Guidance is being provided at this stage following publication of the CCLG Relapsed PNET Study (Study No. CNS 2000 01).

The relapsed PNET study was principally designed for those patients suffering a PNET relapse following prior radiotherapy. The situation with patients who relapse having not received prior radiotherapy generally requires a different treatment approach.

Disclaimer:
The CCLG does not sponsor nor indemnify the treatment detailed herein. These clinical guidelines are provided by the tumour working group or specialist committee to inform and for use at the sole discretion of treating clinicians who retain professional responsibility for their actions and treatment decisions. Treatment recommendations are based on current best practice and not what is necessarily proposed for any forthcoming clinical trial.
# Table of Contents:

1.0.  **BACKGROUND** ....................................................................................................................................................... 3  

1.1.  **Relapsed Medulloblastoma - un-irradiated patients** ................................................................................................. 3  
   1.1.1. **High Dose Chemotherapy and Focal Radiotherapy** ............................................................................................... 3  
   1.1.2. **Craniospinal Radiotherapy** ......................................................................................................................................... 3  

1.2.  **Relapsed Medulloblastoma—previous posterior fossa radiotherapy** ........................................................................... 3  

1.3.  **Relapsed Medulloblastoma/StPNET – previous craniospinal radiotherapy** ................................................................. 4  

1.4.  **Discussion** ................................................................................................................................................................... 4  

2.0  **International Consensus Meeting** ............................................................................................................................... 7  

3.0.  **Guidelines for the Treatment of Recurrent CNS PNETs in Children and Young People** ............................................. 8  

3.1.  **General comments:** ....................................................................................................................................................... 8  

3.2.  **Previously un-irradiated patients with relapsed Medulloblastoma** .............................................................................. 8  

3.3.  **Previously un-irradiated patients with relapsed Supratentorial PNET** .............................................................. 9  

3.4.  **Patients with relapsed Medulloblastoma—previous posterior fossa radiotherapy** ........................................................... 9  

3.5.  **Relapsed supratentorial PNET in previously irradiated patients (CSRT)** ................................................................. 10  

3.6.  **Relapsed Medulloblastoma in previously irradiated patients (CSRT)** .......................................................... 10  

3.7.  **Palliative and Experimental Therapy** .......................................................................................................................... 11  

3.8.  **Biological Studies** ............................................................................................................................................................ 11  

**References** ............................................................................................................................................................................. 13
1.0. Background

1.1. Relapsed Medulloblastoma - un-irradiated patients

1.1.1. High Dose Chemotherapy and Focal Radiotherapy

The French group have significant experience of treating previously un-irradiated patients with relapsed medulloblastoma, being part of the strategy for treating ‘standard risk’ infant patients with medulloblastoma i.e. those treated with the SFOP Baby Brain Protocol.

Results from this approach were published in 2007 [1]. The generally used regimen was conventional chemotherapy with a combination of carboplatin (800mg/m²) and etoposide (500mg/m²). This was followed by high dose chemotherapy (HDCT) with a combination of busulfan (600 mg/m²) and thiotepa (900 mg/m²) followed by autologous stem cell transplantation (ASCT). For patients relapsing in the posterior fossa, PF RT was delivered at doses from 50 Gy to 55 Gy on Day +70 after ASCT. The authors reported 27 patients who developed a local recurrence of an initially completely resected medulloblastoma. Twelve further patients had local residual disease after surgery and were enrolled into the salvage protocol at the time of local disease progression following conventional chemotherapy. Two toxic deaths (5%) from infections were reported. The 5-year OS rate after this salvage treatment for the 39 children who were treated was 68.8% (95% CI 53-81.2%).

Whilst this approach appears appropriate for previously un-irradiated patients with a relapse in the primary tumour site (posterior fossa), results of this therapy for patients with metastatic relapse are said to be disappointing.

Furthermore, there is the consideration of the severe long-term neuropsychological associated with radiotherapy to supratentorial sites. The use of a combination of HDCT with busulfan and thiotepa in conjunction with radiotherapy to sites of supratentorial relapse of medulloblastoma may be associated with very severe neuropsychological sequelae.

1.1.2. Craniospinal Radiotherapy

An alternative approach to the treatment of previously un-irradiated patients with relapsed medulloblastoma is the use of cranio-spinal radiotherapy (CSRT) with a boost to the PF and sites of relapse where appropriate. There is a paucity of data on the outcomes for patients receiving CSRT in addition to surgery and chemotherapy, although clearly this approach may cure a proportion of patients.

