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Preoperative chemotherapy in medulloblastoma: a change in treatment paradigm?

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See the article by Guerrini-Rousseau et al. in this issue, pp. 1686–1695.

Medulloblastoma is the most common malignant brain tumor among children. Over successive studies, our improved understanding of the disease has allowed the development of a risk stratification taking into account age, disease staging, residual disease, and molecular profile. Currently, with this approach, survival ranges from approximately 70% for high risk patients to up to 85% for standard risk patients. For the survivors, the long-term physical and cognitive effects of the disease and its treatment can have a devastating impact on their lives. In a long-term follow-up study, Brinkman and colleagues showed that 60% of patients previously treated for a brain tumor struggled to live independently, to maintain employment, and to have long-term relationships.[1] Consequently, it is critical that clinicians have in mind the long-term costs when designing new therapy.

In this issue of *Neuro-Oncology*, Guerrini-Rousseau and colleagues interrogated the place of neoadjuvant chemotherapy prior to surgery in pediatric patients with metastatic medulloblastoma.[2] They conducted a monocentric retrospective study where 92 patients were assigned "pragmatically" by their neurosurgeon into group A (upfront maximal safe resection; n = 54) or group B (neoadjuvant chemotherapy; n = 38). Because of the lack of randomization, higher-risk patients tended to be more prevalent in group B. Although the patients received the same chemotherapy backbone (carboplatin/etoposide), the number of cycles received varied from 1 to 8 based on the therapeutic response and improved resectability of the tumor. Importantly, the rate of ventriculoperitoneal shunt insertion was similar between the 2 groups, as well as the rate of disease progression while on treatment. Five-year progression-free survival (PFS) and overall survival (OS) were also comparable, confirming that this approach was safe. A higher rate of complete tumor resection was achieved after neoadjuvant chemotherapy (93.3% in group B vs 57.4% in group A). This finding was important because extent of resection is traditionally seen as an important risk factor for poorer outcome.[3] Molecular subgrouping was conserved when assessed. Importantly, Guerrini-Rousseau and colleagues also reported a trend toward better long-term neuropsychological outcome in children with a delayed definitive surgical resection, using longitudinal Full-Scale Intelligence Quotient (FSIQ) and Perceptual Reasoning Index (PRI) measures.

Several groups have previously reported improved neurosurgical outcomes with neoadjuvant chemotherapy, particularly in infants and young children with various tumor types.[4] The improved resection was related to the devascularization of the tumor as well as reduction in size. Furthermore, delaying surgery to a time when patients were clinically more stable also facilitated its proceedings. A residual disease >1.5 cm^2 is a well-established risk factor of poorer outcome, thus most protocols currently treat these patients with increased doses of craniospinal irradiation (CSI),[3] and maximal safe resection remains a major therapeutic goal. On the other hand, aggressive surgical resection is likely to be associated with increased morbidities, such as increased incidence of posterior fossa syndrome.[5] More recently, the impact of resection has been revisited by MAGIC (Medulloblastoma Advanced Genomics International Consortium) in the light of molecular subgrouping. In multivariable analysis, a near total resection (NTR) did not increase the risk of progression compared with a gross total resection (GTR), independently of the molecular subgroup.[6] The authors concluded that although a GTR should be the surgical goal, it should not be pursued over a risk of neurologic sequelae. In this study, Guerrini-Rousseau and colleagues considered the surgery as R0 in the absence of residual tumor during surgery and on postoperative MRI, while resection was R1 when there was a macroscopic residue and/or a residual tumor >1.5 cm^2 was identified on postoperative imaging. It is unclear where the patients with NTR, defined as a residual tumor <1.5 cm^2, would be. However, the largely improved incidence of R0 tumors confirms the role of neoadjuvant therapy on surgical resectability, with no impact on PFS and OS.

In this study, similar to other "sandwich" approaches where chemotherapy was given after surgery and before radiation,[7]

outcome for patients with metastatic disease was not improved or worsened by neoadjuvant chemotherapy. Here, the benefit seems to rely on a possibly less damaging surgery. Some predictive factors recognized to influence long-term neurocognitive disability such as the tumor location or the age at diagnosis are not amenable to intervention. However, others are, such as the occurrence of posterior fossa syndrome, hydrocephalus, irradiation, or some environmental factors, and several groups are currently developing innovative approaches[8] and posttreatment interventions to improve this outcome. Promising results have been shown with exercise training[9] or with the potential role of metformin in promoting cognitive recovery.[10] In this respect, this study reported valuable longitudinal neuropsychological evaluations over 7 years for 75% of the cohort and confirmed that the FSIQ and PRI scores decreased significantly over time as previously known. However, group B tended to have a better neuropsychological outcome. Despite these encouraging results, only a prospective randomized trial with longitudinal neuropsychology follow-up could confirm the advantage of a delayed surgical strategy.

This study raises several questions which we feel warrant further investigation. With residual disease being an important factor of poor outcome justifying a higher CSI dose, would a neoadjuvant chemotherapy approach leading to a GTR/NTR avoid increased CSI? Only children with metastatic disease were included in this study. Previous clinical trials have confirmed that neoadjuvant "sandwich" chemotherapy was an independent factor of adverse outcome for patients with M0 or M1 disease.[7] However, it would be interesting to study the impact of neoadjuvant therapy on patients with localized disease where GTR/NTR is not achievable, notably if it would allow a decreased dose of radiation.

Finally, as discussed by the authors, given the unchanged PFS/OS in this high-risk group and a trend for an improved long-term neurocognitive outlook, novel agents could be assessed during the neoadjuvant phase in a modified "phase zero" approach for high-risk medulloblastoma. By adapting such an approach, a new drug may be tested in combination with conventional chemotherapy through paired pharmacodynamic studies in children planned to have further tumor resection, and where analysis of the molecular targets is feasible.

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