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**THERAPEUTIC INTERVENTIONS FOR PERIPHERAL
NEUROPATHY/NEUROPATHIC PAIN INDUCED BY VINCERISTINE TREATMENT
FOR CHILDHOOD ALL ON TOTAL XVI PROTOCOL
IND# 113597**

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TINALL - Therapeutic Interventions for Peripheral Neuropathy/Neuropathic Pain Induced by Vincristine Treatment for Childhood ALL on Total XVI Protocol

Principal Investigator: Doralina Anghelescu, MD

IND Holder: St. Jude Children's Research Hospital; IND #113597

Brief Overview: Neuropathic pain / peripheral neuropathy (NP/PN) is a known painful complication of vincristine (VCR) therapy; evidence supporting the best treatment plan for pediatric patients is limited. Gabapentin is frequently used for VCR-related NP/PN, with variable dosing and scheduling regimens, and with varying measures of success. The hypothesis of the study is that gabapentin will reduce the severity of NP/PN in patients receiving vincristine during treatment for ALL on the Total XVI protocol, as measured by two outcome measures: the daily dose of morphine used as needed for pain in addition to either gabapentin or placebo, as randomized, and the pain scores assessed daily.

Intervention: Randomized, placebo-controlled study of gabapentin 20mg/kg/day divided in three doses; open label morphine for breakthrough pain as needed for both arms.

Brief Outline of Treatment Plan:

Patients with ALL on Total XVI or "as per TOTXVI" who experience NP/PN after specific doses of vincristine are eligible to enroll in the study as soon as the diagnosis of NP/PN related to VCR is established. The qualifying doses of vincristine have been selected because they fall in the schedule of weekly vincristine doses as per Total XVI, and 2 additional weekly vincristine doses are anticipated according to the protocol. Participants will be randomized to receive gabapentin or placebo upon enrollment. Morphine will be available to both groups as needed for pain at any time on the study. At the time of enrollment, and daily thereafter until completion of the study drug, data will be collected for pain assessment, and the daily dose of oral morphine used will be collected. Data regarding the pain type, quality, and location, as well as treatments used to manage pain will be assessed on a daily basis for the diagnostic event and for the period following the next two administrations of VCR treated with the study drug.

Objectives:

Primary Objective:

To assess the analgesic efficacy of gabapentin in controlling VCR-related NP/PN in participants with ALL, by comparing the morphine daily dose (mg/kg/day) used to control NP/PN as a primary or a rescue regimen in the gabapentin vs. placebo groups.

Secondary Objective:

To compare the pain scores in the gabapentin and placebo groups as recorded by pain score right now and pain score average for previous 24 hours.

Responsible Investigator: Doralina Anghelescu, MD

Statistician: Cheng Cheng, Ph.D.

Estimated date for completion of data collection: December 2015

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Hypotheses/Estimates: The hypothesis is that treatment with gabapentin has better analgesic efficacy than placebo in the treatment of VCR-related NP/PN. Based on the current enrollment on the Total XVI protocol, the projected enrollment, the incidence of NP/PN of 34.9% as determined in our previous study of NP/PN associated with the Total XV protocol, we estimate that 60 study participants will be eligible to enroll in this study during the duration of the Total XVI study. To achieve a total of 60 evaluable patients, up to 80 participants may be enrolled.

Criteria for Evaluation:

Safety: Any adverse events will be recorded and reported.

Efficacy: Efficacy will be evaluated based on two outcome measures: the daily dose of oral morphine used as needed for pain (mg/kg/day) and the pain scores daily, during the treatment course with either gabapentin or placebo.

Study Design: Randomized placebo controlled phase II study**Study Population:**

Inclusion Criteria:

1. Participant is enrolled on Total XVI or “as per TOTXVI”.
2. **Participant is 1 year of age or older.**
3. Participant has symptoms of NP/PN with onset no more than 7 days after one of the following vincristine doses dates \pm 3 days: protocol week 1, week 2 (induction), week 7 (reinduction I), or week 17 (reinduction II).
4. Patient is expected to receive 2 doses of vincristine in weekly intervals as outlined by the Total XVI or “as per TOTXVI” protocol while on study drug (i.e. no known dosage reductions or planned missed doses).
5. Participant is able and willing to take oral medications.

Exclusion Criteria:

1. Previous participation in this study
2. Participant is receiving gabapentin for another indication at the time of diagnosis of NP/PN or has received gabapentin previously.
3. Pregnancy. Female participants of childbearing potential must have documented negative urine or serum pregnancy test result not older than 7 days. Male patients with reproductive potential will be counseled not to procreate during the study.
4. **Impaired renal function: decreased eGFR (< 60ml/min/1.73m² as estimated by the Schwartz equation).**
5. Participant has allergy or other contraindication for either morphine or gabapentin therapy.
6. Inability or unwillingness of research participant or legal

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guardian/representative to give written informed consent.

Sample Size: The sample size will depend on the incidence of NP/PN in the eligible population. Based on our retrospective data from Total XV, we expect a sample size of 60, with 30 to be randomized to the gabapentin arm or the placebo arm, respectively. However we will enroll and randomize all eligible and consented patients in the remainder of Total XVI. To achieve a total of 60 evaluable patients, up to 80 participants may be enrolled.

