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HYPERTENSION INTERVENTION TO REDUCE OSTEONECROSIS IN CHILDREN WITH ACUTE LYMPHOBLASTIC LEUKEMIA/ LYMPHOMA

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Protocol Summary

HYPERION: Hypertension Intervention to Reduce Osteonecrosis in Children with Acute Lymphoblastic Leukemia
Principal Investigator: Seth Karol, MD
IND Holder: N/A
Brief Overview: This is a randomized Phase II clinical trial evaluating the impact of intensive antihypertensive control (targeted to the 50-75th percentile for age, sex, and height) compared to conventional antihypertensive control (targeted to the 90-95th percentile for age, sex, and height) on the incidence of radiographically extensive osteonecrosis in children and young adults receiving treatment for newly diagnosed acute lymphoblastic leukemia/lymphoma (ALL).
Intervention: Patients will be treated for hypertension to achieve the goal systolic blood pressure indicated by their intervention arm.
Brief Outline of Treatment Plan: Patients will be randomized on day 4 of induction therapy to either conventional or intensive blood pressure goals. Patients will be treated with the long-acting antihypertensive lisinopril to achieve blood pressure control as indicated by their randomized arm. Long-acting therapy will be adjusted every 3-4 days as needed to achieve targeted control based on the median of blood pressures obtained in that period. Treatment of hypertension to the target will continue until the completion of reinduction II therapy. Patients will be evaluated for osteonecrosis as indicated in their primary therapeutic protocol using MRI during reinduction II.
Study Design: Randomized unblinded trial of conventional vs. intensive hypertensive control. Evaluation of the MRIs defining the primary endpoint will be performed by a blinded radiologist.
Sample Size: We will randomize 160 evaluable patients (180 total).
Data Management: Data management and statistical analysis will be provided locally by the Comprehensive Cancer Center Hematological Malignancies Program and the Biostatistics Department at St. Jude Children's Research Hospital.
Human Subjects: The risks to subject will be related to the toxicity of antihypertensive therapy. Side effects are anticipated to be mild and limited to reversible orthostatic/postural hypotension and transient increases in creatinine. Patients will be informed of this and other minor side effects during informed consent discussion. Adverse events will be monitored and reported and treated appropriately.

St. Jude Children's Research Hospital
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1.0 OBJECTIVES

1.1 Primary Objective

1.1.1 Compare the frequency of radiographically extensive osteonecrosis in patients receiving intensive compared to conventional antihypertensive therapy.

1.2 Secondary Objectives

1.2.1 Evaluate the efficacy of intensive antihypertensive control compared to conventional antihypertensive control in the prevention of clinically significant (CTCAE Grade 2 or higher) and radiologically extensive osteonecrosis, overall and stratified by joints.

1.2.2 Compare the frequency of clinically significant and radiographically extensive osteonecrosis in patients receiving antihypertensive therapy and historical controls.

1.2.3 Compare blood pressures achieved in intensive and conventional arms using both pressures obtained as part of routine patient care and ambulatory blood pressure monitoring.

1.2.4 Compare levels of vascular dysfunction as measured physiologically, radiographically, and in blood samples in patients receiving intensive compared to standard antihypertensive therapy.

1.3 Exploratory Objectives

1.3.1 Identify predictive patterns of blood biomarkers which identify patients at high-risk of developing clinically significant osteonecrosis.

1.3.2 Identify MRI findings during late induction which correlate with osteonecrosis lesions seen during reinduction.

1.3.3 Identify patterns of diurnal blood pressure variation as measured by ambulatory blood pressure monitoring associated with the later development of osteonecrosis.

1.3.4 Compare induction blood pressure control and intervention arm to echocardiographic changes at reinduction II.

1.3.5 Evaluate patient-reported, health-related quality of life in patients during induction and after 1.5 years of therapy when many experience the symptoms of osteonecrosis.

2.0 BACKGROUND AND RATIONALE

2.1 Background

Advancements in the treatment of acute lymphoblastic leukemia (ALL) have pushed the cure rate to greater than 90%.[1] Intensifying glucocorticoid use (i.e. prednisone and dexamethasone) has been key in accomplishing these outcomes. However, glucocorticoid-induced osteonecrosis (ON) is one of the most common dose-limiting toxicities of ALL therapy in children.[2-6] Symptomatic cases (defined as Common Terminology Criteria for Adverse Events (CTCAE) grade 2-4) often occur during the first two years of treatment, and may result in early discontinuation of glucocorticoids from treatment. Age is the most significant risk factor, with ALL patients greater than 10 years of age at higher risk of developing ON.[2,3,5,6] The most common affected joints are the hip, knee, and shoulder.[7-9] In both Total XV[3] and Total XVI[10], the rate of symptomatic osteonecrosis in children age 10 or older was ~40%.

Recent work has demonstrated that patients with ALL age 10 or older at diagnosis who develop hypertension during glucocorticoid containing phases of therapy were more likely to develop osteonecrosis. Among 235 children treated on Total XV and Total XVI, osteonecrosis occurred in 52% of the 94 who developed hypertension compared to 38% of those who were normotensive [p=0.037, odds ratio (OR) 1.75, 95% confidence interval (95% CI) 1.02-3.01.[11] The association was maintained in a multivariable analysis of all known factors associated with either hypertension or osteonecrosis (p=0.03, OR 1.88, 95% CI 1.1-3.22). When the analysis was restricted to osteonecrosis that developed during protocol therapy, 52% of patients with hypertension developed osteonecrosis compared to 34% of normotensive patients (p=0.006, OR 2.11, 95% CI 1.2-3.6). Hypertension was also associated with an increased frequency of extensive epiphyseal involvement (≥30% of the surface effected) of the hip and knee joints on screening MRIs; this is significant as this degree of involvement is associated with joint collapse and the need for surgical intervention.[12,13]

In preclinical models, dexamethasone and asparaginase produced hypertension as in patients with ALL. The use of either an angiotensin enzyme inhibitor or hydralazine reduced the frequency of osteonecrosis (15% vs. 38% and 3% vs. 36%, p<0.01 for both) through reductions in osteonecrosis-inducing arteriopathy.[11] The same regimen did not impact the antileukemic efficacy of chemotherapy *in vitro* or *in vivo*.

2.2 Rationale

Based on the retrospective clinical and prospective preclinical data, undertreatment of hypertension is associated with an approximately 2-fold increased risk of developing osteonecrosis after accounting for other known risk factors. Data from both adult[14,15] and pediatric[16] populations shows a benefit to more intensive blood pressure control compared to conventional control. Due to the risks of complications from untreated hypertension (e.g. posterior reversible encephalopathy syndrome), it is both impractical and unethical to randomize patients to no treatment for their hypertension. We will therefore test the efficacy of intensive hypertensive control (targeted to the 50-75th

percentile for age, sex, and height, systolic) compared to conventional antihypertensive control (targeted to the 90-95th percentile for age, sex, and height, systolic). We have chosen slightly higher systolic blood pressure goals for the intensive arm compared to the ESCAPE trial[16] due to the presence of anemia and risk for infection in pediatric ALL patients, both of which may predispose to an increased risk of symptomatic hypotension.

The Children's Oncology Group AALL0232 and CCG1961 trials demonstrated differences in osteonecrosis in patients receiving dexamethasone instead of prednisone during induction, or continuous instead of alternate week dexamethasone during delayed intensification, respectively.[2,5] These data support the critical role that these two steroid-intensive phases of therapy (termed induction and reinduction in St. Jude Total Therapy protocols) play in the development of osteonecrosis. The planned intervention will therefore encompass these two periods.

Although TOT17 includes an optional randomization for vincristine and dexamethasone duration (49 weeks vs. 101 weeks), the primary endpoint in this study (Reinduction II MRI) occurs prior to that randomization. Thus, the randomization will not impact the primary outcome of the study. Furthermore, review of symptomatic osteonecrosis timing on TOTXVI suggests that the majority of patients develop symptoms prior to this timepoint. For secondary endpoints including CTCAE symptomatic osteonecrosis, we will consider dexamethasone duration as a covariate.

2.3 Background and Rationale for Ancillary and Exploratory Studies

Screening magnetic resonance imaging has a higher sensitivity than traditional radiographs for detecting early osteonecrosis.[12,17] Data from prior Total Therapy studies indicates that involvement of ≥30% of the epiphyseal surface of either the hip or knee is associated with the need for surgical intervention and/or collapse of the articular surface.[12](Inaba et al, in submission).

