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Treatment of recurrent central nervous system primitive neuroectodermal tumours in children and adolescents: Results of a Children's Cancer and Leukaemia Group study

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ABSTRACT

Background: The treatment of previously irradiated patients with recurrent central nervous system primitive neuroectodermal tumours (PNETs) is a considerable challenge. A study was undertaken to attempt to improve the outcome for such patients using a high dose chemotherapy (HDCT) based strategy.

Methods: Between 2000 and 2007, 40 patients with relapsed medulloblastoma (MB) and 5 with relapsed supratentorial PNETs (StPNETs) were accrued. All but one had received prior craniospinal radiotherapy. Patients were initially treated with cyclophosphamide (4 g/m^2) together with surgery or local radiotherapy where appropriate. If complete or near complete remission was achieved, the patient proceeded to receive two sequential courses of HDCT with stem cell rescue. The first course consisted of thiotepa (900 mg/m^2) and the second carboplatin (AUC 21).

Results: All five patients with StPNET died of tumour progression with a median OS of 0.4 years. Nineteen of the 40 patients with relapsed MB underwent surgery. Radiotherapy was administered to eight patients. All patients received at least one course of cyclophosphamide. Only 22 MB patients progressed to the HDCT phase; 10 patients received thiotepa only and 12 thiotepa and carboplatin. At a median follow-up of 7.4 years (Range 2.8–8.2 years), only three MB patients are still alive, one following a further relapse. Three and 5 year OS was 22.0% and 8.2%, respectively and 3 and 5 year EFS was 14.6% and 8.7%, respectively.

Conclusion: This national study based on a strategy including a particular tandem HDCT regimen showed no benefit for previously irradiated patients with relapsed StPNET and very limited benefit for patients with relapsed medulloblastoma.

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1. Introduction

Medulloblastoma (MB), a cerebellar tumour, is the most common malignant brain tumour in childhood accounting for 15–20% of central nervous system (CNS) neoplasms. It shares clinical characteristics with histologically similar tumours leading to the concept of 'primitive neuroectodermal tumours' (PNETs),[1] that include both MB (>80% of PNETs) and supratentorial PNETs (StPNETs) which are typically either cortical or arise in the region of the pineal gland (pineoblastomas).

Treatment approaches to MB/StPNET are determined by the patient's age and extent of disease at diagnosis. Children less than 3–5 years of age are treated with chemotherapy regimens that avoid the use of whole brain or craniospinal radiotherapy (CSRT).[2,3] For older children, therapy includes chemotherapy and risk-adapted CSRT with a boost to the primary tumour bed.[4,5]

For MB, the predominant site of relapse is distant leptomeningeal, either alone or in combination with relapse at the primary site.[4,6] In contrast, the majority of StPNETs relapse locally.[7,8]

The treatment of recurrent MB/PNET is a considerable challenge. Infants who have been previously irradiated and have a local relapse can be salvaged by surgical resection and local RT with or without high dose chemotherapy (HDCT).[3] The outcome is, however, extremely poor for patients who relapse following previous CSRT and who are retreated with 'conventional therapy'.[9,10]

In 1996, Finlay et al. reported a study showing that a subset of patients with recurrent brain tumours could be salvaged with HDCT followed by autologous stem cell rescue.[11] Subsequently other investigators have tested the efficacy of HDCT in patients with recurrent MB and StPNETs.[12,13]

Based on these reports, the United Kingdom Children's Cancer Study Group (UKCCSG) (now the Children's Cancer and Leukaemia Group, CCLG) initiated an observational study, the principle aim of which was to test a strategy including HDCT for recurrent CNS PNETs in children and adolescents.

2. Methods

The study was approved by a multi-centre research ethics committee, and written informed consent from each participant or each participant's guardian was obtained.

2.1. Patients

Eligible patients were aged less than 21 years with either relapsed MB or StPNET, with the study being particularly designed for patients who had received prior CSRT.