Randomization: Patients with ALL on Total XVI or “as per TOTXVI” who experience NP/PN after certain doses of vincristine are eligible to enroll in the study as soon as the diagnosis of NP/PN related to VCR is established. Participants will be randomized to receive gabapentin or placebo and continue taking the study drug until 2 doses of vincristine have been completed, and for 7 days after the second dose of vincristine. Morphine will be available to both groups as needed for pain at any time on the study.

Data Analyses: Two efficacy measurements will be analyzed: the average daily morphine dosage and the average daily pain score during the maximum 21-day treatment period. We will test the null hypothesis that the expected average daily morphine dosage and pain score are the same in the gabapentin and the placebo group vs. a one-sided hypothesis that the expected average daily morphine dosages and pain scores are lower in the gabapentin group.

Anticipated Primary Completion Date: December 2016

Anticipated Study Completion Date: December 2018

Timeframe for Primary Outcome Measure:

Data Management: Data management and statistical analysis will be provided locally by the Department of Anesthesiology and Biostatistics Department at St. Jude Children’s Research Hospital, respectively.

Human Subjects: The risk to subjects is related to the side effects of gabapentin. The most common side effect is somnolence. Patients will be informed of this and other minor side effects during informed consent. Adverse events will be monitored and reported and treated appropriately.

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1.0 **OBJECTIVES**

The investigators propose to study the analgesic efficacy of gabapentin for the treatment of neuropathic pain/peripheral neuropathy (NP/PN) associated with vincristine therapy in the context of treatment of childhood ALL on Total XVI protocol.

1.1 **Primary Objective**

To assess the analgesic efficacy of gabapentin in controlling VCR-related NP/PN in participants with ALL, by comparing the morphine daily dose (mg/kg/day) used to control NP/PN as a primary or a rescue regimen in the gabapentin vs. placebo groups.

1.2 **Secondary Objective**

To compare the pain scores in the gabapentin and placebo groups as recorded by pain score right now and pain score average for previous 24 hours.

2.0 **BACKGROUND AND RATIONALE**

2.1 **Background**

Children with cancer experience a significant symptom burden during the course of treatment^{1,2}, and pain is the most frequent, most severe and most distressful of symptoms. The impact of pain experienced during treatment for cancer has long term implications after completion of therapy^{3,4}.

Neuropathic pain and related neuropathy symptoms have been directly correlated with chemotherapeutic agents⁵, vincristine in particular⁶ and have been reported during therapy for childhood cancers^{7,8}.

Neurotoxicity, the dose-limiting side effect of vincristine, most often causes mixed sensorimotor neuropathy (loss of deep tendon reflexes, paresthesias, neuritic pain, and wrist or foot drop) or autonomic neuropathy (constipation, abdominal pain, paralytic ileus, bladder atony with retention of urine, and orthostatic hypotension). On the rare occasions in which vincristine-associated neurotoxicity involves the cranial nerves, it produces transient cortical blindness, oculomotor nerve dysfunction with ptosis and diplopia, jaw pain, facial palsy, hearing loss, and vocal cord paresis or paralysis⁵.

The incidence of peripheral neuropathy related to vincristine during treatment of childhood ALL per protocol Total XIIIB in our institutional experience has been 17.5% (42 of 240)⁹ and peripheral neuropathy/neuropathic pain were identified as adverse events in 34.9% of

children treated on protocol Total XV (174 of 498)¹⁰. Due to the higher vincristine dose used in our current institutional protocol for treatment of childhood ALL, Total XVI, and knowing that vincristine toxicity is related to higher individual doses as well as cumulative dose, we expect an even higher incidence during Total XVI treatment.

2.2 Rationale

Given the significance of the problem of neuropathic pain during cancer treatment in children, the associated suffering, and the long term impact, we propose to prospectively investigate the value of two therapeutic intervention arms for NP/PN, in children with ALL treated per Total XVI or “as per TOTXVI” protocol. Furthermore, our retrospective analysis did not demonstrate conclusively the analgesic efficacy of gabapentin, although clinical applications of gabapentin for VCR-neuropathy continue to persist with varying treatment regimens and despite the lack of data from relevant clinical trials.

The design of the study is a randomized placebo-controlled study, comparing a regimen based on opioid only to a regimen comprised of opioid and gabapentin. Existing data from clinical trials has failed to show the best treatment regimen to control or prevent VCR-induced NP/PN in children. There are indications in the literature in adult neuropathic pain syndromes such as diabetic neuropathy and postherpetic neuralgia that dual therapy of opioid and gabapentin has better analgesic efficacy than either individual therapy¹¹; nevertheless, no such investigations have explored therapies for neuropathic pain in children.

Rationale for dose selection and duration of gabapentin therapy

The gabapentin dose selection for this study is based on the data in the literature describing the clinical use of gabapentin in children with neuropathic pain¹²⁻¹⁹ and on our institutional experience with gabapentin in a retrospective study evaluating neuropathic pain in children with ALL during Total XV therapy¹⁰. There are no PK data supportive of gabapentin dose regimens for neuropathic pain in children.

