

## **ABSTRACT**

This internship practicum report evaluates clinical outcomes of high-risk acute lymphoblastic leukemia in young patients who underwent myeloablative hematopoietic stem cell transplant as an alternate to chemotherapy in hopes of long term cure. Scientific literature reveals that presence of specific progressive disease features during therapy and at diagnosis of acute lymphoblastic leukemia categorizes few patients as high-risk ALL. These patients respond poorly to chemotherapy and require durable potential alternatives for long term survival. The use of myeloablative allogeneic hematopoietic stem cell transplant may be offered as an option for potential long term cure. However following transplant remains considerable likelihood of serious post-transplant complications which may jeopardize chances of survival. Longitudinally drawn statistically significant retrospective studies may uncover valuable information and possibly impact decisions when considering a myeloablative allogeneic transplant once a young patient is considered high-risk ALL.

RETROSPECTIVE ANALYSIS OF SURVIVAL AND TREATMENT  
RELATED MORTALITY FOLLOWING A MYELOABLATIVE  
HEMATOPOIETIC STEM CELL TRANSPLANT IN  
CHILDHOOD ACUTE LYMPHOBLASTIC  
LEUKEMIA

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SREEJETA DASGUPTA, M.S.

Fort Worth, Texas

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# **CHAPTER I**

## **INTRODUCTION**

In partial fulfillment of the curriculum requirement for a Masters Degree in Clinical Research Management, I have conducted a six month internship from June 15, 2009 to November 6, 2009 in the Department Hematology-Oncology of Cook Children's Medical Center. I was under the supervision of on-site mentor, Professor W. Paul Bowman, M.D and Senior Clinical Research Associate, Kathy Tankersley, C.C.R.P. During the internship I performed the day to day work activities expected from a clinical research coordinator/associate.

During this time, Cook Children's was evaluating four on-going Children's Oncology Group (COG) clinical trials on newly diagnosed Acute Lymphoblastic Leukemia (ALL) patients and three other clinical protocols/studies for a subgroup of high risk patients who had responded poorly to treatment and are at higher risk for relapse. Such pediatric patients may be considered for a myeloablative hematopoietic stem cell transplant (HSCT). I actively participated in these ongoing Phase II & III clinical trials. These trials are multicenter, randomized , open label, parallel assignment, efficacy and safety trials of risk-directed combination chemotherapy in patients newly diagnosed with standard risk, intermediate risk and high risk acute lymphoblastic leukemia who are either in age ranges of less than 1 year, within 1 and 9 years of age or 10 to 30 years of age. According to the eligibility criteria of the study protocols, the patients were enrolled according to their age, clinical presentation at diagnosis and risk features identified after completing induction chemotherapy regimens. The Phase II/III clinical trials are being conducted across 199 study locations in the COG and intended to enroll more than 5,000 subjects in United States and several other countries by December, 2009.

ALL is the most common of all childhood cancers. The peak age of incidence is 3 to 4 years and ALL accounts for 23% of cancer diagnosed in children younger than 15 years of age (Murphy et al. 2<sup>nd</sup> edition). The National Cancer Institute (NCI) and the National Surveillance Epidemiology and End Results (SEER) database estimates at least 2000 cases of children and adolescents younger than 20 years age diagnosed with ALL each year in the United States, and there has been a gradual increase in the occurrence of this disease in children in the past 25 years in United States (Xie et al. 2229-2235).

It is also known that the incidence of ALL is significantly higher in white children than in black children, with a nearly three-fold increased prevalence in white children compared to black children of 2-4 years of age (McNeil et al. 554-7; discussion 552-3). Such epidemiological differences could be due to genetic predisposition or environmental factors. It has also been evident that boys are more likely than girls to develop ALL (Murphy et al. 2<sup>nd</sup> edition). The occurrence of ALL also appears to be highest in Hispanic children in the United States (43 per million) (McNeil et al. 554-7; discussion 552-3). According to the SEER Program and National Cancer Institute, ALL occurs most often in the first decade of life from 1 to 4 years and an increased incidence is noted in older individuals.

Increased risk of ALL has been linked with congenital disorders such as Down syndrome, autosomal recessive chromosomal abnormalities including Ataxia-telangiectasia and in children with Bloom syndrome. Children with congenital or acquired immunodeficiencies may also be at increased risk ALL possibly due to impaired system of immune surveillance (Murphy et al. 2<sup>nd</sup> edition).



### ***Clinical presentation of ALL can be variable***

An asymptomatic onset of ALL or extramedullary spread of disease at time of diagnosis reflect the extent of disease. Some patients also suffer from prolonged illness before they get diagnosed with ALL. Common symptoms at diagnosis are fever, pallor, petechiae, enlarged lymph nodes, hepatosplenomegaly, nephromegaly and bone pain. Abnormal blood cell counts of WBC and neutrophils clearly identify with the presence of morphological lymphoblasts and are diagnostic features of early onset of ALL (Murphy et al. 2<sup>nd</sup> edition).

Clinically significant features such as cytogenetic abnormalities (lesser chromosomes and chromosomal translocations) and central nervous system (CNS) involvement at diagnosis predispose patients to poor outcome to standard chemotherapy and are used to categorize high risk subtypes of ALL. Such tailoring of childhood ALL therapy directed by extramedullary spread of disease, cytogenetic subtypes and certain risk factors at the time of diagnosis that identifies appropriate risk stratification which may further help to define a potential role of hematopoietic stem cell transplant. Most studies reveal translocations at the 22q- marker Philadelphia (Ph) chromosome have a range of 3% – 5% occurrence in childhood ALL and is an adverse high-risk factor (Murphy et al. 2<sup>nd</sup> edition). Improvements in risk classifications of the disease subtypes based on clinical presentation and response to chemotherapy have led to more effective treatment approaches (Jabbour E., et al. Chapter I: Acute Lymphoblastic Leukemia) (Pui et al. 2730-2741).

Epidemiological studies have indicated certain predisposition for the incidence of ALL in identical twins of ALL patients. Also inherited diseases including excessive chromosomal aberrations such as Fanconi's Anemia have a higher incidence of developing ALL. Recent studies have also suggested that gene polymorphisms (MethyleneTetraHydroFolate Reductase

gene) in infants could be targeted as susceptibility genes in infant ALL (Jabbour E. et al. Chapter I: Acute Lymphoblastic Leukemia).

### ***Introduction of thesis project***

Many clinical trials on pediatric ALL are in progress worldwide. Survival rates have established that success of therapy vary significantly with the clinical presentation of the disease at diagnosis and depends on the risk-adjusted chemotherapy utilized in the treatment (Murphy et al. 2<sup>nd</sup> edition). With tremendous advances in modern intensive chemotherapeutic regimens, the overall event free survival (EFS) rates in children diagnosed with ALL who are receiving risk-adapted chemotherapy have been improving to 86.5% (Pui et al. 2730-2741). However, certain subgroups of these children still have a lower survival rate using risk-adjusted chemotherapy (Nachman et al. 1663-1671) (Wheeler et al. 94-103)(Chessels et al. 93-100).

Currently, factors that are predictive of poor prognosis have been identified as those that indicate a very high risk for relapse and treatment-related mortality using standard therapy. Major factors include: chromosomal abnormalities such as Philadelphia (Ph) chromosome with Bcr/Abl translocations, MLL rearrangements, lesser chromosomes and failure or slow response to primary treatment (Schultz et al. 926-935). Many ALL clinical studies have indicated a poor outcome of these very high risk patients with an estimated event free survival lower than 45% using intensive chemotherapy regimens (Schultz et al. 926-935). Out of the majority of children who are treated with intensive chemotherapy, 25% of these patients eventually relapse (Smith et al. 1086-1093). Risk adjusted standard chemotherapy have not led to sustainable improvements in survival rates of these very high risk patients (Smith et al. 1086-1093). Often these patients

suffer from progressive disease with poor response to the already available standard and risk-adjusted chemotherapeutic regimens (Schultz et al. 926-935). Thus, it becomes essential to conduct new studies with alternative and potential therapeutic approach seeking to achieve long term cure among very high risk ALL patients (Pui and Evans 166-178)(Bailey et al. 873-883). Patients who do not achieve remission even by the end of consolidation chemotherapy have a very poor prognosis and require major alterations in treatment approach (Schultz et al. 926-935). Past few decades had very little progress of successful application of intensive chemotherapy alone and thus makes it necessary to incorporate some equivalent or modified optimal options in the available treatment modalities used for very high risk ALL patients subgroup (Schechter et al.).

Currently, collaborative nonrandomized studies are attempting to develop novel treatment strategies aimed at this subgroup of patients. The use of novel and investigational intensified chemotherapeutic regimens to achieve a complete leukemia-free status (Pui and Evans 166-178)(Bailey et al. 873-883) followed by a subsequent allogeneic transplant of hematopoietic stem cells from a suitable well matched donor are often offered as an optimal equivalent treatment option to these patients, when appropriate donors are available (Bailey et al. 873-883)(Bleakley, Shaw and Nielsen 1-7)(Tomblyn et al. 3634-3641). Such an allogeneic hematopoietic stem cell transplant (HSCT) is usually offered in hopes of long-term favorable outcome with minimal complications (Jabbour E. et al. Chapter I: Acute Lymphoblastic Leukemia).

The major potential benefit of allogeneic HSCT is a significant reduction in the relapse rates, when compared to intensive chemotherapy (Bleakley, Shaw and Nielsen 1-7). However,

these benefits can be offset by higher treatment and/or transplant related mortality (Tomblyn et al. 3634-3641) and complications that may affect the incidence of survival in these patients.

New technologies and better tracing techniques aimed to identify suitable donors have led to increasing availability of transplant option for these patients. The generation of national networks of donor databases such as National Marrow Donor Program (NMDP) and Center for International Blood and Marrow Transplant Research (CIBMTR) for availability of appropriate donors and convenient methodologies used to match related donors has made allogeneic HSCT a favorable option for potential long-term cure in very high risk ALL patients (Tomblyn et al. 3634-3641).

Unfortunately, an allogeneic HSCT may be associated with major treatment complications due to the myeloablative nature of pre-transplant chemotherapeutic regimens. Myeloablative regimens usually include intensive chemotherapy along with single or fractionated doses of total-body radiation, which may affect the long term prognosis of these transplant survivors (Tomblyn et al. 3634-3641). Prior to an allogeneic transplant, myeloablation is often considered necessary since it aids in normal restoration of the patient immune system. Myeloablative regimens are associated with a significant reduction in relapse rates; however, myeloablative regimen-related toxicities may lead to treatment related complications which are major causes of undesirable morbidity and mortality in these patients (Tomblyn et al. 3634-3641). Treatment related complications often include acute and chronic graft-versus-host-disease and severe infections. As our need arises to better understand how prognosis and survival outcome gets affected by the treatment and/or transplant related morbidities, it is essential to

analyze the major treatment related complications incurred following a myeloablative allogeneic HSCT.

Very few published studies on very high risk ALL population have evaluated the overall impact of a myeloablative HSCT in each complete remission (CR) status or each stage of disease status. Some reports have recommended an allogeneic HSCT in first complete remission (CR 1) for best outcome (Schechter et al). According to some reports, clinical outcomes of patients who have received HSCT beyond second complete remission (CR 2) or in third complete remission (CR 3) are significantly worse due to relapse and non-relapse reasons, in comparison to patients who received a transplant in CR 1 or CR 2 (Tomblyn et al. 3634-3641)(Gassas et al. 86-89). The problem lies in how to best identify a timely transplant for these patients in each CR whose prognosis may be bad enough to justify the risk of undesirable morbidities caused by allogeneic HSCT. Comparisons between the therapies used for each CR group will be necessary to understand the relative benefits over the possible risks, offered by a myeloablative allogeneic HSCT at each stage of disease.