All tumours must have been histologically proven at first diagnosis. All patients must have had an MRI of brain and spine with gadolinium enhancement prior to study entry. Post-operative MRI had to be performed within 72 hours of any neurosurgical procedure. It was stipulated that CSF be collected and examined for tumour cells as part of the diagnostic work-up, either at surgery before tumour handling or by lumbar puncture.

2.2. Treatment

Particularly for patients with a solitary relapse, it was recommended that surgery be undertaken as the initial therapy, with the aim of obtaining a complete surgical excision. It was suggested that surgery might also be appropriate following cytoreductive chemotherapy, again with the aim of removing residual disease.

For patients not in a surgical CR a cytoreductive phase was undertaken with the principle aim of obtaining a second complete remission (CR). Based on previous reports,[11,13] it was suggested that only those patients reaching a radiological second CR should generally proceed to the second, myeloablative phase, consisting of HDCT with autologous stem cell rescue.

In certain individuals focal radiotherapy (RT) was considered appropriate local therapy, Guidelines for RT were included in the protocol and were based on the site of relapse. For cranial relapse, the suggested RT was with between 30 and 40 Gy in 1.74 Gy fractions and for localised recurrence involving the spinal cord, then suggested RT was with 20 Gy in 1.67 Gy fractions.

2.3. Cytoreductive phase

The cytoreductive phase consisted of cyclophosphamide chemotherapy and local therapy where appropriate cyclophosphamide was given at a dose of 4 g/m^2 per course over 2 days, with intravenous fluids and mesna followed by G-CSF (5 μg/kg daily). Two to four courses of cyclophosphamide were recommended dependent on the pattern of relapsed disease and the effect of surgery in producing a second CR.

Peripheral blood stem cell (PBSC) harvesting was undertaken during this phase with the aim of storing at least two collections of 2×10^6/kg CD 34+ cells which was considered the minimum acceptable to proceed with HDCT. It was strongly encouraged that harvesting be performed as early as possible in relation to the cytoreductive phase using the high dose cyclophosphamide dose as priming for the stem cell mobilisation.

2.4. Myeloablative phase

High dose chemotherapy comprised two courses of sequential, single-agent high dose therapy. It was hoped that by using such sequential treatment, toxicity would be lower than that noted following previously reported regimens, in which two or more agents are given concurrently.

The first course of HDCT consisted of thiotepa at a dose of 900 mg/m^{2}given over three days. The second was with high dose carboplatin given on count recovery (neutrophil count $>1 \times 10^9$/L and platelet count $>80 \times 10^9$/L). Carboplatin was dosed to an intended AUC of 21 mg/ml min, given over three days, based on body weight and half-life of ^{51}Cr EDTA clearance.[14]

Following each course of HDCT, it was recommended that at least 2×10^6/kg CD 34+ cells be reinfused 48 hours after the last dose of drug and G-CSF 5 μg/kg started 5 days after the PBSC infusion.

2.5. *Statistical methods*

The primary end-point to be used to assess the effectiveness of the protocol was event-free survival. Stopping rules were established to close the study should the toxic death rate exceed the theoretical acceptable rate, which was set at 15%.

Response to cytoreductive therapy was defined according to the accepted International Society of Paediatric Oncology (SIOP) Brain Tumour Committee definition of response.[15] Overall survival (OS) and Event Free Survival (EFS) were calculated using the Kaplan–Meier method in consideration of the time from relapse to death, further relapse or progression or the time of last follow up. To allow comparison with those studies that report outcome from the time of HDCT, a separate analysis for both OS (OS-HDCT) and EFS (EFS-HDCT) for patients receiving this treatment modality was conducted, calculated from day 1 of thiotepa therapy.