Three case reports¹⁷⁻¹⁹ and 5 small series¹²⁻¹⁶ describe the use of gabapentin as an adjuvant analgesic in children with NP under diverse circumstances: after thoracotomy¹⁷, after multilevel orthopedic surgery¹⁴, and for complex regional pain syndrome^{15,18}, systemic lupus erythematosus¹³, cancer-related pain^{12,19}, neck pain¹², and phantom limb pain¹⁶. These studies included 24 children, and the dose regimen of gabapentin was described for only 17 of them^{12,14,16,17}. Analgesic efficacy was reported at 22.5 mg/kg/day in a 12-year-old with post-thoracotomy NP¹⁷, 14-40 mg/kg/day in 7 patients 7 to 28 years old with phantom limb pain¹⁶, 19-32.6 mg/kg/day in 4 children 11 to 17 years old with NP after

multilevel orthopedic surgery¹⁴, and 10-30 mg/kg/day in 5 children with cancer-related pain (n=4) or neuropathic neck pain (n=1)¹².

Dosing and safety information for the pediatric use of gabapentin has been defined only for anti-seizure therapy²⁰. Most pediatric pain specialists recommend the anti-seizure dose regimen for children with NP, starting at 10 mg/kg/day and titrating upward to 50 to 70 mg/kg/day. Gabapentin is currently the first-line therapy for NP at our institution. In our retrospective review of neuropathic pain during Total XV protocol for ALL at St. Jude, we found treatment data for 180 of 207 episodes of NP in 153 of 174 patients; the missing data reflect treatment at a site other than St. Jude. Gabapentin was used to treat 62.2% of episodes (112 of 180) in 65.4% of patients (100 of 153); the remaining 37.8% of episodes (68 of 180) in 34.6% of patients (53 of 153) were treated with opioids. The selection of gabapentin or opioids did not appear to be influenced by the pain intensity score at the time of diagnosis of NP (p=0.91). The mean starting dose used for the 112 episodes was 15.5 mg/kg/day (SD 7.9)¹⁰. In this study we found the median starting dose to be 14.2 mg/kg/day. In the absence of a uniform approach to the use of gabapentin, prospective studies are needed to determine the optimal regimen. There is some evidence that concurrent use of gabapentin and morphine provide better analgesia at doses lower than those used for single-agent therapy¹¹.

The duration of gabapentin therapy of up to 21 days is based on the pattern of administration of the trigger agent for neuropathic pain in ALL. We have selected the phases of the Total XVI or “as per TOTXVI” protocol during which VCR is administered most intensely, in weekly doses. Indeed, data from Total XV and preliminary data from Total XVI or “as per TOTXVI support the highest cumulative incidence of neuropathic pain at the time of induction, reinduction I and II. The duration of gabapentin therapy reflects the duration of vincristine administration.

3.0 RESEARCH PARTICIPANT ELIGIBILITY CRITERIA AND STUDY 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 Participant is enrolled on Total XVI
- 3.1.2 Participant is age 1 year or older.
- 3.1.3 Participant has symptoms of NP/PN with onset within 7 days after one of the following vincristine doses dates ± 3 days: protocol week 1 or week 2 (induction), week 7 (reinduction I), or week 17 (reinduction II).

- 3.1.4 Patient is expected to receive 2 weekly doses of vincristine as outlined by the Total XVI or “as per TOTXVI” protocol while on study drug (i.e. no known dosage reductions or planned missed doses).
- 3.1.5 Participant is able and willing to take oral medications.

3.2 **Exclusion Criteria**

- 3.2.1 Previous participation in this study
- 3.2.2 Participant is receiving gabapentin for another indication at the time of diagnosis of NP/PN or has received gabapentin previously
- 3.2.3 Pregnancy. Female participants of childbearing potential must have documented negative urine or serum pregnancy test result not older than 7 days. Male patients with reproductive potential will be counseled not to procreate during the study.
- 3.2.4 Decreased GFR (<60ml/min/1.73m² as estimated by the revised Schwartz equation^{21,22}).
- 3.2.5 Participant has allergy or other contraindication for morphine or gabapentin therapy.
- 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**

Participants will be identified by referral to the study team (Pain Service) from the primary clinical team (Leukemia Service), upon diagnosis of NP/PN. In addition to referrals from the Leukemia Service, the study team will screen the clinical notes of potentially eligible Total XVI or “as per TOTXVI patients for documentation of new onset NP/PN and determine eligibility. With the agreement of the primary clinical team, a study team member will approach the potentially eligible participant to initiate informed consent discussions.

When informed consent is obtained and the patient is enrolled, a member of the study team will inform the pharmacy and the randomization procedure will be initiated. The pharmacy order sets will be activated for the study drug and open label oral morphine.