Blood pressures obtained as part of routine care have historically been the standard for evaluation of hypertension in children with ALL.[11,18-20] However, ambulatory blood pressure monitoring (ABPM) has been shown to better predict end-organ damage in patients with hypertension and to identify patients with masked hypertension during office visits.[21-23] This modality has not been previously evaluated in children receiving leukemia treatment and so its predictive value in this population is unknown. These data also demonstrate echocardiographic changes seen in patients with hypertension detected by ABPM would not have been predicted by clinical monitoring.

Measurements of small and large elasticity are associated with cardiovascular events in the general population[24,25] and are feasible in childhood cancer survivors.[26] These vascular properties change across age and vary between boys and girls.[27] We will measure these vascular properties non-invasively to assess their changes during therapy as well as their association with osteonecrosis and other vascular biomarkers.

Plasma markers of vascular health have been associated with a variety of adverse cardiovascular outcomes. Synthesis of nitric oxide, a potent vasodilator, acts as a marker of cardiovascular stent re-stenosis risk.[28] Other plasma markers shown to predict adverse cardiovascular events include von Willebrand Factor, tumor necrosis factor alpha,[29], D-dimer, [30] PAI-1, E-selectin, and ICAM-1.[31] These markers of endothelial function and vascular health have not been previously studied in this population and so their association with osteonecrosis risk remains unknown.

Although osteonecrosis is considered a significant contributor to the intermediate- and long-term morbidity of ALL therapy, patient perspectives on the impact of osteonecrosis are lacking. We will thus evaluate the impact of therapy and osteonecrosis on the patient experience using the validated patient-reported tool PROMIS tools.[32-35] We will further assess the impacts of therapy on patient quality of life with semi-structured interviews.[36,37]

3.0 RESEARCH PARTICIPANT ELIGIBILITY CRITERIA AND ENROLLMENT

According to institutional and NIH policy, the study will accession research participants regardless of gender and ethnic background. Institutional experience confirms broad representation in this regard.

3.1 Inclusion Criteria

3.1.1 Patient is being treated for newly diagnosed acute lymphoblastic leukemia or lymphoma (ALL) on the TOT17 protocol. Patients do not need to be hypertensive to enroll.

3.1.2 Patient is 10 years of age or older at the time of enrollment on TOT17.

3.1.3 Patient has completed $\leq$ 4 days of protocol therapy (patients are eligible on Day 4 of TOT17 therapy).

3.2 Exclusion Criteria

3.2.1 Moderate-severe renal dysfunction (glomerular filtration rate <45 ml/min/1.73m^2).

3.2.2 Down's syndrome (germline Trisomy 21) or other syndrome resulting in growth delay or alterations in stature.

3.2.3 Chronic inability to ambulate. Patients with limitations in movement due to acute complications of leukemia/lymphoma are not excluded.

3.2.4 Permanent contraindication to MRI evaluation.

3.2.5 Participants who are pregnant or lactating. Males or females of reproductive potential must agree to use effective contraception for the duration of study participation.

3.2.6 Inability or unwillingness of research participant or legal guardian/representative to give written informed consent.

3.3 Research Participant Recruitment and Screening

Five institutions will collaborate in the proposed project: St. Jude Children's Research Hospital (SJCRH); Cook Children's Medical Center; Stanford University; Children's Hospital of Michigan; Rady Children's Hospital – San Diego and Novant Health Hemby Children's Hospital – Charlotte NC.

3.4 Enrollment on Study at St. Jude

A member of the study team will confirm potential participant eligibility and complete all sections of the Participant Eligibility checklist, print, and sign. If the enrollment will be entered by Clinical Trials Operations (CTO), then the study team must send the completed checklist to CTO by email [redacted] or fax [redacted] (follow fax by a phone call to [redacted] to ensure receipt).

The Study Team or CTO will enter the Eligibility checklist information into the central enrollment system and release an informed consent form. The study team will provide a copy of the study informed consent form (ICF) to the participant family for their consideration and reference. The entire signed ICF must forwarded to CTO: [redacted] or faxed [redacted] so that the enrollment will show in the protocol Milli tab and for study-specific orders to be generated in Milli.

To assist with enrollments and consent release, the CTO staff is available during office hours. After hours, weekends, and holiday patient enrollment issues please call the St. Jude study coordinator or refer to the CTO intranet site for additional resources and instructions: [redacted].

3.5 Enrollment Instructions for Collaborating Sites

Before the collaborating or enrolling affiliate sites screen or enroll a study participant, the site completes a RIN request form and submits it to CTO by e-mail: [redacted] or fax [redacted] (follow fax by a phone call to [redacted] to ensure receipt). A RIN is an eight-digit automated number beginning with an "R". Once the form is received, St. Jude will register the research participant and then email the RIN to the email address provided on your registration form. This will register the participant only; it will not enroll the participant on the study. After hours, holidays, and weekends the site RIN request will be answered by the Patient Registration team.

To *enroll* the study participant, after the RIN is obtained, the site study team will complete an eligibility checklist and fax it to [redacted] or by email [redacted] (follow with a phone call to [redacted] to ensure receipt). The CTO will enter the Eligibility Checklist information into the central enrollment system to officially enroll the participant on the trial. Collaborating sites are not required to forward a fully executed (signed) Informed Consent Form to St. Jude.

4.0 TREATMENT PLAN

4.1 Treatment

Following enrollment and randomization, a target systolic blood pressure range will be chosen for each participant based on their randomization arm, age, sex, and height. Target blood pressures for girls randomized to standard and intensive blood pressure control are shown in Tables 1a and 1b, respectively. Target blood pressures for boys randomized to standard and intensive blood pressure control are shown in Tables 2a and 2b, respectively. For patients ages 10-12 years, select the height column closest to their true height. If two columns are equidistant from their true height, select the lower height.

Patient randomization will be stratified based on patient's location (Memphis vs. other), use of antihypertensives prior to randomization, and factors known to influence osteonecrosis risk, specifically sex and self-declared race (non-Hispanic white vs. other).

Patients will begin antihypertensive therapy to achieve the targeted blood pressure on day 4. Patients already receiving antihypertensive therapy prior to day 4 should have their therapy adjusted according to the guidelines below. **Patients requiring an antihypertensive should be started on lisinopril** (initial dose 2.5mg daily) unless there is a contraindication to its use. Lisinopril dose may be escalated as indicated. Recommended second line agents for use when lisinopril is contraindicated include angiotensin receptor blockers (e.g. losartan 25mg daily), beta-blockers (e.g. carvedilol 3.125mg BID or, if cardiac rate control is required, metoprolol 12.5mg BID) or a calcium channel blocker (e.g. amlodipine 2.5mg daily).

Table 1a: Girls' Standard Arm Systolic Blood Pressure Targets

Age/Height (cm)	Height 5%	Height 10%	Height 25%	Height 50%	Height 75%	Height 90%	Height 95%
10 years	130 cm	132 cm	136 cm	141 cm	146 cm	150 cm	153 cm
Standard Low End Target (mmHg)	109	110	111	112	113	115	116
Standard High End Target (mmHg)	113	114	114	116	117	119	120
11 years	136 cm	138 cm	143 cm	148 cm	153 cm	157 cm	160 cm
Standard Low End Target (mmHg)	111	112	113	114	116	118	120
Standard High End Target (mmHg)	115	116	117	118	120	123	124
12 years	143 cm	146 cm	150 cm	155 cm	160 cm	164 cm	166 cm
Standard Low End Target (mmHg)	114	115	116	118	120	122	122
Standard High End Target (mmHg)	118	119	120	122	124	125	126
13+ years	All heights						
Standard Low End Target (mmHg)	130						

Standard High End Target (mmHg)	135

Table 1b: Girls' Intensive Arm Systolic Blood Pressure Targets

Age/Height (cm)	Height 5%	Height 10%	Height 25%	Height 50%	Height 75%	Height 90%	Height 95%
10 years	130 cm	132 cm	136 cm	141 cm	146 cm	150 cm	153 cm
Intensive Low End Target (mmHg)	96	97	98	99	101	102	103
Intensive High End Target (mmHg)	103	103	105	106	108	109	110
11 years	136 cm	138 cm	143 cm	148 cm	153 cm	157 cm	160 cm
Intensive Low End Target (mmHg)	98	99	101	102	104	105	106
Intensive High End Target (mmHg)	105	106	107	109	110	112	113
12 years	143 cm	146 cm	150 cm	155 cm	160 cm	164 cm	166 cm
Intensive Low End Target (mmHg)	102	102	104	105	107	108	108
Intensive High End Target (mmHg)	108	109	110	112	113	114	114
13+ years	All heights						
Intensive Low End Target (mmHg)	110						
Intensive High End Target (mmHg)	120						