Baseline variables at relapse that could potentially influence EFS were explored by Cox proportional hazard modelling where the variables of interest were gender, age at relapse, relapse type, the presence of metastases, treatment with chemotherapy for treatment at initial diagnosis and the time between original diagnosis and relapse. A 5% significance level was used for variable selection and all analyses were performed using STATA version 11.[16]

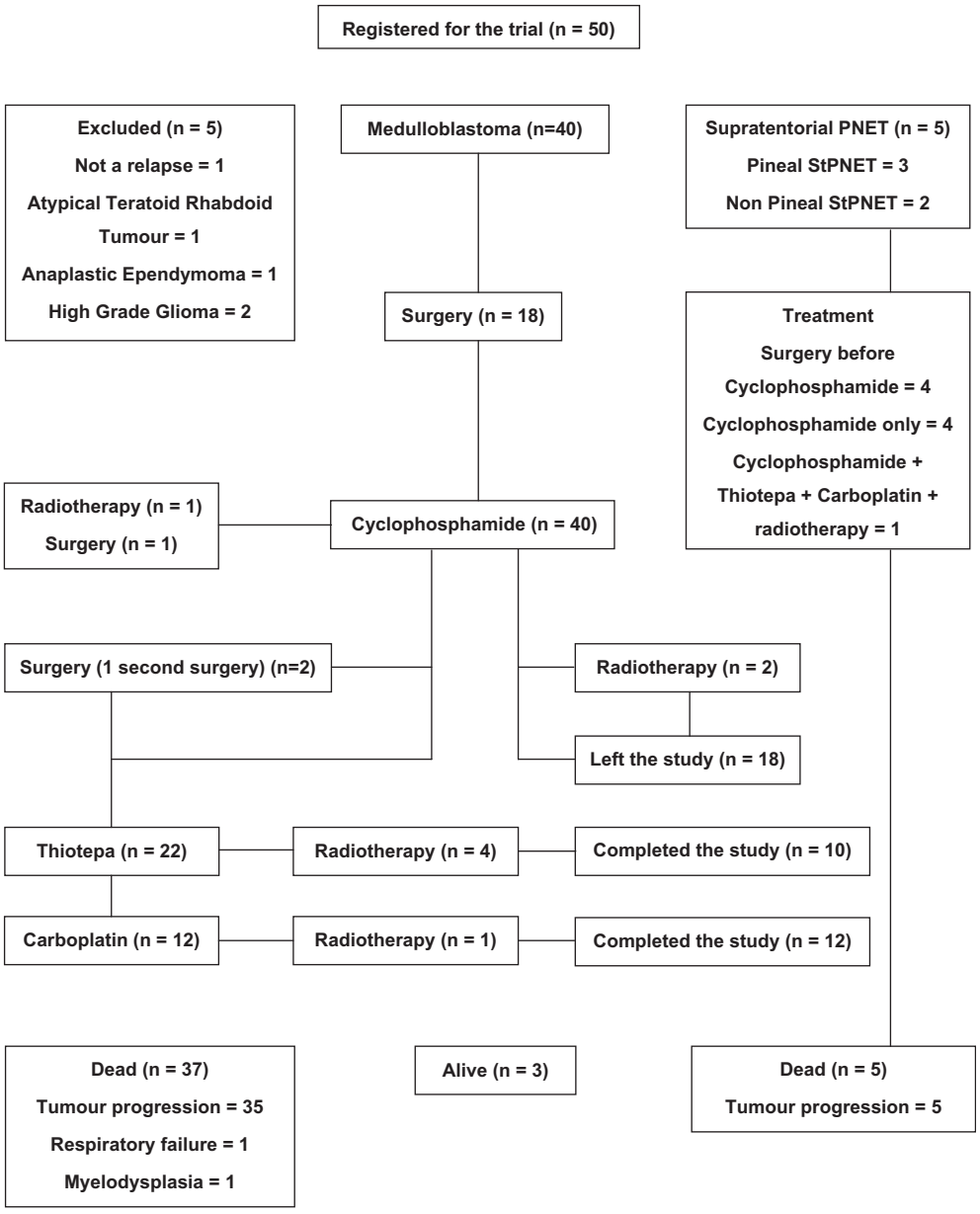

Fig. 1 – Patients progression through the trial.

