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Phase 3 randomized trial of high-dose methotrexate for young children with high-risk embryonal brain tumors: A report from the Children's Oncology Group

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Abstract

Background: Embryonal brain tumors are the leading cause of cancer death in young children.

Methods: ACNS0334 was a phase 3 randomized study evaluating high-dose methotrexate in young children < 36 months old with newly diagnosed high-risk embryonal brain tumors. Treatment included three cycles of induction chemotherapy with or without methotrexate followed by three cycles of high-dose consolidation chemotherapy with hematopoietic stem cell infusion. Primary endpoint was complete response (CR) at end of therapy. Secondary endpoints included comparison of event-free survival (EFS) between arms and to historical controls. Molecular characterization was conducted retrospectively. Tests of significance were one-sided.

Results: Of 77 eligible patients, 59 with detectable disease were evaluable for response and 28 (47.5%) achieved CR, 15/30 (50%) treated with methotrexate compared to 13/29 (45%) without methotrexate ($p=0.35$). For MB, CR was 12/19 (63%) with methotrexate compared to 6/20 (30%) without methotrexate ($p=0.039$). Considering molecular diagnosis, all SHH MB ($n=11$) were survivors. Five-year EFS was 70% [90% CI:39.6-87.2] for 10 Group 3 MB with methotrexate versus 33.3% [90% CI:15.0-52.9] for 15 without ($p=0.037$). In other embryonal tumors, CR was 3/11 (27%) with methotrexate compared to 7/9 (78%) without ($p=0.99$). No benefit with methotrexate was observed for Embryonal Tumor with Multilayered Rosettes ($n=14$, EFS 20.0% [90% CI:1.8-52.5] with methotrexate versus 33.3% [90% CI:10.8-58.1] without, $p=0.58$), or pineoblastoma ($n=9$, EFS 16.7% [90% CI:1.6-46.1] with methotrexate versus 0% without, $p=0.52$).

Conclusions: The addition of methotrexate to intensive chemotherapy improved CR and EFS for young children with high-risk Group 3 MB, but not other diagnoses.

Keywords: embryonal tumor with multilayered rosettes; medulloblastoma; methotrexate; pediatric brain tumor; pineoblastoma.