3.4 **Enrollment on Study at St. Jude**

A member of the study team will confirm potential participant eligibility as defined in Section 3.1-3.2, complete and sign the ‘Participant Eligibility

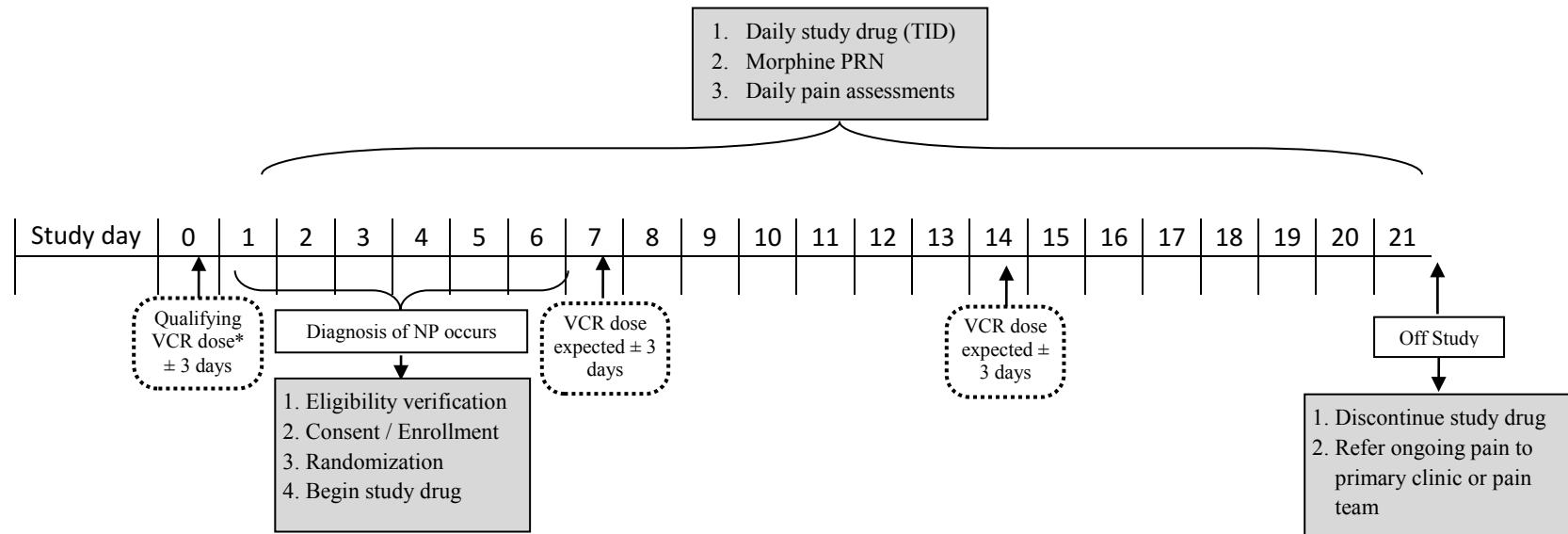
Checklist'. The study team will enter the eligibility checklist information into the Patient Protocol Manager (PPM) system. Eligibility will be reviewed, and a research participant-specific consent form and assent document (where applicable) will be generated. The complete signed consent/assent form(s) must be faxed to the CPDMO to complete the enrollment process.

The CPDMO is staffed 7:30 am-5:00 pm CST, Monday through Friday. A staff member is available by pager Saturday, Sunday, and holidays from 8:00 am to 5:00 pm.

3.5 Procedures for Identifying and Randomizing Research Participants

The PI or other study team member will approach the parent and participant regarding the study. If both the research participant and parent agree to participate, the randomization plan established by the study biostatistician will be accessed according to Section 11.

4.0 TREATMENT PLAN



*Qualifying VCR dose – dose falling on a weekly interval with at least 2 more weekly doses expected. Includes vincristine dose dates: Induction week 1 ± 3 days, Induction week 2 ± 3 days, Reinduction I (week 7) ± 3 days or Reinduction II (week 17) ± 3 days.

4.1 Study treatment

Upon each participant's enrollment, study staff will randomize the participant to one of 2 possible treatment arms (see section 11 for randomization procedure) and order the study treatment. The pharmacy will dispense a supply of the study treatment (gabapentin vs. placebo) sufficient to last through the end of the study (not more than 21 days), as well as the oral morphine for use as needed.

The pharmacy order will read "Gabapentin/Placebo study drug (TINALL)" and doses will be calculated as 20 mg/kg/day PO divided into 3 doses and rounded to the nearest 100 mg for capsules and 10 mg for liquid preparation. Neither the ordering clinician nor the participant / family will be informed of the treatment assignment.

Study treatment order entry will be managed by study staff according to pharmacy and institutional policy for medication administration. Any modifications to the study treatment (dose, duration, frequency, or discontinuation) will be done by the study team.

4.1.1 Active treatment arm

Participants randomized to the active treatment arm will receive gabapentin 20mg/kg/day PO divided into 3 doses and rounded to the nearest 100 mg for capsules and 10 mg for liquid preparation.

4.1.2 Placebo treatment arm

Participants randomized to the placebo treatment arm will receive look-alike capsules or liquid in a respective capsule size or liquid measure equivalent to the active treatment arm, but which contain no active treatment.

4.2 Breakthrough pain control

All participants, regardless of treatment assignment, will receive open-label oral morphine (0.15 mg/kg/dose every 2 hours, **rounded to the nearest tablet size or measurable liquid quantity**), as needed for pain. Morphine orders and dosages will be managed by the pain team according to clinical indication and following institutional and pharmacy policy for prescription and administration of controlled substances.

Substitution of other opioids for morphine should be avoided and performed only upon consultation with the PI.