Table 1 – Demographic information at study entry.

Variable (%)	Medulloblastoma (n = 40)	Supratentorial PNET (n = 5)	Total (n = 45)
Gender			
Male	25 (62.5)	2 (40.0)	27 (60.0)
Female	15 (37.5)	3 (60.0)	18 (40.0)
Age at original diagnosis (years)			
Median	8.4	8.9	8.6
Range	1.7–16.0	5.2–14.3	1.7–16.0
Age at relapse (years)			
Median	10.5	12.9	1.8
Range	2.3–17.5	9.4–15.8	2.3–17.5
Time between original diagnosis and relapse (years)			
Median	2.5	4.2	2.5
Range	0.5–6.8	1.4–5.6	0.5–6.8
Relapse type			
Solitary primary site	13 (32.5)	2 (40.0)	15 (33.3)
Solitary metastatic site	10 (25.0)	1 (20.0)	11 (24.4)
>1 site with metastases	12 (30.0)	0 (0.0)	12 (26.7)
>1 site not at primary	5 (12.5)	2 (40.0)	7 (15.6)
Metastases present			
Yes	22 (55.0)	1 (20.0)	23 (51.1)
No	18 (45.0)	4 (80.0)	22 (48.9)
Initial treatment			
Chemotherapy only	1 (2.5)	0 (0.0)	1 (2.2)
Radiotherapy only	9 (22.5)	2 (40.0)	10 (22.2)
Chemotherapy + radiotherapy	30 (75)	3 (60.0)	34 (75.6)

3. Results

The study recruited between 1/1/2000 and 3/28/2007. Data for analysis wereas extracted on 7/9/2009. The study accrued 50 patients, 45 of whom are eligible for analysis. One patient was excluded because they were treated at first presentation and four after central pathological review (Fig. 1). Of the 45 eligible patients, there were 27 males and 18 females. Forty had MB, and five a StPNET (3 pineal and 2 non-pineal).

The results were considered separately for MB and StPNET, as over the course of this study there was increasing evidence of clinical and biological differences between these tumour types[7,17] and to enable a clear comparison with other studies.

3.1. *Supratentorial PNET patients*

Of the five patients with StPNET, two relapsed only at the primary site, one patient at a solitary metastatic site and two with more than one site of metastatic relapse. Three had received both chemotherapy and radiotherapy (RT) for their original tumour and two RT alone. The median age at relapse was 12.9 years and the median time from original diagnosis to relapse was 4.2 years (Table 1). Four patients had surgery prior to cytoreductive therapy; two had a complete resection and two a partial resection. All five patients started cytoreductive therapy with one receiving HDCT followed by RT. All five patients died due to tumour progression with a median OS of 0.4 years (range 0.1–1.7) (Fig. 1) and median EFS of 0.2 years (range 0.1–1.6).

3.2. *Medulloblastoma patients*

Of the 40 MB patients, 25 were male and 15 were female. The median age at original diagnosis was 8.4 years and at relapse was 10.5 years. The median time between original diagnosis and relapse was 2.5 years (Table 1).

The majority of patients had received treatment for their initial tumour according to the SIOP PNET 3 protocol that compared 12 weeks of pre-irradiation chemotherapy (carboplatin, cyclophosphamide, etoposide and vincristine) with radiotherapy alone.[6] Thirty patients received chemotherapy and RT, nine patients received RT alone and one patient received chemotherapy alone (Table 1). Thirteen (32.5%) relapsed isolated at the primary site and ten (25%) with a solitary mass at a metastatic site. Seventeen (42.5%) relapses involved more than one site, 12 of which involved the primary site.

3.3. *Treatment and trial progress (Fig. 1)*

3.3.1. *Cytoreductive therapy*

Nineteen (47.5%) patients with MB underwent surgery, 18 prior to and one after cyclophosphamide. Fifteen patients had a complete resection, one a partial resection and three a biopsy only. All 40 patients received at least one course of cyclophosphamide, 39 at least two courses and 19 at least four courses.