## BACKGROUND & RATIONALE

Cancer is rare among children and adolescents, with ALL being the most common childhood cancer. This disease occurs in about one of every 29,000 children in the United States every year (NCI website).

Clinical trials in childhood ALL have been designed to compare currently accepted standard therapy, with an investigational risk-based treatment approach seeking to increase the cure rate and possibly decrease toxicities associated with standard chemotherapeutic regimens. Historical approaches used for treatment of childhood ALL proves the importance of a risk-adjusted assignment of patients to clinical protocols. Such an approach has allowed children with a very good outcome to be treated with standard therapy and hence spared from more intensive and toxic treatment, while allowing children with a poor prognosis and low survival to receive more risk adjusted intensive therapy that may increase their chance of cure (Gaynon et al. 2223-2233). The National Cancer Institute defines “survival for children with ALL has improved over the past 35 years is one of the great success stories of cancer treatment. In the 1960s, less than 5 percent of children with ALL survived for more than five years. Today, about 85 percent of children with ALL live five years or more” (quoted by N.C.I website).

### ***Implications of chemotherapy used:***

Significant improvements in combination chemotherapy for treatment of childhood ALL have led to dramatic increases in cure rates over the past few decades (Harned and Gaynon 453-458). Due to tremendous advances in modern risk-adjusted intensified chemotherapeutic regimens and

supportive care techniques, estimated survival data suggest that children with ALL will attain an overall 90% cure rates in future (Pui and Evans 166-178). One recent report has published a 5-year event free survival approaching 86.5% in childhood ALL (Pui and Evans 166-178)(Moricke et al. 4477-4489)(Pui et al. 2730-2741). A published report on the Total XV clinical trial has recently reported a superior overall survival rate of 93.5% using risk-adjusted treatment (Pui et al. 2730-2741). However, subgroups of these children still have a poor prognosis with a lower survival rate with estimated event free survival of 45% and lower using such intensive risk-adjusted chemotherapy regimens (Pui and Evans 166-178)(Chauvenet et al. 1105-1111)(Silverman et al. 1395-1404).

### **Factors predictive of poor prognosis with chemotherapy**

Recent risk adjusted ALL trials sponsored by the Children's Oncology Group and others have reported great improvements in survival rate in childhood ALL, but specific patient subsets continue to not fare well (Schultz et al. 926-935). These patients share several specific very high risk features leading to treatment failure even to intensive extended induction or consolidation chemotherapy treatment and, as a result, never attain complete remission (Silverman et al. 1395-1404). Those patients, who cannot achieve both hematological and molecular remission within six weeks of diagnosis or respond slowly to induction chemotherapy, have an even poorer prognosis (Silverman et al. 1395-1404). Such patients constitute of only 3% of cases, can be attributed to advanced and refractory disease causing treatment failure or relapse primarily due to drug resistance (Murphy et al. 2<sup>nd</sup> edition). Patients who do not achieve a complete remission by the end of consolidation phase of chemotherapy have a very poor prognosis with chemotherapy alone, and such patients may be benefited when offered intensive chemotherapy followed by an

equivalent treatment option of allogeneic HSCT for potential long term cure(Bleakley, Shaw and Nielsen 1-7).

Randomized clinical trials using risk adjusted combination chemotherapy and prophylactic CNS treatment methodologies have led to increased cure rates in childhood ALL (Pui CH, Nejm, 2006). First-line intensive chemotherapy has yielded first complete remission rates in about 60-70% of patients, while a small subgroup of children carry a very high risk for relapse later in life with unfavorable long term prognosis with a reported cure rate ranging from 20% to 31% with chemotherapy alone (Vaidya et al. 599-603)(Bleakley, Shaw and Nielsen 1-7). Of all the children treated with intensive chemotherapy, 20% – 25 % of patients will eventually relapse later in life (Smith et al. 1086-1093). These patients suffer from recurrent disease at sites such as bone marrow, CNS, testis or other extramedullary sites and, have low survival rate and risk-adjusted intensive chemotherapeutic agents (Bailey et al. 873-883). Intensive extended re-induction chemotherapy will lead to a second complete remission (CR 2) in > 70% of patients (Smith et al. 1086-1093); however with an apparent risk of a possible second or third relapse after completing therapy. Prospective nonrandomized trials suggest a favorable advantage of allogeneic hematopoietic stem cell transplantation (HSCT) over extended chemotherapy in patients who have relapsed once or more than once, due to significant reduction in relapse rates (Smith et al. 1086-1093).

Relapse is the greatest barrier to long term cure for childhood ALL (Murphy et al. 2<sup>nd</sup> edition). This disease usually recurs in bone marrow, CNS, testis or other extramedullary sites. However, bone marrow relapse is the most common form of treatment failure, with a reported reoccurrence rate in 10%-15% of patients and, has a very grave prognosis. Patients with



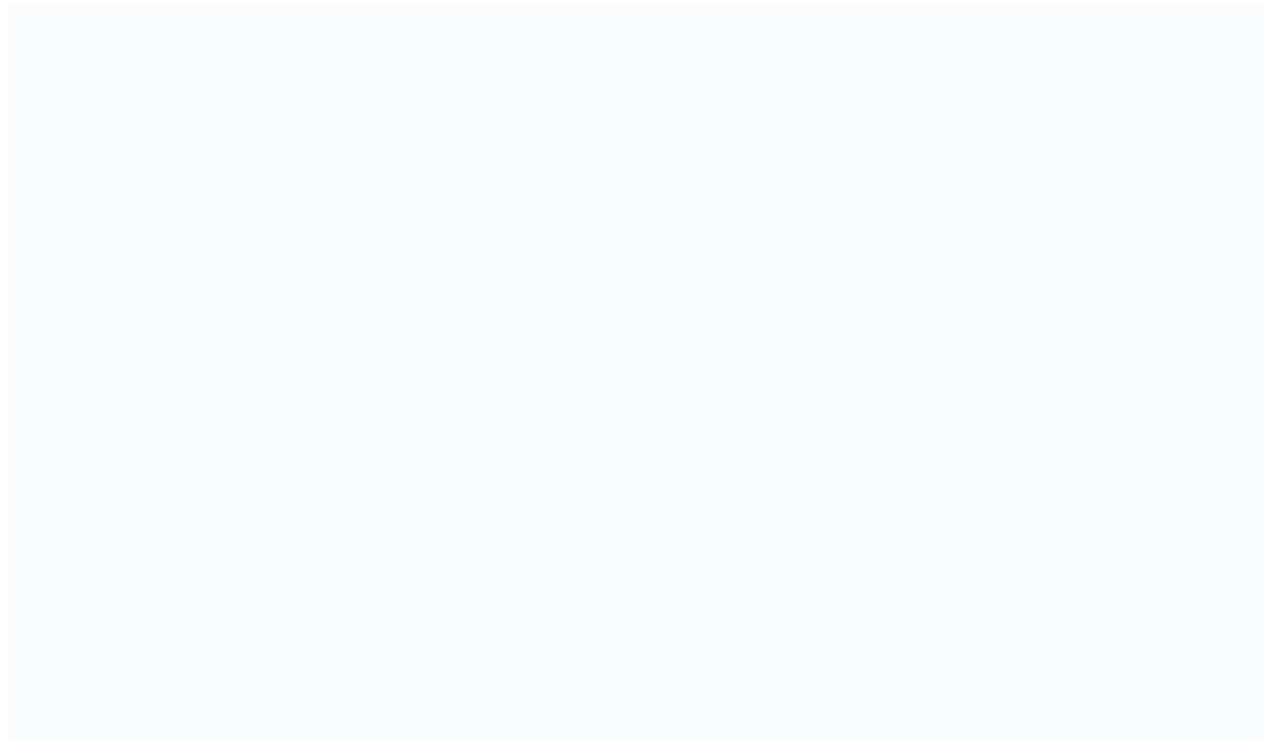
symptomatic isolated marrow relapse undergo bone marrow examinations and molecular assessments to detect persistent minimal residual leukemic cells using flow cytometry and RT-PCR and this provides evidence that help to determine cellular origins and observe distinct patterns of relapse. Historically, an isolated bone marrow relapse carries the worst prognosis (Bailey et al. 873-883); while an isolated CNS or testicular relapse carries a better prognosis compared to a combined marrow and testicular relapse (von Stackelberg et al. 2573-2580)(Lawson et al. 531-543).

Other unfavorable adverse factors which can be categorized as very high risk at time of initial diagnosis and/or once the patient achieves first complete remission (CR 1) includes high risk genetic chromosomal alterations (Bcr-Abl translocation or MLL rearrangements in infants), hypodiploid ALL with 45 or fewer chromosomes and patients who are slow early responders and do not achieve an M1 status ( $< 5\%$  blasts by histology and  $< 1\%$  marrow blasts by immunophenotyping). A minimal residual disease  $> 1\%$  by flow cytometry and RT-PCR at the end of extended induction chemotherapy in slow early responders correlates with a poor prognosis even after attaining morphological remission and carry a very high risk for relapse (Bailey et al. 873-883)(Coustan-Smith et al. 2399-2402). Specific subsets of patients with a positive Philadelphia chromosome ( $\text{Ph}^+$ ) with Bcr-Abl translocation occurs in only 3-5% of children with ALL. Often  $\text{Ph}^+$  patients have aggressive disease and typically respond to standard intensive chemotherapeutic regimens but remission may not be long term. Intensive chemotherapy followed by transplant of hematopoietic stem cell from a suitable donor have yielded better survival rates in  $\text{Ph}^+$  patients (Schechter et al. ).

## **Alternatives to intensive chemotherapy**

Such factors including relapse on therapy and refractory disease at end of induction and presence of very high risk features at diagnosis are predictive of poor prognosis and curing such high-risk disease with chemotherapy is difficult. Published reports have demonstrated significantly favorable survival rates in this group of patients using myeloablative hematopoietic stem cell transplantation (HSCT) after attaining complete hematological and molecular remission (Tomblyn et al. 3634-3641)(Smith et al. 1086-1093).

Most clinicians recommend an allogeneic HSCT to improve outcome in this group of high risk ALL. However, scientific literature cites considerable heterogeneity in the clinical outcomes following transplantation with many instances of disease-related and treatment-related complications affecting the overall long term prognosis in these patients, even after HSCT (Armand et al. 28-35).



## **CHAPTER II**

### **Specific Aims and Methods of the Internship Practicum Report**

#### **Specific Aim 1**

Overall survival of childhood ALL varies with the clinical presentation and characteristics of disease at diagnosis, immunophenotypic, cytogenetic and molecular features of the disease, age at diagnosis playing an important role. With tremendous advances in chemotherapeutic regimens for treatment, there has been incredible surge in the overall event free survival rates in these children receiving risk-adapted chemotherapy, with a success rate up to 93.5% (Pui et al. 2730-2741). However, subgroups of these children have a lower probability of survival (less than 45%) utilizing such chemotherapeutic regimens (Schultz et al. 926-935).