Table 2a: Boys' Standard Arm Systolic Blood Pressure Targets

Age/Height (cm)	Height 5%	Height 10%	Height 25%	Height 50%	Height 75%	Height 90%	Height 95%
10 years	130 cm	133 cm	137 cm	141 cm	146 cm	150 cm	153 cm
Standard Low End Target (mmHg)	108	109	111	112	113	115	116
Standard High End Target (mmHg)	112	113	114	116	118	120	121
11 years	135 cm	137 cm	142 cm	146 cm	151 cm	156 cm	159 cm
Standard Low End Target (mmHg)	110	111	112	114	116	117	118
Standard High End Target (mmHg)	114	114	116	118	120	123	124
12 years	140 cm	143 cm	148 cm	153 cm	158 cm	163 cm	166 cm
Standard Low End Target (mmHg)	113	114	115	117	119	121	122
Standard High End Target (mmHg)	116	117	118	121	124	126	128
13+ years	All heights						
Standard Low End Target (mmHg)	130						

Table 2a: Boys' Standard Arm Systolic Blood Pressure Targets							
Age/Height (cm)	Height 5%	Height 10%	Height 25%	Height 50%	Height 75%	Height 90%	Height 95%
Standard High End Target (mmHg)	135						

Table 2b: Boy's Intensive Arm Systolic Blood Pressure Targets							
Age/Height (cm)	Height 5%	Height 10%	Height 25%	Height 50%	Height 75%	Height 90%	Height 95%
10 years	130 cm	133 cm	137 cm	141 cm	146 cm	150 cm	153 cm
Intensive Low End Target (mmHg)	97	98	99	100	101	102	103
Intensive High End Target (mmHg)	104	104	106	107	108	108	109
11 years	135 cm	137 cm	142 cm	146 cm	151 cm	156 cm	159 cm
Intensive Low End Target (mmHg)	99	99	101	102	103	104	106
Intensive High End Target (mmHg)	105	106	107	108	109	111	112
12 years	140 cm	143 cm	148 cm	153 cm	158 cm	163 cm	166 cm
Intensive Low End Target (mmHg)	101	101	102	104	106	108	109
Intensive High End Target (mmHg)	107	108	109	110	112	114	115
13+ years	All heights						
Intensive Low End Target (mmHg)	110						
Intensive High End Target (mmHg)	120						

Patients will begin antihypertensive therapy to achieve the targeted blood pressure on Day 4 of Remission Induction on TOT17. Patients already receiving antihypertensive therapy prior to Day 4 should have their therapy adjusted according to the guidelines below.

During outpatient visits, blood pressures measured should be performed after the patient has been sitting at rest for at least 10 minutes and is not experiencing pain or anxiety.

During induction, blood pressure adjustments will be made for each patient based on the mean blood pressure over the preceding 4 days (minimum 2 measurements) unless indication for immediate change is met (listed below). Blood pressures obtained while a patient is sedated for procedures should not be included in the evaluated blood pressures when determining whether to adjust antihypertensive medications. Patients with mean blood pressures outside of the target range should have antihypertensive therapy adjusted in an attempt to reach the goal range. However, if prior changes to medication have been made within 7 days and blood pressures are both 1) closer to the target range than at the time of prior medication change and 2) within 10mmHg of the goal range following that change, further modifications can be delayed until a subsequent visit.

Immediate changes to antihypertensive therapy are indicated if:

1) systolic pressures are more than 15mmHg above the high end target,
2) patients are experiencing headache, vision changes, or neurologic symptoms attributable to hypertension,
3) the patient has experienced an episode of syncope,
4) the patient's systolic pressure is below 90, or
5) the patient is experiencing unacceptable toxicity from their current antihypertensive therapy.

Patients will continue antihypertensive therapy (as needed to achieve the targeted blood pressure range) during phases of therapy with scheduled glucocorticoids (i.e. Induction and Continuation, including Reinduction 1 & 2). Patients should continue antihypertensive therapy during other phases if tolerated. Caution is warranted in consolidation (due to the risk of altered renal perfusion or kidney injury) and during immunotherapy (due to the risk of cytokine release induced hypotension).

All antihypertensive agents are FDA approved and commercially available. See package inserts or published references or guidelines for drug information on individual medications.

The completion of Reinduction II dexamethasone marks the completion of the intervention. Following this, physicians should discontinue antihypertensive therapy or continue treatment according to their clinical judgement.

Patients will be evaluated for variations in vascular function due to chemotherapy and the antihypertensive intervention according to the calendar in Table 3 (Section 5.2). Adherence should be verified by the research team utilizing the proportion of days covered at least weekly.[38]

The term "day" does not refer to an absolute calendar day. It refers to a general 24-hour period. Variations in scheduled evaluations of up to 2 days outside the indicated time points are acceptable if needed for good patients care.

4.2 Participation of St. Jude Affiliates in the Treatment Plan

Patients treated at affiliate sites will participate in the hypertension randomized intervention. They may participate in correlative studies based on the availability of required equipment at each affiliate institution.

4.3 Treatment Modifications for Collaborating Sites

Patients treated at collaborating sites will participate in the hypertension randomized intervention. They may participate in correlative studies based on the availability of required equipment at each collaborating institution. Induction MRI will only be performed for St. Jude patients.

4.4 Supportive Care

Patients should receive supportive care per institutional standard and as directed in the TOT17 protocol.

4.5 Symptom Survey and Semi-structured Interviews

All patients will be asked to complete a symptom survey comprised of the PROMIS Ped 25 profile, PROMIS pain interference 8a, PROMIS physical activity 8a, and PROMIS mobility 8a during induction (day 23-28), during week 17 of continuation (+/- 2 weeks), and continuation week 49 (+/- 3 weeks).

Patients electing to participate in patient interviews about their treatment and symptom burden will be contacted by a study team member. They will be asked to speak about the impact treatment and symptoms have had on their lives. The semi-structured interview will be recorded, with verbal consent at the time of the recording from the patient and, if present, family members confirming the written consent obtained at protocol entry. The semi-structured interview will include the following prompts:

- Tell me about a time when your leukemia treatment changed the way that you did an activity.
    - e.g., Has your leukemia ever made it harder to do something that you wanted to do?
    - Has your leukemia ever prevented you from doing something that you wanted to do?
    - Conversely, has your leukemia ever made it easier to do something that you wanted to do?
- Can you tell me a time when a side effect from treatment impacted your life?
    - e.g., Have you ever felt pain during treatment? If so, tell me about how this affected your ability to live your life.
    - Have you ever experienced nausea or vomiting during treatment? If so, tell me about how this affected your ability to live your life.
    - Are there other symptoms which have affected your ability to live your life?
- What has been the hardest part of treatment for you?
    - What part of treatment has made you feel the most sad?
    - What part of treatment has made you feel the most angry?
    - What part of treatment has made you feel the most frustrated or helpless?
    - As a last resort, if the interviewee is unable to come up with a response despite the question item and the above prompts:
        - Some people tell us that dealing with physical symptoms is the hardest part. Others tell us that feeling anxious or sad is the hardest part. Others say that being away from family/school/friends is the hardest part. And there are so many other things about treatment that are hard. What feels like the hardest part for YOU, personally?

- Tell me about something positive that has happened as a result of your treatment.
    - Has your treatment ever helped you feel better? Tell me about this experience.
    - Has your treatment ever helped you feel relieved? Tell me about this experience.
    - Has your treatment ever helped you feel hopeful? Tell me about this experience.

All interviews will be audio-recorded and transcribed into written narratives for grounded theory qualitative analysis. Patient specific identifiers will be replaced with a code for transcription.

Qualitative analysis of interviews will be performed using the well-described methodology of content analysis.[36] Text transcripts will be reviewed in depth by multiple coders to discover similarities and trends related to each interview question item; this process will inform the development of an a priori coding schemata. Through a rigorous, iterative process of memoing and development of codes and code definitions, a preliminary codebook will be created. This codebook will be pilot tested through serial application across pre-selected rich transcripts by multiple coders, with subsequent assessment of inter-rater reliability (goal IRR >0.7). Based on pilot testing feedback, revisions will be made to the codebook to improve content and face validity. Following codebook finalization, codes will be applied across all transcripts by multiple coders working in silos to ensure at least 2 coders per transcript. The unit of analysis will be a segment inclusive of a single sentence or stand-alone phrase. Rigorous reconciliation processes will be conducted to reach consensus, with an objective third-party present to assist with adjudication. Codes will ultimately be organized and collapsed into broader categorized, with the goal of identifying emerging themes upon which to develop concepts and theories.[37] As per the inclusion standard in qualitative methodology that investigates descriptive life experiences, if a theme occurs in one interview by one person, it is reported and considered legitimate.[36]

5.0 REQUIRED EVALUATIONS, TESTS, AND OBSERVATIONS

5.1 Pre-Study Evaluations

All entry/eligibility studies must be performed within 10 days prior to entry onto the trial (unless otherwise specified). Evaluations performed as part of TOT17 evaluation and therapy should be used when feasible to avoid duplicate studies.

