Unacceptable severe (grade 3-4) toxicity that is possibly related to the study drug and persists despite dose optimization and optimal management of toxicity.

Patient choice

Failure to comply with study schedule

Statistical Considerations

The primary outcome of the study will be response rate. Time to recurrence of CNS leukemia and overall survival will be secondary outcomes. Time to recurrence and survival will be considered from the date of CNS relapse diagnosis.

There is no well-defined metric to measure response to treatment in patients with peripheral nerve involvement only. Clinical and radiologic response will be recorded and it is expected that few to no patients with only peripheral nerve involvement will actually be involved and therefore the statistical analysis will not be affected.

A maximum of 25 patients will enrolled in this phase I/II study, with about 12 patients/year.

Phase I

First, phase I study is performed to assess the safety of two dose levels for rituximab: 10mg and 25mg. These two dose levels have been previously in a small series (12). A 3+3 design will be used to for dose escalation. Detailed dose escalation rules are described in the following section. A maximum of 12 patients will enroll in the phase I study.

Dose Escalation Procedures

The dose of treatment agent will be escalated in successive cohorts of patients. The starting dose is at dose 0 as shown in table 1. Enroll 3 patients at the dose level and proceed to the next higher dose level with a cohort of 3 patients until at least 1 patient experiences a dose-limiting toxicity (DLT).

DLT is defined as a clinically significant adverse event or abnormal laboratory value assessed as unrelated to disease progression, intercurrent illness, or concomitant medications and meeting the NCI common terminology criteria that are CTCAE Grade 3 or 4.

An adverse event must be clinically significant to define DLT e.g. alopecia, study drug-related fever, electrolyte abnormalities (including K, Na, Cl, HCO3, Mg, Ca) that are < Grade 3 will not define the DLT. Drug-related Grade 3-4 nausea and vomiting not controlled with adequate therapy will be considered DLTs.

If only 1 of 3 patients experiences a DLT at a given dose level, enter 3 additional patients at the current dose level. If only 1 of 6 patients experiences a DLT at a given dose level, proceed to the next higher dose level with a cohort of 3 patients. If at least 2 of 3 or 2 of up to 6 patients experience a DLT at a

given dose level, then the MTD has been exceeded (stopping dose). Once the MTD has been exceeded, treat another 3 patients at the previous dose level if there were only 3 patients treated at that dose level. The MTD is defined as the highest dose level in which 6 patients were treated with at most 1 experiencing a DLT during the 1st cycle.

In summary, our dose escalation plan is as follows: during phase I, the starting dose is 10 mg and dose escalation will follow a 3 + 3 design. After three patients have received 10 mg, if there is no DLT, the next cohort of three patients will receive 25 mg. If there is one DLT in the initial three patients, an additional three patients will be treated at 10 mg. If 2/6 patients experience a DLT at 10 mg, the study will be closed. If less than or equal to 1/6 at 10 mg experience a DLT, we will enroll the next three patients at 25 mg. The maximum dose on this protocol is 25 mg, thus, no further dose escalation will occur. If 1/3 patients at 25 mg experience a DLT, we will enroll three additional patients at 25 mg. If 2/6 experience a DLT, all subsequent patients will receive 10 mg, and that will be the final dose. If less than or equal to 1/6 experience a DLT at 25 mg, the remainder of the patients enrolled will receive 25 mg. If 2/3 or 2/6 patients experience a DLT at the 10 mg dose, the study will be terminated.

Table 1. Dose levels of rituximab

Dose level	rituximab
0 (starting dose)	10 mg
1	25 mg

Phase II

Phase II part is a single arm study using the dosage level recommended from phase I. The patients treated at the MTD in phase I will be included in phase II part, and the sample size for phase II can be up to 22. The trial will be continuously monitored for efficacy and toxicity (non-hematological ≥grade 3). The method of Thall, Simon, and Estey will be used to perform interim efficacy and safety monitoring (15).

Efficacy

The primary endpoint is the response defined as the CNS is without evidence of blast cells after four lumbar punctures with rituximab. The historical data suggested the response rate by chemotherapy (methotrexate and/or cytarabine) is about 10%. The targeted improved overall response rate is 25%, The trial will be continuously monitored. The study will be stopped early if the data suggest that:

$$\Pr(\pi > 0.1 \mid \text{data}) < 0.05$$

Here π is the response rate. That is, if at any time during the study we determine that there is a less than 5% chance that the response rate is greater than 10%, we will terminate the study. The response