4.3 Dose Modifications

The most common side effect of gabapentin is sedation/drowsiness. Participants who experience unacceptable side effects will have dosage adjustments at the discretion of the PI, or will be taken off therapy. If dose adjustment is indicated, study treatment will be reduced by 5-10 mg/kg/day.

Elimination of gabapentin can be affected by renal impairment which could increase drug exposure. Patients who are found to have renal impairment while on the study (defined as GFR < 60ml/min/1.73m² as estimated by the Schwartz equation^{21,22}) will be taken off therapy. Renal function of participants will be reviewed at least weekly while on study.

4.4 Definitions of Dose-Limiting Toxicity

The most common side effect of gabapentin is sedation/drowsiness. Participants who experience unacceptable side effects will have dosage adjustments or will be removed from the study (see section 4.3)

4.5 Concomitant Therapy

It is expected that participants in this study will receive numerous concomitant therapies unrelated to the research interests of this study. Only the study treatment and pain control treatments will be analyzed to determine the study outcomes. Exposure to vincristine (dose preceding NP event, as well as total cumulative dose) will be recorded.

4.6 Supportive Care

Morphine is prescribed for use as needed for breakthrough pain. See sections 4.1 and 4.3.

5.0 DRUG/DEVICE/BIOLOGIC AGENT INFORMATION

5.1 GABAPENTIN (Neurontin®)

Source and Pharmacology: Gabapentin is a white to off-white crystalline solid that is freely soluble in water. Its mechanism of action in preventing seizures is not known. Gabapentin is not appreciably metabolized in humans; pharmacological effects are from the activity of the parent compound. It is eliminated unchanged in the urine. Patients with renal impairment should have dosage adjustments. Higher doses are less bioavailable than lower doses after oral administration, but across the recommended dose range of 300 mg to 600 mg T.I.D., the bioavailability

is approximately 60%. Administration with food has little effect on absorption of gabapentin.

Formulation and Stability: Gabapentin is supplied as 100 mg, 300 mg, and 400 mg capsules, and as an oral solution containing 50 mg/ml. The tablets and capsules can be stored at room temperature, and the oral solution must be refrigerated.

Toxicity: Patients 3 – 12 years old treated with gabapentin for epilepsy reported the following central nervous system related adverse events: emotional lability, hostility, thought disorder and hyperkinesia in addition to CNS depression (dizziness, somnolence, fatigue, ataxia, and nystagmus). In placebo controlled trials of gabapentin in children taking other antiepileptic drugs, the following were also seen at higher frequency in the treatment group than the placebo group: viral infection, bronchitis, pharyngitis, rhinitis, respiratory infection, coughing, otitis media, fever, nausea and/or vomiting, diarrhea, depression, headache, diplopia, blurred vision, nervousness, seizures, pruritus, dyspepsia, constipation, weight gain, anorexia, leukopenia, back pain, and peripheral edema.

Supplier: Commercially available

Dosage and Route of Administration: Participants randomized to the active treatment arm will receive gabapentin 20mg/kg/day PO divided into 3 doses and rounded to the nearest 100 mg for capsules and 10 mg for liquid preparation.

Do not administer within two hours of aluminum or magnesium containing antacids. Abrupt withdrawal of gabapentin therapy may precipitate seizures.

5.2 PLACEBO

Placebo capsules contain microcrystalline cellulose as filler to a weight equivalent to the active agent. The capsules should be stored at room temperature in the pack provided. The expiration date will be listed on the product label. Placebo capsules will be compounded for patients by Regel PharmaLab (a local compounding pharmacy) to match the active capsules in appearance as closely as possible. St Jude pharmacy will dispense the capsules and keep accountability records as per randomized assignment.

Placebo syrup will be compounded with simple syrup diluted with normal saline with flavoring added. The solution should be stored in the refrigerator. The expiration date will be listed on the product label. Placebo syrup will be prepared by the St. Jude Children's Research Hospital Pharmacy for distribution to the patient.

To allow for the study team and participants to remain blinded to the treatment assignment, the study drug will be labeled by the pharmacy as “TINALL study treatment (gabapentin vs. placebo)” followed by applicable dose and administration instructions.

6.0 REQUIRED EVALUATIONS, TESTS, AND OBSERVATIONS

Subsections of 6.0 are outlined in tabular form in Appendix I.

6.1 Pre-Study Evaluations

The eligibility depends on establishing the initial diagnosis of NP/PN related to vincristine; this is a clinical diagnosis that is documented in the medical record and does not require any additional tests. Documentation of NP/PN made in the medical record by any St. Jude clinician will serve as the source for this diagnosis and for determining eligibility.

Female participants of childbearing potential must have documentation of a negative pregnancy test not older than 7 days at the time of enrollment; if this is not available, the study team will order the test to be performed and reviewed prior to starting study drug.

Clinically obtained creatinine levels will be used to estimate the GFR using the Schwartz equation^{21,22}. Patients with estimated GFR <60ml/min/1.73m² will not be enrolled.

