Medulloblastoma in infants: the critical issues of the dilemma

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Brain tumours have now become the leading cause of cancer death in children under the age of 18. Although advances in management have resulted in improvements in survival, pediatric oncologists face a number of challenges in dealing with childhood brain tumours, particularly when they affect younger patients.

In an earlier issue of *Current Oncology,* Lafay–Cousin *et al.* reviewed a 22-year institutional experience of medulloblastoma management in infants and young children under the age of 3 years [1]. That series encompassed several eras during which significant changes occurred in the treatment of medulloblastoma. In the late 1980s, the Pediatric Oncology Group set a benchmark by using prolonged postoperative chemotherapy in an attempt to delay radiation in infants and young children with malignant brain tumours—including medulloblastoma [2]. The planned duration of chemotherapy was 24 months for children under 24 months of age and 12 months for children 24–36 months of age at diagnosis; the radiation therapy was started 3–4 weeks after the last cycle of chemotherapy. Although this cooperative effort was associated with significant hope and enthusiasm, the effectiveness of the strategy was soon questioned, because most enrolled children with medulloblastoma experienced early relapse (within the first 6–8 months of therapy). In addition, the incidence of late effect and second malignancy among survivors raised additional concerns [3].

A subsequent generation of protocols was developed in an attempt to avoid radiation, generally through intensification of chemotherapy with or without the use of autologous bone marrow or stem-cell transplant. The results of these second-generation studies were recently reported, and they set new standards for the treatment of medulloblastoma in infants and young children. In particular, the clinical trial conducted by Kuehl in Germany between 1991 and 1997, reported by Rutkowski, showed that, in a selected subgroup of patients with favourable features (desmoplastic histology and no evidence of metastatic disease), the use of radiation could be avoided in two thirds of the patients [4]. In addition, Rutkowski *et al.* provided results of neuro-intellectual assessments that illustrated the cognitive benefit of the strategy. Their study and others conducted in Europe and North America [5–7] generated new enthusiasm, and efforts are currently directed to the development of international collaboration, with the aim of achieving a consensus on common strategies.

In this context, the relevance of the institutional report from Lafay–Cousin *et al.* might be questioned, because the cooperative studies have provided extensive information on a rather rare disease. In reality, the institutional work provides insight that may not be captured by cooperative clinical trials. The first observation was that a number of infants do not receive any postoperative management after diagnosis. In the experience of Lafay–Cousin and colleagues, 5 of 24 patients (15%) received postoperative palliation because of extensive disease and poor surgical recovery. The second important point was related to the high proportion of patients with metastatic disease at the time of diagnosis—more than 50% in the institutional series. Comparison with the aforementioned cooperative studies suggests some selection bias, because the proportion of patients with metastatic disease is substantially lower (30%) in the experiences reported by the Foundation of Paediatric Cancer Research [Stichting Kindergeneeskundig Kankeronderzoek (SKK)] [4] and the Children's Cancer Group (CCG) 9921 protocol (33%) [6]. Another striking difference concerns the proportion of patients with desmoplastic histology: 24% in the report from Lafay–Cousin *et al.* compared with 46% in the SKK experience. This difference may reflect either a selection bias or, more worrisome, a difference in the histologic criteria used to define the desmoplastic entity. If the criteria are different, significant problems in future protocols might be anticipated because, following from the results of the SKK study,

histology is likely to become the cornerstone for allocation of treatment in infant medulloblastoma.

In the series reported by Lafay–Cousin *et al.,* 12 of 29 patients who received postoperative treatment are long-term survivors, and only 4 surviving patients did not receive radiation. An additional 2 patients received limited-field or limited-dose radiation. Although the management of patients has evolved over time, the proportion of patients successfully treated with chemotherapy alone or with chemotherapy in association with reduced-dose or limited-volume radiation does not contrast with recent reports. In the CCG 9921 study, 20 of 92 medulloblastoma patients (22%) enrolled were alive and radiation-free 5 years after the initial diagnosis [6]. In the French experience, among children without metastatic disease at diagnosis, the proportion of non-irradiated patients at 5 years was 22%.

Certainly one of the very important points from the experience of Lafay–Cousin and colleagues relates to neurocognitive outcome. The subgroup of patients treated with chemotherapy alone or with chemotherapy in association with reduced-dose or limited-volume radiation showed overall functioning within the normal range for age. By contrast, neurocognitive outcomes in children successfully treated with craniospinal radiation was dramatically lower, and physicians should be aware that, despite significant progress in radiation techniques, cure does not come without a cost for infants who fail chemotherapy-only strategies.

Finally, one important aspect of the work by Lafay–Cousin and colleagues is its confirmation of the need for prospective clinical trials for "orphan" diseases of this kind. Small numbers obviously limit the power of a study to identify prognostic variables and the possibility to envisage institutional, provincial, or even national studies. A recent work from the Canadian Paediatric Brain Tumour Consortium recorded 96 cases of medulloblastoma in infants and children under the age of 3 years during the period 1990–2005 [8]—a figure could be multiplied by a factor of approximately 10 to account for all children 3 years of age or younger diagnosed with medulloblastoma during the same period in North America. During that time, only four publications appeared, reporting a total of slightly more than 100 patients [6,7,9,10]. Although final results of other cooperative North American studies conducted during the same period are awaited, the scarcity of publications suggests that, overall, fewer than 20% of all cases of medulloblastoma in infants and children under 3 years of age are treated in cooperative clinical trials.

With the discovery of signal transduction pathways that are critical in the development of the cerebellum, dramatic breakthroughs are being made in the current understanding of the biology of medulloblastoma. Evidence is also increasing that medulloblastoma is not a single disease entity, but rather a complex group of molecularly distinct tumours despite their morphologic similarities under the microscope [11]. These findings suggest that the future treatment of medulloblastoma will be tailored according to the underlying molecular biology, leading ideally to an increased chance of cure with minimally toxic therapy and reduced long-term morbidity. This prospect reinforces the critical importance of clinical trials, even if the complexity of these innovative treatments may require the transfer of these patients to supraregional centres. Similarly, the development of proton therapy units will have a significant effect on the management of these young patients who are likely to benefit from these modern techniques of radiation.

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