Among these very high risk ALL patients with poor prognostic features, information regarding the clinical impact of myeloablative hematopoietic stem cell transplantation at each complete remission is sparse and incomplete. Therefore it becomes imperative to evaluate the clinical outcomes of these patients following myeloablative hematopoietic stem cell transplantation at each complete remission or disease status.

The goal of this practicum project is to evaluate the benefits affecting clinical outcomes of very high risk pediatric ALL survivors following myeloablative hematopoietic stem cell transplantation (HSCT) in each complete remission status as a treatment modality. The following specific aim was addressed:

**Examine the post-transplant outcome(s) in very high risk pediatric acute lymphoblastic leukemia and assess the frequency of survival in each complete remission status following myeloablative hematopoietic stem cell transplant.**

Relevant literature was comprehensively reviewed and print journal articles were made available through the Edwin G. Schwarz Health Sciences Library and Gibson D. Lewis Health Science Library. Literature was reviewed to identify specific variables which address the clinical outcomes and affects the prognosis of the very high risk pediatric ALL patients who underwent myeloablative hematopoietic stem cell transplantation. Pub Med, Google and Cooknet were mainly used as the search engines to locate journals that addressed survival outcomes of myeloablative transplant in pediatric ALL. Literature was compiled and thoroughly reviewed. In addition, knowledge and experience gained during the internship, was also used to address the research question. To address this specific aim, it was imperative to examine the overall clinical outcomes at each status of complete remission, following hematopoietic stem cell transplantation, in all patients primarily diagnosed with ALL, who did not achieve long-term cure with standard chemotherapy.

A comprehensive data collection sheet was created, by extracting specific baseline data from the available electronic medical records, research databases and also review the patient medical charts. Patients who were transplanted onwards 1986 at Cook Children's, their medical records were unavailable and had to be requested from off-site locations. Specific data that were missing or incomplete in database(s) were added into the spreadsheet, in order to ensure completeness and accuracy of data collection sheet. The development of the data collection procedure was based on comprehensive literature review and criteria(s) suggested by Dr. W.

Paul Bowman and Kathy Tankersley. The content of the data collection sheet was focused on overall outcomes of ALL transplant recipients, with an emphasis on a considerable follow up period; until date(s) of last encounter documented in the medical record.

## **Significance**

Prognosis of pediatric patients with very high risk ALL treated with chemotherapy has been historically poor (Yoshihara et al. 25-31). Because chemotherapy has detrimental long-term outcomes, allogeneic hematopoietic stem cell transplantation (HSCT) with pre-transplant myeloablative regimens has been developed as an option for potential long-term cure. However, information on the long-term clinical outcome of transplant recipients in each CR are limited (Yoshihara et al. 25-31). The results obtained from this retrospective analysis may help gain insight and identify a possible timely approach for myeloablative transplant which may be associated with the long term clinical outcomes in these transplant recipients.

## **Specific Aim 2**

The choice of the myeloablative regimen utilized has a considerable impact on the survival after transplant (Schrauder et al. S71-4). The choice of myeloablative conditioning regimen may often be associated with major complications which may lead to undesirable morbidity and mortality in these patients (Schrauder et al. S71-4)(Holler 281-294). Regimen-related toxicities are often associated with progressive opportunistic infections that affect the survival and quality of life among these immune compromised patients (Holler 281-294); however acute and chronic forms of moderate to severe Graft-versus-host disease or GvHD also can affect the long-term clinical

outcomes in these transplant recipients (Holler 281-294). Therefore, in order to identify an optimum conditioning regimen for myeloablative HSCT and to solve the problem of treatment complications such as GvHD, it is important to evaluate the incidence of major treatment complications associated with the conditioning regimens utilized in each CR status of these transplant recipients.

Thus, the second goal of this practicum project was to evaluate the incidence of major treatment and/or transplant-related complications on the basis of type of myeloablative conditioning regimen utilized, in each CR status in HSCT recipients. The following specific aim was addressed:

**Identify the most commonly occurred complications which affected clinical outcomes in each complete remission or disease status following myeloablative hematopoietic stem cell transplantation (HSCT).**

To address the above specific aim, data on major treatment and/or transplant related complications that had occurred in each complete remission status that may have directly affected the clinical outcomes in these patients were reviewed and collected.

### **Significance**

After having received transplant, patients affected with only milder acute and chronic forms of GvHDs demonstrated a decreased incidence of treatment failure due to relapse or non-relapse reasons (Holler 281-294). Substantial improvement in long term clinical outcomes has been demonstrated in patients with minor acute and chronic GvHDs grade I only. Whereas in

contrary, patients with none or moderate to severe acute and chronic GvHD grade III and IV had poor long term outcomes (Holler 281-294). Hence the results obtained from this retrospective analysis may help gain insight and identify the most commonly occurred grade of treatment complications in each remission status that may have affected the clinical outcomes of transplant recipients.

### CHAPTER III

The use of intensive risk-adjusted chemotherapy employed by the Children's Cancer Group (CCG) and the Pediatric Oncology Group (POG) for treatment of children  $\geq 1$  year of age with high risk acute lymphoblastic leukemia (ALL) has resulted in long term better survival outcomes (Nachman et al. 1663-1671)(Chessells et al. 93-100)(Chessells et al. 565-568). However subgroups of these children do not experience an increased survival rate, despite promise shown by major advances in risk-adjusted (salvage) chemotherapy for overall treatment of high risk ALL (Chessells et al. 93-100)(Nachman et al. 1663-1671). The presence of rare features is predictive of poor prognosis, even with the help of re-intensified chemotherapeutic regimens (Silverman et al. 1395-1404). Prospective nonrandomized trials have used myeloablative hematopoietic stem cell transplantation (HSCT) over extended chemotherapy, which has yielded in significant reduction of relapse rates (Smith et al. 1086-1093)(Tomblyn et al. 3634-3641).

When a trial involves the pediatric population certain factors varying from age of a subject, clinical presentation of disease at diagnosis, abnormal chromosomal numbers and alterations, slow response to chemotherapy causing induction failure, and one or more relapses are reasons given to consider the option of myeloablative hematopoietic stem cell transplantation (HSCT) as an alternative to standard chemotherapy. Following a myeloablative HSCT, several factors hitherto seem to influence the prognosis and play an important role in long term survival of the very high risk ALL patients (Tomblyn et al. 3634-3641). Therefore, to examine the benefits and risks of a myeloablative HSCT among a very high risk ALL, it is very important to identify these factors.



In my report, I will focus on key variables which will help gain insight into the clinical outcomes of the transplant recipients. This may assist in future recommendations for using a myeloablative HSCT for potential curative therapy in these patients.

## **Factors suggestive of prognosis in very-high-risk ALL transplant recipients**

### **Patient age**

Childhood ALL trials often consider age at diagnosis or relapse, as an important prognostic factor. Children up to 10 years of age have a reported long-term survival of 80%, whereas in young adults and adolescents outcomes do not reach such high proportions (Ribera and Oriol 1033-42, vi). However, no distinct age group is marked with poor prognosis, but age at the time of diagnosis and relapse continue to be of prognostic significance among ALL patients (Ribera and Oriol 1033-42, vi). Although an older age > 18 years, as well as male gender and being of Hispanic ethnicity, have showed an increased incidence of transplant related mortality or TRM due to severe GvHDs or reoccurring infections (Tomblyn et al. 3634-3641).

### **Site and time of relapse**

Common findings from collaborative groups have identified similar outcomes with chemotherapy and autologous transplantation. Autologous HSCT is associated with low transplant-related mortality but a high risk for relapse (Tomblyn et al. 3634-3641). Unlike autologous HSCT and standard chemotherapy which has shown similar results until now, cooperative groups have illustrated increased leukemia free survival (LFS) in patients who have received an allogeneic HSCT from a well matched suitable donor (Bailey et al. 873-883).

The greatest barriers to long term cure after having received a hematopoietic stem cell transplant are further relapse at sites such as bone marrow, CNS, testis or other extramedullary sites (Bailey et al. 873-883). Researchers have also observed the length of time following first complete remission to determine potential long term prognosis. Individuals with a shorter time (less than 18 – 24 months) into CR 1 to enter first complete remission have a poorer prognosis than those who relapse beyond 36 months of first complete remission (Bailey et al. 873-883).

Minimal residual disease (MRD) is of potential prognostic value prior to hematopoietic stem cell transplantation as it influences the risk of reoccurrence of disease after transplant (Bailey et al. 873-883). The most recent markers used in prognosis in ALL are time taken to eradicate residual leukemia and extent of minimal residual disease (Bailey et al. 873-883). In patients with MRD, after receiving substantial immunosuppressive prophylaxis, the major determining factor of outcome is the balance between Graft-versus-host-disease (GvHD) and Graft-versus-leukemia (GvL) effect (Flowers et al. 277-282). The overall efficacy is determined by the antitumor effects mediated by the donor immune cells (donor T cells) ultimately responsible for eradication of the residual leukemic cells in the recipient, causing morbid GvHDs (Flowers et al. 277-282). Superior immunosuppressive prophylactics report fewer clinical evidences of GvHD, but at the expense of higher relapse rates (Holler 281-294). Some studies have shown that the greatest leukemia free survival rates were among patients with milder GvHD grade I and II, compared to worse outcomes in patients without any GvHDs or with severe GvHD grade III and IV (Holler 281-294)(Flowers et al. 277-282).

Recent studies aim to investigate whether higher doses of hematopoietic stem cells decreases the risk of relapse, even after transplantation and this needs further randomized investigations (Bailey et al. 873-883).

Thus duration of first remission, time taken to relapse, site of relapse, incidence of GvHD and grades of GvHD are significant prognostic variables in these transplant recipients.

### **Induction failure**

Induction failure is defined by the presence of measurable persistent leukemia even after four to six weeks of remission induction chemotherapy (Silverman et al. 1395-1404). Slow response to chemotherapy, due to refractory disease is highly predictive of poor prognosis (Silverman et al. 1395-1404). Transplantation of hematopoietic stem cells from a suitable donor is often regarded as definitive therapy in this group (Schechter et al. )(Schultz et al. 926-935). Some studies by Children's Oncology Group have reported better event free survival rate of 77.8% in patients with induction failure following allogeneic HSCT (Schechter et al. ).

After a patient has achieved morphological remission or M1 status (< 5% blasts by histology and <1% marrow blasts by immunophenotyping), further assessments are done to detect minimal residual disease (Sutton et al. 292-299). Very few trials done by collaborative groups such as Children's Oncology Group have shown persistent MRD levels prior to transplant as a poor prognostic variable in HSCT recipients (Sutton et al. 292-299)(Bailey et al. 873-883)(Coustan-Smith et al. 2399-2402).

## **Disease status at time of transplant**

Published studies have shown an allogeneic transplant from a matched related/unrelated donor in first complete remission (CR 1) yielded superior survival rates (Tomblyn et al. 3634-3641)(Schechter et al. ). However, allogeneic transplant in CR 1 is associated with higher incidences of complications associated with severe forms of GvHDs and infections (Tomblyn et al. 3634-3641). Patients who received allogeneic transplants in second complete remission (CR 2), with a shorter duration of CR 1 of less than 1 year had poor outcomes (Tomblyn et al. 3634-3641). Patients who had received an allogeneic transplant at CR 2, with a greater duration of CR 1 of more than 1 year, had better outcomes. It was also observed that patients transplanted in CR 2, who had a duration of CR 1 of more than 1 year, had rare occurrences of relapse and were able to maintain durable remissions (Tomblyn et al. 3634-3641). Allogeneic HSCT in third complete remission (CR 3) had worse outcomes and comprised of more deaths associated to treatment, infections, septic shock, organ failures, relapses and severe GvHD grade III and IV (Gassas et al. 86-89).