6.2 Evaluations During Therapy

Participants will be evaluated daily by pain intensity assessments, using age appropriate tools, until completion of the study treatment. The maximum duration of the study cannot exceed 21 days. The pain assessment tools are the FLACC scale (0-10) for participants younger than years of age or other children who cannot self report²³, the Faces Pain Scale-Revised (FPS-R) (0-10) for ages 4-7²⁴, and the numeric scale (0-10) for ages older than 7^{25,26}. This assessment can be obtained during a clinical evaluation or by phone interview, if a clinical visit is not feasible.

Additional data will be obtained regarding location and descriptors of pain (daily) and the daily dose of morphine used during the study.

The GFR of participants will be monitored at least weekly while on study, using clinically obtained creatinine levels to estimate GFR using the Schwartz equation^{21,22}. Patients who develop renal impairment (estimated GFR < 60ml/min/1.73m²) will be taken off therapy.

6.3 Response Evaluations

Evaluations will continue as described in section 6.2.

6.4 Off-Study Evaluations

Patients will be off study when the patient has completed the study treatment and applicable pain assessments have been collected. If pain symptoms persist at the completion of the study, the patient will continue to be treated as needed, with gabapentin and/or morphine, either by the pain team or the leukemia team, but no additional data will be collected for this study.

6.5 Long-Term Follow-up Evaluations

This study will not evaluate NP events or long term results beyond the off study evaluation.

Participants will be notified of their treatment assignment (gabapentin or placebo) after the completion of data collection for the last participant enrolled. Notification will be performed by a member of the study team in person (when feasible) or by letter at the earliest convenience of the study team and documented in the study files.

7.0 EVALUATION CRITERIA

7.1 Response Criteria

The response to therapy will be measured by pain intensity scores and daily use of morphine doses for breakthrough pain as described in the study objectives. Daily assessments will continue during treatment with the study drug (gabapentin or placebo) irrespective of patient response to study treatment.

7.2 Toxicity Evaluation Criteria

Participants who experience unacceptable side effects will have dosage adjustments or will be removed from the study (see section 4.4). The decision to adjust the study treatment dose or to discontinue study treatment will be made by the PI and in the context of the participant's clinical situation.

8.0 CRITERIA FOR REMOVAL FROM PROTOCOL THERAPY AND OFF-STUDY CRITERIA

8.1 Off-study criteria

- 8.1.1 Completion of study therapy and assessments
- 8.1.2 Death
- 8.1.2 Lost to follow-up
- 8.1.3 Request of the Patient/Parent
- 8.1.4 Discretion of the Study PI, such as the following
 - The researcher decides that continuing in the study would be harmful
 - New information is learned that a better treatment is available, or that the study is not in the participant's best interest

8.2 Off-therapy criteria

- 8.2.1 Development of unacceptable toxicity during treatment
- 8.2.2 Development of renal impairment, defined as GFR less than 60ml/min/1.73m² as estimated by the Schwartz equation^{21,22}.**
- 8.2.3 Refusal of therapy
- 8.2.4 Unblinding of participant or study team to participant's treatment assignment (see section 9.3)**

9.0 SAFETY AND ADVERSE EVENT REPORTING REQUIREMENTS

9.1 Reporting Serious Adverse Events

9.1.1 IRB Notification by Investigator

Adverse events (AEs) will be graded according to the CTCAE version 4.0. All study-related anticipated AEs of grade 3 or higher will be reported to the IRB via institutional reporting mechanisms. Those AEs grade 2 or below will be reported to the IRB at the time of continuing review. All serious, related (or possibly related), and unexpected AEs of all grades will be reported to the IRB within 48 hours of discovery of the event. Others will be reported within 10 working days of discovery of the event.

Adverse events determined by the PI to be unrelated to the study treatment will be reported by the procedures outlined in the primary treatment protocol (Total XVI).

9.1.2 Recording Adverse Events and Serious Adverse Events

Adverse events will be submitted by a member of the study team to the IRB using the existing institutional online reporting mechanisms. All study-related AEs will be collected in the database, regardless of their grade.

9.2 Reporting to the IRB

In addition to the continuing review reports to the IRB, the Principal Investigator is responsible for reporting all serious **and** unexpected adverse events that impact the safety of risk to study research participants. Unexpected death will be reported to the IRB office immediately at SJCRH. Serious unexpected events will be reported within 48 hours, and all others within 10 working days.

9.3 Emergency Unblinding

In the case of a medical emergency or in the event of a serious medical condition, when knowledge of the investigational product is essential for the clinical management or welfare of the subject, an investigator or other physician managing the subject may decide to unblind that subject's treatment code.

The physician managing the medical emergency or serious condition should attempt to contact the principal investigator to discuss options prior to unblinding, and the principal investigator should approve the unblinding, when applicable. However, ensuring patient safety is the primary objective when the decision to unblind the treatment assignment is made.

The principal investigator or designated study personnel will complete an off therapy request with the rationale to unblind study drug listed. The principal investigator or designated study personnel will contact pharmacy to determine the unblinding information.

Any patient whose treatment assignment is unblinded will be removed from study treatment and followed off-therapy. The study team will continue to follow the patient status regarding the serious adverse event(s) for which the patient's treatment was unblinded until resolved or improved to baseline. The patient can receive off-study treatment as necessary.

All occurrences of emergency unblinding will be reported to the IRB according to the criteria established in protocol section 9.0, and the FDA, when applicable.

