive is the chemotherapy regimen [11].

The first stage of chemotherapy is 4-6 weeks of remission induction. The initial treatment and regimen are established in the hospital until complications subside allowing the patient to be discharged and will receive outpatient follow-up. The first stage is aimed to complete remission induction which sets a benchmark to about 95% of all pediatric patients upon completion [6]. Those patients who fail to receive complete remission by the end of induction are prone to either induction failure or surrender to treatment-related mortality. The patients who do not achieve remission and experience induction chemotherapy failure are subjected to allogeneic bone marrow transplant. Drugs used for induction chemotherapy include corticosteroids, vincristine, and asparaginase [11]. Moreover, a great number of therapy regimens use anthracyclines such as doxorubicin or daunorubicin in addition to the previously mentioned drugs. Doxorubicin and daunorubicin were found to have the same efficacy and toxicity in randomized trials. Therefore, some therapy groups do not use these anthracyclines with lower-risk groups to avoid their toxicity and further complications [1].

The two types of corticosteroids commonly used in chemotherapy are prednisolone and dexamethasone. While dexamethasone shows improvement in central nervous system penetration and reduced risk of relapse, it maximizes the occurrence of toxicity leading to infection, reduction in linear growth, and avascular necrosis [12]. Several forms of L-asparaginase are currently used for the pediatric treatment of ALL for asparagine depletion. These forms include Pegasparagase (PEG-asparaginase), asparaginase Erwinia chrysanthemi (Erwinia L-asparaginase), and native Escherichia coli (E. coli) L-asparaginase. The native Escherichia coli (E. coli) L-asparaginase is not used in the United States. L-asparaginase agents are the cornerstone of ALL
treatment regimens in children and these agents adequately improve event-free survival (EFS) [13]. The covalent attachment of polyethylene glycol has been used to modify the E. coli enzyme in Pegaspargase. Pegaspargase is the most common type used both intramuscularly (IM) and intravenously (IV) for both induction and postinduction stages of treatment in children newly diagnosed with ALL. A single dose of Pegaspargase injected for the first time, as part of an induction multiagent regimen, leads to a serum asparaginase enzyme activity level that exceeds 100 IU/L and is associated with prolonged asparagine depletion [14]. As for Erwinia L-asparaginase, it is normally used with children who are allergic to Pegaspargase. Due to the shorter half-life of Erwinia L-asparaginase, it should be frequently administered to allow asparagine depletion [15].

The second phase of chemotherapy that follows remission induction is consolidation. Consolidation is meant to eliminate the submicroscopic residual disease that exists after complete remission. The phase of consolidation lasts from 6-9 months based on the protocol used and level of risk. Whereas this phase of chemotherapy is administered mainly in outpatient care, a more aggressive regimen can be required using inpatient care. For children with ALL who are at higher risk, the consolidation phase is more intense and lasts for a longer period of time. Several chemotherapeutic agents such as cyclophosphamide, cytarabine, thioguanine, methotrexate, etoposide, and one of the thiopurine drugs such as mercaptopurine are integrated and administered in the consolidation phase. These agents are mainly used to increase synergy and reduce drug resistance in the consolidation phase, and they are often not part of the initial induction phase [6].

The third stage of therapeutic treatment in pediatric ALL is the maintenance chemotherapy phase. This phase is the last and longest stage of treatment that lasts approximately two years. However, boys need longer treatment that reaches three years. Maintenance chemotherapy is less
intensive, is associated with less disruptive toxicity, and aims toward minimizing the risk of relapse. This phase is an antimetabolite therapy involving drugs such as methotrexate and 6-mercaptopurine as a thiopurine drug which can be administered orally through outpatient care [16]. Several randomized studies demonstrated that longer periods of maintenance therapy are associated with a reduced risk of relapse. However, elevated risk of developing second cancers has been associated with longer periods of maintenance therapy and higher doses of both methotrexate and 6-mercaptopurine [17]. Furthermore, reducing maintenance therapy duration to less than two years was found to lower the event-free survival possibility. To acquire the cytotoxic effect of the 6-Mercaptopurine drug, metabolic activation is necessary. The activity of this drug is utilized by its transformation into thioguanine nucleotides (TGN) and its incorporation into the DNA of multiplying cells, thus elevating the levels of DNA-TGN. The DNA-TGN is the endpoint metabolite of 6-mercaptopurine and is responsible for its cytotoxic effect and its short-term and long-term adverse events. These adverse events include fatal myelosuppression and second malignant neoplasia [18]. There is evidence from studies that the risk of relapse is associated with the degree of myelosuppression. Therefore, several regimens provide instructions for dose change to balance the risk of myelosuppression with the risk of severe pancytopenia. Moreover, other regimens use vincristine and steroids too [16].