In total, 18 MB patients left the study without progressing to the myeloablative phase (Table 2). Twenty-two patients continued to the myeloablative phase; 7 after 2 courses, 3 after 3 courses, 8 after 4 courses and 4 after 5 or more courses of cyclophosphamide.

Table 2 – Patients progress through the cytoreductive phase.

	Number of courses of cyclophosphamide					
	1	2	3	4	⩾5	Total
Reason for not progressing to HDCT						
Progression	1	5	0	0	0	6
Inadequate response	0	0	0	5	2	7
Toxicity	0	0	2	0	0	2
Clinicians decision	0	2	1	0	0	3
Total	1	7	3	5	2	18
Progressing to HDCT	0	7	3	8	4	22

Of the 33 MB patients who were eligible for response to cyclophosphamide, the best response was: 5 CR, 12 PR, 3 OR, 6 SD and 7 PD giving a CR + PR response rate of 51.5%. There was no statistically significant difference in best response to cyclophosphamide with respect to whether or not treatment at initial diagnosis included chemotherapy.

Cyclophosphamide was generally well tolerated. Serious adverse events (SAEs) included electrolyte imbalance resulting in seizures in three patients and septic shock in one patient. These events were reversible and there were no toxic deaths in this phase of treatment.

3.3.2. *Stem cell harvesting*

Stem cell harvesting was undertaken at varying points during the cytoreductive phase and was attempted in 35 patients and was deemed successful in 20 of these (57.1%). 13 patients had a failed stem cell harvest. A second attempt at mobilisation took place in some patients where an inadequate number of cells were harvested but in five cases a decision was made to carry out a bone marrow harvest instead (data unavailable in two patients).

3.3.3. *High dose chemotherapy*

At the start of HDCT, 12 patients were in CR and 10 were in near CR. Twenty-two patients received thiotepa, all but one at the recommended dose of 900 mg/m^2. Twelve patients also received carboplatin with 7 of these receiving a dose of 21 AUC and. five at varying lower doses because of a limited number of stem cells or with respect to poor count recovery after high dose thiotepa. The reasons why 10 patients did not receive carboplatin were; 4 poor marrow recovery, 2 unsuccessful harvest, 1 toxicity, 2 progressive disease and 1 due to parents' wishes.

Following high dose thiotepa, the median time to achieve a neutrophil count of $>1.0\times10^9$/L was 15 days (maximum 35 days). Recovery of platelets following thiotepa was slow with a median time to achieve an unsupported platelet count of $>50\times10^9$/L of 26 days, with four patients failing to reach this platelet level within 60 days post stem cell infusion.

Following high dose carboplatin, the median time to achieve a neutrophil count of $>1.0\times10^9$/L was 15 days (maximum 67 days) and to achieve a platelet count of $>50\times10^9$/L was 18 days, but with two patients failing to reach a platelet count of $>50\times10^9$/L within 60 days.

SAEs associated with thiotepa also included skin hyperpigmentation and haematuria in one patient each. SAEs associated with carboplatin included grade 3 ototoxicity in one patient. One patient developed fatal respiratory failure.

3.3.4. *Radiotherapy*

Radiotherapy was administered to eight patients, all of whom had been previously irradiated; three during or after cyclophosphamide and five after HDCT. The mean dosage of RT administered was 29.8 Gy, (Range 18.0–40.0 Gy). The median dose per fraction was 1.8 Gy (Range 1.5–2.0) and the median total number of fractions was 17.5 (Range 10–20). The mean duration of RT was 26.1 days (Range 13.0–56 days).

3.4. *Survival*

3.4.1. *Overall survival*

At the time of analysis, 37 patients with relapsed MB have died; 35 due to tumour progression, 1 from respiratory failure and 1 from post-treatment myelodysplasia (Fig. 1). The median follow up was 7.4 years (Range 2.8–8.2 years).