Thus, the stage of disease or remission status prior to transplant has a variable significance on the clinical outcomes and prognosis among transplant recipients. Therefore it is imperative to compare between survival and outcomes in each remission status and stage of disease of very high risk ALL patients who had received a myeloablative allogeneic HSCT.

## High-risk cytogenetic features

Often rare, a small group of patients are considered very high risk at diagnosis or CR 1 due to the presence high risk genetic features such as: Philadelphia (Ph<sup>+</sup>) positive chromosome with Bcr/Abl translocation and MLL rearrangements usually found in infants < 1 year of age (Schechter et al. ). Another high risk feature, hypodiploidy with less than 45 chromosomes is of considerable prognostic significance in children (Heerema et al. 4036-4045). Such patients may typically respond to treatment, but their remissions are not long-term with chemotherapy (Heerema et al. 4036-4045)(Laport et al. 903-909).

Some very high-risk patients are known to have better outcome with a matched related or unrelated allogeneic transplant in CR1, particularly for Ph<sup>+</sup> patients (Laport et al. 903-909). However, no data were available on prognosis of patients with hypodiploidy with lesser chromosomes, who underwent an allogeneic transplant (Heerema et al. 4036-4045).

Patients having a favorable chance of survival due to allogeneic HSCT in CR 1 include those with high-risk genetic features such as Ph<sup>+</sup> chromosome, infants with MLL rearrangements, hypodiploidy with 45 and fewer chromosomes (Uckun et al. 2030-2039)(Heerema et al. 4036-4045)(Laport et al. 903-909)(Schechter et al. ). The presence of small number of patients prevent any large scale recommendations on the timing of transplant in this very high risk group. The prognostic significance in patients following HSCT with such high-risk cytogenetic features can be evaluated, with further investigations in a large cohort of patients, which is beyond scope of this practicum report.

## **Myeloablative conditioning regimen(s) utilized**

The choice of the myeloablative conditioning regimen, including total-body irradiation (TBI) has a significant impact on survival after HSCT (Schrauder et al. S71-4). Irradiation-free conditioning regimens have shown inferior outcomes due to higher incidences of relapses and treatment-related complications. In younger patients, TBI gets substituted by other effective myelosuppressive agent, such as busulfan (Schrauder et al. S71-4). Standard myeloablative conditioning regimens constitute of a combination of drugs (Busulfan, Cytosan, etc.) along with TBI, have shown promising results (Schrauder et al. S71-4). However such a significant impact on outcome is dependent on the combination of drugs used, with or without radiation (Schrauder et al. S71-4).

Thus, this report will evaluate the impact of the myeloablative conditioning on the survival frequencies in each CR status in very high risk ALL.

## **Graft and donor type**

Nonrandomized trials utilizing allogeneic HSCT have repeatedly established a survival advantage in patients who do not fare well with chemotherapy (Bleakley, Shaw and Nielsen 1-7). Transplant of hematopoietic stem cells from a matched family donor (MFD), usually sibling (Tomblyn et al. 3634-3641), is the preferred transplant option and is associated with significantly better outcome and disease-free-survival (Tomblyn et al. 3634-3641)(Bleakley, Shaw and Nielsen 1-7). However, only 15-20% of all patients have access to a matched related donor (MRD) (Schrauder et al. S71-4)(Tomblyn et al. 3634-3641). Therefore, it becomes important to evaluate alternative stem cell sources and whether a well matched or partially-matched unrelated

donor is equivalent to a MRD (Schrauder et al. S71-4). Unmanipulated stem cell from bone marrow from a matched donor is always a preferred option (Schrauder et al. S71-4).

Because a small proportion of patients become eligible for allogeneic HSCT having a related and well matched sibling, other allogeneic stem cell sources such as unrelated donors with well-matched and partially-matched bone marrow and umbilical cord blood may be acceptable alternatives (Schrauder et al. S71-4)(Tomblyn et al. 3634-3641).

Thus, the type of allogeneic graft, source of graft and the degree of histocompatibility or human leukocyte antigen (HLA) match may significantly affect the clinical outcomes of HSCT recipients in each CR status and are important variables. Thus it is necessary to investigate to evaluate the effect of graft variables on the clinical outcome in a large cohort of patient population to help draw significant conclusions in future.

## CONCLUSION

The nationally accredited Stem Cell Transplant Program at Cook Children's Medical Center had already reported 23 years of experience in using myeloablative HSCT with total-body irradiation (TBI) for patients with high-risk ALL. This opened a unique opportunity to assess the clinical transplant outcomes from a single center institution utilizing different preparative and myeloablative conditioning regimens. In this analysis, I had intended to retrospectively assess the clinical outcomes of all 179 consecutive high-risk ALL pediatric patients who had undergone a myeloablative transplant at the Stem Cell Transplant Unit at Cook Children's. The retrospective analysis would also evaluate the survival and incidence of major complications which lead to death in these patients. This study would also examine the regimens associated with the incidence of treatment complications in each of these 179 patients.

Within context of this practicum project I have reported the clinical transplant outcomes in 22 consecutive high risk ALL patients who underwent myeloablative HSCT using different preparative regimens, with a maximum long term 3-year follow up duration. This report includes an estimate of possible relationships between myeloablative regimens used prior to transplant, incidence of treatment related complications causing death, and survival in the results obtained from the most recently transplanted 22 consecutive patients.



## **Overview of Methods used, Results and Discussion**

Due to time constraints and off-site location of several patients' records that were treated before the year 2004, we chose to review the readily available records accessible electronically on Meditech and through the Medical Records at Cook Children's. This report includes the consecutive pediatric ALL patients that underwent myeloablative HSCT utilizing different preparative and myeloablative regimens at the Cook Children's Medical Center between April 1, 2006 and December 31, 2008. All patients' records were accessed electronically and therapy charts were requested from the Medical Record Department at Cook Children's. Apart from therapy charts and electronic records, primary research database(s) such as Leukemia/Lymphoma Access Database, Clinical Research Access Database and Stemsoft software were also accessed to appropriately identify the patient population.

### **Result**

The medical records of twenty-two consecutive patients with ALL who underwent HSCT comprising different preparative and myeloablative conditioning regimens were reviewed. As indicated in Table 1, the proportions of patients were equal among males and females. The median age of the patients at diagnosis was 6.1 years, with a range of 1.2 to 15.6 years. Nineteen out of twenty two patients were diagnosed with the B-precursor phenotype of ALL, two with T-cell and one with B-cell phenotype ALL. Table 1 shows the demographic characteristics found in these 22 patients.

**Table 1: Population Demographic Characteristics:**

Median Age at Diagnosis:	6.1 yrs (Range 1.2 – 15.6 years)
Number of Females:	11
Number of Males:	11
Median Age at Transplant:	8.7 yrs (Range 2.1 – 18.7 years)

All patients had either a B-Precursor, B-cell or T-cell phenotype ALL. These patients underwent myeloablative HSCT in either first complete remission (CR 1), second complete remission (CR 2), third complete remission (CR 3) or when they had poorly responded to chemotherapeutic induction regimen, which is known as Induction failure.

As shown in Table 2, cytogenetic results at diagnosis with a normal karyotype were common. Considerable heterogeneity in the clinical outcomes was observed in each remission group of transplant recipients, which showed marked differences in survival.

**Table 2: Characteristics such as stage of disease and status of remission observed**

Remission Status	Definition	Cytogenetic Features	Number of Deaths
Complete Remission 1 ( <i>n</i> = 2)	Achieves both hematological & molecular remission	Both were Hypodiploid (< 45)	1
Complete Remission 2 ( <i>n</i> = 7)	Achieves both hematological & molecular remission after first relapse	5 normal karyotype 1 Hyperdiploid (> 50) 1 TEL/AML	1
Complete Remission 3 ( <i>n</i> = 7)	Achieves both hematological & molecular remission after second relapse	6 normal karyotype 1 Hyperdiploid (> 47)	2 1
Induction Failure ( <i>n</i> = 6)	Achieves morphological remission with persistent levels of MRD	4 normal karyotype 1 Hyperdiploid (> 47) Down Syndrome	1
Total patients = 22			6

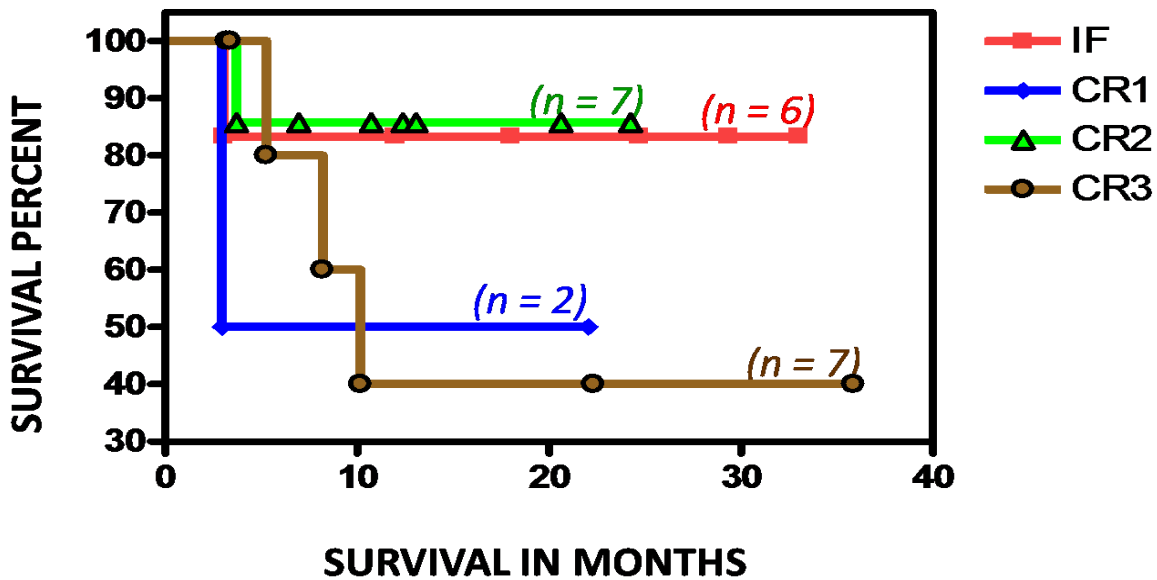
**Survival Percent in each Remission Status**

As shown in Table 2 and Figure 3, the remission group CR 3 showed worse clinical outcome with greatest proportions of deaths (*n* = 3) and a lowest survival percentage less than 40%,

following a myeloablative HSCT. Major causes of death in CR 3 were reported as severe infections, GvHDs and relapse.

Remission group of CR 2 and Induction failure had one death each, indicated an advantage of better survival percentage of 80%, compared to CR 3. In remission group of CR 1, only one death had occurred.

Overall, as shown in Figure 3, the survival percentage in CR 2 and Induction failure were higher with 80 % survival, unlike CR 3. However, it is difficult to critique the survival percent in CR 1 group, since the number of patients in this group was too small to help draw any significant conclusion.