Evaluation– must be obtained before enrollment	**Within 10 days prior to enrollment**
History and physical exam with height (cm), weight (kg), and BSA	X
Diagnosis of acute lymphoblastic leukemia/ lymphoma (ALL)	X
Laboratory studies: CBC with Diff, Chem 18, Urinalysis, PT, PTT	X
Echocardiogram	X
Pregnancy test for females of childbearing potential	X

5.2 Evaluations during Therapy

Evaluation	**Timing during Induction**	**Timing post-Induction**
Ambulatory blood pressure monitoring (ABPM)	Once for 12-30 hours on day 4-7, once for 12-30 hours on day 23-28	-
Magnetic resonance imaging of hip and knee	Once during Days 23-28#	Reinduction 2 per Total 17 protocol
Vasomotor testing (arterial elasticity, pulse wave velocity) #	Once during Days 23-28	Once between Early Intensification day 57 and Consolidation day 28, (optional) once Continuation week 120 ±2 weeks
Serum for vascular biomarkers[&]	Day 22 +/- 2 days	Week 17 of Continuation (Reinduction II)
Echocardiogram		Once during week 17-19 of Continuation (Reinduction II)#
Symptom survey (PROMIS: Ped 25 Profile, Pain interference 8a, Physical activity 8a, Mobility 8a)	Once on day 23-28	Week 17 of Continuation (Reinduction II) ± 2 weeks, week 49 ± 3 weeks
Semi-structured interview of treatment and symptom burden #		Week 49 ± 3 weeks (with symptom survey)

All days/ weeks refer to the date of Total 17 therapy (i.e. day 22 refers to day 22 of Total 17, not the 22nd day since HYPERION entry or randomization).
***The St. Jude IRB requires that a female patient of childbearing potential must have a negative pregnancy test as a condition of clinical research eligibility.*

 # SJCRH Memphis patients only
&See HYPERION Manual of Operations for collection, processing and shipping instructions.

Obtain other studies as needed for good patient care and per the TOT17 protocol.

5.3 Response Evaluations

Osteonecrosis will be graded according to CTCAE v4 (to coincide with CTCAE version used in TOT17). Patients will receive MRI screening during Reinduction II as prescribed in the TOT17 protocol. Pain will be ascribed to osteonecrosis or an alternative cause by the treating physician based on clinical history, radiographic findings, and response to therapeutic interventions. MRIs obtained at other times due to clinical concerns/symptoms will be recorded in the research database. MRIs will be evaluated by a pediatric radiologist blinded to the hypertension randomization.

Induction MRIs will only be performed in patients able to complete the study without sedation.

5.4 Off-Study Evaluations

A symptom survey (Pediatric PROMIS Ped 25 Profile, Pain interference 8a, Physical activity 8a, Mobility 8a) and a brief interview to assess patient symptom burden will be performed at week 49 ± 3 weeks. Patients also have the option of completing vasomotor testing at week 120 ± 2 weeks.

5.5 Long-Term Follow-up Evaluations

Patients will be followed for the development of osteonecrosis as per the TOT17 protocol.

5.6 Modifications for Collaborating Sites

All sites will complete ambulatory blood pressure monitoring, Reinduction 2 MRI evaluations, serum vascular biomarkers, and symptom surveys for all patients. Vasomotor testing, echocardiography at week 17, and patient interviews will be performed only at St. Jude. Induction MRI may be performed at collaborating sites based on scanner design and sequence availability. Induction MRI may be performed at collaborating sites based on scanner design and sequence availability.

5.7 Participation of Affiliate Sites

All sites will complete ambulatory blood pressure monitoring, Reinduction 2 MRI evaluations, serum vascular biomarkers, and symptom surveys for all patients. Vasomotor testing, echocardiography at week 17, and patient interviews will be performed only at St. Jude.

6.0 EVALUATION CRITERIA

6.1 Response Criteria

All patients will be evaluated clinically and radiographically for the development of osteonecrosis. Patients with radiographic (MRI or plain film x-ray) findings of osteonecrosis will be assessed for symptoms by the treating physician or designee. CTCAE version 4 criteria will be used to categorize the severity of osteonecrosis. MRI imaging will be centrally reviewed by a radiologist blinded to treatment assignment to assess the involvement of epiphyseal surfaces (0, <30%, ≥30%) which will be determined for each effected joint.

Blood pressures for each patient will be documented in the research database as the median of each week during induction and the median of each post-induction phase.

6.2 Toxicity Evaluation Criteria

CTCAE version 4 (to coincide with CTCAE criteria used in TOT17) will be used to document all toxicities which occur on study.

6.3 Missed Doses

For the planned analyses, patients within targeted blood pressure ranges (or below target without the use of any antihypertensives) at least 80% of the time will be considered as part of the per-protocol analysis. All patients will be evaluated in the intention to treat analysis regardless of the blood pressure range achieved or number of doses of antihypertensives given as long as imaging to assess osteonecrosis is available.

7.0 OFF TREATMENT AND OFF STUDY CRITERIA

7.1 Off-Study Criteria

- Death
- Lost to follow-up
- Request of the patient/parent/LAR
- Completion/discontinuation of Total 17 therapy
- Discretion of the Study PI, such as the following
- The researcher decides that continuing in the study would be harmful, such as:
  - A treatment is needed that is not allowed on this study
  - The participant misses so many appointments that the data cannot be used in the study
  - The participant’s condition gets worse
  - New information is learned that a better treatment is available, or that the study is not in the participant’s best interest
  - Study evaluations are complete

7.2 Off-Therapy Criteria

- Completion of prescribed therapy duration (completion of week 19 dexamethasone).
- Discontinuation of TOT17 therapy
- Treatment with high-risk arm therapy (i.e. chimeric antigen receptor T-cell therapy, Reintensification, or transplant)
- Development of unacceptable toxicity during treatment
- Refusal of therapy
- A research participant may also be taken off treatment or off of the study at the discretion of the study PI if persistent non-adherence with protocol directed therapy is documented.

8.0 SAFETY AND ADVERSE EVENT REPORTING REQUIREMENTS

8.1 Reporting Adverse Experiences and Deaths to St. Jude IRB

Only "unanticipated problems involving risks to participants or others" referred to hereafter as "unanticipated problems" are required to be reported to the St. Jude IRB promptly, but in no event later than 10 working days after the investigator first learns of the unanticipated problem. Regardless of whether the event is internal or external (for example, an IND safety report by the sponsor pursuant to 21 CFR 312.32), only adverse events that constitute unanticipated problems are reportable to the St. Jude IRB.

As further described in the definition of unanticipated problem, this includes any event that in the PI's opinion was:

- Unexpected (in terms of nature, severity, or frequency) given (1) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document, as well as other relevant information available about the research; (2) the observed rate of occurrence (compared to a credible baseline for comparison); and (3) the characteristics of the subject population being studied; and
- Related or possibly related to participation in the research; and
- Serious; or if not serious suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

Unrelated, expected deaths do not require reporting to the IRB. Though death is "serious", the event must meet the other two requirements of "related or possibly related" and "unexpected/unanticipated" to be considered reportable.

Deaths meeting reporting requirements are to be reported immediately to the St. Jude IRB, but in no event later than 48 hours after the investigator first learns of the death.

The following definitions apply with respect to reporting adverse experiences:

Serious Adverse Event: Any adverse event temporally associated with the subject's participation in research that meets any of the following criteria:

- results in death;
- is life-threatening (places the subject at immediate risk of death from the event as it occurred);
- requires inpatient hospitalization or prolongation of existing hospitalization;
- results in a persistent or significant disability/incapacity;
- results in a congenital anomaly/birth defect; or
- any other adverse event that, based upon appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition (examples of such events include: any substantial disruption of the ability to conduct normal life functions, allergic bronchospasm requiring intensive treatment in the emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse), a congenital anomaly/birth defect, secondary or concurrent cancer, medication overdose, or is any medical event which requires treatment to prevent any of the medical outcomes previously listed.

