Comparison of high-dose methotrexate (HD-MTX) with Capizzi methotrexate plus asparaginase (C-MTX/ASNase) in children and young adults with high-risk acute lymphoblastic leukemia (HR-ALL): A report from the Children's Oncology Group Study AALL0232

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Background/Introduction

- There are approximately 5,300 new cases of acute lymphoblastic leukemia (ALL) diagnosed every year in the United States; 60% of these cases are in children and young adults (age < 20), while 40% of these cases are in patients over the age of 20.
- ALL represents the most common malignancy in children, but is relatively rare in adults.
- The survival of children with ALL has increased dramatically over the last 60 years, as ALL was uniformly fatal in the 1950s. There has been incremental improvement in the survival of patients diagnosed with ALL, from approximately 10% in the late 1960s to 75—85% more recently. This rapid improvement in outcomes has resulted from incremental refinement of multi-agent chemotherapy regimens.
- However, outcomes in children with high-risk ALL are less encouraging, and the outcomes of adults with ALL are relatively poor with long-term leukemia-free survival of only 40%.
- The issue of central nervous system (CNS) control in ALL is relatively important, because while only 10% of patients have CNS involvement at the time of diagnosis, as control of disease in the bone marrow has improved, over time there has been a proportionally higher rate of CNS relapse.
- Historically, prevention of CNS relapse involved a combination of cranial irradiation, intrathecal (IT) methotrexate (MTX), and IV MTX, but the combination of these led to unacceptably high rates of clinical leukoencephalopathy.
- The current protocol (COG HR-ALL - AALL0232) was designed to evaluate systemic treatments with the potential to increase CNS control, in particular:
  - Dexamethasone during induction therapy (results of which were reported in a separate abstract #9504), and
  - High-dose MTX during interim maintenance, which is the focus of this abstract.
- MTX has been the cornerstone of maintenance therapy since the early folate analogue aminopterin induced the first remission in ALL patients in 1947.
- There have been 2 attempts to intensify MTX chemotherapy:
  - High dose MTX with leucovorin rescue, and
  - Escalating IV MTX followed by L-asparaginase (Capizzi MTX)
  - Both treatments are very effective in ALL therapy, but have never been compared head to head

Methods

- AALL0232 was a Phase III, randomized trial for patients age 1-30 years old, with newly diagnosed high risk B-precursor ALL.
  - High risk patients included those aged 1-9 years with WBC > 50k, or age 10-30 with any WBC count
Very high risk ALL patients were removed from protocol at the end of induction.

- **Schema:** This study employed a 2 x 2 factorial design using a Children's Oncology Group (COG) augmented intensity Berlin-Frankfurt-Münster (BFM) backbone, consisting of:
  - 4-drug induction therapy including randomization between prednisone and dexamethasone, then
  - Augmented BFM consolidation, then
  - Interim Maintenance #1, where patients were randomized between Capizzi MTX and high dose (HD) MTX with leucovorin rescue, then
  - Delayed intensification #1
  - At this point Rapid Early Responders (RER) went directly to maintenance therapy, and Slow Early Responders (SER) went into Interim Maintenance #2 with Capizzi MTX and then a second Delayed intensification cycle before proceeding to maintenance therapy.
  - Cranial irradiation was used in this study, at a dose of 1800 cGy in patients with CNS disease, and a dose of 1200 cGy in patient who were SER without frank CNS disease.

- Patients randomized to Capizzi MTX received increasing doses of MTX every 10 days without leucovorin rescue, beginning at 100 mg/m2 and increased 50 mg/m2/dose as tolerated. They also received PEG-asparaginase on days 2 and 22, intrathecal MTX on days 1 and 31, and Vincristine every 10 days with MTX.
- Patients randomized to the HD-MTX arm received 5 grams/m2 with leucovorin rescue every 2 weeks for a total of 4 doses. They also received IT MTX and Vincristine.
- 3154 patients were enrolled on the study, and to date 2104 of these patients have completed Interim Maintenance #1.

**Results**

- The key finding in the study was fewer treatment failures in the HD-MTX regimens compared to the Capizzi regimens:
  - Marrow relapse occurred in 68 patients treated with Capizzi MTX, vs 42 treated with HD MTX
  - Isolated CNS relapse occurred in 32 treated with Capizzi MTX, vs 22 treated with HD MTX
  - Improved Event Free Survival (EFS) was observed for patients treated HD MTX regimens at 5 years: 82% for HD MTX versus 75.4% for Capizzi MTX (p = .006).
  - For Rapid Early Responders (RER), smaller benefit to HD MTX (5 year EFS 86.6% vs. 82.7%, p = .09) was observed.
  - For Slow Early Responders (SER), more pronounced benefit to HD MTX (5-year EFS 79.5% versus 65.4%, p = .04) was observed.
- **Key Toxicities:**
  - There was no difference in incidence of mucositis between the 2 arms.
  - The febrile neutropenia rate was higher in the Capizzi MTX arm: 8.2% versus 5.2% for HD-MTX arm (p = .005).
  - There were low rates of neurological toxicity and they were equal between the 2 arms.
  - In summary HD-MTX was well-tolerated and overall had less toxicity than Capizzi MTX.

**Authors' Conclusions**

- The authors conclude that high dose MTX is superior to escalating Capizzi MTX for children and young adults with high risk B-cell precursor ALL.
- The magnitude of the benefit is more pronounced in Slow Early Responders compared to Rapid Early Responders.
- HD MTX is well tolerated, with less toxicity when compared to Capizzi MTX.
- The authors note that the improvement in outcomes demonstrated in this trial was the result of optimizing chemotherapy (MTX) that has been in use for 50 years, but future progress in ALL will more likely result from therapies directed at molecular targets.

**Clinical/Scientific Implications**

- This was a large, well-designed study that establishes a new standard of care for children with high-risk ALL.
The use of HD MTX during the interim maintenance phase led to a 7% improvement in event free survival at 5 years, and demonstrated both fewer marrow relapses and fewer isolated CNS relapses.

The inclusion of patients up to 30 years of age in this study is to be commended, as it fosters a common treatment approach between children and adults.

- Historically, clinical trials have imposed somewhat arbitrary age cut-offs.
  - There is now evidence that certain populations of young adults treated on pediatric protocols fare better than those treated in adult centers or on adult protocols.
  - Nevertheless, only 2% of the patients accrued were between the age of 20 and 30, so it is unclear how well these patients will tolerate the regimen overall.

Limitations of the study include that it does not provide information about the treatment of T-cell ALL, another disease where HD-MTX appears important.

Furthermore, there is no information regarding molecular genetics, although these studies are underway.

In general, this study demonstrates the importance of sequential studies building on previous results, a paradigm which has been well-established in serial trials investigating treatment regimens for leukemia. In addition, this trial exemplifies the potential for improved outcomes when a high proportion of patients are enrolled in trials.

- 60% of children with ALL are enrolled in trials versus <5% of adolescents and adults diagnosed with ALL.
- Massive improvements in outcomes for children with ALL over the past 60-70 years speak to the importance of investigation of treatments in the setting of cooperative group settings, a model that should be mimicked within the environment of adult oncology inasmuch as possible.