Resident Scholarly Project

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Title of Project: Meta-analysis analyzing different treatment options for large cell/anaplastic medulloblastoma and their effect on survival.

Study Purpose and Rationale:
Medulloblastoma is one of the most common pediatric brain neoplasms, comprising 63% of childhood intracranial embryonal tumors and ~10% of all pediatric CNS tumors. Medulloblastoma is a heterogeneous group of neoplasms ranging from their histologic appearance to their genetic heterogeneity. Classically, risk stratification had been based on three factors: age of presentation, extent of disease at presentation (Modified Chang criteria), and outcome of surgical resection (subtotal vs total resection), while classification of medulloblastoma was based on histologic subtypes. Recently genetic subtyping has played a larger role in risk stratification and classification of medulloblastoma tumors. Although the components of the classic risk stratification are falling out of favor for molecular genetics, the 2016 WHO classification of medulloblastoma still includes the histologic subtypes.

The four histologic subtypes are classic, desmoplastic/nodular (DNMB), extensive nodularity (MBEN), and large cell/anaplastic (LC/A). Of these, LC/A is of particular interest because these patients consistently have the poorest prognosis. One study that controlled for stage of metastases and extent of surgical resection, demonstrated that DNMB and MBEN showed better survival when compared to classic histology and LC/A showed significantly worse survival when compared to classic histology[1]. Even with this information, high-risk medulloblastoma, regardless of their histology, are usually treated the same.

There is a gap in knowledge about which treatment regimens confer the best prognosis for LC/A medulloblastoma, specifically. In this study we aim to review the medulloblastoma literature and shed light on which treatments have yielded the best survival for patients with LC/A medulloblastoma.

Methodology:
We performed a literature review on PubMed and Google Scholar with search terms “High risk medulloblastoma”, “Large cell/anaplastic medulloblastoma”, and “Pediatric medulloblastoma”. We compiled 31 studies, of which 16 met inclusion criteria. We included RCTs as well as retrospective and prospective case control studies due to the dearth of RCTs. Many of the studies had overlapping patient cohorts, so we decided to take individual subject data for those who had LC/A disease and compiled them for statistical analysis.

Inclusion Criteria:
- At least one documented LC/A subject
- Age up to 25 years
- Primary disease only (no recurrent disease, secondary neoplasms, etc.)

Statistical Analysis:
Statistical analyses will be conducted with Microsoft Excel and R. We will use overall survival (OS) and event-free survival (EFS), in months, as primary outcomes. We will compare OS and EFS against different regimens of RT dose, RT fractions, extent of surgical resection, intraventricular/intrathecal chemotherapy, and use of different classes of systemic chemotherapy agents. Comparisons will be made by utilizing

Kaplan Meier Curves and Cox Proportional Hazards Modeling. Groups will be stratified for age (<3 year and >3 years) and Chang classification at presentation to control for initial risk, since not all studies sequenced the tumors.

Study Drugs:
Drugs and therapies that are studied include: Etoposide, vincristine, cisplatin, carboplatin, ifosfamide, cyclophosphamide, radiation therapy, and surgical resection.

Medical Devices:
N/A

Potential Conflict of Interests:
No conflicts of interest to report.

Potential Benefits:
Through this study we can hopefully contribute to the pediatric neuro-oncology community more information about how to treat LC/A medulloblastoma. Eventually we hope this research can lead to better treatments for this disease that, for now, has a very grim prognosis.

References:

1. Rutkowski S, von Hoff K, Emser A, et al. Survival and prognostic factors of early childhood medulloblastoma: an international meta-analysis. *J Clin Oncol*. 2010;28(33):4961-4968. doi:10.1200/JCO.2010.30.2299
2. Northcott PA, Robinson GW, Kratz CP, et al. Medulloblastoma. *Nat Rev Dis Primers*. 2019;5(1):11. Published 2019 Feb 14. doi:10.1038/s41572-019-0063-6
3. von Hoff K, Hartmann W, von Bueren AO, et al. Large cell/anaplastic medulloblastoma: outcome according to myc status, histopathological, and clinical risk factors. *Pediatr Blood Cancer*. 2010;54(3):369-376. doi:10.1002/pbc.22339
4. Sirachainan N, Pakakasama S, Anurathapan U, et al. Outcome of newly diagnosed high risk medulloblastoma treated with carboplatin, vincristine, cyclophosphamide and etoposide. *J Clin Neurosci*. 2018;56:139-142. doi:10.1016/j.jocn.2018.06.028
5. Huang PI, Lin SC, Lee YY, et al. Large cell/anaplastic medulloblastoma is associated with poor prognosis-a retrospective analysis at a single institute. *Childs Nerv Syst*. 2017;33(8):1285-1294. doi:10.1007/s00381-017-3435-9
6. Campen CJ, Dearlove J, Partap S, et al. Concurrent cyclophosphamide and craniospinal radiotherapy for pediatric high-risk embryonal brain tumors. *J Neurooncol*. 2012;110(2):287-291. doi:10.1007/s11060-012-0969-2
7. Dufour C, Kieffer V, Varlet P, et al. Tandem high-dose chemotherapy and autologous stem cell rescue in children with newly diagnosed high-risk medulloblastoma or supratentorial primitive neuro-ectodermic tumors. *Pediatr Blood Cancer*. 2014;61(8):1398-1402. doi:10.1002/pbc.25009
8. Sung KW, Lim DH, Son MH, et al. Reduced-dose craniospinal radiotherapy followed by tandem high-dose chemotherapy and autologous stem cell transplantation in patients with high-risk medulloblastoma. *Neuro Oncol*. 2013;15(3):352-359. doi:10.1093/neuonc/nos304