9.4 Criteria for Unblinding

The occurrence of a serious adverse event that is both unexpected and considered by the reporting investigator to be associated with the use of study drug, and the knowledge of the treatment assignment is deemed essential for the patient's care in treatment of the event. This criteria includes known overdose of study drug.

10.0 DATA COLLECTION, STUDY MONITORING, AND CONFIDENTIALITY

10.1 Data Collection

A member of the TINALL study team will complete documentation in MILLI for each study encounter (“anesthesia research note”). Data will then be entered into a secure database, which serves as the electronic case report forms (eCRFs). Records from the study which identify the study participant will be kept confidential in a secured area.

10.2 Study Monitoring

Source document verification of eligibility for all SJCRH cases will be performed within two weeks of completion of enrollment. This will include verification of appropriate documentation of consent. Monitoring of timeliness of adverse and serious adverse event reporting will be done as events are reported. Monitoring of protocol compliance, adverse event reporting, and data completeness will be conducted according to recommended schedule for this study.

10.3 Confidentiality

Study 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/or in a password protected database 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, clinical research monitors, etc.

11.0 STATISTICAL CONSIDERATIONS

11.1 Primary Objective

This study has the following single primary objective:

To assess the analgesic efficacy of gabapentin in controlling VCR-related NP/PN in participants with ALL, as reflected by the morphine daily dose (mg/kg/day) used to control NP/PN as a primary or a rescue regimen, and by daily pain scores in the gabapentin vs. placebo groups.

Accrual: The eligibility criteria requires that a patient can be enrolled in this study only if a VCR-induced NP not previously treated by gabapentin occurred after vincristine doses administered at the following time points: Induction Week 1 ± 3 days, Induction week 2 ± 3 days, Continuation Week 7 (Re-induction I) ± 3 days or Week 17 (Re-induction II) ± 3 days of Continuation. A review of Total XVI or “as per TOTXVI” patients up to the date of this protocol development showed that respectively 33, 29, 5, and 1 patient satisfied the condition at the time points. A review of Total XV showed a similar pattern. Thus we expect to enroll for this study at least 60 patients in the remainder of Total XVI or “as per TOTXVI. We will enroll and randomize all eligible and consented patients in the remainder of Total XVI or “as per TOTXVI”. To achieve a total of 60 evaluable patients, up to 80 participants may be enrolled.

Study Design: Placebo-controlled, randomized Phase-II trial. Sixty (60) participants will be randomized into the treatment (gabapentin) and the placebo group, with 30 patients per group.

Analysis: For each subject a pre-treatment (baseline) pain score will be obtained from the leukemia clinic. This score serves as the baseline level of pain and is used in stratified randomization (see below); and if necessary, as a covariate in modeling the daily morphine dosage used for pain control. The daily morphine dosage will be modeled as longitudinal observations with treatment (gabapentin vs. placebo) group, and if necessary, other clinical factors such as age category for pain assessment (0-3yr, 4-7yr, >7yr), baseline pain score, and ALL risk classification, as explanatory factors, using repeated measure linear models.

Multiple test adjustment will not be made. Participants **whose doses of vincristine are delayed or those who are taken off study drug** will be included in the analysis according to “intent to treat”.

11.2 Randomization

Randomization will be performed in SJCRH pharmacy by a research pharmacist, using the randomization program developed by the Department of Biostatistics. The randomization will be stratified by the three age categories for which distinct pain assessment tools are applied, and by two categories of the baseline pain score (<5, ≥5). The joint distribution of the age and baseline pain score categories in the enrolled

patients may be skewed with either null or small odd-numbered (1, 3, 5) cell sizes, and consequently stratification may still not able to guarantee balance. If it so happens, the age categories and baseline pain score will be included in the longitudinal model as covariates (see above).

11.3 Secondary Objective

Daily “pain score right now” and “pain score average last 24 hours” will be compared between the gabapentin and place groups using longitudinal models, with pain treatment group and if necessary, other clinical factors as explanatory variables. For “pain score right now”, time since last morphine use will be used as an explanatory variable as well. The pain scores are discrete, thus a proper link function (such as Poisson) will be applied.

12.0 OBTAINING INFORMED CONSENT

Eligible patients will be approached by a member of the study team regarding the study purpose, methods and design details. Both verbal and written assent and consent procedures will be completed in a private room and follow our institutional guidelines. Verbal assent will be obtained from participants 7 to less than 14 years old and written assent from participants 14 to less than 18 years old.

The consent/assent process will be documented in the medical record per institutional guidelines. Research participants and parents may decline participation without repercussions. Refusals will be documented in the research records and examined for any possible patterns. All research participants who meet eligibility criteria regardless of gender or minority status are fully eligible to participate in this study. All data will be kept confidential and stored in a locked file inside locked offices.

12.1 Consent at Age of Majority

The age of majority in the state of Tennessee is 18 years old. The PI/designee will identify study participants requiring consent at age 18 years. Active research participants must be consented at the next clinic visit after their 18th birthday.