Unexpected Adverse Event: Any adverse event for which the specificity or severity is not consistent with the protocol-related documents, including the applicable investigator brochure, IRB approved consent form, Investigational New Drug (IND) or Investigational Device Exemption (IDE) application, or other relevant sources of information, such as product labeling and package inserts; or if it does appear in such documents, an event in which the specificity, severity or duration is not consistent with the risk information included therein; or the observed rate of occurrence is a clinically significant increase in the expected rate (based on a credible baseline rate for comparison); or

The occurrence is not consistent with the expected natural progression of any underlying disease, disorder, or condition of the subject(s) experiencing the adverse event and the subject's predisposing risk factor profile for the adverse event.

Internal Events: Events experienced by a research participant enrolled at a site under the jurisdiction of St. Jude IRB for either multicenter or single-center research projects.

External Events: Events experienced by participants enrolled at a site external to the jurisdiction of the St. Jude Institutional Review Board (IRB) or in a study for which St. Jude is not the coordinating center or the IRB of record.

Unanticipated Problem Involving Risks to Subjects or Others: An unanticipated problem involving risks to subjects or others is an event which was not expected to occur, and which increases the degree of risk posed to research participants.

Such events, in general, meet all of the following criteria:

- unexpected;
- related or possibly related to participation in the research; and
- suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized. An unanticipated problem involving risk to subjects or others may exist even when actual harm does not occur to any participant.

Consistent with FDA and OHRP guidance on reporting unanticipated problems and adverse events to IRBs, the St. Jude IRB does not require the submission of external events, for example IND safety reports, nor is a summary of such events/reports required; however, if an event giving rise to an IND safety or other external event report constitutes an "unanticipated problem involving risks to subjects or others" it must be reported in accordance with this policy. In general, to be reportable external events need to have implications for the conduct of the study (for example, requiring a significant and usually safety-related change in the protocol and/or informed consent form).

Although some adverse events will qualify as unanticipated problems involving risks to subjects or others, some will not; and there may be other unanticipated problems that go beyond the definitions of serious and/or unexpected adverse events. Examples of unanticipated problems involving risks to subjects or others include:

- The theft of a research computer containing confidential subject information (breach of confidentiality); and
- The contamination of a study drug. Unanticipated problems generally will warrant consideration of substantive changes in the research protocol or informed consent process/document or other corrective actions in order to protect the safety, welfare, or rights of subjects or others.

The principal investigator has the obligation to report all serious adverse events to the FDA and IRB.

The following adverse events that are commonly observed in this patient population will not be reported as individual expedited reports, but with annual continuing review and progress reports:

- Grade 3 or 4 infection or fever
- Grade 3 or 4 fever and neutropenia with or without infection
- Grade 3 or 4 elevation in hepatic transaminases, alkaline phosphatase, GGT, bilirubin, and triglycerides that resolve to less than grade 3 within 5 days
- Grade 3 or 4 elevation of amylase or lipase
- Grade 3 electrolyte disturbances and Grade 4 electrolyte disturbances that resolve to < grade 3 within 24 hours allowing for replacement as needed
- Grade 3 and 4 electrolyte disturbances due to tumor lysis

- Grade 3 hyperglycemia or hypoglycemia and Grade 4 hyperglycemia or hypoglycemia that resolve to < grade 3 within 24 hours, allowing for replacement or insulin as needed
- Grade 3 fatigue and nausea.
- Grade 3 vomiting or diarrhea that resolves to ≤ Grade 2 within 7 days with supportive care as needed (antiemetics, antidiarrheal medications)
- Grade 3 or 4 hypotension explained by sepsis, pancreatitis, or infusion reaction
- Grade 3 mucositis that resolves to ≤ Grade 2 within 14 days
- Grade 3 anorexia
- Grade 3 hypertension
- Grade 3 enterocolitis, typhlitis, or colitis
- Grade 3 gastric hemorrhage, gastric ulcer, gastritis, and/or upper GI bleed
- Grade 3 glucose intolerance
- Grade 3 leukoencephalopathy and/or seizures secondary to intrathecal chemotherapy
- Any Grade 3 event not specified above as an exception which resolves within 48 hours
- Any Grade 3 event secondary to an infectious process or thrombocytopenia

This is an investigator-initiated study. The principal investigator, Seth Karol and St. Jude are conducting the study and acting as the sponsor. Therefore, the legal/ethical obligations of the principal investigator include both those of a sponsor and those of an investigator.

8.2 Recording Adverse Events and Serious Adverse Events

Adverse events (AEs) will be evaluated and documented by the clinical staff and investigators throughout inpatient hospitalizations and each outpatient visit. CRAs are responsible for reviewing documentation related to AEs and entering directly into TrialMaster protocol-specific database. The data to be recorded are 1) the event description, 2) the NCI CTCAE v4.0 code and grade, 3) the onset date, 4) the resolution date (or ongoing), 4) action taken for event, 5) patient outcome 6) relationship of AE to protocol treatment/interventions, 7) if AE was expected or unexpected, and 8) comments, if applicable.

AEs that are classified as serious, unexpected, and at least possibly related will be notated as such in the database as “unanticipated problems”.

Attribution of an Adverse Event

Not related – The lack of a temporal relationship of the event to study treatment makes a causal relationship not reasonably possible, or other drugs, therapeutic interventions or underlying conditions provide a sufficient explanation.

Unlikely related – The temporal relationship of the event to study treatment makes a causal relationship reasonably unlikely, and other drugs, therapeutic interventions or underlying conditions may not provide sufficient explanation for the observed event.

Possibly related – The temporal relationship of the event to study treatment makes a causal relationship reasonably possible, and the event is more likely explained by exposure to the study treatment than by other drugs, therapeutic interventions or underlying conditions.

A cumulative summary of all non-hematologic Grade 3-5 AEs, and expected/unrelated deaths that occur more than 30 days after protocol treatment will be reported to all sites with study progress report at the time of continuing review.

For the purpose of safety analyses, all AE's that are classified as unlikely or possible will be considered treatment-related events.

8.3 Process for Reporting Adverse Events To and From St. Jude and Collaborating Sites/Affiliates

Adverse events from collaborating sites will also be reviewed by the PI and discussed in study team meetings as described above. SAE reports from collaborating sites for AEs that are serious, unexpected, and at least possibly related to protocol treatment or interventions will be reported to site IRB and the St. Jude IRB within the reporting requirements described above. The PI will determine if this is an event that will need to be reported expeditiously to all participating sites, considering the following criteria:

- Is the AE serious, unexpected, and related or possibly related to participation in the research?
- Is the AE expected, but occurring at a significantly higher frequency or severity than expected?
- Is this an AE that is unexpected (regardless of severity that may alter the IRB's analysis of the risk versus potential benefit of the research *and*, as a result, warrant consideration of substantive changes in the research protocol or informed consent process/document?

With the submission of the "Reportable Event" in St. Jude iRIS application, the PI will indicate if all sites should be notified to report to their IRBs, and if the protocol and/or consent should be amended (consent will be amended if event is information that should be communicated to currently enrolled subjects). Generally, only events that warrant an amendment to the protocol and/or consent will be reported expeditiously to all sites. However, any event may be reported expeditiously to all sites at the discretion of the PI. A cumulative summary of all non-hematologic Grade 3-5 AEs, and expected/unrelated deaths that occur more than 30 days after protocol treatment will be reported to all sites with study progress report at the time of continuing review.
For collaborating sites: Serious AND unexpected events are to be reported to the St. Jude PI (Dr. Seth Karol) within 48-72 hours via fax or email.

All treatment-related deaths and unexpected deaths must be reported to the St. Jude PI at HYPERION study team by e-mail or phone call to Dr. Karol within 24 hours of the event. A written report must follow.

The study team should be copied on all correspondence regarding the event. Sent report to:

Seth Karol, MD
Department of Oncology
Leukemia/Lymphoma Division
St. Jude Children's Research Hospital
262 Danny Thomas Place
Memphis, TN 38105
Phone: [redacted]
FAX: [redacted]
Email: [redacted]
Email: [redacted]

9.0 DATA COLLECTION, STUDY MONITORING, AND CONFIDENTIALITY

9.1 Data Collection

Electronic case report forms (e-CRFs) will be completed by the clinical trials staff from the Cancer Center Comprehensive Center, Hematological Malignancies Program. Data will be entered from record directly into a secure, protocol-specific TrialMaster database, developed and maintained by St. Jude Clinical Research Informatics.

