TREATMENT OF CHILDREN AND ADOLESCENTS WITH METASTATIC MEDULLOBLASTOMA AND PROGNOSTIC RELEVANCE OF CLINICAL AND BIOLOGIC PARAMETERS.


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Abstract

Purpose To assess an intensified treatment in the context of clinical and biologic risk factors in metastatic medulloblastoma. Patients and Methods Patients (4 to 21 years old, diagnosed between 2001 and 2007) received induction chemotherapy, dose-escalated hyperfractionated craniospinal radiotherapy, and maintenance chemotherapy. Subgroup status and other biologic parameters were assessed. Results In 123 eligible patients (median age, 8.2 years old; median follow-up, 5.38 years), 5-year event-free survival (EFS) and overall survival (OS) were 62% (95% CI, 52 to 72) and 74% (95% CI, 66 to 82), respectively. OS was superior compared with the precedent HIT '91 trial. The 5-year EFS and OS were both 89% (95% CI, 67 to 100) for desmoplastic/nodular (n = 11), 61% (95% CI, 51 to 71) and 75% (95% CI, 65 to 85) for classic (n = 107), and 20% (95% CI, 0 to 55) and 40% (95% CI, 0 to 83) for large-cell/anaplastic (n = 5) medulloblastoma (P < .001 for EFS; P = .001 for OS). Histology (hazard ratio, 0.19 for desmoplastic/nodular and 45.97 for large-cell/anaplastic medulloblastoma) and nonresponse to the first chemotherapy cycle (hazard ratio, 1.97) were independent risk factors (EFS). Among 81 (66%) patients with tumor material, 5-year EFS and OS differed between low-risk (wingless...
[WNT], n = 4; both 100%), high-risk (MYCC/ MYCN amplification; n = 5, both 20%), and intermediate-risk patients (neither; n = 72, 63% and 73%, respectively). Survival rates were different between molecular subgroups (WNT, n = 4; sonic hedgehog [SHH; n = 4]; group 4 [n = 41]; group 3 with [n = 3] or without [n = 17] MYCC/MYCN amplification; P < .001). All cases showed p53 immuno-negativity. There was no association between patients with nonresponding tumors to induction chemotherapy and WNT (P = .143) or MYCC/MYCN status (P = .075), histologic subtype (P = .814), or molecular subtype (P = .383), as assessed by Fisher’s exact test. Conclusion This regimen was feasible and conferred overall favorable survival. Our data confirm the relevance of subgroup status and biologic parameters (WNT/MYCC/ MYCN status) in a homogeneous prospective trial population, and show that metastatic group 3 patients do not uniformly have poor outcomes. Biologic subgroup, MYCC/ MYCN status, response to induction chemotherapy, and histologic subtype may serve for improved treatment stratification.