1.2. Relapsed Medulloblastoma– previous Posterior Fossa Radiotherapy

The treatment of patients that relapse following a treatment regimen that contains posterior fossa radiotherapy (as opposed to whole CNS radiotherapy) such as the CCLG Infant PNET Protocol is a difficult issue. There is a distinct lack of data with respect to the most appropriate management for these patients.

There is increasing experience based on the St Jude approach to relapsed ependymoma that second radiotherapy to the posterior fossa may be an appropriate treatment approach in
relapsed ependymoma [2]. The experience of such an approach in relapsed medulloblastoma cases is more limited as is the experience of whole CNS radiotherapy with a posterior fossa boost in patients that have received prior radiotherapy to the posterior fossa alone.

1.3. Relapsed Medulloblastoma/StPNET – previous Craniospinal Radiotherapy

The following is an abstract of the results of the CCLG study as published recently in the European Journal of Cancer.


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 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 (4g/m²) 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/m²) 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.

1.4. Discussion

Commensurate with their relative rarity, only 5 patients with StPNET were entered into the CCLG study, all of who died within a relatively short time. The very poor outcome for these patients may reflect differences in biology, poor sensitivity to chemotherapy and possibly
difficulties in applying second local treatment. Because of very small numbers, caution must be attached to the interpretation of the CCLG study with respect all patients with relapse StPNET but it would appear that new approaches are needed for relapsed StPNET.

In the CCLG study, all but one of the 40 patients with relapsed MB had undergone prior CSRT. For the MB patients, the 5-year EFS was 8.7% and OS was 8.2% demonstrating a poor outcome using a treatment with the intention of cure. There are only 3 survivors, one of whom has recently suffered a second relapse and is thus unlikely to be cured.

The outcome observed in the CCLG study is less good than that from the initially encouraging 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 10 with StPNETs [3]. 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 Dunkal et al. reported a study that included 23 patients with recurrent MB treated with HDCT [4]. 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%).

Reports of the use of HDCT in relapsed PNETs must be interpreted with caution with respect to the impact of this approach to the whole cohort of relapsed patients. As in the United Kingdom, studies will generally not include patients in whom a decision has been made not to apply therapy with curative intent. It is likely that 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 CCLG and other studies.

Another national study of relapsed PNETs is the German, HIT REZ 97 study. Results from which have not been published but have been widely presented [5]. 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. Seventy-two patients were entered into the second, ‘curative arm’ of which only 26 subsequently received HDCT. Results of HIT REZ 97 are similar to those of the CCLG 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.

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 the CCLG 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.

More recent reports from single institutions have also shown disappointing results.
In a St Jude’s study, of 14 previously irradiated patients with recurrent PNETs treated with a HDCT-based strategy, there was only one survivor, a child with relapsed pinealoblastoma who received second RT [6].

Similarly, in a recent report from Duke University there were no survivors of 12 previously irradiated MB patients who received HDCT at relapse [7].

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 [8].

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 previously irradiated patients were alive and disease-free [9].

In the CCLG study, the two event free surviving patients had a localised relapse. This is consistent with the study from Graham et al referred to above [3] 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. 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) [10].

The CCLG relapsed tumour protocol recommended that patients should, if possible receive further RT following relapse. In recent years it has become clear that following an initial course of RT, there is a degree of recovery of tolerance of the CNS to further RT over at least a one to two year recovery period [2]. 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. 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 the investigation of 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 [11].

Studies of intraventricular/intrathecal chemotherapy should also be considered with the aim of treating diffuse leptomeningeal relapse using such regional chemotherapy. There have indeed been several reports, principally from single institutions or from consortia of a limited number of institutions of the feasibility and tolerability of this approach. A number of drugs have been investigated in this respect including: maphosphamide, etoposide, thiopeta, and liposomally encapsulated cytarabine (Depocyt™) [12, 13]. It is of note, however, that in these studies, the majority of the patients have been treated with systemic chemotherapy and
or radiotherapy in conjunction with intraventricular/intrathecal chemotherapy and in this respect the pure Phase 2 data for this approach is limited. Hence there is considerable interest amongst both European and North American brain tumour groups in developing formal Phase 2 studies of the use of intraventricular/intra-lumbar chemotherapy in medulloblastoma/PNETs.

Palliative chemotherapy is frequently used; most commonly with oral etoposide. Early small studies (<10 patients) showed very encouraging response rates [14]. However, larger formal Phase II studies showed response rates of 15-20 % [15, 16], including the UKCCSG NAG 8 study which investigated the now standard regimen of 21 days of oral etoposide (50 mg/m²/day) followed by a 7 day rest [16].