Data Management will be supervised by the Director of Clinical Trials Management, and Manager of Clinical Research Operations for the Hematological Malignancies Program, working with Dr. Karol or his designee. All protocol-specific data and non-hematologic grade 3-5 adverse events during glucocorticoid phases will be recorded by the clinical research associates into the protocol-specific database, ideally within 2-4 weeks of completion of study phase. Osteonecrosis (CTCAE Grade 2 or higher) will be recorded. All questions will be directed to the attending physician and/or PI and reviewed at regularly-scheduled working meetings. Data collection for adverse events will be captured for 4 weeks after participant is removed from treatment.

The attending physicians (or their designees) are responsible for keeping up-to-date roadmaps in the patient's primary St. Jude medical chart. Regular (at least monthly) summaries of toxicity and protocol events will be generated for the PI and the department of Biostatistics to review.

9.2 Study Monitoring

This study is considered moderate risk for monitoring purposes. Protocol and regulatory compliance, including essential regulatory documentation, will be assessed as well as the accuracy and completeness of data points related to the primary study objective semi-annually. If the study design has strata, accrual will be tracked continuously. The first two enrollees and then 10 % of participants will be monitored semi-annually.
The PI and study team are responsible for protocol and regulatory compliance, and for data accuracy and completeness. The study team will meet at appropriate intervals to review case histories or quality summaries on participants and retain copies of the minutes which are signed by the PI.

Clinical Trials Operations (CTO) will verify informed consent documentation of and eligibility status for 50% of trial participants within 5 days of enrollment. Additionally, a quality review will be performed by CTO personnel on 100% of St. Jude participants' informed consent forms to assure completeness.

Overall study conduct, compliance with primary objectives, age of majority consenting, safety assessments and reporting, and the timeliness and accuracy of database entries are monitored routinely. Study documents routinely monitored on selected participants include medical records, database entries, study worksheets, and case report forms. Study documents are monitored for participant status, demographics, staging, subgroup assignment, treatments, investigational drug accountability, evaluations, responses, participant protocol status, off-study and off-therapy criteria, and for all other specifics as detailed in a separate study-specific monitoring plan. The study-specific monitoring plan may be revised over time, to adapt monitoring frequency and/ or intensity to a changing environment when appropriate (for example: new safety signals; positive history of compliance; all participants are in long term follow-up; or the enrollment period has ended).

The recording and reporting of Adverse Events, Serious Adverse Events (SAEs), and Unanticipated Problems (UPs) to include type, grade, attribution, duration, timeliness and appropriateness will be reviewed by the Monitor/ CRM. The CRM will generate a formal report which is shared with the Principal Investigator (PI), study team and the Internal Monitoring Committee (IMC).

Continuing reviews by the Institutional Review Board (IRB) and Scientific Review Committee (CT-SRC) will occur at least annually. In addition, unanticipated problems are reviewed in a timely manner by the IRB.

9.3 Confidentiality

Research Identification numbers will be used in place of an identifier such as a medical record number. No research participant names will be recorded on the data collection forms. The list containing the study number and the medical record number will be maintained in a locked file and will be destroyed after all data have been analyzed.

The medical records of study participants may be reviewed by the St. Jude IRB, FDA, and clinical research monitors.

10.0 STATISTICAL CONSIDERATIONS

10.1 Sample size and accrual

It is logistically realistic and statistically sound (see below) to randomize 160 patients (80/arm) to the intensive or the standard antihypertensive arms. Patients who are randomized but drop out due to reasons as defined in Sections 7.1 and 7.2 before ON is observed or before the reinduction 2 MRI, are considered as inevaluable for the primary endpoint, and should be replaced. Based on past experience, we anticipate ~60 eligible patients to be randomized annually. Conservatively postulating a 12% drop out rate, we need to randomize 180 patients altogether. We thus anticipate a full accrual within 3.5 years.

10.2 Randomization

Open-label, stratified block randomization with block size of 4[39]. Randomization will be stratified by site (SJCRH and other), gender, self-declared race/ancestry (White Non-Hispanic and other) and hypertension requiring >1 dose of medication before Day 4 (Yes/No).

Analyses for the primary and secondary objectives will not be stratified. If it is determined that certain important factors are not balanced between the two treatment arms, appropriate regression models (such as logistic or integer response models) will be applied. The power assessment below is based on an unstratified Chi-square test.

10.3 Monitoring

To monitor the safety of therapy intensification, we will monitor for the following targeted toxicities: acute kidney injury (CTCAE grade 3 or higher not resolving to grade 0-1 within 72 hours) and syncope resulting in any injury. We will count events occurring during glucocorticoid containing phases only.

The intensive BP control arm (experimental) will be closely monitored for adverse effects and clinically suboptimal efficacy. The monitoring rules are constructed according to the Binomial group sequential design. We shall suspend the trial and investigate if any threshold defined in the rules is crossed.

AE monitoring in the intensive treatment arm: Probabilities of suspending trial to monitor > 25% targeted AE:

	True targeted AE probability			
	0.20	0.25	0.30	0.35
Suspend if number of AEs >7/20	0.03	0.07	0.23	0.40
Suspend if number of AEs >13/40	0.01	0.03	0.14	0.22
Suspend if number of AEs >25/80	0.00	0.01	0.12	0.18

Monitoring of missing the target in the intensive treatment arm: against <70% Probability of stopping

	True success probability			
	0.55	0.60	0.70	0.75
Suspend if number of successes <12/20	0.59	0.40	0.11	0.04
Suspend if number of successes <24/40	0.17	0.13	0.07	0.03
Suspend if number of failures <51/80	0.19	0.24	0.04	0.00

Efficacy monitoring of failures at reinduction II MRI (failure defined as ≥30% involvement in any joint) against >50% failure rate.

	True success probability				
	0.35	0.40	0.45	0.50	0.55
Suspend if # successes <7/20	0.42	0.25	0.13	0.06	0.02
Suspend if # successes <16/40	0.31	0.23	0.13	0.05	0.01
Suspend if # successes <33/80	0.17	0.17	0.08	0.02	0.00

10.4 Primary Objective

To compare the frequency of radiographically significant osteonecrosis in patients receiving intensive compared to conventional antihypertensive therapy.

The primary endpoint is the number of major joints (hips and knees) with extensive epiphyseal osteonecrosis (≥30% affected surface[12,13,17]) on MRI after approximately 9 months of chemotherapy (during reinduction 2). All randomized patients with appropriate imaging are considered evaluable and all analyses will be done according to intent-to-treat.

A chart review of 140 TOTXVI patients meeting the eligibility criteria of this study showed the following distribution of the number of affected joints in the low BP within-target group vs. the above-target group:

	Number of affected joints					
	0	1	2	3	4	Total
Above-target (proportion, n)	0.583, 70	0.083, 10	0.233, 28	0.017, 2	0.083, 10	120
Within-target (proportion, n)	0.80, 16	0.05, 1	0.10, 2	0.00, 0	0.05, 1	20

Clearly in each BP group the distribution is bi-modal with local modes at 0 and 2.

The primary analysis will consist of two parts. In the first part the distribution of the number of affected joints will be compared by the exact one-sided Chi-square test comparing the probability of having at least 1 affected joint. Let P0(k) and P1(k) be the probability of k affected joints among patients above- and within-target respectively (k=0,1,2,3,4). We have noted in the preliminary data that the BP of 14.6% of the eligible patients was within target without any treatment. Therefore, the distribution of the number of affected joints in the control group is anticipated to be PC(k)=0.854*P0(k)+0.146*P1(k), and the distribution in the treatment group is anticipated to be PT(k)=P1(k), k=0,1,2,3,4. Applying the preliminary data displayed above to this model, we obtain the anticipated distribution in the control and treatment group as follows:

	Number of affected joints k	
	0	1+
Control	0.615	0.385
Treatment	0.8	0.2

With n=80 subjects per group, the one-sided test has the exact power of 78.7% to detect the above anticipated difference at the 5% significance level. The power is calculated using Cytel Studio II.

In the second part, the mean number of affected joints within the treatment and control group will be estimated by the sample mean and a 95% confidence interval based on the t statistic. Difference in the mean number of affected joints between the two groups will also be estimated by the point estimate of the difference of two sample means and the t-statistic based 95% confidence interval. We note that although the sample space is discrete, the relatively large sample size (n=80/group) renders valid t statistic-based confidence intervals.

Bootstrap will be applied to check if the sample mean behaves similarly to a normally distributed random variable, and bootstrap confidence intervals will be applied if the t-distribution approximation is questionable. Additionally, we will compare the two arms by the two-sided chi-square test for ordered columns.