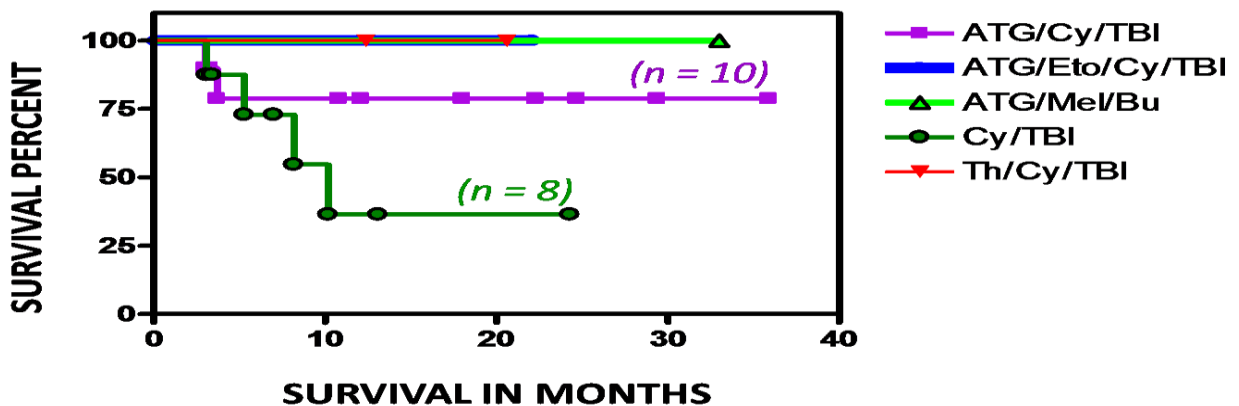
(Between date achieved remission – Last follow up visit post transplant)

Figure 3: Kaplan-Meier graph showing survival percent in CR 1, CR 2, CR 3 and Induction Failure

Figure 3 survival curve shows that three patients who were transplanted in CR 3 had worse clinical outcomes and died due to treatment-related mortality (TRM). Causes of death were relapse, severe GvHDs and overwhelming infections. Deaths also occurred in remission groups CR 1, CR 2 and Induction failure due to severe GvHDs and infections, but were fewer. This graph also helps to further hypothesize that transplant at an early stage of disease may be a better option in comparison to a late transplant.

### Effect of Myeloablative regimens utilized on Survival Percent

Clinical outcomes in each remission group may be directly attributed to the choice of myeloablative conditioning regimens used prior to HSCT (Schrauder et al. S71-4). So our next goal was to analyze the survival percentage based on the different preparative and myeloablative conditioning regimens utilized prior to transplant. As shown in the Figure 4 Kaplan-Meier survival graph, the choice of the myeloablative conditioning regimen utilized possibly indicated an impact on the overall percent of survival.



(Between date achieved remission – Last follow up visit post transplant)

Figure 4: Kaplan-Meier graph showing relationship between the type of myeloablative regimen used and percent survival

This Figure 4 survival graph shows the effect of different preparative and myeloablative regimens used, on the frequency of survival. It was observed that myeloablative regimen comprising of Antithymic Globulin (ATG), Cyclophosphamide (Cy) and Total-body irradiation (TBI) and the other myeloablative regimen comprising of Cyclophosphamide (Cy) and Total-body irradiation (TBI) had poor outcomes in comparison to other regimens used.

**Table 5: Composition of Myeloablative regimen utilized prior to transplant in each disease or remission status**

Remission Status	Myeloablative Regimen used	Other irradiation(s) used	Number of Death(s)
Complete Remission 1 (n = 2)	ATG/Cy/TBI ATG/Eto/Cy/TBI		1
Complete Remission 2 (n = 7)	ATG/Cy/TBI Th/Cy/TBI Cy/TBI		1
Complete Remission 3 (n = 7)	ATG/Cy/TBI Cy/TBI	2 had CNS irradiation 3 had CNS irradiation	3
Induction failure (n = 6)	ATG/Cy/TBI ATG/Mel/Bu Cy/TBI		1
Total n = 22			Total Deaths = 6

Prior to HSCT, the preparative conditioning regimens comprises a combination of standard backbone of myeloablative drugs such as Antithymic Globulin (ATG), Cytosan or Cyclophosphamide (Cy), Etoposide (Eto), Thiotepa (Th), Melphalan (Mel), along with total-body irradiation (TBI). Often Busulfan is also used in an irradiation-free conditioning regimen (Schrauder et al. S71-4). All male patients' also receive an additional gonadal irradiation as standard therapy and prophylactic cranial irradiation, if any overt CNS leukemia blasts are found. The permissible level of dose of radiations administered to these patients is always calculated according to their body mass index or BMI.

As shown in Table 5, one interesting finding was identified with the myeloablative conditioning regimen consisting of Cy/TBI. In remission group CR 3, five patients had received cranial irradiation with a dose ranging up to 1800 cGy. All three patients who received Cy/TBI with prophylactic cranial irradiation with dose up to 1500 cGy died from treatment-related mortality (TRM). Causes of death were overwhelming infections, relapse and severe acute and chronic GvHDs.

### **Effect of Graft-versus-Host-Disease on Survival Percent**

The major complications associated with HSCT comprising myeloablative conditioning regimens were acute and chronic forms of graft-versus-host-disease. As shown in Table 6, patients who had severe clinical manifestations of acute GvHD grade III and IV, along with mild or severe chronic GvHD showed poor outcomes, when compared to patients with GvHDs of grade I and II.

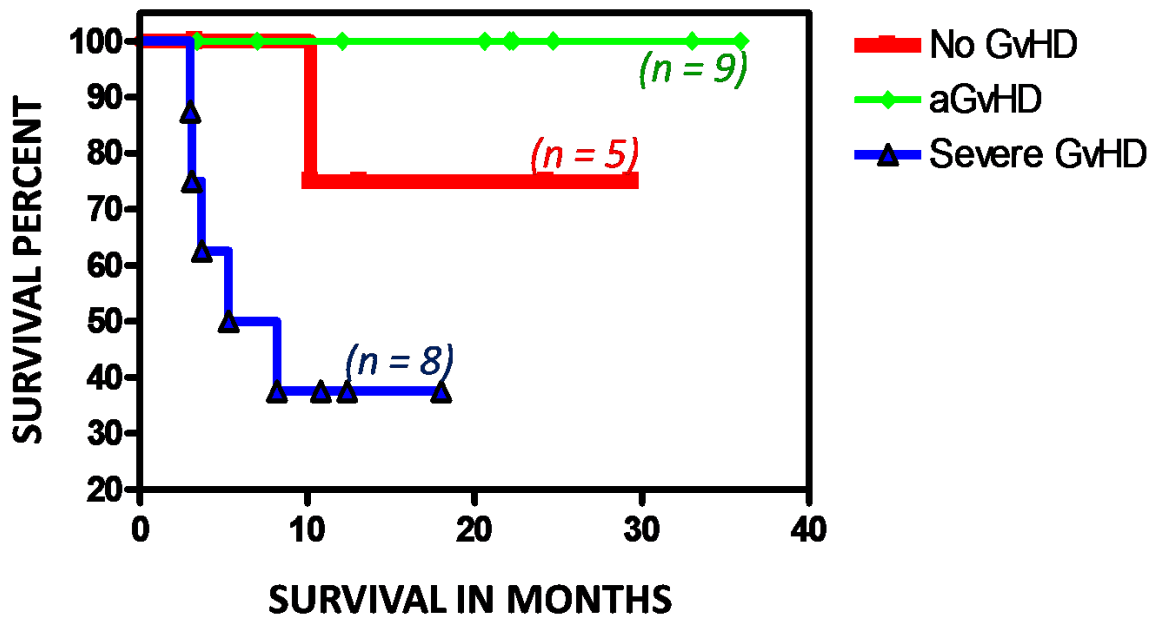
**Table 6: Clinical evidence of Graft-versus-Host Disease and its grades occurred in patients**

Remission Status	aGvHD/Grade	cGvHD/Grade	Outcome
Complete Remission 1 (n = 2)	Yes/ I	No	1 Alive
	Yes/III-IV	Severe	1 Dead
Complete Remission 2 (n = 7)	No aGvHD	No	2 Alive
	Yes/I	No	2 Alive
	Yes/III-IV	Severe	1 Dead
	Yes/III-IV	Mild	2 Alive
Complete Remission 3 (n = 7)	No aGvHD	No	Both Relapsed
	Yes/I-II	Mild	3 Alive
	Yes/III-IV	Mild	2 Dead
Induction failure (n = 6)	No aGvHD	No	1 Alive
	Yes/I	Mild	3 Alive
	Yes/III-IV	Mild	1 Alive, 1 Dead
		Total number of death(s) due to severe GvHDs = 5	Death(s) = 6

*Keywords used: Acute GvHD Grade I & II (aGvHD); Severe GvHD Grade III & IV with chronic GvHD (cGvHD)*

Of the five patients who died of TRM, the causes of death were acute GvHD grade III and IV, along with mild to severe chronic GvHD in five patients and overwhelming infections in two patients. After receiving transplant, two patients had relapse with no clinical manifestations of GvHD. Out of the two relapsed patients, one patient died and the other patient is still alive using hospice and palliative supportive care measures.





(Between date achieved remission – Last follow up visit post transplant)

**Figure 7: Kaplan-Meier Survival graph showing relationship between grade of GvHD and survival percent**

As shown above in Table 6 and Figure 7, patients with clinical manifestations of acute GvHD grade I and II had better outcomes. Patients with clinical manifestations of severe acute and chronic GvHD, grade III and IV had very poor survival outcomes. However, five patients had no clinical manifestations of GvHD probably due to continuous administration of effective superior GvHD prophylactics such as cyclosporine, cellcept, prograf and tacrolimus. Two patients in CR 3 with no clinical evidence of GvHD post-HSCT relapsed and one died and the other patient is undergoing chemotherapy and is still alive with hospice and palliative care.

**Table 8: Summary of Treatment-related complications occurred in each status of CR 1, CR 2, CR 3 and Induction Failure**

<b>Remission Status</b>	<b>Cause of Death</b>
<b>CR 1</b> (n = 2)	<ul style="list-style-type: none"> <li>• Both Hypodiploid</li> <li>• <b>1 died of TRM</b> (EBV infections accompanied with severe acute grade 3 GvHDs)</li> <li>• <b>1 patient alive</b> 22 months post HSCT with no major complications</li> </ul>
<b>CR 2</b> (n = 7)	<ul style="list-style-type: none"> <li>• <b>1 died of TRM</b> (Severe GvHD with acquired bloodstream and viral infections)</li> <li>• <b>6 were survivors</b> between 7 and 24 months post HSCT</li> <li>• Out of these survivors, 4 had acute GvHD w/ cGvHD and 2 had no GvHD post HSCT and were alive</li> </ul>
<b>CR 3</b> (n = 7)	<ul style="list-style-type: none"> <li>• <b>2 died of TRM</b> (Infections: multiple bacteremia, septic shock, respiratory failure with metabolic acidosis accompanied with grade III-IV GvHD with cGvHD)</li> <li>• <b>1 died of relapse</b> (no GvHD)</li> <li>• <b>Another 1 has relapsed</b> post HSCT and is alive on supportive care</li> <li>• <b>3 were survivors</b> between 3.4 and 36 months post HSCT, aGvHD and infections were easily resolved and have been followed up till now</li> </ul>
<b>IF</b> (n = 6)	<ul style="list-style-type: none"> <li>• <b>1 died of TRM</b> (Chronic pneumonitis, multiple bacteremia, pulmonary hemorrhage accompanied with grade III-IV GvHD and cGvHD)</li> <li>• <b>5 were survivors</b> between 12 and 33 months post HSCT</li> <li>• Out of the 5 survivors, 4 had significant aGvHD with cGvHD which were resolved and 1 had no GvHD and all of them were alive</li> </ul>

**Conclusion:** Six patients had died from relapse, TRM or severe GvHDs. Figure 2 survival graph showed considerable heterogeneity between the clinical outcomes in each remission group of Induction failure, CR 1, CR 2 and CR 3.

