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Review

What have we learnt from previous phase II trials to help in the management of childhood brain tumours?

P. Chastagner[a,*], E. Bouffet[b], J. Grill[c], C. Kalifa[c]

[a]*Department of Paediatric Oncology, Hôpital d'Enfants, CHU Nancy, 54500 Vandoeuvre, France*
[b]*Paediatric Oncology Unit, Children's Department, The Royal Marsden NHS trust, Downs Road, BS28BJ, Sutton, Surrey SM2 5PT, UK*
[c]*Department of Paediatric Oncology, Institut Gustave Roussy, Villejuif 94805, France*

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Abstract

Contrary to major advances in cure rates observed for almost all childhood cancers, progress in reducing brain tumour survival rates remains very limited. Although new drug development in oncology is founded on principles outlined in the organised methodology of phase I, II, and III trials, based on rigorous study design using standardised criteria, this approach has been applied very slowly in the field of neuro-oncology. There are multiple explanations for the paucity of well-conducted prospective clinical trials, such as the rarity and the heterogeneity of these tumours, and the reluctance of some investigators to enrol their patients in constraining trials. Data from the past two decades shows that several methodological problems preclude the drawing of any definite conclusions for the majority of drugs assessed. Among them, the necessity of a central neuropathological and neuroradiological review has been highlighted in, at least, two multicentric studies. Changes in histological diagnosis and grade have been reported in a proportion as high as 20%, and changes in response rate in 14% of the cases. This review of phase II trials for brain tumours reveals a wide array of sometimes arbitrary response definitions, that is if response is defined at all, and most series have enrolled small numbers of patients. We report on the different problems encountered in childhood brain tumours in these phase II trials, and their impact on phase III trials.

Keywords: Brain tumours; Chemotherapy; Phase II trials; Children

1. Introduction

Brain tumours constitute the largest group of childhood solid neoplasms [1]. However, progress made in the treatment of children with malignant brain tumours has not been in keeping with the major advances observed in treating childhood malignant tumours over the past two decades. The impact of adjuvant chemotherapy in improving survival has been essential in most childhood malignancies. However, the precise role of chemotherapy for brain tumours still remains ill defined at the beginning of the 21st century. Few drugs have been developed and most phase II trials have consisted of assessing the efficacy of some old drug combinations, and, more recently, in assessing the use of dose-intensity regimens. Problems remain with the development of treatment plans and the evaluation of results. The aim of this review was to critically analyse the problems raised by tumour location in the brain, scarcity of each tumour type using the results of most of the relevant phase II studies over the last 20 years, with specific emphasis on the methodology used.

2. The role of chemotherapy in the treatment of brain tumours

Despite recent advances in neuro-imaging, neuro-anaesthesia and neurosurgical techniques, the prognosis of patients with malignant brain tumours is dismal. Only approximately 80% of brain tumours are accessible to surgery resulting in the need for further therapy after subtotal resection and this has prompted investigators to assess the use of postoperative radiation and chemotherapy. Several studies showed a significant survival advantage for patients receiving postoperative radiation. However, neuro-intellectual and endocrine

* Corresponding author. Tel.: +33-3-8315-4632.
E-mail address: p.chastagner@chu-nancy.fr (P. Chastagner).

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sequels consecutive to radiotherapy are frequent and sometimes severe. A new indication for chemotherapy treatment has emerged in the last 10 years. Chemotherapy has assumed precedence over radiotherapy for postoperative treatment in young children with malignant brain tumours and in the patients with unresectable low grade gliomas, often allowing radiation to be deferred for several years. However, background data justifying the choice of each drug is often unavailable or not well established. Finally, it is not yet clear whether chemotherapy regimens with response rates as high as 72% [2] will prolong survival for all tumour types and in all age groups.

3. Special problems of brain tumours

3.1. Neuropathology

The objective grading of primary brain tumours in order to accurately reflect clinical behaviour remains one of the most difficult problems facing the neuropathologist. The need for a central review has recently been emphasised for gliomas. Out of 250 gliomas described and treated as malignant gliomas according to the Children's Cancer Group (CCG)-945 study, 46 (18.4%) were deemed on central neuropathology review to be low grade gliomas [3]. In a French pilot study, out of 51 gliomas considered as malignant, 12 (24%) were graded as low grade gliomas after central review (data not shown). The intratumoral histological heterogeneity of gliomas was described in a quantitative study investigating small and large biopsies punched from 50 unembedded supratentorial gliomas, with 48% differently typed and 82% differently graded samples among two observers who independently reviewed 1000 samples [4].