A very crucial component of pediatric ALL treatment is the therapy against the CNS disease, whether it is detected at diagnosis or developed during the course of ALL disease. This therapy includes integration between chemotherapy and other drugs for CNS prophylaxis. CNS regimen involves potent intrathecal prophylactic chemotherapy that starts during the remission induction phase of treatment [19]. The intrathecal chemotherapy can include methotrexate only or
incorporate cytarabine and hydrocortisone in the intrathecal therapy with methotrexate which is called the triple intrathecal therapy [20].

Table 1

Phases of ALL Treatment

<table>
<thead>
<tr>
<th>Phase</th>
<th>Duration</th>
<th>Effect</th>
<th>Drugs Involved</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Remission Induction</td>
<td>4-6 weeks</td>
<td>Sets a benchmark to about 95% of all pediatric patients upon completion and improve event-free survival (EFS)</td>
<td>Corticosteroids, vincristine, and asparaginase, in addition to anthracyclines such as doxorubicin or daunorubicin</td>
<td>[6, 11]</td>
</tr>
<tr>
<td>Consolidation</td>
<td>6-9 months</td>
<td>eliminate the submicroscopic residual disease that exists after complete remission</td>
<td>Chemotherapeutic agents such as cyclophosphamide, cytarabine, thioguanine, methotrexate, etoposide, and thiopurine drugs such as mercaptopurine</td>
<td>[6]</td>
</tr>
<tr>
<td>Maintenance</td>
<td>2-3 years</td>
<td>Minimizes the risk of relapse.</td>
<td>methotrexate and 6-mercaptopurine</td>
<td>[16]</td>
</tr>
<tr>
<td>CNS Therapy</td>
<td>Throughout the therapy duration</td>
<td>Less CNS relapse frequency</td>
<td>Potent intrathecal prophylactic chemotherapy using methotrexate only or triple intrathecal therapy by incorporating cytarabine and hydrocortisone to methotrexate, cranial irradiation</td>
<td>[19, 20]</td>
</tr>
<tr>
<td>Allogenic hematopoietic stem cell transplant (HSCT)</td>
<td>After remission induction failure</td>
<td>Increases survival rates and beneficial for patients with evidence of higher risk of relapse and remission induction failure</td>
<td>Total body irradiation (TBI) before stem cell transplant</td>
<td>[21]</td>
</tr>
</tbody>
</table>

Studies have reported no difference in outcomes of both therapy regimens, such as overall survival and event-free survival. However, evidence shows that triple intrathecal therapy has delivered less CNS relapse frequency. Chemotherapy that is composed of high-dose methotrexate,
dexamethasone, cytarabine, and asparaginase is known to be CNS effective [20]. Peripheral hyperleukocytosis is one of the risk factors of CNS disease development in ALL upon diagnosis in addition to T-cell immunophenotype. Some CNS regimens can include additional cranial irradiation if ALL patients are at increased risk for CNS infiltration. Cranial irradiation is known to maximize the risk of neurocognitive deficits and secondary malignancies [19].

Another protocol that enhances survival rates is the allogeneic hematopoietic stem cell transplant (HSCT) regardless of the stem cell source whether it is matched related, matched unrelated, cord blood, or haploidentical donor. Allogenic HSCT is considered beneficial for pediatric ALL patients with evidence of a higher risk of relapse and remission induction failure. It is believed that exposure to total body irradiation (TBI) as a preparation phase for HSCT improves patients’ outcomes after achieving a condition of MRD-negative disease [21].