Seven patients were transplanted in CR 3, of which three patients died. Causes of death in CR 3 were TRM and relapse. Two patients died of treatment related mortality caused due to overwhelming infections with *Candida*, multiple bacteremia and septic shock, renal failure, acute respiratory failure with metabolic acidosis, accompanied with severe GvHDs grade III and IV with mild to severe chronic GvHD. One patient in CR 3 with no evidence of GvHD post myeloablative HSCT relapsed and died. This patient was on continuous effective immunosuppressive GvHD prophylactics, and as a result probably did not develop any clinical manifestations of GvHD and hence suffered a relapse. Another patient in CR 3, with no evidence of GvHD has relapsed post-HSCT, and at the time of writing this report, the patient is still alive on hospice and palliative care. Three patients were long-term survivors between 3.4 and 36 months post-HSCT. All had mild to moderate acute GvHD grades I or II and infections which were easily resolved. These patients are still being followed up with the Life After Cancer Program at Cook Children's.

Seven patients were transplanted in CR 2, of which one patient died. Cause of death was severe GvHD with overwhelming, acquired bloodstream and viral infections post-HSCT. Six patients were long-term survivors between 7 and 24 months post HSCT. Four of these patients had moderate to severe acute GvHD grade I along with none or few clinical symptoms of chronic GvHD. Two patients did not develop any clinical manifestations of GvHD and were still alive.

Two patients were transplanted in CR 1. Both patients were hypodiploid with less than 45 chromosomes, and were considered high-risk soon after hematological remission. One patient died from TRM and cause of death was overwhelming Epstein Barr viral (EBV) lymphoproliferative infections, accompanied with severe acute grade 3 GvHDs. One patient is still alive without any major complications, at 22 months post-HSCT.

Six patients were transplanted in Induction failure, as they were poor responders to initial chemotherapy. With extended re-intensified chemotherapy, all the patients had achieved morphological remission, yet had persistent levels of minimal residual disease (MRD). These patients had a high risk for relapse. One Down syndrome patient died within 3 months post-HSCT. Cause of death was chronic pneumonitis and multiple bacteremic infections, pulmonary hemorrhage, associated with severe acute GvHD grade III-IV with chronic GvHD and multiorgan system failure. Five patients became MRD negative and were long-term survivors between 12 and 33 months, post-HSCT. Four patients had significant moderate to severe acute or chronic GvHD and, one patient did not develop any clinical symptom of GvHD, and was on GvHD prophylactics.

## **Discussion**

Clinical outcomes of patients in CR 3 were worse with greater proportions of deaths concomitant with a survival percent less than 40% post-myeloablative HSCT. Patients in CR 2 and Induction failure had a better outcome post-HSCT. Unlike CR 3, patients in CR 2 and Induction failure demonstrated an advantage of survival of more than 80%, post-myeloablative HSCT. Major causes of death were treatment-related mortality (TRM) and may be attributed to toxicities related to myeloablative conditioning regimens or prior chemotherapy. Greater proportions of death were reported in patients who received myeloablative regimens Cy/TBI and ATG/Cy/TBI, because of incidences of relapse as well as TRM. Causes of death were significant TRM such as overwhelming infections and severe grade III and IV along with chronic GvHDs. This report had also intended to evaluate the relationship between graft donor source and survival; however it was not feasible due to insufficient number of patients. The cohort had a limited population of 22 patients and hence statistically significant conclusions could not be drawn. Consequently, it becomes difficult to depict the overall survival outcomes in each remission group and draw definitive conclusions.

However these preliminary results helped to generate a hypothesis that a timely approach to transplant, type of regimen used prior to HSCT and GvHD grade may affect the likelihood of survival in very high risk ALL patients. To test the hypothesis and validate the above results, further investigations on a large cohort of patient population are necessary to help draw statistical significant conclusions. Considerable heterogeneity observed in clinical outcomes obtained in results of this study, with marked differences in each remission group post-HSCT, not only

reaffirms our research hypothesis, but also justifies further retrospective studies to validate the above results in future.

Overall analysis of the benefits and complications occurring in each remission group of very high risk ALL may better expose the need and warrant a timely approach for considering a myeloablative HSCT. This may be a step further to justify the need of myeloablative HSCT once a patient is considered high risk ALL and requires alternate therapy.

## **CHAPTER IV**

### **INTERNSHIP EXPERIENCE**

The site where I completed my six month clinical research internship was located at the Cook Children's Medical Center in the Clinical Research Office at the Department of Hematology & Oncology. The Hematology/Oncology department has a specialized clinic where patients come in for treatment and specialized care. The Hematology & Oncology clinic provides care to more than 2000 patients and their families ranging from age of  $\leq 1$  to 30 years, who come from various cultures and represent many nationalities. Clinical trials conducted at this site are specifically aimed at either testing the safety and efficacy of investigational drug, interventions or researching disease stages predominantly found within pediatric population of children, adolescents and young adults. The pediatric practice and research is led by Professor W. Paul Bowman, M.D, Chairman of the Hematology & Oncology Leukemia/Lymphoma Program, with assistance of Kathy Tankersley – Manager and Supervisor of H/O Program Support and Senior Clinical Research Associate, and my mentor(s) during my internship. Holly Lawrence, CRA was also a constant guide throughout my internship. During the period of my internship, this site dealt with four on-going Children's Oncology Group (COG) sponsored childhood ALL clinical trials.

The overall purpose of the internship was to gain knowledge and experience of how to manage a clinical research trial on human subjects. During my internship I performed day to day activities expected from a clinical research associate. The basis of my experience was through four on-going Children's Oncology Group (COG) sponsored clinical trials that focused on

childhood ALL and three other clinical protocols open for a subgroup of high risk childhood ALL. The internship experience spanned various areas of clinical research management including coordination, protocol implementation, administrative duties, regulatory affairs, IRB interactions, data collection, data management, maintaining study files, interaction with study personnel, subject recruitment and budget information. The following is the narrative account of the individual experiences gained during internship.

**Training and Certification:**

In order to participate in clinical research with human subjects and to have access patient treatment information, I completed the CCMC institutional Collaborative IRB Training Initiative (CITI) and Health Insurance Portability and Accountability Act (HIPAA) training. The CITI training, in particular, was very helpful in understanding the ethical aspect of human trials.

**Recruitment of Subjects:**

For a successful completion of trial recruitment is often the most critical aspect of clinical coordination. During this internship I was able to actively participate in subject recruitment.

Subject referrals mainly came through physician referrals from the Hematology & Oncology clinic at Cook Children's. The subjects are referred to this site by the physician network and are screened for eligibility before enrollment by the clinical research associates. Along with Holly Lawrence, C.R.A, I reviewed several subject's lab reports and medical charts to ensure their eligibility before enrollment.



Tissue specimen submission forms are to be completed and biological specimens are collected by our laboratory personnel and sent to the sponsor laboratories each time a patient was enrolled on a study. During the duration of my internship, I completed more than 20 such forms.

For subjects who did not qualify for a particular study a separate list was made and sent to every CRA to consider those subjects for the alternative and future studies at the site.

**Implementing the Protocol Procedure:**

During my internship I was able to witness several times Andrea Horsch and Carol Roberts, nurse research coordinators going over the *informed consent* with subject and his/her family.

Before the subject was administered Informed Consent, I helped Holly in *preparing copies of IRB approved consents and processing tissue specimen submission reports for laboratory personnel*. After administering of Informed Consent, it is essential to ensure completeness and accuracy of written approval in consent document. I was able to participate in such an activity more than 15 times.

I learned procedures for updating and verifying information in study files from patient medical charts. During my internship I was able to help Holly more than 20 times in *recording, updating and verifying appropriate drug information on patient charts* and *updating specific roadmaps* of induction, consolidation, maintenance and intensification cycles of therapy. In the end, I was confident and was able to independently verify and update patient study files and keep it ready for subsequent patient follow up clinic visits.

I also learned specific procedures required for data collection and verifying information in patient medical charts. During my internship I was able to help Holly several times in *collecting data and verifying data from medical charts related to pharmacokinetics of the drugs* given to the patient. I was equipped with appropriate training which helped me to independently administer data collection on pharmacokinetics on more than 20 patients, appropriate filing and then faxed to the sponsor.

I also actively participated in *budgeting of three new trials*. Both the trials were sponsored by pharmaceuticals. Kathy T., Manager and Senior CRA at the Hematology & Oncology, CCMC gave me training on how to create budgets using specific information provided by sponsor protocols. Kathy T. gave me ample encouragement and space to incorporate new ideas and changes to the budgeted information, related to study visits, before approval. This helped me to understand the budgeting issues of a trial.

I also actively participated in weekly Study Analysis Meetings with Kathy T., Dr. James Marshall and Dr. Leigh Donahue which gave me a *clear understanding over trial management and criteria for inception of new pharmaceutical studies*. This knowledge also proved useful while creating budgets.

## **Regulatory and Administrative Duties:**

### **IRB Interaction:**

The major portion of the internship experience was based on the regulatory and administrative duties done in trial initiation and during the execution of the trial.

Before I started my internship, the clinical trials in which I was actively involved were already IRB approved. However, once a trial gets approved by the IRB, it needs to go again in front the full board for continuing review IRB approval, every twelve months. For this, the paperwork has to be completed, signed and submitted as a part of IRB packet. The packet include a copy of budget, protocol, Protocol Synopsis, Conflict of Interest form(s) of investigators involved in the study, their CV'S and CITI certificates and completed FDA 1572 form. During my internship I gathered, completed and submitted these forms for continuing reviews.

I was fortunate to work with Dionne Rogers, Research Regulatory Specialist on the IRB submission requirements of a new study. She guided me through the initial paperwork of the study. I felt confident and was independently able to gather and complete important regulatory documents. I had ***submitted regulatory documents required for submission to both Cook IRB and study sponsor***. The completion of documents ensured and helped me to understand the qualifications for the inception of a new pharmaceutical trial.

The regulatory duties also involved the process of development of informed consent & assent documents for a study. In this process, I was able to independently *draft informed consents and assent documents* for a new sponsored study.

I received an opportunity to sit in one New Research Full Board IRB meeting, for the new study I had worked on. I also received an opportunity to sit in three Continuing Review Full Board IRB meetings. The IRB for this site meets twice a month to review potential new research studies, continuing reviews, changes to protocols, reported events and adverse events. This meeting gave me insight into the different perspective and concerns from the community, researchers, legal representatives have when reviewing the typical study designs.

### ***Study Initiation Visits:***

Before a sponsor selects a site, a study initiation visit is undertaken by a CRO to ensure the correct choice of study site. This survey gathers information on the availability of potential study subjects, competitor's studies going on at the site and insight of professional experience and capabilities of those involved in a study. I had a chance to participate in such study initiation visits for three forthcoming trials for this site.