9. von Bueren AO, Kortmann RD, von Hoff K, et al. Treatment of Children and Adolescents With Metastatic Medulloblastoma and Prognostic Relevance of Clinical and Biologic Parameters. *J Clin Oncol*. 2016;34(34):4151-4160. doi:10.1200/JCO.2016.67.2428
10. Massimino M, Antonelli M, Gandola L, et al. Histological variants of medulloblastoma are the most powerful clinical prognostic indicators. *Pediatr Blood Cancer*. 2013;60(2):210-216. doi:10.1002/pbc.24225
11. von Bueren AO, von Hoff K, Pietsch T, et al. Treatment of young children with localized medulloblastoma by chemotherapy alone: results of the prospective, multicenter trial HIT 2000 confirming the prognostic impact of histology. *Neuro Oncol*. 2011;13(6):669-679. doi:10.1093/neuonc/nor025
12. Pompe RS, von Bueren AO, Mynarek M, et al. Intraventricular methotrexate as part of primary therapy for children with infant and/or metastatic medulloblastoma: Feasibility, acute toxicity and evidence for efficacy. *Eur J Cancer*. 2015;51(17):2634-2642. doi:10.1016/j.ejca.2015.08.009
13. Goschzik T, Schwalbe EC, Hicks D, et al. Prognostic effect of whole chromosomal aberration signatures in standard-risk, non-WNT/non-SHH medulloblastoma: a retrospective, molecular analysis of the HIT-SIOP PNET 4 trial. *Lancet Oncol*. 2018;19(12):1602-1616. doi:10.1016/S1470-2045(18)30532-1
14. Gajjar A, Chintagumpala M, Ashley D, et al. Risk-adapted craniospinal radiotherapy followed by high-dose chemotherapy and stem-cell rescue in children with newly diagnosed medulloblastoma (St Jude Medulloblastoma-96): long-term results from a prospective, multicentre trial [published correction appears in Lancet Oncol. 2006 Oct;7(10):797]. *Lancet Oncol*. 2006;7(10):813-820. doi:10.1016/S1470-2045(06)70867-1
15. Brown HG, Kepner JL, Perlman EJ, et al. "Large cell/anaplastic" medulloblastomas: a Pediatric Oncology Group Study. *J Neuropathol Exp Neurol*. 2000;59(10):857-865. doi:10.1093/jnen/59.10.857
16. Korshunov A, Remke M, Kool M, et al. Biological and clinical heterogeneity of MYCN-amplified medulloblastoma. *Acta Neuropathol*. 2012;123(4):515-527. doi:10.1007/s00401-011-0918-8
17. Yoon JH, Park KD, Kang HJ, et al. Treatment of pediatric average-risk medulloblastoma using craniospinal irradiation less than 2500 cGy and chemotherapy: single center experience in Korea. *World J Pediatr*. 2017;13(4):367-373. doi:10.1007/s12519-017-0044-3
18. Jiang T, Zhang Y, Wang J, et al. A Retrospective Study of Progression-Free and Overall Survival in Pediatric Medulloblastoma Based on Molecular Subgroup Classification: A Single-Institution Experience. *Front Neurol*. 2017;8:198. Published 2017 May 12. doi:10.3389/fneur.2017.00198
19. Ramaswamy V, Remke M, Bouffet E, et al. Risk stratification of childhood medulloblastoma in the molecular era: the current consensus. *Acta Neuropathol*. 2016;131(6):821-831. doi:10.1007/s00401-016-1569-6
20. Shih DJ, Northcott PA, Remke M, et al. Cytogenetic prognostication within medulloblastoma subgroups. *J Clin Oncol*. 2014;32(9):886-896. doi:10.1200/JCO.2013.50.9539
21. Eberhart CG, Kratz JE, Schuster A, et al. Comparative genomic hybridization detects an increased number of chromosomal alterations in large cell/anaplastic

medulloblastomas. *Brain Pathol*. 2002;12(1):36-44. doi:10.1111/j.1750-3639.2002.tb00420.