Other commonly used palliative chemotherapy is with oral temozolomide. Although there are anecdotal reports of a positive effect of this drug in recurrent medulloblastoma, results from a formal COG Phase II study of oral temozolomide (180-200 mg/m²/day for 5 days) were disappointing, with a response rate of only 16 % (4/26) [17].

Finally, work is 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.

2.0 International Consensus Meeting

At an International Consensus Meeting in Milan (2008), a number of institutions and groups from Europe and North America presented their experience on use of a variety of HDCT based strategies for treating relapsed PNET. All the reports of the outcome of patients from the studies presented showed very poor survival for relapsed PNET.

The consensus from the meeting was that the prognosis for patients with relapsed PNET was extremely poor. However, a very small proportion of patients are curable. Although it is not entirely clear, the consensus was that a curative approach including HDCT may be appropriate for those patients in who second local therapy i.e. surgery or radiotherapy is applicable in respect of providing disease control. Such patients include, for example, a solitary localised relapse or possibly a solitary metastatic relapse.
3.0. **Guidelines for the Treatment of Recurrent CNS PNETs in Children and Young People**

3.1. **General comments:**

- It is extremely difficult to give categorical recommendations for the treatment of relapsed medulloblastoma and StPNET. This is due to the high number of variables that may be considered in formulating a treatment plan.

- These variables include the prior use of posterior fossa or craniospinal radiotherapy, other previous treatment, the age of the patient, the site/s and pattern of relapse and others.

- The possibility of achieving a surgical CR will be a major factor to consider in planning a treatment strategy.

- Management must thus be decided on an individual basis taking a number of factors into account and with full engagement of the patient’s carers and the patient where appropriate.

- In this respect, myself and other members of the CCL CNS sub group and Special Interest Group (particularly those involved with the former CCLG PNET group) would be willing to give management advice in individual cases.

- These guidelines give only broad principles with respect to management of patients with relapsed medulloblastoma / StPNET.

3.2. **Previously un-irradiated patients with relapsed Medulloblastoma**

- Complete resection of a localised area of relapse amenable to surgery should be undertaken.

- Craniospinal radiotherapy (CSRT) with a boost to the primary tumour and site of relapse (as in the treatment of newly diagnosed older children with this disease) should be considered.

- Clearly the risk of neuropsychological and other sequelae is age dependent and should be considered in formulating a treatment plan containing CRST, and the parents should be appropriately counselled in this respect.

- The use of conventional chemotherapy with this approach is unclear, and its indication should be determined on an individual basis.

- An alternative approach would be a management plan including HDCT and focal radiotherapy as in the SFOP Study of patients relapsing off the SFOP Baby Brain
3.3. **Previously un-irradiated patients with relapsed Supratentorial PNET**

- The management of these patients present a considerable challenge. Generally the prognosis for infants with StPNET is poor and there is limited evidence on the salvage of such patients who relapse.

- Nevertheless, as with the initial treatment of older children with supratentorial PNET and depending on individual patient circumstances, a treatment regimen containing CSRT or focal radiotherapy should be considered.

- As with medulloblastoma patients, the risk of age dependent neuropsychological and other sequelae should be considered in formulating a treatment plan containing CRST, and the parents should be appropriately counselled in this respect.

- If a curative approach is to be attempted, resection of the site of relapse should be undertaken.

- There is a lack of evidence as to the use of chemotherapy in this situation, although treating clinicians may wish to consider an approach that uses chemotherapy in a similar fashion to that used in relapse of medulloblastoma in previously un-irradiated patients.

- The use of HDCT in such patients should be treated with a degree of caution, particularly regimens containing busulphan and thiotepa, which appear to result in a high risk of severe, long term neuropsychological sequelae, particularly when given in combination with radiotherapy to supratentorial sites.

- For patients in whom a curative approach is not to be attempted – please see section below on relapsed medulloblastoma in previously irradiated patients and section on Palliative and Experimental Therapy.

3.4. **Patients with Relapsed Medulloblastoma – previous Posterior Fossa Radiotherapy**

As discussed above, there is a lack of data with respect to appropriate management for patients that relapse following a treatment regimen that contains posterior fossa radiotherapy (as opposed to whole CNS radiotherapy) such as the CCLG Infant PNET Protocol.

- If a curative approach is to be adopted, then surgical resection of the relapsed tumour should be undertaken.

- The application of a curative approach to chemotherapy requires careful consideration.