3.2. Neuro-imaging

While computed tomography (CT) and magnetic resonance imaging (MRI) scans both offer good sensitivity for central nervous system (CNS) tumours, their specificity is variable. On a given date, it is possible to slice through the widest portion of a multilobulated tumour, but then to miss the same section plane on a scan performed subsequently. The problem may become more serious if patients are serially imaged with different scanners, if a subsequent scanning procedure is performed in an entirely different imaging plane, or if CT and MRI scans are alternated. A study of CNS tumours correlating CT abnormalities with pathological findings showed that radiotherapy that is only targeted at the contrast enhancement area would miss the tumour in 75% of patients [5]. Furthermore, careful stereotactic biopsies in the zones of abnormal CT density or MRI signal that surround the areas of contrast enhancement on CT or MRI scans have often revealed infiltrating tumour cells.

4. Methodological problems

4.1. Phase II trials in childhood

The conventional objective of phase II trials is to determine whether a new agent appears to be active enough to justify further study. It is generally advisable to limit phase II studies to small numbers of patients in order to ensure testing of the maximum number of programmes that require evaluation. Sample sizes for phase II studies have traditionally been set at 25–40 patients, but that does not always make accurate estimation of the tumour response rate possible. For many of the clinical trials of brain tumours published so far, results are often difficult to interpret, and conclusions are often unclear on account of several methodological problems in the study design. These problems include prohibitive statistical constraints, enrolment of patients who are heterogeneous both for prognostic factors and histology, and lack of uniform response criteria. In many of the earliest phase II trials, the characteristics of the patient population studied, including factors such as histology and grade, extent of disease, age restrictions, available prior therapy, physiological and performance status are not reported. According to the high frequency of histology and grade changes and decrease in response rates after central review, neuropathology and neuroimaging central review would be mandatory to validate the results of phase II trials.

4.2. Limited number of patients

Most often the investigator may wish to restrict study entries to a homogeneous patients population, but biological variability precludes this possibility. Thus, numerous phase II or pilot studies reports concern unicentric trials that enrolled two to ten patients per histology group which precludes answering the study question.

4.3. Heterogeneity of tumour types

Brain tumours are a tumour group in which differences in histology, histological grade and biological behaviour are most important. While some tumours are known to be 'benign' (i.e. low grade gliomas and papilloma plexus choroid), and some are malignant (i.e. high grade gliomas and medulloblastomas), other tumours are difficult to classify as 'benign' or 'malignant', such as ependymomas. One additional weakness of phase II studies of paediatric brain tumours is the fact that most patients are included on the basis of their original diagnosis without considering a second biopsy during

disease progression. The risk of treating a different disease is small, but the likelihood of treating a tumour with a different biology does exist and has been illustrated in medulloblastoma studies [6].

4.4. Newly-diagnosed versus relapsed patients

Phase II studies should ideally be conducted with previously untreated patients to avoid the problems of acquired drug resistance and diminished tolerance associated with prior treatment. Because traditional phase II chemotherapy studies in children with recurrent CNS tumours have produced no active agents except for platinum analogues, an increasing number of new drug evaluations need to be performed for example, as phase II windows before initiating standard therapy in newly diagnosed patients. Thus, in the last 10 years, neoadjuvant (pre-irradiation) chemotherapy has been increasingly used postoperatively to allow agent activity to be assessed separate from the irradiation effect and also to facilitate drug access to the tumour before radiotherapy-induced vascular changes occurred. This strategy seems justifiable for most paediatric patients with CNS malignancies, but a clear concern is that delay in starting definitive therapy may compromise the patient's outcome if the agent used in the 'upfront window' is inactive. This especially concerns patients in medulloblastoma trials have tested both the role of a 'sandwich chemotherapy' that delayed irradiation and the decrease of the prophylactic craniospinal radiation dose [7]. The role of time from diagnosis to relapse or disease progression (e.g. less then 3 months to up to 106 months in a phase II study) and the relationship between prior chemotherapy and the subsequent response to new drugs should also be analysed. In a review of patients with recurrent medulloblastoma, Bouffet and colleagues have shown that the delay between diagnosis and relapse significantly influenced the response to salvage chemotherapy, with a 60% response rate for late relapses versus 30% for the early ones [8].

