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Comments and Critique

Treatment of Brain Tumours in Children Less Than 3 Years of Age

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SUCCESSFUL TREATMENT of brain tumours in very young children has to achieve the impossible—cure without toxicity. A tall order when radiation, which is the mainstay of treatment in older children and adults, is particularly damaging to the developing brain. In children under 3 years, the serious consequences of brain irradiation make radiotherapy unacceptable [1–3] and chemotherapy, despite its relatively limited overall role in the treatment of brain tumours, requires testing.

Brain tumours in this age group are infrequent, but the distribution of tumour types is similar to older children. The prognosis in younger children is generally considered worse, although this may reflect the inability to give adequate treatment, such as the increased technical difficulty of complete surgical resection or giving lower doses of radiation, rather than a difference in biology *per se* [4]. The rarity of this disease and consequently the small number of children in individual studies make consensus information difficult to obtain. The Paediatric Oncology Group has accrued a large number of patients treated in a uniform manner—a model for multicentre co-operation in rare tumours. Between 1986 and 1992, 198 children under 3 years old with a variety of brain tumours, reflecting the distribution of tumours in the paediatric age group, were treated with initial combination chemotherapy comprising two cycles of cyclophosphamide and vincristine, alternating with cisplatin and etoposide [5]. Children under 2 years received chemotherapy for 2 years, and those aged between 2 and 3 years received 1 year of chemotherapy. External beam radiotherapy was given either at completion of chemotherapy or at disease progression, the aim being to delay the administration of radiation for as long as possible without jeopardising survival.

When considered in terms of response, the results are reasonably successful with a 39% overall response rate in evaluable patients. Apparent complete disappearance of tumour does occur following chemotherapy, but anyone familiar with the assessment of radiological responses of patients with brain tumours will realise the difficulty of such measurement. Despite the large overall number of patients, the results broken down into individual histological subtypes have very large confidence intervals, although brain stem gliomas and primitive neuroectodermal tumours (PNET) did seem to do particularly badly. Progression-free survival is a valid, and perhaps more appropriate method of assessing the effectiveness of chemotherapy, and is reported as 45% at 1 year and 37% at 2 years.

These results can certainly be considered a measured success, as radiation could be delayed until the fourth year of life in around 40% of children. At what cost was this success achieved? The treatment was not without toxicity, in terms of nausea and vomiting, neutropenic sepsis and haemorrhagic cystitis. There were four treatment-related deaths and two second malignancies. The observation that 21 children were withdrawn by their parents from the study suggests that subjective toxicity was not minimal. More long-term toxicity, as measured by growth delay and change in neurodevelopmental function before and after chemotherapy, was acceptable although cognitive development was abnormal in 64% of those tested prior to chemotherapy (after neurosurgery), and the majority of patients went on to receive radiotherapy. Thus, long-term survivors may accrue damage from the tumour, neurosurgery and radiotherapy. The contribution of chemotherapy to the long-term damage would, however, seem to be acceptable and is largely cisplatin related.

The survival results reflect the effectiveness of the whole treatment approach of combined chemotherapy and radiotherapy. The overall survival of 74% at 1 year and 53% at 2 years appears favourable, but the inspection of survival curves shows continued attrition, with 3-year survival falling to 40% with no obvious plateau reached. Results by individual histology show a potentially cured population only among patients with medulloblastoma, with a survival rate similar to older children. Direct comparison of other histological subtypes with published studies is difficult, but in terms of survival the results are comparable to conventional treatment approaches [1,2,6].

There is no clear information about possible differences in tumour biology and tumour chemosensitivity in very young children compared to older children and adults. Aggressive chemotherapy regimens, such as high-dose myeloablative chemotherapy or the 8-in-1 regimen (reviewed by Finlay [7]), given to older patients, have failed to live up to their early expectations [8]. However, many chemotherapy programmes, both in children and in adults, have been examined in the context of relapsed or progressive disease, and require testing as the primary therapy. This study is valuable as patients with a wide variety of tumours received primary chemotherapy, yielding information about primary chemosensitivity. For example, the high response rate observed in children with high-grade gliomas suggests possible new approaches to older patients with the disease. The use of chemotherapy prior to radiotherapy may allow more effective delivery of drugs to the tumour as the blood–tumour barrier may be disrupted at diagnosis, and may subsequently repair in responsive tumours following radiotherapy [9]. This strategy is applied in the current International

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Society of Paediatric Oncology (SIOP) PNET III trial, where in one arm of a randomised study 3 months of chemotherapy using cyclophosphamide, carboplatin, vincristine and etoposide precedes irradiation.

Where do we go from here? Initial chemotherapy is likely to remain the first-line treatment in very young children presenting with brain tumours and possibly warrants further evaluation in older patients with certain histological subtypes. This study also confirms the prognostic significance of the degree of tumour resection, which suggests that local tumour control remains an important aim. Advances in microsurgical and stereotactic technology may improve resection rates without increasing morbidity.

More precise targetting of radiotherapy may be an alternative strategy for avoiding toxicity in selected patients. Whole brain irradiation, as part of craniospinal axis radiotherapy, significantly adds to treatment-related damage. It has become increasingly apparent that it may be unnecessary in patients with ependymoma [10, 11]. However, it is likely to remain part of the treatment of PNET as reduction of neuraxis dose in "good" prognosis patients with medulloblastoma results in an unacceptable relapse rate outside the posterior fossa, and inferior survival [12]. High-precision localised irradiation can be achieved with the use of stereotactic technology as fractionated stereotactic radiotherapy [13]. It provides an opportunity for reducing toxicity by treating less normal tissue, and this should be a general aim for all paediatric cranial irradiation. To improve tumour control and survival, the technique allows for dose escalation without increasing morbidity, and this approach also requires testing.

It is not clear if primary chemotherapy can reduce the rate of distant seeding and provide durable local control. An experimental strategy, currently being explored by the United Kingdom Children's Cancer Study Group (UKCCSG), is to omit radiotherapy in infants under 3 years who have no evidence of disease at completion of chemotherapy. A regimen similar to that used in the SIOP PNET III study is given, but with increased dose intensity achieved by the addition of cisplatin, and high-dose methotrexate given between courses of myelosuppressive chemotherapy. Durable responses have been seen, and the salvage rate of delayed radiotherapy seems acceptable [14]. 11 of 13 children, in the study by Duffner *et al.* under review, who had no evidence of disease at completion of chemotherapy, and in whom radiotherapy was declined, remained disease-free at a median interval of 1 year [5]. On the other hand, the poor results seen in children with brain stem gliomas suggest that, for some children, initial radiotherapy may be the only viable treatment option.

The prognosis of young children with brain tumours remains poor, and the management continues to be difficult. Current chemotherapy regimens used as first-line treatment do allow for delays in radiotherapy in a significant proportion of cases, and reduce the risk of radiation injury to the developing brain. However, the overall results are poor, and the main challenge remains. Future advances are likely to parallel those in older patients and we have to await the results of new technological developments of conventional treatments as well as new biological approaches. This study shows that initial chemotherapy can be an effective approach for some patients and it is a good and worthwhile start—but there is still a long way to go.

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