**Complications Associated with ALL Treatment**

Although current approaches to the treatment of ALL have enhanced the event-free survival rates among children to be more than 80% and 5-year survival rates to be more than 90%, there is a higher risk for children to develop treatment-related toxicity and complications [1, 22, 23]. While the higher rates of survival reflect an increased response to chemotherapy regimens, unfortunately, the toxicity of treatment can develop complications that can affect every organ in the child’s body and even can cause death [24]. Chemotherapy regimens have the ability to cure tumors whether they are in initially diagnosed or more advanced cases. Such treatment is crucial to the survival of many ALL patients by effectively destroying malignant cells. However, chemotherapy regimens do not differentiate between malignant cells and normal healthy cells in different parts of the body including the hematopoietic tissue, gastrointestinal tract, and oral mucosa [25]. Accordingly, a variety of complications are experienced at a very large scale in ALL
pediatric patients due to treatment toxicity [22]. Some of these complications are addressed in this thesis, and they include pulmonary embolism, concurrent diabetic ketoacidosis and pancreatitis, cancer-related fatigue, steroid-induced glaucoma, osteonecrosis, tumor lysis syndrome, varicella-zoster virus infection, invasive fungal infections, and oral mucositis. Several studies have investigated these complications as discussed below.

**Pulmonary Embolism**

One of the toxicities related to ALL treatment in children is a thromboembolism, which is associated with pulmonary embolism. Pulmonary embolism is a very dangerous and fatal event that can affect the sequence of ALL treatment. An observational study was conducted to investigate the incidence of pulmonary embolism using a group of pediatric patients who were treated by following the Nordic Society of Pediatric Hematology and Oncology (NOPHO) ALL2008 protocol [24]. This study reported that the incidence of pulmonary embolism reached its peak with infants less than 1-year-old and adolescents who were treated with asparaginase and steroids. Asparaginase was found to cause a reduction in procoagulant, anticoagulant, and fibrinolytic protein levels. Thus, increasing the risk of thrombosis. In addition to asparaginase, factors related to thromboembolism and pulmonary embolism include obesity, T-cell leukemia, and dexamethasone use in the induction phase of treatment. Patients who develop thromboembolic events discontinue asparaginase treatment, and they are reimaged before resuming this treatment. However, asparaginase treatment is resumed after the end of the thromboembolic events [24].

**Concurrent Diabetic Ketoacidosis and Pancreatitis**

When ALL adolescents are treated during the induction stage with L-asparaginase-based chemotherapy, there is a possibility that an incidence of diabetic ketoacidosis with pancreatitis is likely to occur. There is a 15% chance for chemotherapy treated ALL children to develop
infections, pancreatitis, and hyperglycemia [26]. L-asparaginase was found to be an effective addition in treatment that results in better clinical outcomes. However, some studies revealed adverse events associated with L-asparaginase use in ALL treatment. These adverse events include hypersensitivity reactions such as diabetic ketoacidosis and pancreatitis in addition to other complications such as hepatotoxicity, intracranial hemorrhage, hyperglycemia, and hypersensitivity reactions among others [26].

Hyperglycemia is a consequence of using L-asparaginase- and prednisolone-based treatment mainly with children > 10 years old. Hyperglycemia incidence due to the use of L-asparaginase was reported by one study to be approximately 9.7% [26]. Treatment of ALL in children using L-asparaginase was found to hinder the production of insulin as a consequence of its amino acid asparagine depletion effect. The precise pathogenesis of L-asparaginase that results in complications is not known yet. However, its asparagine depletion effect is the consequence of deamidation of asparagine to ammonia and aspartic acid or iso-aspartic acid which can reduce protein synthesis in malignant lymphoblasts [22].

