Isolated CNS relapse of acute lymphoblastic leukemia (ALL) treated with intensive systemic chemotherapy and delayed CNS radiation: A Pediatric Oncology Group Study

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Background
- Event-free survival for patients suffering isolated CNS relapse of ALL after initial therapy has improved.
- The previous POG 9061 study showed an excellent 4 year EFS of 71% with 6 months of intensive chemotherapy and delayed craniospinal radiation (CSI). Duration of remission was an important prognostic factor. Bone marrow, not the CNS, was the most common site of failure.
- This study investigated whether 12 months instead of 6 months of intensive chemotherapy could decrease the risk of bone marrow failure. Radiotherapy (RT) was delayed by 12 months and RT doses were tailored to the length of the initial remission duration (CR1).
- A secondary goal was to test whether up-front thiotepa could be useful in clearing CSF blasts.

Materials and Methods
- Eligible patients were age > 6 months and younger than 21 years with first isolated CNS relapse of T or B precursor cell ALL.
- 78 patients were enrolled with a median age of 7.4 years.
- Pre-irradiation chemotherapy included agents with high CNS penetration: Induction (Dex, VCR, daunorubicin and triple intrathecals), consolidation (ARA-C, L-Asparaginase), intensification (CTX, VP-16, MTX, ARA-C, L-asparaginase and re-induction. Early CNS relapse patients received 24 Gy cranial, 15 Gy spinal radiation. Late CNS relapse patients received 18 Gy cranial radiation only.

Results
- 24 patients had a CR1 < 18 months and 51 had a CR1 > 18 months. 19 patients received up-front thiotepa.
- At a dose rate of 65mg/m2, 7/9 patients had a clinical response to thiotepa.
- 3 year EFS was 42% for early relapse patients and 77% for late relapse patients. Overall, only one patient had a second CNS relapse prior to receiving RT.
- 4 toxic deaths occurred. Almost all patients had Grade III/IV hematologic toxicity.

Author's Conclusions
- 12 months of intensive chemotherapy is well tolerated and allows for reduced cranial RT in selected patients without compromise of EFS. This promising data will allow future trials in which RT is eliminated.
- This trial showed EFS results comparable to the POG 9061 trial.
- Thiotepa is effective in reducing CSF blast burden.

Clinical/Scientific Implications
- This study shows that additional intensive chemotherapy can allow for RT delay, reduction of RT dose and the elimination of spinal irradiation in patients with a late (>18 months) CR1 without compromise of outcome. However, in patients with an early CR1 (< 18 months) results of this trial are no better than in the previous POG 9061 trial in which only 6 months of chemotherapy were used. This trial indicates that future research is needed into alternative treatments for early CR1
patients who continue to have significant second relapses. Elimination of radiation may be considered in future protocols for late CR1 patients.

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