22. Eberhart CG, Cohen KJ, Tihan T, Goldthwaite PT, Burger PC. Medulloblastomas with systemic metastases: evaluation of tumor histopathology and clinical behavior in 23 patients. *J Pediatr Hematol Oncol*. 2003;25(3):198-203. doi:10.1097/00043426-200303000-00004
23. Pérez-Martínez A, Lassaletta A, González-Vicent M, Sevilla J, Díaz MA, Madero L. High-dose chemotherapy with autologous stem cell rescue for children with high risk and recurrent medulloblastoma and supratentorial primitive neuroectodermal tumors. *J Neurooncol*. 2005;71(1):33-38. doi:10.1007/s11060-004-4527-4
24. Ramaswamy V, Remke M, Adamski J, et al. Medulloblastoma subgroup-specific outcomes in irradiated children: who are the true high-risk patients?. *Neuro Oncol*. 2016;18(2):291-297. doi:10.1093/neuonc/nou357
25. Abd El-Aal HH, Mokhtar MM, Habib E, El-Kashef AT, Fahmy ES. Medulloblastoma: conventional radiation therapy in comparison to chemo radiation therapy in the post-operative treatment of high-risk patients. *J Egypt Natl Canc Inst*. 2005;17(4):301-307.
26. Esbenshade AJ, Kocak M, Hershon L, et al. A Phase II feasibility study of oral etoposide given concurrently with radiotherapy followed by dose intensive adjuvant chemotherapy for children with newly diagnosed high-risk medulloblastoma (protocol POG 9631): A report from the Children's Oncology Group. *Pediatr Blood Cancer*. 2017;64(6):10.1002/pbc.26373. doi:10.1002/pbc.26373
27. Jakacki RI, Burger PC, Zhou T, et al. Outcome of children with metastatic medulloblastoma treated with carboplatin during craniospinal radiotherapy: a Children's Oncology Group Phase I/II study. *J Clin Oncol*. 2012;30(21):2648-2653. doi:10.1200/JCO.2011.40.2792
28. Tarbell NJ, Friedman H, Polkinghorn WR, et al. High-risk medulloblastoma: a pediatric oncology group randomized trial of chemotherapy before or after radiation therapy (POG 9031). *J Clin Oncol*. 2013;31(23):2936-2941. doi:10.1200/JCO.2012.43.9984
29. Robinson GW, Orr BA, Wu G, et al. Vismodegib Exerts Targeted Efficacy Against Recurrent Sonic Hedgehog-Subgroup Medulloblastoma: Results From Phase II Pediatric Brain Tumor Consortium Studies PBTC-025B and PBTC-032. *J Clin Oncol*. 2015;33(24):2646-2654. doi:10.1200/JCO.2014.60.1591
30. Taylor RE, Howman AJ, Wheatley K, et al. Hyperfractionated Accelerated Radiotherapy (HART) with maintenance chemotherapy for metastatic (M1-3) Medulloblastoma--a safety/feasibility study. *Radiother Oncol*. 2014;111(1):41-46. doi:10.1016/j.radonc.2014.01.022
31. Packer RJ, Zhou T, Holmes E, Vezina G, Gajjar A. Survival and secondary tumors in children with medulloblastoma receiving radiotherapy and adjuvant chemotherapy: results of Children's Oncology Group trial A9961. *Neuro Oncol*. 2013;15(1):97-103. doi:10.1093/neuonc/nos267
32. Conroy S, Garnett M, Vloeberghs M, Grundy R, Craven I, Walker D. Medulloblastoma in childhood: revisiting intrathecal therapy in infants and children. *Cancer Chemother Pharmacol*. 2010;65(6):1173-1189. doi:10.1007/s00280-009-1127-1

33. Packer RJ, Gajjar A, Vezina G, et al. Phase III study of craniospinal radiation therapy followed by adjuvant chemotherapy for newly diagnosed average-risk medulloblastoma. *J Clin Oncol*. 2006;24(25):4202-4208. doi:10.1200/JCO.2006.06.4980