- Conventional chemotherapy (e.g. cisplatin, carboplatin/etoposide or moderate dose cyclophosphamide as in the CCLG Relapsed PNET study) should be considered.
although it should be borne in mind that the patient may have already been exposed to a number of chemotherapeutic agents.

- The use of HDCT should be considered, particularly if CSRT is not being given.
- As discussed above, the evidence base for the use of second focal radiotherapy as part of CSRT in this situation is very limited, although data from relapsed ependymoma does suggest that this approach is at least feasible.
- It is suggested that the use of second radiotherapy in this situation should be discussed with an appropriately experienced Radiation Oncologist.

### 3.5. Relapsed supratentorial PNET in previously irradiated patients (CSRT)

- The CCLG study showed a fatal outcome in all of the 5 patients with StPNET. There is however, insufficient evidence base to suggest that previously irradiated patients with relapsed supratentorial PNET are incurable.
- A number of individual factors must be considered in formulating an appropriate treatment plan, particularly whether an approach with curative intent will be attempted.
- In broad terms, patients who may be deemed suitable for a curative attempt include those patients who relapse in a localised fashion, where the site of relapse can be completely resected and possibly second radiotherapy to the site of relapse can be applied.
- There is a lack of a good evidence base for the use of conventional dose or high dose chemotherapy in this situation, although generally chemotherapy should be considered if a curative approach is to be attempted.
- Possible conventional chemotherapy options would include a combination of carboplatin and etoposide or moderate dose cyclophosphamide as used in the CCLG relapsed PNET study.

### 3.6. Relapsed medulloblastoma in previously irradiated patients (CSRT)

- There have been a number of studies as to the treatment of relapse in medulloblastoma patients who have previously undergone radiation to the craniospinal axis.
- As in the CCLG relapsed PNET study, the majority of studies, particularly those more recent, show a poor outcome for such patients, whatever treatments are given.
- Although not conclusively shown, those patients who appear to have a reasonable chance of cure following relapse, are those who relapse in a localised fashion, either at the primary tumour site (posterior fossa) or at a metastatic site. In these cases it would seem reasonable to consider a treatment approach based on cure.
If a curative approach is to be adopted, then surgical resection of the relapsed tumour should be undertaken followed by conventional chemotherapy (e.g. carboplatin/etoposide or moderate dose cyclophosphamide as in the CCLG Relapsed PNET study).

The use of second radiotherapy to the site/s of the relapse should be considered. A CCLG clinical oncologist experienced in this situation should be consulted.

The use of HDCT in this situation is contentious. The paediatric oncologists listed below would be willing to advise with respect to this issue.

The current evidence and consensus from the Milan meeting on HDCT would suggest that patients who suffer a diffuse relapse of medulloblastoma e.g. sugar coating of the brain or spinal cord or multiple metastatic sites of relapse have a very dismal outcome. In such patients an attempt of cure following relapse is probably not justifiable, although such an approach may be appropriate in individual patients.

3.7. Palliative and Experimental Therapy

If an attempt at curative therapy is not to be considered in patients with relapsed medulloblastoma/StPNET, then entry into an appropriate Phase 1 and Phase 2 study should be strongly considered.

The most commonly used palliative chemotherapy is with oral etoposide or oral temozolomide, although as discussed above, response rates reported in Phase II studies are somewhat disappointing.

So-called metronomic multi-agent chemotherapy regimens are gaining increased interest (11). A multinational metronomic chemotherapy is currently being developed.

In terms of a palliative approach to treatment the treating clinicians may wish to consider use of intraventricular/intralumbar chemotherapy. The UK group with most experience of this approach are the Nottingham team and Professor David Walker would be happy to give advice with regard to the use of intraventricular / intralumbar chemotherapy.

3.8. Biological Studies

Progress in the treatment of de novo and relapsed PNETs require a greater understanding of the tumour biology associated with this group of tumours. This is needed to understand the processes that govern response to treatment and to develop novel therapies. A current biological study of relapsed medulloblastoma/PNET is being led by Professor Steve Clifford in collaboration with a number of CCLG centres. If biological material is available from surgery from the time of initial presentation and at the time of relapse, then clinicians are encouraged to contact Professor Clifford to discuss participation in this work.

In view of the difficulties in devising a treatment strategy for relapsed PNET without taking each individual case scenario into consideration, myself and other members of the former
CCLG PNET Group would be happy to discuss any patient with relapsed medulloblastoma/StPNET.

In this respect clinicians are invited to contact the following for discussion of individual cases.

**Paediatric Oncologists**
Barry Pizer
Heidi Traunecker
Anthony Michalski
Sue Picton

**Clinical Oncologist**
Frank Saran
References