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APPENDIX I
EXAMPLE OF A SCHEDULE OF EVALUATIONS:

Upon confirmation of eligibility (any time between days 1 and 7 after qualifying vincristine dose, see section 3.0):

- Informed consent discussion
- Enrollment data obtained by study team
- Baseline pain assessment by study team
- Participant receives prescription for morphine PRN (see section 4.2)
- Participant is randomized and begins study drug (see section 4.1)

Enrollment through Day 21

- Daily pain assessment by study team
- Daily AE assessment by study team
- Refill morphine if needed
- Patient/family education regarding study drug

Day 21

- Complete last dose of study drug
- Complete last daily pain assessment and AE assessment
- Refer persistent pain to pain team or primary clinic for treatment as clinically indicated

APPENDIX II
RESEARCH ACTIVITIES

Study day	Confirm enrollment criteria	Informed consent	Randomization	VCR dose (expected or actual)	Pain score right now	Average Pain for 24h	Pain location	Pain descriptor	Order Morphine PRN	Study drug TID	Assess opioid use	Assess study drug use	Assess AE	Off Study
pre-enrollment				actual										
Diagnosis of NP (any day between 1 and 7)	x	x	x		x	x	x	x	x	x	x	x	x	
					x	x	x	x	x	x	x	x	x	
					x	x	x	x	x	x	x	x	x	
					x	x	x	x	x	x	x	x	x	
					x	x	x	x	x	x	x	x	x	
7				expected	x	x	x	x	x	x	x	x	x	x
8					x	x	x	x	x	x	x	x	x	x
9					x	x	x	x	x	x	x	x	x	x
10					x	x	x	x	x	x	x	x	x	x
11					x	x	x	x	x	x	x	x	x	x
12					x	x	x	x	x	x	x	x	x	x
13					x	x	x	x	x	x	x	x	x	x
14				expected	x	x	x	x	x	x	x	x	x	x
15					x	x	x	x	x	x	x	x	x	x
16					x	x	x	x	x	x	x	x	x	x
17					x	x	x	x	x	x	x	x	x	x
18					x	x	x	x	x	x	x	x	x	x
19					x	x	x	x	x	x	x	x	x	x
20					x	x	x	x	x	x	x	x	x	x
21					x	x	x	x	x	x	x	x	x	x

APPENDIX III PAIN ASSESSMENT TOOLS

The pain assessment scoring tools for this study are currently used at St. Jude in standard care as directed by the hospital policy; they are included here for reference purposes.

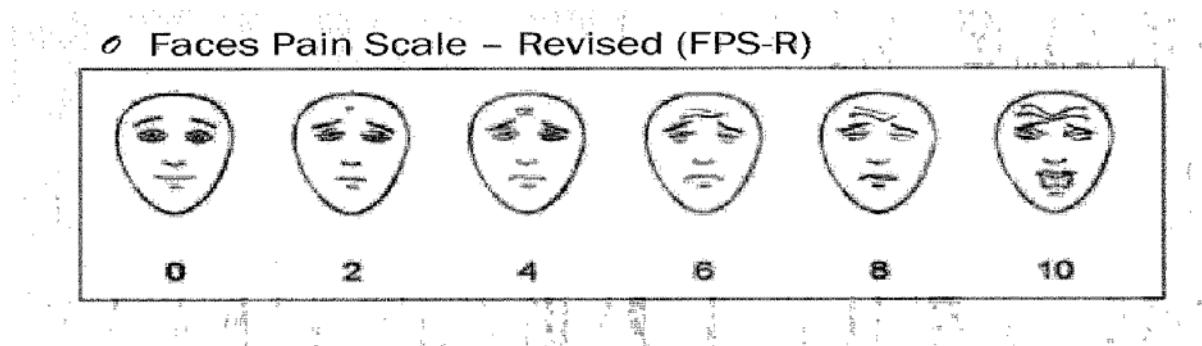
Assessment

- Always assume child's pain report is valid
- Infants and toddlers (less than age 4 years) or other children who cannot self report, use the FLACC Scale
- Score each component as a subscore (face, legs, activity, cry, consolability)
- Total subscores to determine FLACC score

FLACC scale

Categories	Scoring		
	0	1	2
Face	No particular expression or smile	Occasional grimace or frown, withdrawn, disinterested	Frequent to constant quivering chin, clenched jaw
Legs	Normal position or relaxed	Uneasy, restless, tense	Kicking or legs drawn up
Activity	Lying quietly, normal position, moves easily	Squirming, shifting back and forth, tense	Arched, rigid or jerking
Cry	No cry (awake or asleep)	Moans or whimpers; occasional complaint	Crying steadily, screams or sobs, frequent complaints
Consolability	Content, relaxed	Reassured by occasional touching, hugging or being talked to distractible	Difficult to console or comfort
Each of the five categories (F)Face; (L)Legs; (A)Activity; (C)Cry; (C) Consolability is scored from 0-2, resulting in a total score range of 0 to 10.			

- Older children (ages 4 to 7 years) who can self-report, use the Faces Pain Scale-Revised (FPS-R)



Say to the child, "The first face (*point to face 0*), has no pain. The last face, (*point to face 10*), has the worst pain ever. Point to the face that shows how you are feeling."

- Ages >7 years, Self report using a numeric scale 0-10 without reference to Faces Pain Scale-Revised (FPS-R)