The presence of pancreatitis among pediatric ALL patients results in dysfunction of β cells which is associated with a decline in insulin production from these cells in the pancreas. Moreover, some metabolic abnormalities, such as hyperglycemia and diabetes mellitus are associated with ALL patients with pancreatitis. It is documented that the incidence of pancreatitis developed due to L-asparaginase was 2-18% with 8% of pediatric ALL patients who have developed pancreatitis due to this treatment need to obtain insulin therapy. Also, it is reported that 0.75-2.3% of ALL cases can develop diabetic ketoacidosis [26]. A study revealed that ALL patients developed diabetic ketoacidosis in the induction phase after sixteen days from receiving the first dose of L-asparaginase.
While diabetic ketoacidosis has short-term morbidity, it can cause permanent consequences. However, the incidence of acute pancreatitis is 2% in children who developed diabetic ketoacidosis [26]. Studies show that inflammation in the pancreas is associated with pancreatic enzyme leakage [26]. Pancreatitis is confirmed if two of the three following principles are attained: 1. Test of pancreatic amylase and lipase enzymes is $\geq 3$ times the upper normal limit, 2. Imaging of the pancreas shows pancreatitis, 3. Patient suffers from abdominal pain [22]. A study by Jameel et al. was conducted on a 14-year-old female with B-cell ALL. The girl received vincristine, prednisolone, daunomycin, intrathecal methotrexate, and non-pegylated L-asparaginase in the induction phase of chemotherapy. After 20 days of therapy, a sonogram of the abdomen revealed a bulky pancreas as shown in figure 1. It has been postulated that excessive dosage of L-asparaginase and higher risk stratification associated with ALL can increase the risk
for developing pancreatitis. Acute lymphoblastic leukemia patients who develop both pancreatitis and diabetic ketoacidosis are significantly exposed to morbidity and mortality [26].

If glucose levels are acceptable in ALL patients with insulin treatment, asparaginase therapy can be continued. Therefore, for ALL patients who receive L-asparaginase, frequent follow-up and monitoring of blood glucose levels are crucial for detecting hyperglycemia which can be an indication for potential pancreatitis as well. In addition, insulin therapy is recommended for severe cases to avoid nonketotic hyperosmolar coma and enhance wound healing [26]. Due to the importance of not interrupting or discontinuing the use of asparaginase treatment, it is significant to identify any toxicities associated with this treatment. In the case of pancreatitis associated with asparaginase treatment in ALL pediatric patients, a mild condition can be managed by holding the asparaginase treatment for a while until all symptoms are diminished and normal amylase levels are reached. However, asparaginase should be stopped if pancreatitis is acute or hemorrhagic and resumed again once symptoms subside because premature discontinuation can affect a patient’s survival [27].

**Cancer-Related Fatigue**

Cancer-related fatigue is a multidimensional complication of cancer treatment including ALL treatment and is associated with impaired sleep-wake rhythms. Cancer-related fatigue is a distressing uncomfortable condition that hinders children from properly function in school and decreases their activity level. Its fundamental mechanism is not accurately perceived; however, a biopsychosocial model that includes biological, medical, and behavioral factors can contribute to this fatigue condition. Accordingly, evaluating the sleep-wake rhythm using actigraphy (ACT) with some biopsychosocial factors can lead to an improvement in cancer-related fatigue in pediatric ALL patients [28]. Although polysomnography (PSG) is the gold standard for sleep
assessment, it is easier to use the non-invasive ACT assessment tool with children to record the sleep-wake patterns [29]. Another factor for assessing circadian dysregulation is the production of melatonin which is influenced by light. While the melatonin production in children is not affected by ALL, other factors such as chemotherapy, toxicity due to therapy, and hospitalization could jeopardize melatonin production through increasing light exposure. There is evidence that there is an association between unstable and impaired sleep-wake rhythm and high levels of cancer-related fatigue in ALL patients. Such evidence can assist in developing suitable interventions to improve children’s sleep quality and hygiene to improve their health outcomes and reduce cancer-related fatigue [28].

**Steroid-Induced Glaucoma**

Glaucoma is a chronic and escalating optic neuropathy that affects more than 60 million patients worldwide. Glaucoma is considered one of the main causes of irreversible vision loss due to its damaging effect on the optic nerve. Elevated intraocular pressure is the major risk factor for developing glaucoma. In the first stages of glaucoma, the patient is asymptomatic with no clue that the peripheral field of vision is affected. However, the patient becomes symptomatic with impaired vision in the advanced stages when the central field of vision is affected. When intraocular pressure is monitored and regulated, glaucoma can be controlled and curbed without reversing the impaired vision [30].