### ***Protocol Amendments and Consent Modifications:***

It is very common for sponsors to make modifications in protocol and consents during a study. During my internship, I got several chances to submit to the IRB the sponsor suggested track changes in protocol design, informed consent and assent documents. The experience I gained was very valuable because it familiarized me the problems a sponsor faces during a trial execution and the site faces during its implementation.

### ***Correspondence:***

During the course of working on the regulatory aspects of a new study, I corresponded regularly with the study sponsor personnel to get answers to certain questions regarding the protocol design, consent and assent documents, and answered their queries they had for the site. In the end, I was in a position to respond to any questions regarding the new study.

### ***Meetings:***

During the course of my internship, I had the opportunity to attend almost every departmental, institutional and sponsor study and coordinator meetings. These opportunities helped me to experience and realize the challenges of the jobs that were not as obvious to me as a beginner.

The Clinical Research Department at Hematology & Oncology at Cook Children's held monthly meetings with coordinators and physicians so that they can discuss various problems clinical research associates face in their jobs. These meetings also included the IRB regulatory staff. Among the most pressing of these problems discussed during these meetings was a new software development and problems faced with electronic medical records.

Meetings with all clinical research associates and research coordinators allowed me to instantly become a part of the working team and benefit from years of experience of other CRAs and endure the challenges that come in profession of clinical research.

As I was actively involved in ALL studies, I was given a privilege to attend the Children's Oncology Group Investigator study meeting in Dallas. This meeting was one of the most valuable experiences I had during the course of my internship. The investigational meeting was sponsored by the sponsor Children's Oncology Group. This meeting gave me an opportunity to learn new information and to see the problems with therapy and compare our site problems with other sites conducting the same trial.

In addition I also participated in I also participated in weekly and monthly meetings for with all study coordinators, physician and clinical research associates. This kept me updated on the latest information on the study.

I was very fortunate to get an opportunity to participate in coordination of oncology clinical trials. Six month internship exposed me to every possible problematic domain within a clinical trial management. I feel I am now confident enough to manage successfully a clinical trial independently.

## **DAILY JOURNAL**

### **APPENDIX A**

#### **June 15, Monday**

Dr. Bowman introduced me to Kathy Tankersley, Senior CRA, H/O Clinical Research Dept

Kathy T. introduced me to all other CRA and staff members at H/O Clinical Research

Amy oriented me with AE, ADVEER forms & Roadmaps for XXX670

Learnt about the CTCAE version 3.0

Kathy T. spoke about potential studies I could work

Assigned to create a new study budget

#### **June 16, Tuesday**

Attended Grand Rounds on Atresia

Jennifer, CRA, oriented me with the process of patient enrollment & registration for COG

Read the XXXH protocol

#### **June 17, Wednesday**

Learnt how to use the clinical research access and leukemia/lymphoma database

Tammy oriented me on how to use the meditech software

Went through all the ongoing ALL protocol schemas & Roadmaps

### **June 18, Thursday**

Started to work on assigned budget based on sponsor's protocol

Attended a Study Analysis meeting at Burnett Plaza

Met Dr. Marshall, Dr. Leigh, Dr. James and Susan Caskey

Attended a Leukemia/Lymphoma Team meeting

### **June 19, Friday**

Worked on assigned XXXH budget based on sponsor's protocol

Met Dr. Bowman to give an update on the whole week

### **June 22, Monday**

Had committee meeting with Dr. Gwartz, Dr. Bowman, Dr. Kim at Patient Care Center,  
UNTHSC



Collected and read study progress reports on two studies

**June 23, Tuesday**

Attended Grand rounds

Alice oriented me on patient recruitment, eligibility, enrollment and follow up process on her studies

**June 24, Wednesday**

Read XXX08 protocol

Read AAXXXXXX protocol

**June 25, Thursday**

Read Literature journals

Attended Leukemia/Lymphoma meeting

Worked on assigned budget based on sponsor's protocol

**June 26, Friday**

Holly oriented me how to use and update the iRIS

Discussed with Kathy T. about new projects

### **June 29, Monday**

Updated information on 9 patients in follow up in one study, into iRIS database

Worked on the assigned study budget

Met Dr. Bowman to discuss course of project

### **June 30, Tuesday**

Updated status on 90 patients in follow up in another study, into iRIS database

Attended the Neuro/Onc meeting

Worked on the assigned study budget

### **July 1, Wednesday**

Read Journals

Attended Study Analysis meeting

Learnt about an interesting patient case at H/O case conference

**July 2, Thursday**

Submitted study budget to Kathy T.

Updated IRB reimbursements of 2 studies on clinical research database

**July 3, Friday**

Read literature on risks and benefits of transplantation

Updated IRB reimbursements of one study on clinical research database

**July 6, Monday**

Got feedback on submitted budget

Re- worked on the budget and completed all covered amounts and costs

**July 7, Tuesday**

Verified and updated 4 patient charts from their clinic roadmaps.

Printed out updated & verified roadmaps and filed them appropriately

Updated IRB reimbursements for Kathy T. on 3 studies on clinical research database

**July 8, Wednesday**

Verified and updated 4 patient charts from their clinic roadmaps.

Printed out updated & verified roadmaps and filed them appropriately

Re-submitted budget to Kathy T.

**July 9, Thursday**

Registered for taking the CITI training on Cooknet/Cook Children's Intranet

Verified and updated 3 patient charts from their clinic roadmaps.

Printed out updated & verified roadmaps and filed them appropriately

**July 10, Friday**

Verified and updated 2 patient charts from their clinic roadmaps.

Printed out updated & verified roadmaps and filed them appropriately

Completed all modules for CITI certification

**July 13, Monday**

Read Journals

Verified and updated 2 patient charts from their clinic roadmaps.

Printed out updated & verified roadmaps and filed them appropriately

Familiarized myself with sponsor website for a new study

Collected and printed all S00 forms required for regulatory submissions for a study

**July 14, Tuesday**

Trained for data collection procedure of Pharmacokinetics for a study

Verified and updated 1 patient chart from their clinic roadmaps

**July 15, Wednesday**

Feedback on new budget submitted on July 8

Participated in the TTXV Videoconference with St. Jude Children Hospital

**July 16, Thursday**

Collected pharmacokinetics data on 3 patients on TTXV study

Faxed the collected data to St. Jude

Filed the faxed copies in the study files

Verified and updated 4 patient charts from their clinic roadmaps.

Made copies of updated & verified roadmaps and filed them appropriately

Received my CITI training certificate

### **July 17, Friday**

Tracked all documents for XXXH study initiation & regulatory submissions on sponsor website

Read Journals for Pre-Research Proposal

### **July 20, Monday**

Discussed with Kathy T. about new project ideas for pre-proposal

Received positive feedback from Kathy T. on ideas and on design of pre-proposal

Met Dionne Rogers, Research Regulatory Specialist at the Burnett Plaza

Discussed with Dionne, about how to complete the regulatory documents for XXXH study

### **July 21, Tuesday**

Participated in a teleconference with St. Jude on a new protocol: XXX08 study initiation visit

During the teleconference, the P.I went over all the sections of the protocol

Sent research proposal for review by Dr. Bowman and Kathy T.

### **July 22, Wednesday**

Discussed with Dionne on RICH study

Completed the FDA 1572 form for a new study

### **July 23, Thursday**

Met Dr. Bowman for his corrections in Pre-Research Proposal

Discussed with Dr. Bowman about my research questions for pre-proposal

Gave updates on day-to-day activities

Verified and updated 4 patient charts from their clinic roadmaps.

Printed out updated & verified roadmaps and filed them appropriately

### **July 24, Friday**

Included all investigators names in FDA 1572 form

E-mailed Andrea, IRB manager inquiring about renewed FWA number

### **July 27, Monday**

Completed the Shipping Information with help from sponsor's protocol

Collected duplicate copies to be sent to sponsor and kept in regulatory binder

### **July 28, Tuesday**

Received the FWA numbers from Andrea

Completed the S003 and S004 forms for sponsor

Collected duplicate copies to be sent to sponsor and kept in regulatory binder

### **July 29, Wednesday**

Completed Financial Disclosure forms

Made 11 copies and filed them correctly in appropriate packet for fedex



**July 30, Thursday**

Verified and updated 4 patient charts from their clinic roadmaps.

Printed out updated & verified roadmaps and filed them appropriately

**July 31, Friday**

Verified and updated 4 patient charts from their clinic roadmaps.

Printed out updated & verified roadmaps and filed them appropriately

**August 3, Monday**

Sent the final copy of pre-proposal to Dr. Bowman for feedback

Met Kathy Loinette, Transplant Coordinator at the BMT Unit

Discussed with Kathy L. about internship project

Discussed on methods to track all the patients for the study

Sent e-mail to Andrea, IRB Manager, requesting consent template of Cook's IRB

**August 4, Tuesday**

Attended the Doc/CRA meeting at H/O, where several potential studies were discussed

Assigned to work on regulatory affairs of a new study

Updated all members on status of regulatory submissions for the same study

### **August 5, Wednesday**

Collected pharmacokinetics data on 2 patients on the TTXV study

Sent e-mails to sponsor with questions on the XXXH consent

Communicated Kathy T. and Dionne on the sponsor's response on the XXXH consent

### **August 6, Thursday**

Collected pharmacokinetic data on 1 patient on the TTXV study

Started writing the XXXH consent according to the template provided by Cook's IRB

### **August 7, Friday**

Collected pharmacokinetics data on 3 patients on TTXV study

Faxed the collected data to St. Jude nurse

Filed the faxed copies in the study files

Verified and updated 4 patient charts from their clinic roadmaps.

Made copies of updated & verified roadmaps and filed them appropriately

Met Dr. Bowman for feedback on design of pre-proposal and pre-proposal document

Continued working on XXXH consent

### **August 10, Monday**

Collected pharmacokinetics data on 3 patients on TTXV study

Faxed the collected data to St. Jude nurse

Filed the faxed copies in the study files

Sent e-mails to sponsor with questions on sponsor version of XXXH consent

Verified with sponsor to include certain risks of study, not mentioned in sponsor version of consent

Communicated about sponsor's response to Kathy T. and Dionne

Included missing information on risks in the XXXH consent, as mentioned in sponsor protocol

### **August 11, Tuesday**

Sent e-mail to sponsor, verifying about re-imbusement information to be included in the Cook's XXXH consent

Sponsor communicates back to include the verified and approved budget re-imbusement amount for each patient

Verified with Kathy T. about approved re-imbusement amount to be paid by Cooks to each patient

Included all pertinent information communicated by sponsor into consent

Completed the XXXH consent and sent it to Dionne

### **August 12, Wednesday**

Attended TTXV Videoconference with St. Jude

Went over all toxicities of 90 patients in TTXV protocol

Requested Andrea, IRB Manager for the assent template of Cook's IRB

### **August 13, Thursday**

Attended the Leukemia/Lymphoma Team Admin Meeting

Learnt about a potential study

Started working on the Cook XXXH assent document

Met Kathy Loinette for tracking the subject population in my study

Received a complete list of 702 patients who were transplanted at Cook Children's

**August 14, Friday**

Continued working on the Cook XXXH assent document

Met Kathy Loinette to discuss about the transplant survival project

**August 17, Monday**

Continued working on the Cook XXXH assent document

Learnt from Kathy L. how to use Stemsoft software

**August 18, Tuesday**

Completed and sent the final XXXH assent document to Dionne

Pre-Screened 10 patients according to eligibility criteria using Stemsoft for a study

Read a new XXX- Naive protocol

**August 19, Wednesday**

Read a new XXX- Naive protocol

Created a new XXX-Naive budget based on protocol requirement

Sent the XXX-Naive budget to Kathy T. for feedback

Pre- Screened 10 patients according to eligibility criteria using Stemsoft for a study

**August 20, Thursday**

Met Sara and discussed how to obtain PHI for subject population in self project

Worked on one Amendment of consent for AALLXXX, using the sponsor consent

Highlighted track changes that needs to be included in modified consent

E-mailed Jacqueline, Transplant Data Coordinator

Requested Jackie for the complete subject population of ALL transplant recipients till 2008

Created an a simple data sheet according to all the requirements for study

**August 21, Friday**

Received a list of 179 patients for self project

Collected pharmacokinetic data on 2 patients on the TTXV study

Read a paper on outcome in transplant recipients

Collected data on 4 patients in treatment/transplant follow up

**August 24, Monday**

Worked on Protocol Summary for chart analysis for IRB submission

Collected data on 4 patients in treatment/transplant follow up

Feedback from Kathy T. for XXX-Naive budget, submitted on August 19

**August 25, Tuesday**

Collected pharmacokinetics data on 3 patients on TTXV study

Faxed the collected data to St. Jude nurse

Filed the faxed copies in the study files

Verified and updated 4 patient charts from their clinic roadmaps.