Time frame: The analysis will begin within 6 months after the MRI assessments of the last randomized patient is completed.

Responsible investigators: Seth Karol, Cheng Cheng

10.5 Secondary Objectives

Evaluate the efficacy of intensive antihypertensive control compared to conventional antihypertensive control in the prevention of clinically significant (CTCAE Grade 2 or higher) and radiologically extensive osteonecrosis, overall and stratified by joints.

A one-sided Chi-square test will be performed on a 2x2 contingency table similar to that in the primary objective, only now the columns are CTCAE Grade 2 ON (No/Yes). This analysis will also be performed for the knees and hips separately. MRI-defined extensive osteonecrosis will also be performed as described above, for knees and hip separately using Chi-square test on contingency tables.

Compare the frequency of clinically and radiographically significant osteonecrosis between patients receiving antihypertensive intervention and historical controls.

The historical control cohort consists of all patients enrolled on TOT-XV and TOT-XVI studies with age at diagnosis 10 years or older. The rate of clinically significant (CTCAE Grade 2+) ON and radiographically significant findings (number of affected joints) will be compared between the intensive BP treatment arm and the historical cohort by Chi-square tests.

Compare blood pressures achieved in intensive and conventional arms using both pressures obtained as part of routine patient care and ambulatory blood pressure monitoring.

The comparison will be done by regression modeling using mixed effect models to account for intra-patient repeated blood pressure measurements. The response variable is blood pressure, the explanatory variables include the BP control arm (intensive vs. conventional), age, sex, race and a random effect with AR(1) working covariance structure.

Compare levels of vascular dysfunction as measured physiologically, radiographically, and in blood samples in patients receiving intensive compared to standard antihypertensive therapy.

The levels of vascular dysfunction are measured by markers such as MRI, eNO synthetase, Von Willebrand Factor, TNF-alpha, D-dimer, PAI-1, E-selectin and ICAM-1; the measurements are all continuous. Each marker will be compared between the intensive BP treatment arm and the standard care arm by Wilcoxon rank-sum test.

Time frame: The analysis will begin within 6 months after the MRI assessments of the last randomized patient is completed.

Responsible investigators: Seth Karol, Cheng Cheng

10.6 Exploratory Objectives

Identify predictive patterns of blood biomarkers which identify patients at high-risk of developing clinically significant osteonecrosis.

Associations between the blood biomarkers and CTCAE grade 2 or higher ON will be analyzed using mixed-effect logistic regression models.

Identify MRI findings during late induction which correlate with osteonecrosis lesions seen during reinduction.

The MRI finding during late induction is represented by a 3-level ordinal variable (none, small, large). The ON lesions seen during reinduction are represented by a binary variable (large, less than large). The association will be tested by the Chi-square test on a 3-by-2 contingency table with ordered rows.

Compare induction blood pressure control and intervention arm to echocardiographic changes at reinduction II.

Echocardiographic changes at reinduction II is measured by the LV strain which is a continuous variable. Comparison of the LV strain between the intensive BP treatment and standard care arms will be performed by Wilcoxon rank-sum test.

Evaluate patient-reported, health-related quality of life in patients during induction and after 1.5 years of therapy when many experience the symptoms of osteonecrosis.

Survey response scores will be summarized by descriptive statistics including mean, standard deviation, minimum, maximum, quartiles, range and inter-quartile range.

Time frame: The analysis will begin within 6 months after the MRI assessments of the last randomized patient is completed, except for the last exploratory objective for which the analysis will begin within 6 months after the last randomized patient is followed for 1.5 years after completion of chemotherapy.
Responsible investigators: Seth Karol, Cheng Cheng

10.7 Anticipated Completion Dates

Anticipated primary completion date: 3/2023
Anticipated study completion date: 3/2025

10.8 Summary of Primary and Secondary Objectives

Objective#	Objective Type	Analysis#	Resp Party	Stat	Safety	Analysis Measure	Analysis Title	Data Collection Time Frame	# of Participants
1.1.1	P	1	SEK	CC	N	Patient	Intensive vs. conventional hypertension control effect on osteonecrosis	Time on therapy	160
1.2.1	S	2	SEK	CC	N	Patient/ Joint	Antihypertensive intervention patients over time	Time on therapy/ Reinduction II	160
1.2.2	S	3	SCK/CM	CC	N	Patient/ Joint	Antihypertensive treated patients vs. historic control	Time on therapy/ Reinduction II	160
1.2.3	S	4	ND	CC	N	Patient	Blood pressure achieved by intervention arm	Through reinduction II	160
1.2.4	S	5	CM	CC	N	Patient	Induction MRI	Induction	80
1.2.4	S	6	DM	CC	N	Patient	Vascular function by vasomotor testing	Induction, consolidation, off therapy	80
1.2.4	S	7	SEK	CC	N	Patient	Blood markers of vascular dysfunction	Induction, reinduction II	160
1.3.1	E	7	SEK	CC	N	Patient	Blood markers of osteonecrosis risk	Induction, reinduction II	160
1.3.2	E	3/5	SCK/CM	CC	N	Patient	Early vs late MRI findings of osteonecrosis	Induction, Reinduction	80
1.3.3	E	8	ND	CC	N	Patient	ABPM blood pressures vs osteonecrosis	Induction	160
1.3.4	E	7	GB	CC	N	Patient	Echo changes at reinduction vs induction blood pressure	Reinduction II	80
1.3.5	E	9	EK	CC	N	Patient	HRQoL and symptom survey	Induction, reinduction II, week 49	160
1.3.5	E	10	EK	NA	N	Patient	Narrative symptom description	Week 49	80

11.0 OBTAINING INFORMED CONSENT

11.1 Consent at Enrollment

The process of informed consent for HYPERION will follow institutional policy. The informed consent process is an ongoing one that begins at the time of enrollment and ends after the completion of therapy. Informed consent should be obtained by the attending physician or his/her designee, in the presence of at least one non-physician witness.

Throughout the entire treatment period, participants and their parents receive constant education from health professionals at St. Jude and are encouraged to ask questions regarding alternatives and therapy. All families have ready access to chaplains, psychologists, social workers, and the St. Jude ombudsperson for support, in addition to that provided by the primary physician and other clinicians involved in their care.

We will also obtain verbal assent from children 7 to 14 years old and written assent for all participants ≥14 years of age

11.2 Consent at Age of Majority

The age of majority in the state of Tennessee is 18 years old. Research participants must be consented at the next clinic visit after their 18th birthday. If an affiliate or collaborating site is located in a country or state where a different age of majority applies, that location must consent the participants according to their local laws.

11.3 Consent When English is Not the Primary Language

When English is not the patient, parent, or legally authorized representative's primary language, the Social Work department will determine the need for an interpreter. This information documented in the participant's medical record. Either a certified interpreter or the telephone interpreter's service will be used to translate the consent information. The process for obtaining an interpreter and for the appropriate use of an interpreter is outlined on the Interpreter Services, OHSP, and CTO websites. Collaborating sites should follow institutional policy.