While glaucoma mainly affects adults, steroid-induced glaucoma can affect any patient receiving corticosteroids by any route regardless of age. The main concern with steroid-induced glaucoma is the rise of intraocular pressure that can last for a few hours after steroid administration or for many years with continuous steroid use [30]. It is reported that the response of intraocular pressure to steroids is higher, more frequent, and severe in children [31]. Without adequate
monitoring of elevated intraocular pressure with steroid administration, steroid-induced glaucoma can be developed [30]. A study was conducted on a group of children between the ages of 4 and 15 years old who were receiving chemotherapy for ALL. Some of these children received only doses of dexamethasone or prednisolone while the others were administered both medications during the period of study. The mean value of the intraocular pressure was about 30 mmHg in 90% of pediatric patients who were administered dexamethasone, while prednisolone did not raise the intraocular pressure more than 15.5 mmHg. For those children who were under the age of 9 years old, the mean intraocular pressure was significantly high (40.5 mmHg) compared to those who were more than ten years old where the mean intraocular pressure was 23 mmHg [31].

Typically, young ALL children are unable to complain about symptoms associated with high intraocular pressure such as headache, impaired vision, or photophobia. Therefore, it is crucial to monitor children who are under steroid therapy, especially dexamethasone, for high intraocular pressure even in the absence of accompanying symptoms. There is always a probability for ALL pediatric patients of developing glaucoma with therapy containing corticosteroids [31]. In such cases, topical anti-glaucoma medications are started with the patient such as brimonidine, brinzolamide, and latanoprost with temporarily discontinuing steroids from the chemotherapy regimen. Steroids are discontinued to reduce intraocular pressure and avoid optic nerve damage. However, if the use of steroid therapy cannot be avoided, it is effective to closely monitor intraocular pressure and intervene promptly whenever it is necessary since glaucoma can lead to loss of vision that cannot be reversed [30].

**Osteonecrosis**

Osteonecrosis is one of the most occurring complications related to ALL treatment in children that negatively impacts the quality of patients’ lives for many years. Osteonecrosis is a
result of impaired vascular support in bone tissues leading to mechanical failure. Corticosteroid treatment is believed to be associated with the etiology of osteonecrosis. However, some studies reported that the combination of corticosteroids and other drugs of ALL chemotherapy regimen, such as asparaginase and methotrexate, could contribute to the development of osteonecrosis [32]. Children who are aged ten or older are prone to osteonecrosis 10-20 times more than those children under the age of 10 and more than adults. Gender and race pose another risk for developing osteonecrosis. Female gender and Caucasian race are two more risk factors for children with ALL to develop osteonecrosis. Moreover, osteonecrosis due to ALL treatment is mainly developed in the lower extremities and shoulders as shown in figure 2 [33].

Some patients are symptomatic, and they constitute 1-18% of ALL patients with osteonecrosis. Some patients are asymptomatic or have mild symptoms. However, others are disabled due to experiencing severe pain from multiple affected joints. This pain can result from osteoarthritis, bone marrow edema, subchondral collapse with cartilage delamination, and microfracture associated with osteonecrosis. As with the case of glaucoma, the combination of dexamethasone and asparaginase was found to be a higher risk factor for developing osteonecrosis. If the ALL treatment is associated with musculoskeletal pain for more than a week, it is recommended that the patient is assessed for osteonecrosis [33]. Effective decisions about osteonecrosis treatment and surgical procedures with ALL patients is very complicated because it involves other factors such as the chemotherapy phase and other health issues that should be taken into consideration. These decisions must be compatible with pediatric ALL treatment, and they need the collaboration of physicians from multiple disciplines such as orthopedic, oncology, and anesthesiology [33].
Figure 2

Osteonecrosis in the Hip: Difference between a normal hip joint & a necrotic hip joint. They were adopted from the Mount Sinai website. 

Treatment recommendations from previous clinical studies were based on idiopathic osteonecrosis treatment with children or adults. It is not well documented how effective is the combination of osteonecrosis surgical treatment and ALL treatment on the healing process of the child’s bones. Also, invasive procedures are not the best decision for children who are exposed to excessive infection and poor healing due to chemotherapy. Nonoperative treatment is basically recommended for patients who are less than 10 years old or have smaller lesions. Larger lesions in patients older than ten years old can be the source of pain and osteoarthritis and might require operative treatment and total hip arthroplasty. Better outcomes are associated with early diagnosis and intervention to avoid joint deformity. There is no reliable clinical data for the treatment of pediatric ALL patients with osteonecrosis [33].

