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Primary postoperative chemotherapy without radiotherapy for treatment of brain tumours other than ependymoma in children under 3 years: Results of the first UKCCSG/SIOP CNS 9204 trial

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ABSTRACT

Background: Radiotherapy is an effective adjuvant treatment for brain tumours arising in very young children, but it has the potential to damage the child's developing nervous system at a crucial time – with a resultant reduction in IQ leading to cognitive impairment, associated endocrinopathy and risk of second malignancy. We aimed to assess the role of a primary chemotherapy strategy in avoiding or delaying radiotherapy in children younger than 3 years with malignant brain tumours other than ependymoma, the results of which have already been published.

Methods: Ninety-seven children were enrolled between March 1993 and July 2003 and, following diagnostic review, comprised: medulloblastoma ($n = 31$), astrocytoma (26), choroid plexus carcinoma [CPC] (15), CNS PNET (11), atypical teratoid/rhabdoid tumours [AT/RT] (6) and ineligible (6). Following maximal surgical resection, chemotherapy was delivered every 14 d for 1 year or until disease progression. Radiotherapy was withheld in the absence of progression.

Findings: Over all diagnostic groups the cumulative progression rate was 80.9% at 5 years while the corresponding need-for-radiotherapy rate for progression was 54.6%, but both rates varied by tumour type. There was no clear relationship between chemotherapy dose intensity and outcome. Patients with medulloblastoma presented as a high-risk group, 83.9% having residual disease and/or metastases at diagnosis. For these patients, outcome was related to histology. The 5-year OS for desmoplastic/nodular medulloblastoma was 52.9% (95% confidence interval (CI): 27.6–73.0) and for classic medulloblastoma 33.3% (CI: 4.6–67.6); the 5-year EFS were 35.3% (CI: 14.5–57.0) and 33.3% (CI: 4.6–67.6), respectively.

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All children with large cell or anaplastic variants of medulloblastoma died within 2 years of diagnosis. The 5-year EFS for non-brainstem high-grade gliomas [HGGs] was 13.0% (CI: 2.2–33.4) and the OS was 30.9% (CI: 11.5–52.8). For CPC the 5-year OS was 26.67% (CI: 8.3–49.6) without RT. This treatment strategy was less effective for AT/RT with 3-year OS of 16.7% (CI: 0.8–51.7) and CNS PNET with 1-year OS of 9.1% (CI: 0.5–33.3).

Interpretation: The outcome for very young children with brain tumours is dictated by degree of surgical resection and histological tumour type and underlying biology as an indicator of treatment sensitivity. Overall, the median age at radiotherapy was 3 years and radiotherapy was avoided in 45% of patients. Desmoplastic/nodular sub-type of medulloblastoma has a better prognosis than classic histology, despite traditional adverse clinical features of metastatic disease and incomplete surgical resection. A subgroup with HGG and CPC are long-term survivors without RT. This study highlights the differing therapeutic challenges presented by the malignant brain tumours of early childhood, the importance of surgical approaches and the need to explore individualised brain sparing approaches to the range of malignant brain tumours that present in early childhood.

1. Introduction

Young age at diagnosis has long been considered a powerful and adverse prognostic factor for both survival and quality of survival from malignant brain tumours arising in childhood. The reasons are multifactorial, and include ethical considerations of embarking upon high-risk therapies in young and extremely vulnerable infants or toddlers, clinical presentation of a protracted time to diagnosis, acute and delayed toxicities of chemotherapy and cranial and spinal radiotherapy, the latter being particularly high-risk for profound cognitive damage at an early age.[1–3]

The adverse late effects of radiotherapy in young patients reflect the vulnerability of an immature CNS to treatment related damage.[2,4] Whilst the ultimate objective of treatment with chemotherapy might be the avoidance of radiotherapy, pioneering work in the mid 1980s suggested that it was at least possible to delay irradiation by this means.[5,6] Subsequent studies attempted to delay radiotherapy to beyond 3 years of age,[7,8] representing a physiological end-point at which time cell division of the CNS is largely complete in order to preserve cognitive capacity.[9] CNS 9204 was a United Kingdom Children's Cancer Study Group (UKCCSG) and International Society of Paediatric Oncology (SIOP) co-operative trial, initially open to all histopathological sub-types of brain tumour aged less than 3 years. The aims of this study were to improve the duration of survival of very young children with brain tumours by using a chemotherapy strategy aimed at avoiding or delaying radiotherapy. The outcomes of children with ependymoma have already been reported.[10] This paper describes the outcomes of children with other malignant brain tumour types using the same therapeutic approach.

2. Methods

2.1. Participants

Criteria for recruitment included histological diagnosis of primary intracranial malignant brain tumour or radiological findings consistent with a brainstem astrocytoma, age 3 years or younger at diagnosis and no prior adjuvant drug or radiation therapy. Fig. 1 shows the trial profile. The trial was approved by UKCCSG/SIOP and national ethical approval was obtained. Informed consent was obtained from parents or guardians of each child, in accordance with national guidelines at the time of this trial, and noted in the hospital records. Children were registered and monitored through the CCLG Data Centre and followed until censor point or death.

2.2. Procedures

After maximal surgical resection, the chemotherapy schedule comprised blocks of alternating myelosuppressive and non-myelosuppressive drugs repeated at 14-d intervals to produce a high-intensity regimen with modest individual drug-dose intensity (Table 1). Drugs chosen had different mechanisms of cytotoxic action in an attempt to prevent the early emergence of drug resistance. Each course lasted for 56 d and a total of seven cycles were given. Children weighing 10 kg or more were dosed by surface area, those weighing less than 10 kg were dosed by weight as shown. Course 1; carboplatin (550 mg/m^2 or 20 mg/kg) over 4 h and vincristine (1.5 mg/m^2 or 0.05 mg/kg) intravenous bolus; course 2; methotrexate (8000 mg/m^2 or 250 mg/kg) and vincristine (1.5 mg/m^2 or 0.05 mg/kg); course 3; cyclophosphamide (1500 mg/m^2 or 50 mg/kg) over 4 h with prehydration and mesna; course 4; cisplatin (40 mg/m^2 for 48 h or 1.3 mg/kg). Further details of administration are given in Table 1. 10% of the total dose of methotrexate was given over the first hour then the remaining 90% was given intravenously over 23 h. Hydration with 0.18% NaCl + 2.5% dextrose + $NaHCO_3$ 50 mmol/L + KCl 20 mmol/L was given before, during and for at least 48 h after the methotrexate infusion was completed. Methotrexate serum concentration was measured at 24 h, 48 h and 72 h post infusion. Folinic acid rescue was a fixed dose of 15 mg starting 36 h after the beginning of the methotrexate infusion 3-hourly for five doses, then 6-hourly until serum methotrexate concentration was under 0.1 μmol/L ($<1 \times 10^{-7}$ M). Mesna was given alongside the cyclophosphamide (1800 mg/m^2 or 60 mg/kg) and was given intravenously commencing with prehydra-