12.0 REFERENCES

1. Pui CH, Campana D, Pei D, et al: Treating childhood acute lymphoblastic leukemia without cranial irradiation. N Engl J Med 360:2730-41, 2009
2. Karol SE, Yang W, Van Driest SL, et al: Genetics of glucocorticoid-associated osteonecrosis in children with acute lymphoblastic leukemia. Blood 126:1770-6, 2015
3. Kawedia JD, Kaste SC, Pei D, et al: Pharmacokinetic, pharmacodynamic, and pharmacogenetic determinants of osteonecrosis in children with acute lymphoblastic leukemia. Blood 117:2340-7; quiz 2556, 2011
4. Mattano LAJ, Devidas, M.; Winick, N.; Raetz, E.; Hunger, S. P.; Carroll, W. L.; Larsen, E.C.: Effects of dexamethasone (DEX) vs prednisone (PDN) and high-dose methotrexate (HD-MTX) vs Capizzi methotrexate/asparaginase (C-MTX/ASNase) on osteonecrosis (ON) incidence in children and young adults with high risk acute lymphoblastic leukemia (HR ALL): a report from the Children's Oncology Group (COG) Study AALL0232. Blood ASH Abstract 665, 2012
5. Mattano LA, Jr., Devidas M, Nachman JB, et al: Effect of alternate-week versus continuous dexamethasone scheduling on the risk of osteonecrosis in paediatric patients with acute lymphoblastic leukaemia: results from the CCG-1961 randomised cohort trial. Lancet Oncol 13:906-15, 2012
6. Mattano LA, Jr., Sather HN, Trigg ME, et al: Osteonecrosis as a complication of treating acute lymphoblastic leukemia in children: a report from the Children's Cancer Group. J Clin Oncol 18:3262-72, 2000
7. Mogensen SS, Harila-Saari A, Makitie O, et al: Comparing osteonecrosis clinical phenotype, timing, and risk factors in children and young adults treated for acute lymphoblastic leukemia. Pediatr Blood Cancer 65:e27300, 2018
8. Kuhlen M, Kunstreich M, Krull K, et al: Osteonecrosis in children and adolescents with acute lymphoblastic leukemia: a therapeutic challenge. Blood Advances 1:981-994, 2017
9. Powell C, Chang C, Gershwin ME: Current concepts on the pathogenesis and natural history of steroid-induced osteonecrosis. Clin Rev Allergy Immunol 41:102-13, 2011
10. Jeha S, Pei D, Choi J, et al: Improved CNS Control of Childhood Acute Lymphoblastic Leukemia Without Cranial Irradiation: St Jude Total Therapy Study 16. J Clin Oncol 37:3377-3391, 2019
11. Janke LJ, Van Driest SL, Portera MV, et al: Hypertension is a modifiable risk factor for osteonecrosis in acute lymphoblastic leukemia. Blood 134:983-986, 2019
12. Kaste SC, Pei D, Cheng C, et al: Utility of early screening magnetic resonance imaging for extensive hip osteonecrosis in pediatric patients treated with glucocorticoids. J Clin Oncol 33:610-5, 2015
13. Karimova EJ, Wozniak A, Wu J, et al: How does osteonecrosis about the knee progress in young patients with leukemia?: a 2- to 7-year study. Clin Orthop Relat Res 468:2454-9, 2010
14. Group SR, Wright JT, Jr., Williamson JD, et al: A Randomized Trial of Intensive versus Standard Blood-Pressure Control. N Engl J Med 373:2103-16, 2015
15. Beddhu S, Chertow GM, Greene T, et al: Effects of Intensive Systolic Blood Pressure Lowering on Cardiovascular Events and Mortality in Patients With Type 2 Diabetes Mellitus on Standard Glycemic Control and in Those Without Diabetes Mellitus: Reconciling Results From ACCORD BP and SPRINT. J Am Heart Assoc 7:e009326, 2018
16. Group ET, Wuhl E, Trivelli A, et al: Strict blood-pressure control and progression of renal failure in children. N Engl J Med 361:1639-50, 2009

17. Karimova EJ, Rai SN, Howard SC, et al: Femoral head osteonecrosis in pediatric and young adult patients with leukemia or lymphoma. J.Clin.Oncol. 25:1525-1531, 2007
18. Kamdem LK, Hamilton L, Cheng C, et al: Genetic predictors of glucocorticoid-induced hypertension in children with acute lymphoblastic leukemia. Pharmacogenet Genomics 18:507-14, 2008
19. Louis CU, Butani L: High blood pressure and hypertension in children with newly diagnosed acute leukemia and lymphoma. Pediatr Nephrol 23:603-9, 2008
20. Schmiegelow K, Attarbaschi A, Barzilai S, et al: Consensus definitions of 14 severe acute toxic effects for childhood lymphoblastic leukaemia treatment: a Delphi consensus. Lancet Oncol 17:e231-e239, 2016
21. Flynn JT: Differentiation between primary and secondary hypertension in children using ambulatory blood pressure monitoring. Pediatrics 110:89-93, 2002
22. Richey PA, DiSessa TG, Hastings MC, et al: Ambulatory blood pressure and increased left ventricular mass in children at risk for hypertension. Journal of Pediatrics 152:343-348, 2008
23. Gimpel C, Wuhl E, Arbeiter K, et al: Superior consistency of ambulatory blood pressure monitoring in children: implications for clinical trials. J Hypertens 27:1568-74, 2009
24. Mitchell GF, Hwang SJ, Vasan RS, et al: Arterial stiffness and cardiovascular events: the Framingham Heart Study. Circulation 121:505-11, 2010
25. Vlachopoulos C, Aznaouridis K, Stefanadis C: Prediction of cardiovascular events and all-cause mortality with arterial stiffness: a systematic review and meta-analysis. J Am Coll Cardiol 55:1318-27, 2010
26. Mulrooney DA, Ness KK, Solovey A, et al: Pilot study of vascular health in survivors of Hodgkin lymphoma. Pediatr Blood Cancer 59:285-9, 2012
27. Senzaki H, Akagi M, Hishi T, et al: Age-associated changes in arterial elastic properties in children. Eur J Pediatr 161:547-51, 2002
28. Piatti P, Di Mario C, Monti LD, et al: Association of insulin resistance, hyperleptinemia, and impaired nitric oxide release with in-stent restenosis in patients undergoing coronary stenting. Circulation 108:2074-81, 2003
29. Ceconi C, Fox KM, Remme WJ, et al: ACE inhibition with perindopril and endothelial function. Results of a substudy of the EUROPA study: PERTINENT. Cardiovasc Res 73:237-46, 2007
30. Ceconi C, Fox KM, Remme WJ, et al: ACE inhibition with perindopril and biomarkers of atherosclerosis and thrombosis: results from the PERTINENT study. Atherosclerosis 204:273-5, 2009
31. Massot A, Giralt D, Penalba A, et al: Predictive value of ankle-brachial index and PAI-1 in symptomatic intracranial atherosclerotic disease recurrence. Atherosclerosis 233:186-9, 2014
32. Hinds PS, Wang J, Cheng YI, et al: PROMIS pediatric measures validated in a longitudinal study design in pediatric oncology. Pediatr Blood Cancer 66:e27606, 2019
33. Cheng AL, Calfee R, Colditz G, et al: PROMIS Physical and Emotional Health Scores Are Worse in Musculoskeletal Patients Presenting to Physiatrists than to Other Orthopedic Specialists. PM R 11:604-612, 2019
34. Varni JW, Magnus B, Stucky BD, et al: Psychometric properties of the PROMIS (R) pediatric scales: precision, stability, and comparison of different scoring and administration options. Qual Life Res 23:1233-43, 2014
35. Hinds PS, Nuss SL, Ruccione KS, et al: PROMIS pediatric measures in pediatric oncology: valid and clinically feasible indicators of patient-reported outcomes. Pediatr Blood Cancer 60:402-8, 2013

36. Krippendorff K: Content Analysis: An Introduction to Its Methodology (ed Second). Thousand Oaks, SAGE Publications, 2004
37. Ulin P RE, Tolley E: Qualitative Methods in Public Health: A Field Guide for Applied Research. San Francisco, Jossey-Bass Wiley Imprint, 2005
38. (PQA) PQA: Adherence Measures [Internet]. 2018
39. Zelen M: The randomization and stratification of patients to clinical trials. J Chronic Dis 27:365-75, 1974

APPENDIX I: PERFORMANCE STATUS CRITERIA

PERFORMANCE STATUS CRITERIA *Karnofsky and Lansky performance scores are intended to be multiples of 10*					
ECOG (Zubrod)		**Karnofsky**		**Lansky**	
Score	**Description**	**Score**	**Description**	**Score**	**Description**
0	Fully active, able to carry on all pre-disease performance without restriction	100	Normal, no complaints, no evidence of disease	100	Fully active, normal
		90	Able to carry on normal activity, minor signs or symptoms of disease	90	Minor restrictions in physically strenuous activity
1	Restricted in physically strenuous activity by ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work	80	Normal activity with effort; some signs or symptoms of disease	80	Active, but tires more quickly
		70	Cares for self; unable to carry on normal activity or do active work	70	Both greater restriction of and less time spent in play activity
2	Ambulatory and capable of self-care but unable to carry out any work activities; up and about more than 50% of waking hours	60	Requires occasional assistance, but is able to care for most of his/her needs	60	Up and around, but minimal active play; keeps busy with quieter activities
		50	Requires considerable assistance and frequent medical care	50	Gets dressed, but lies around much of the day; no active play, able to participate in all quiet play and activities
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours	40	Disabled, requires special care and assistance	40	Mostly in bed; participates in quiet activities
		30	Severely disabled, hospitalization indicated; death not imminent	30	In bed; needs assistance even for quiet play
4	Completely disabled; cannot carry on any self-care; totally confined to bed or chair	20	Very sick, hospitalization indicated. Death not imminent	20	Often sleeping; play entirely limited to very passive activities
		10	Moribund, fatal processes progressing rapidly	10	No play; does not get out of bed