*Tumor Lysis Syndrome*
The list of complications associated with chemotherapy and other ALL treatment drugs is very long and complicated. Another ALL chemotherapy complication is tumor lysis syndrome, which is a life-threatening metabolic abnormality. Tumor lysis syndrome is associated with high morbidity and mortality. It is caused by enormous cytolysis that produces intracellular metabolites such as protein products, potassium, phosphate, purine, and uric acid. The effluence of the intracellular metabolites accumulates in the blood, cannot be renally excreted, and results in abnormalities such as hypocalcemia, hyperuricemia, hyperphosphatemia, hyperkalemia, and acute kidney injury [35].

Laboratory tumor lysis syndrome can be detected within 3-7 days after chemotherapy if more than two of these abnormalities exist. Lab results confirming the presence of tumor lysis syndrome show hypocalcemia with calcium level < 7 mg/dL, hyperuricemia with uric acid > 8 mg/dL, hyperphosphatemia with serum phosphate > 6.5 mg/dL, and hyperkalemia with potassium > 6 mEq/L. However, clinical tumor lysis syndrome is detected when one abnormality exists. For example, the patient experience features of acute kidney injury (serum creatinine exceeds the normal upper limit by 1.5 times and the patient experiences oliguria for 6 hours), severe renal impairment, features of leukostasis such as brain hypoxia, seizures, and intracranial bleeding, cardiac arrhythmias, or death [35].

Figure 3 shows both the laboratory and clinical tumor lysis syndromes with a comparison between the frequency of biochemical and renal abnormalities in both of them. The figure is one of the outcomes of a study by Naeem et al. (2019) that used 57 pediatric ALL patients. In this study, the most common abnormalities were found to be hyperphosphatemia and hyperuricemia in both the laboratory and clinical tumor lysis syndromes. Whereas hypocalcemia and hyperkalemia
were the least common, and acute kidney injury is found only in clinical tumor lysis syndrome [35].

**Figure 3**

A Comparison Between the Frequency of Biochemical and Renal Abnormalities in lab and clinical tumor lysis syndrome. Adopted with permission from Naeem et al., *Pakistan Journal of Medical Sciences, 35*(4), 899–904. [https://doi.org/10.12669/pjms.35.4.715](https://doi.org/10.12669/pjms.35.4.715) (An open access article)

Tumor lysis syndrome can rarely develop spontaneously and if it occurs, serious clinical outcomes will be experienced too [35, 36]. Many factors contribute to increasing the risk for tumor lysis syndrome, such as the stage of ALL at diagnosis, the aggressiveness of the disease, the chemotherapy protocol, the lactate dehydrogenase level, body sensitivity to chemotherapy, and pre-existing conditions before ALL diagnosis. High-risk ALL patients have serum lactate dehydrogenase level (LDH) $\geq 2 \times$ upper level of normal (ULN) [36]. Tumor lysis syndrome develops when chemotherapy incorporates prednisone, asparaginase, vincristine, and daunorubicin. Since tumor lysis syndrome is an oncological emergency that should be handled effectively, it is crucial to identify high-risk ALL patients undergoing chemotherapy early enough,
provide them with prophylactic interventions, and monitor them continuously for complications such as acute kidney injury, arrhythmia, and manifestations of the central nervous system. Early intervention is a major factor in reducing the intensity and frequency of tumor lysis syndrome that can result in more preferable outcomes [35].

**Varicella-Zoster Virus Infection**

Varicella-zoster virus infection is an acute disease that affects children with ALL more than in the general population of children. It may lead to complications specifically with pediatric ALL patients who undergo chemotherapy [37]. In spite of the vaccines given to the general population of children, prophylaxis with acyclovir or immunoglobulins presents a risk factor for children who receive immunosuppression medications. Children with ALL are subject to immune suppression, and they are more prone to develop varicella-zoster virus infection. Chemotherapy administered to children has an impact on reducing the level of immunoglobulins, B-lymphocytes, and T-lymphocytes [38].

