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Analysis of patients with supratentorial primitive neuro-ectodermal tumours entered into the SIOP/UKCCSG PNET 3 study

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ABSTRACT

The SIOP PNET 3 study was designed to determine whether 10 weeks of moderately intensive chemotherapy given after surgery and before radiotherapy (RT) would improve the outcome for patients with primitive neuroectodermal tumours (PNETs) compared with RT alone.

Patients with a histological diagnosis of supratentorial PNET (StPNET) and no radiological evidence of metastatic disease were initially eligible for randomisation to either chemotherapy followed by craniospinal RT 35 Gy in 21 fractions with a boost of 20 Gy in 12 fractions to the primary site, or RT alone. In respect of the increasing recognition that StPNET were high-risk tumours, randomisation for this group closed in November 1999. This analysis includes both randomised and non-randomised patients with StPNET entered into the study database.

Sixty-eight patients aged 2.9–16.6 years (median 6.5 years) were included in the analysis (chemotherapy + RT: 44, RT alone: 24). Fifty-four patients (79%) had a non-pineal and 14 (21%) a pineal site. At a median follow-up of 7.4 years, for all patients overall survival (OS) at 3 and 5 years was 54.4% and 48.3%, respectively. Event-free survival (EFS) at 3 and 5 years was 50.0% and 47.0%, respectively. There was no statistically significant difference in OS or EFS according to treatment received. OS ($P = 0.05$) and EFS ($P = 0.03$) were significantly better for patients with pineal primary sites. EFS for pineal tumours were 92.9% at 3 years and 71.4% at 5 years and for non-pineal primaries 40.7% at 3 years and 40.7% at 5 years. This study confirmed the relatively good survival for non-metastatic pineal PNETs but poor survival of non-pineal StPNETs. There was no evidence that pre-radiation chemotherapy improved outlook. Future treatment programs should be directed at the particular natural history of these tumours, to further define prognostic factors and to explore further biological characteristics.

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1. Introduction

Primitive neuroectodermal tumours (PNETs) are a group of malignant embryonal tumours of unknown aetiology accounting for approximately 20% of central nervous system (CNS) neoplasms in childhood. A histopathological classification of CNS PNETs was proposed by Rorke in 1983,[1] in recognition of the morphological and immunohistochemical characteristics shared by cerebellar PNETs (medulloblastomas) and supratentorial PNETs (StPNETs). These tumours also share common clinical features such as a propensity to leptomeningeal dissemination via the CSF pathways and sensitivity to both radiotherapy (RT) and chemotherapy. StPNETs comprise approximately 2–3% of CNS tumours in childhood.[2,3] Most arise in the cerebral hemispheres with a minority occurring in the pineal region (pineoblastomas).

Until the late 1980s, standard management of both medulloblastoma and StPNETs was maximum surgical resection followed by craniospinal RT (CSRT) to a dose of 35–36 Gy with a 'boost' of around 20 Gy to the primary tumour site. It is clear that using this so-called conventional treatment, StPNETs have a worse prognosis than medulloblastoma with various series reporting a 20–40% survival.[4–6] Very young patients appear to have a particularly poor prognosis possibly as a result of underutilization of adequate doses of RT, a higher rate of metastatic disease or adverse biological features.

There have been no large group-wide studies specifically for StPNET; instead they are generally treated with protocols designed for children with high-risk medulloblastoma. Similarly, prognostic factors for StPNETs are poorly defined although the larger series of patients with StPNETs such as those from the CCG-921[7] and the HIT 91[6] studies show an improved survival for pineal compared with non-pineal StPNETs.

Over the last 30 years the International Society for Paediatric Oncology (SIOP) has conducted a series of randomised controlled trials for medulloblastoma/PNET particularly addressing the role of adjuvant chemotherapy. There are theoretical advantages for giving chemotherapy before RT. The time between surgery and RT is when the tumour has its maximal blood supply and when the blood/brain barrier is maximally disrupted. The delivery of intensive chemotherapy may be more difficult after CSRT because of myelosuppression.

The central question for the SIOP PNET 3 study (from April 1992 to August 2000) was whether the use of intensive pre-RT chemotherapy would improve the outcome for patients with non-metastatic medulloblastoma although those with StPNET were eligible for entry and randomisation into the study.

The results of PNET-3 study for both M0–1 and M2–3 medulloblastoma have been reported.[8,9] This paper reports the results of an analysis of patients with StPNETs entered into the study including the assessment of prognostic factors on survival.

2. Patients and methods

2.1. Selection criteria

Patients eligible for randomisation were those aged 3 and 16 years inclusive with a histologically proven institutional diagnosis of StPNET. Patients should have had no radiological evidence of metastases. As for patients with medulloblastoma, it was recommended that StPNET patients with radiological evidence of leptomeningeal metastases at diagnosis (M2–3) should receive pre-RT chemotherapy.

In respect of the increasing recognition that StPNET were high-risk tumours, randomisation for this group closed in November 1999. Ethical approval for the study was acceptable at contemporaneous standards of the early 1990s.

2.2. Pre-treatment investigations

Patients should have had a spinal MR or myelogram before, or within two weeks after surgery, and a cranial CT or MR scan within 72 h after surgery. The study design did not include central radiological review and tumour size was assessed from institutional reports of the pre-operative imaging.

CSF sampling although recommended was not mandatory, and was inconsistently carried out throughout the study.

2.3. Surgical treatment

The extent of resection was assessed on the basis of institutional reports of post-operative imaging for 59 (87%) patients and by the neurosurgical assessment when an imaging report was not available for 9 (13%) patients and was classified as being either a total, or less than total resection.

2.4. Trial randomisation

Patients with non-metastatic tumours (M0–1) were randomised to treatment with either chemotherapy followed by RT, or RT alone. Randomization was stratified on the basis of extent of tumour resection, treating centre and age grouping (3–7, 8–11 and 12–16 years).

2.5. Chemotherapy protocol

Chemotherapy was intended to commence within 28 days of surgery and consisted of four cycles of treatment at three-weekly intervals using alternating cycles of:

Vincristine 1.5 mg/m^2, days 1, 8, 15.
Etoposide 100 mg/m^2, days 1, 2, 3.
Carboplatin 500 mg/m^2, days 1, 2.

and

Vincristine 1.5 mg/m^2, days 1, 8, 15 (day 1 only for final course).
Etoposide 100 mg/m^2, days 1, 2, 3.
Cyclophosphamide 1.5 g/m^2, day 1.

Count recovery (neutrophils $> 1.0 \times 10^9$/L, platelets $> 100 \times 10^9$/L) should have occurred before each cycle of chemotherapy.

2.6. Radiotherapy protocol

RT commenced with CSRT and was given in daily fractions, five days per week. The CSRT dose was 35 Gy in 21 daily