Three patients are still alive; two in continuing complete remission (2.8 and 8.2 years after relapse, respectively) and one following a further solitary relapse which occurred 6.6 years after their initial relapse. All three had been previously irradiated and had had an initial solitary relapse of

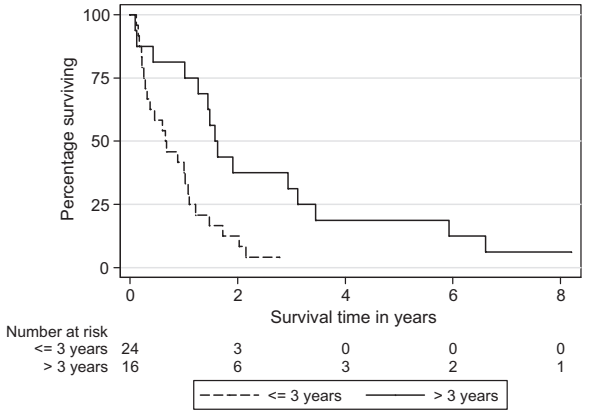

Fig. 2 – Event Free Survival for MB patients by time from original diagnosis to relapse.

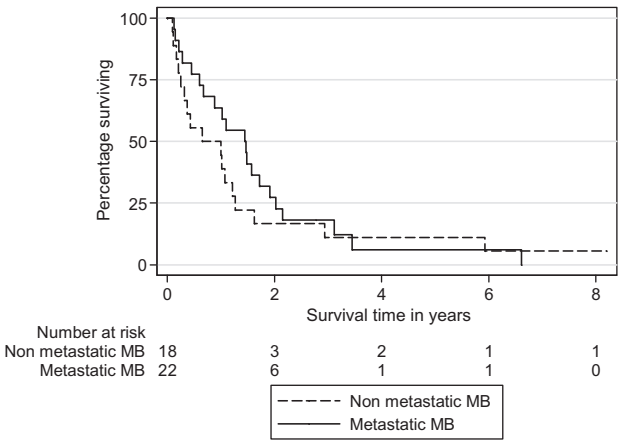

Fig. 3 – Event Free Survival for MB patients with and without metastases.

MB (one at primary site, two at metastatic sites) and received HDCT at relapse.

The median OS was 1.6 years (95% CI: 1.1–2.0 years). The yearly OS rates were 70.0% (95% CI: 53.3–81.7) at 1 year, 22% (95% CI: 10.7–35.8) at 3 years and 8.2% (95% CI: 2.2–19.7) at 5 years.

3.4.2. *Event free survival*

The median EFS was 1.0 years (95% CI: 0.6–1.5 years). The yearly EFS rates were 55% (95% CI: 38.5–68.8) at 1 year, 14.6% (95% CI: 5.7–27.3) at 3 years and 8.7% (95% CI: 2.4–20.4) at 5 years.

Cox proportional hazard modelling identified the time from original diagnosis to relapse as the only significant contributing baseline factor on EFS, whereby the patients whose relapse occurred more than 3 years after original diagnosis had a significantly better EFS than those whose relapse occurred within 3 years of their original diagnosis (Hazard ratio 0.340; 95% CI: 0.159–0.727, $p = 0.005$) (Fig. 2). This difference in EFS remained significant when the time between original diagnosis and relapse was split according to the median (Hazard ratio 0.391; 95% CI: 0.193–0.792, $p = 0.009$). No significant difference in EFS was observed for the other variables tested including the presence of metastases (Fig. 3) and chemotherapy for treatment at initial diagnosis.

3.4.3. *Survival of medulloblastoma patients from the time of high dose chemotherapy*

For the 22 MB patients who received HDCT the median OS-HDCT was 1.4 years (95% CI: 0.8–3.1 years), and the 3-year OS-HDCT was 31.5%. The median EFS-HDCT was 0.8 years (95% CI: 0.6–1.5 years) and the 3-year EFS-HDCT was 22.3%.