The risk for developing varicella-zoster virus infection is even more when chemotherapy is combined with steroids leading to more complications in children with ALL. It is recommended that steroid therapy be postponed until the end of the incubation period of varicella-zoster virus infection. On the other hand, steroid therapy cannot be delayed for patients receiving chemotherapy in the induction period for its significance in this period. Most of the patients who developed varicella-zoster virus infection were on aggressive chemotherapy and steroid therapy and some developed lymphopenia associated with herpes zoster. Moreover, during the first two years after diagnosis of ALL, 80% of pediatric patients are prone to develop Herpes zoster [39]. While chemotherapy was the main cause for developing varicella-zoster virus infection in ALL patients, the type and dosage of steroid therapy were correlated with the intensity of this infection.
Therefore, in the induction period, pediatric ALL patients should be administered varicella-zoster immune globulin along with acyclovir directly after exposure prophylaxis [38].

**Invasive Fungal Infections**

Immunocompromised pediatric ALL patients are exposed to invasive fungal infections which is the main cause of high morbidity and mortality. Invasive fungal infections are predicted in pediatric ALL patients who are exposed to chemotherapy and prolonged corticosteroid therapy, have neutropenia, or have undergone hematopoietic cell transplant [40]. Invasive fungal infections are a consequence of opportunistic fungal pathogens that include fusariosis, aspergillosis, candidiasis, cryptococcosis, trichosporonosis, and mucormycosis [41]. According to Wang et al. (2019), complications experienced by pediatric ALL patients that are associated with fungal infections were assessed in the United States. This assessment revealed that the incidence of invasive fungal infections is maximized during the intensive induction and re-induction phases of treatment. The degree of invasive fungal infections depends on the risk category and chemotherapy and prophylaxis regimens and they ranged from 4% to 35% [40]. Patients with invasive fungal infections can experience an incidence of drug resistance resulting in a higher mortality rate [41].

**Oral Mucositis**

Oral mucositis is the most significant oral complication and the most common associated with chemotherapy regimens that lead to inflammation and ulceration of the oral mucosa. Clinical manifestations of oral mucositis include erythematous and edematous mucosa and atrophy causing much pain, discomfort while eating and drinking, dysphagia, and weakness [25]. Furthermore, oral mucositis causes psychological distress and diminished functionality and quality of life. It is significant to perform oral monitoring for patients during chemotherapy, especially when methotrexate is involved in the treatment regimen. Such oral monitoring can prevent the
treatment’s stomato toxic effect that causes oral lesions and decreases the quantity of saliva and oral functions. After the initiation of chemotherapy by 5-7 days, the oral mucositis becomes visible and continues through the treatment period showing mucosal changes, cellular desquamation, and symptomatic ulcers [25].

A study by Ribeiro et al. (2017) was conducted on a group of children with ALL aged 0-18 years old. These children were monitored and assessed weekly for a period of 10 weeks. The study reported that in the first six weeks of assessment, children who developed oral mucositis experienced pain, impaired voice, and dysphasia. However, dysphagia associated with pain was experienced after the 7th week. Starting from the 8th week, changes were apparent in oral tissues and the tongue leading to difficulty eating and malnutrition in those patients and resulting in comorbidities affecting their quality of life and survival [25].

Lips of the patients showed the presence of ulcerations in almost half the number of patients and ulcerations were obvious in the labial mucosa from the 2nd week to the 10th week of treatment [25]. These changes in the oral mucosa are evaluated using the Oral Assessment Guide (OAG), an 8-item scale: voice, swallowing, lips, tongue, saliva, mucous membrane (buccal mucosa, palate), mucous membrane (labial mucosa), and gingiva [25]. The OAG scores each item as 1(normal), 2 (mild-to-moderate), and 3 (severe impairment) as illustrated in Table 2. Usually, chemotherapy is stopped when oral lesions are present and are resumed after healing, a matter that negatively affects the treatment process of the patient [25]. However, a study by Silva (2020) revealed that ALL pediatric patients who received chemotherapy and were treated with either antimicrobial photodynamic or photobiomodulation therapies had shown positive results in the reduction of pain and time span of oral mucositis [42].
Table 2