Made copies of updated & verified roadmaps and filed them appropriately

Continued with Protocol Summary for chart analysis for next month IRB submission

Extracted the key variables from Leukemia/Lymphoma access research database

Sent the completed protocol summary to Dr. Bowman & Kathy for feedback

### **August 26, Wednesday**

Collected pharmacokinetics data on 3 patients on TTXV study

Faxed the collected data to St. Jude nurse

Filed the faxed copies in the study files

Verified and updated 4 patient charts from their clinic roadmaps.

Made copies of updated & verified roadmaps and filed them appropriately

Learnt how to fill tissue specimen submission reports and send to lab

Interacted with the Lab personnel with questions on specific diagnosis of a new patient

Participated in one patient eligibility screening for all available protocols

Observed patient consenting, with prior approval from patient's parent and consenting nurse

### **August 27, Thursday**

Extracted few more important variables from Leukemia/Lymphoma access database



Created a rough data collection sheet on Leukemia/Lymphoma access database

**August 28, Friday**

Sent the rough data collection sheet to Kathy T. for feedback

Participated in the consented patient's enrollment on the available protocols

Completed and filed 3 tissue specimen submission reports

**August 31, Monday**

Worked on a consent amendment, according to the sponsor consent

Made track changes for approval and submitted it on iRIS

Feedback on XXX-Naive budget sent to Kathy T.

Read Journals

**September 1, Tuesday**

Attended the monthly Doc/CRA meeting

Identified 9 patients lost to follow-up on the access database & Meditech

Learnt about the process of AE reporting from Amy

Screened roadmaps referring to CTCAE version 3.0 for AE reports

### **September 2, Wednesday**

Feedback on data collection variables from Kathy T.

Sent final variables to Kathy T.

Re-modified rough data collection sheet on access clinical research database

Completed a consent amendment, according to the sponsor consent

Learnt about IRB guidelines to follow for AE reporting

Assisted Amy with CTCAE version 3.0 criteria for AE reporting

### **September 3, Thursday**

Did not got to Internship

### **September 4, Friday**

Attended the SCT meeting and, identified 2 patients on follow up, to considered in self project

Met Dr. Bowman at LACP

Gave updates, received approval on the key variables for the data collection sheet

Collected pharmacokinetics data on 3 patients on TTXV study

Faxed the collected data to St. Jude nurse

Filed the faxed copies in the study files

Screened eligibility criteria for 46 patients using Stemsoft

Requested off-site charts of those 46 patients for chart review

### **September 7, Monday**

Happy Labor Day Holiday!

### **September 8, Tuesday**

Worked on another protocol & consent amendment, according to the sponsor template

Feedback on written consent & assent from Dionne

Feedback on Protocol Summary from Dr. Bowman

Incorporated changes into the summary

### **September 9, Wednesday**

Requested 2 patients' charts from Medical Records for review

Collected data on those 2 patients

**September 10, Thursday**

Requested 2 patients' charts from Medical Records for review

Collected data on those 2 patients

**September 11, Friday**

Collected pharmacokinetics data on 3 patients on TTXV study

Faxed the collected data to St. Jude nurse

Filed the faxed copies in the study files

Verified and updated 4 patient charts from their clinic roadmaps.

Made copies of updated & verified roadmaps and filed them appropriately

Requested 2 patients' charts from Medical Records for review

Collected data on those 2 patients

Observed and participated in a patient consenting process, with prior approval from patient's parent and consenting nurse

**September 14, Monday**

Did a consent amendment AOSTXXXX for Jennifer, according to sponsor protocol

Did a assent amendment AOSTXXXX for Jennifer, according to sponsor protocol

Did track changes to the consent & assent, on approval to be submitted on iRIS

Read a new XXXX protocol for tomorrow's study initiation visit

**September 15, Tuesday**

Participated in a study initiation visit for a new study

Both Tammy and I, were able to answer questions on requirements, from visiting CRO personnel

Collected pharmacokinetics data on 3 patients on TTXV study

Faxed the collected data to St. Jude nurse

Filed the faxed copies in the study files

Verified and updated 4 patient charts from their clinic roadmaps.

Made copies of updated & verified roadmaps and filed them appropriately

Requested 2 patients' charts from Medical Records for review

Collected data on those 2 patients

**September 16, Wednesday**

Collected pharmacokinetics data on 3 patients on TTXV study

Faxed the collected data to St. Jude nurse

Filed the faxed copies in the study files

Verified and updated 4 patient charts from their clinic roadmaps.

Made copies of updated & verified roadmaps and filed them appropriately

Requested 2 patients' charts from Medical Records for review

Collected data on those 2 patients

Collected data on those 2 patients

**September 17, Thursday**

Completed collection of pharmacokinetic data on 2 patients on TTXV study

Identified 2 patients on access database and extracted their transplant follow up information

Attended the IRB new research meeting at Cook Children's

**September 18, Friday**

Identified 73 patients according eligibility criteria with no records on Meditech & Medical Records section

Requested the off-site patient charts for review

### **September 21, Monday**

Completed collection of pharmacokinetic data on 2 patients on TTXV study

Requested 2 patients' charts from Medical Records for review

Collected data on those 2 patients

### **September 22, Tuesday**

Completed collection of pharmacokinetic data on 2 patients on TTXV study

Requested 2 patients' charts from Medical Records for review

Collected data on those 2 patients

### **September 23, Wednesday**

Received new feedback on Protocol Summary & Data collection sheet from Dr. Bowman

Incorporated changes into the summary & data collection sheet

Sent the final Protocol Summary & data collection to Dionne for iRIS filing and submission to Cook's IRB

**September 24, Thursday**

Completed collection of pharmacokinetic data on 2 patients on TTXV study

Requested 2 patients' charts from Medical Records for review

Collected data on those 2 patients

Started working on documents of HIPAA Authorization waiver, COIs & IRB application for UNTHSC OHRP/IRB submission

Sent documents to Kathy T. for feedback

**September 25, Friday**

Received and incorporated feedback, completed UNTHSC OHRP/IRB documents

Requested 2 patients' charts from Medical Records for review

Collected data on those 2 patients

**September 28, Monday**

Received few more corrections related to investigator information, from Dr. Bowman



Did final corrections on Protocol Summary & Data collection sheet

Sent the final versions to Dionne

Finalized Defense Date on November 20, with help from Tiffany

### **September 29, Tuesday**

Completed IRB submission on iRIS, with help from Dionne

Requested 2 patients' charts from Medical Records for review

Collected data on those 2 patients

### **September 30, Wednesday**

Attended the COG Fall meeting at Dallas

Talks attended:

- Molecular targeted therapies for Ph+ ALL
- New therapies for T- ALL
- Future of T- ALL Therapy
- ALL Open Session: Each P.I. spoke for 10 mins talk on their ALL protocol

### **October 1, Thursday**

Collected data on 3 study patients

**October 2, Friday**

Attended a SCT meeting

Had 2 patients for a study

Checked Meditech for eligibility requirements of the new patients

**October 5, Monday**

Collected pharmacokinetics data on 3 patients on TTXV study

Faxed the collected data to St. Jude nurse

Filed the faxed copies in the study files

Requested off-site charts

**October 6, Tuesday**

Attended the CRA/Doc meeting

**October 7, Wednesday**

Worked on another amendment, based on sponsor template

Submitted with approved track changes on iRIS

**October 8, Thursday**

Collected pharmacokinetics data on 3 patients on TTXV study

Faxed the collected data to St. Jude nurse

Filed the faxed copies in the study files

**October 9, Friday**

Verified and updated 4 patient charts from their clinic roadmaps.

Holly kept two other charts for me to update next week, since she will be out of office

Made copies of updated & verified roadmaps and filed them appropriately

**October 12, Monday**

Collected data on 4 patients

Discussed the data with Kathy T.

**October 13, Monday**

Collected data on 2 patients

Collected pharmacokinetics data on 3 patients on TTXV study

Faxed the collected data to St. Jude nurse

Filed the faxed copies in the study files

**October 14, Tuesday**

Read Journals

Collected data on 2 patients

**October 15, Thursday**

Collected pharmacokinetics data on 3 patients on TTXV study

Faxed the collected data to St. Jude nurse

Filed the faxed copies in the study files

Collected Conflict of interest forms signatures and filed them separately

**October 16, Friday**

Read Journals

Had a new patient on study

Asked Andrea and Carol to allow me observe IC

**October 19, Monday**

Collected data on 2 patients

**October 20, Tuesday**

Observed Andrea and Carol while administering Informed consent to subject's parent

Learnt Event Reporting from Kathy T.

**October 21, Wednesday**

Verified and updated 2 patient charts from their clinic roadmaps.

Made copies of updated & verified roadmaps and filed them appropriately

**October 22, Thursday**

Collected data on 2 patients on another study

Learnt few occurrences of AE Reporting from Kathy T.

**October 23, Friday**

Collected data on 2 patients on another study

**October 26, Monday**

Read Journals

Verified and updated 2 patient charts from their clinic roadmaps.

Made copies of updated & verified roadmaps and filed them appropriately

**October 27, Tuesday**

Collected data on another study

Faxed new collected data to St. Jude nurse

Filed the faxed copies in the study files

Received Cook IRB Approval on study

**October 28, Wednesday**

Collected data on 5 patients

**October 29, Thursday**

Submitted 2 packets of IRB documents to UNTHSC OHRP/IRB for approval

Collected data on 2 patients

**October 30, Friday**

Collected data on 3 patients

Discussion of analysis of collected data with Lindsey and Dr. Bowman

Received comments from Lindsey on Thesis sections

**November 2, Monday**

Collected data on 2 patients

Worked on Thesis

**November 3, Tuesday**

Showed results of collected data and graphs to Dr. Bowman for approval

Received UNTHSC IRB communication asking for further documentation

Worked on Thesis

### **November 4, Wednesday**

Submitted further required documentations at UNTHSC OHRP/IRB

Worked on Thesis Results

### **November 5, Thursday**

Worked on Thesis

Collected data on one study patient

Gave a written portion of thesis results to Dr. Bowman for approval

Noted graph comments of Lindsey

Received UNTHSC IRB approval

### **November 6, Friday**

Worked on Thesis Results



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