4. Discussion

This national study demonstrates the poor survival for patients treated for relapsed MB and StPNETs in the face of prior CSRT. When the study was designed in the late 1990s the strong similarities between MB and StPNETs were accepted, hence the design of the common study for these two patient groups. Over recent years there have, however, been clear reports of fundamental biological differences between MB and StPNETs.[17]

Commensurate with their relative rarity, only 5 patients with StPNET were entered into this study, all of whom died within a relatively short time. There are few previous papers of the use of high dose chemotherapy in recurrent StPNET. Broniscer et al. reported the New York experience of using a high dose chemotherapy regimen with thiotepa, carboplatin and etoposide in 17 patients with recurrent PNETs, including eight pineal tumours.[18] Whilst four of nine previously unirradiated patients were survivors at the time of reporting, all of whom received radiotherapy following relapse, there was only one survivor of eight patients that had received radiotherapy prior to relapse. The very poor outcome for previously irradiated patients with StPNET may reflect differences in biology, poor sensitivity to chemotherapy and possibly difficulties in applying second local treatment. Clearly new approaches are needed for relapsed StPNET.

Forty patients with relapsed MB were treated, all but one having had prior CSRT. For these 40 patients, the 5-year EFS was 8.7% and OS was 8.2% demonstrating a poor outcome for this study in which the treatment was applied with the intention of cure. Although there was a survival benefit seen for those patients who received HDCT this may well reflect continuing sensitivity to chemotherapy allowing patients to progress to HDCT. The benefit of HDCT did not translate to a useful long-term survival benefit for the strategy as a whole. There are only 3 of the 40 patients alive, one of whom has recently suffered a second relapse and is thus unlikely to be cured.

The outcome observed in this study is less good than that from the initial reports of HDCT-based approaches for relapsed PNETs. In 1997, the Duke University Medical Center described their experience on the use of HDCT that included 19 patients with MB and with 10 StPNETs.[12] Four patients with MB were disease free after HDCT at the time of reporting. Of note is that these four patients belonged to a group of six patients who relapsed solely in the posterior fossa and who had no evidence of disease at the time of HDCT. All twelve patients who relapsed in a disseminated fashion progressed following HDCT.

In 1998 Dunkel et al. reported a study that included 23 patients with recurrent MB treated with HDCT (carboplatin, thiotepa, and etoposide).[13] Three patients died of HDCT-related toxicities. Seven patients were reported as being event-free survivors at a median of 54 months post-stem cell rescue (3 year EFS 34%). More recently, Kadota et al. reported a Pediatric Oncology Group study for patients with recurrent medulloblastoma or germinoma that used a single myeloablative course of chemotherapy with cyclophosphamide plus melphalan supported by autologous hematopoietic stem cells.[19] Of 22 patients with medulloblastoma, there were six survivors at the time of reporting, four of who had received radiotherapy prior to relapse and two, chemotherapy only as initial therapy, one of who had radiotherapy following HDCT.

Reports of the use of HDCT in relapsed PNETs must be interpreted with caution with respect to the impact of HDCT-based strategies to the whole cohort of patients with relapsed PNETs. As in the United Kingdom, studies will gener-

ally not include patients in whom a decision has been made not to apply therapy with curative intent. Despite no competing similar CCLG trials, this study only recruited a minority of UK patients with relapsed PNETs and the outcome for patients not entered, many of whom would have received palliative therapy only, would be probably even less good than that reported for the present and other studies.

Studies that report from the time of HDCT may particularly over-estimate the benefit of HDCT-based strategies to the total population of relapsing patients. Particularly those patients who have disseminated and/or chemoresistant disease may not reach HDCT despite an initial treatment plan to include HDCT with curative intent. In our study only approximately 50% of patients received HDCT with the remainder being withdrawn from the study either through lack of response to induction chemotherapy or other reasons such as toxicity.