<table>
<thead>
<tr>
<th>Item</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Voice</td>
<td>Normal</td>
</tr>
<tr>
<td>Swallowing</td>
<td>Normal swallowing</td>
</tr>
<tr>
<td>Lips</td>
<td>Smooth and moist</td>
</tr>
<tr>
<td>Tongue</td>
<td>Pink and moist and papillae present</td>
</tr>
<tr>
<td>Saliva</td>
<td>Watery</td>
</tr>
<tr>
<td>Mucous Membrane (buccal mucosa, palate)</td>
<td>Pink and moist</td>
</tr>
<tr>
<td>Mucous Membrane (labial mucosa)</td>
<td>Pink and moist</td>
</tr>
<tr>
<td>Gingiva</td>
<td>Pink and stippled and firm</td>
</tr>
</tbody>
</table>

Another study by Driehuis et al. (2020) reported that the use of leucovorin as a pretreatment to starting the methotrexate could reduce the toxicity related to methotrexate and minimize the proliferation of oral mucosa cells [42]. Other therapies, such as administering palifermin and radiation therapy using low-level laser therapy were found effective in the management and treatment of oral mucositis. Palifermin is a recombinant keratinocyte growth factor (KGF) used for severe mucositis. Low-level laser therapy helps in fast healing and in reducing the incidence and duration of severe oral mucositis [43].
CHAPTER 3 CONCLUSION

Acute lymphoblastic leukemia affects a large number of children, and it is diagnosed when lymphoblasts are present in bone marrow or peripheral blood. Treatment regimens of ALL are determined mainly by risk-based stratification leading to the survival of a large number of pediatric patients. High-risk cases demand aggressive and toxic treatments than those with standard-risks. Though these aggressive regimens have better response rates, they accompany a variety of complications including pulmonary embolism, osteonecrosis, tumor lysis syndrome, and many such treatment emergent adverse events. Periodic follow-ups and being vigilant for some of these expectant complications may negate the morbidity and mortality associated with these adverse events in pediatric ALL patients.
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ABSTRACT

POST CHEMOTHERAPEUTIC TREATMENT IMPACT ON PEDIATRIC PATIENTS WITH ACUTE LYMPHOBLASTIC LEUKEMIA

by

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May 2021

Advisor: Dr. Mohammad Ramzi

Major: Medical Research

Degree: Master of Science

Acute lymphoblastic leukemia (ALL) is the most prevalent type of leukemia among children. It is characterized by chromosomal and genetic variations and abnormalities occurring in the leukemic cells. Prognosis predictors of ALL depend on risk-based stratification and the reaction to the initial therapy. Current treatment regimens of ALL contribute to the survival of approximately 80% of pediatric ALL patients with 90% 5-year event-free survival. Based on the patient’s features impacting prognosis and risk of therapy failure, cases can be designated to receive the adequate type of treatment regimens. The higher the risk, the more aggressive, intensive, and toxic is the treatment regimen. Chemotherapy is the base of ALL treatment and it is composed of 4 major phases, remission induction, consolidation, maintenance, and therapy directed mainly to the central nervous system (CNS). There is a high risk for a multitude of complications and medical problems associated with toxic chemotherapy regimens used with pediatric ALL patients. Some of these complications are pulmonary embolism, concurrent diabetic ketoacidosis and pancreatitis, cancer-related fatigue, steroid-induced glaucoma, osteonecrosis, tumor lysis syndrome, varicella-zoster virus infection, invasive fungal infections, and oral
mucositis. However, early detection of these complications can contribute to a lower risk of morbidity and mortality.

**AUTOBIOGRAPHICAL STATEMENT**

Roaa Alfarshooiti is currently a graduate student in the Department of Medical Research at the school of Medicine, Wayne State University. Previously, she has graduated from King Abdul-Aziz University in 2011 with a Bachelor of Medicine and Surgery. Roaa has served as a pediatric medical physician at Maternity and Children Hospital, Ministry of Health, Saudi Arabia. Additionally, Roaa is sponsored by the Ministry of Health in Saudi Arabia to pursue her graduate studies in medical research. She contributed to publishing a paper titled, “Unusual Presentation of Supra cardiac TAPVD in 5 Years Old Boy.” Roaa will be continuing her residency program and fellowship in pediatrics in Saudi Arabia to pursue her goal to be an oncologist.