To our knowledge, this is the first paper describing a truly nationwide strategy of HDCT in the treatment of relapsed MB/StPNET. Another such study is the German, HIT REZ 97 study that, although not yet published, has been widely presented.[20] This study involved two treatment arms one in which the intention was not to apply potential curative therapy but instead to give experimental and/or palliative treatment. The second arm involved a strategy that included HDCT with a conditioning combination of thiotepa, carboplatin and etoposide. A total of 72 patients were entered into the 'curative arm' of which only 26 subsequently received HDCT. Results of HIT REZ 97 are similar to those of the present study in that in terms of long-term disease control a strategy involving HDCT proved to be largely ineffective. Indeed it was of note that in the HIT study of the six survivors in CR at the time of reporting, four had not received HDCT.

More recent reports from single institutions have shown disappointing results for the use of HDCT in relapsed PNET. In a study from St. Jude Children's Research Hospital, 14 previously irradiated patients with recurrent PNETs were treated with a HDCT-based strategy. There was only one survivor, a child with relapsed pinealoblastoma who received second RT.[21] Similarly, in a report from the Duke University Group there were no survivors of 12 previously-irradiated MB patients who received HDCT at relapse.[22] The Milan group reported their experience in treating relapsed MB in 17 patients, 16 of whom had received prior CSRT. 10 patients were treated with HDCT, three underwent complete resection of recurrence, and 10 underwent re-irradiation. There was only one survivor who had had a single spinal metastasis that was excised and irradiated.[23] Finally, Butturini recently reported the Los Angeles experience of children with recurrent PNETs referred for HDCT. Of 33 referred patients, 19 received HDCT. At the time of reporting, 4 of the 13 who had been previously irradiated were alive and disease free.[24]

In the current study the two event free surviving patients had a localised relapse. This is consistent with the study from Graham et al. referred to above and supports the assertion that patients who suffer a localised relapse, where second surgery and possibly second RT can be undertaken, may have a better chance of long term survival than those with a more diffuse pattern of relapsed disease.

An important component of this protocol was the recommendation that patients should if possible receive further RT following relapse. In recent years it has become clear that following an initial course of RT, over at least one-two years there is a degree of recovery of tolerance of the CNS to further RT.[25] This will enable low to moderate doses of RT to be delivered even after prior CSRT that may contribute to tumour response in combination with chemotherapy. In a recently published update of the Memorial Sloan–Kettering Cancer Centre experience of the use of HDCT for patients with previously irradiated recurrent MB, this group reported a trend towards better EFS in the 5 patients who received additional RT as part of their retrieval therapy ($p = 0.07$), in addition to those whose recurrent disease was demonstrated to be sensitive to re-induction chemotherapy ($p = 0.09$).[26] Saran et al. described the use of Hypofractionated stereotactic radiotherapy in the management of recurrent or residual medulloblastoma/PNET. Of the 14 patients, three were surviving event free at the time of reporting.[27] Whether a treatment strategy for patients with a localised relapse requires the inclusion of HDCT is uncertain.

The poor prognosis for previously-irradiated relapsed patients would suggest that phase I or II studies are appropriate. Such studies should include investigation of conventional chemotherapeutic agents but also biological therapies directed against pathways and receptors associated with MB/StPNET. There is also recent interest in so-called 'metronomic' chemotherapy particularly regimens including antiangiogenic agents.[28] Patients with disseminated relapse of PNET would be eligible for inclusion into studies of intraventricular/intrathecal chemotherapy with the aim of treating diffuse leptomeningeal disease using such regional chemotherapy.

In conclusion, further studies are required to determine variables that may predict survival following relapse of medulloblastoma, including the pattern of relapse, tumour chemoresponsiveness at the time of relapse, as well as the impact of various treatment modalities. Work is clearly required to investigate the biology of relapsed medulloblastoma, which will potentially allow refinement of upfront therapy but may also inform new biologically driven strategies for relapsed patients.

Conflict of interest statement

None declared.

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Treatment Centeres participating: the number of patients enrolled from each centere is given in parenthesis.

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