4.5. Response assessments

4.5.1. Diagnostic procedure

Cranial CT without and with contrast enhancement was first made available in the 1970s, which means that the response rates of previous reports are questionable. Furthermore, CT may not be sufficient for brainstem gliomas, infiltrating gliomas, or any posterior fossa tumour in the vicinity of the brainstem. MRI of the brain in three planes, including T1- and T2-weighted image reconstruction without and T1-weighted image reconstruction with gadolinium contrast enhancement has been used since the 1980s. The dramatic breakthrough in imaging techniques has contributed to specific and reproducible definitions of response. Standardised criteria are currently in use in most groups or institutions, as these criteria have been agreed upon at an international level [9]. Although calculations of tumour volume would be ideal for precise base-line evaluation and follow-up, the method does not appear to be either practical or widely applicable and nearly all brain tumour study groups prefer size assessment to be the product of the longest two perpendicular diameters.

For 'upfront window' strategy, the first investigation must be conducted within the first 48 h (or a maximum of 72 h) and include contrast enhancement. Unfortunately, many reports do not clearly define the timing of the first postoperative investigation.

All tumours capable of seeding metastases throughout cerebrospinal fluid (CSF) pathways, and irrespective of the presence or absence of neurological symptoms, should be additionally investigated by (i) CSF cytology following a concentration process. The source of CSF should be the lumbar theca since it has recently been shown that cytological detection of leptomeningeal disease is more appropriate with lumbar rather than shunt CSF [10]; (ii) spinal MRI with and without gadolinium enhancement.

A complete response is defined as no evidence of disease at the primary tumour site or of metastases, and a CSF free from tumour cells in patients with initial evidence of disease. CSF-negativity has to be confirmed at least twice at consecutive samplings if initially positive. A partial response requires a reduction in size of all unequivocal residual tumour manifestations by more than 50% with no progression and no appearance of new tumour lesions at any site. Stable disease is defined as a less than 50% reduction of residual tumour size, with no progression and no occurrence of new tumour lesions at any site. Progression and/or relapse are defined as a more than 25% increase of tumour size or the emergence of new lesions or CSF-positivity.

4.5.2. Relevance of responses

While responses are assessed in almost all the series after two courses of chemotherapy, this period of time is clearly too short to evaluate response rate in slowly growing tumours such as low grade gliomas. In this case, the best observed response, whatever the number of courses, is frequently taken into account. Despite frequently observed poor objective response rates some patients may become clinically and radiologically stable for periods exceeding one year after the experimental treatment has been given. Thus, the relevance of a stable disease is sometimes difficult to interpret, especially in cases of low grade glioma in which stable disease can last for many years, allowing deferral and avoidance of radiotherapy.

Since glucocorticoids have an impact upon cerebral oedema and contrast enhancement as assessed by CT scan and MRI, the doses of steroids at the outset of a

therapy cycle and at the time of reassessment should be compared [11]. However, such information is seldom reported.

5. Selected phase II trials

We screened the MEDLINE database (1966 to October 2000) in search of phase II trials and pilot studies evaluating the efficacy of chemotherapy in children with brain tumours. We also reviewed the literature referenced in the phase II trials and review articles retrieved. The results of these searches were combined to yield a common series of data based on the literature. Only phase II trials with CT and/or MRI were evaluated. Only complete and partial responses were taken into account, while mixed responses were considered as no response. According to Gehan's method [12] concerning the sample size, only trials that included at least 9 patients with the same histological type, were screened. This is the minimum number of patients required at the preliminary stage of evaluation, to authorise rejection of a treatment if activity is demonstrated in less than 30% of cases (with a β probability of 5% of wrongly rejecting the treatment). This means that if no response is observed in the 9 patients included, the trial could be prematurely discontinued and the drug could be declared ineffective (activity $<30\%$). This 30% response rate (RR) was chosen instead of the classic 20% RR, because 28 of the 69 trials reviewed (41%) would have been rejected on the grounds that chemotherapy was administered at conventional doses. As high dose chemotherapy trials are rare, all 69 trials were earmarked for selection.

6. Conventional dose

Among the 69 studies reviewed that evaluated the efficacy of one or several drugs administered at conventional doses, we selected 41 studies published from 1982 to the year 2000, that reported on at least 9 consecutively treated patients presenting the same histological type (30% expected efficacy). Thirty-eight of these studies concerned at least 11 consecutively treated patients (30% expected efficacy) and 25, at least 14 patients, (20% expected efficacy). The results of these phase II studies are presented in Table 1 [13–52]. Although we have mentioned results reported in each series of less that 9 patients, only the results concerning at least 9 patients treated consecutively in each series were taken into account for the analysis of cumulative response rates according to each tumour type.

It is noteworthy that in this selection of phase II trials, among the 82 results that reported on more than 8 patients treated for a similar tumour type, these results concerned from 9 to 11 patients in 15 (18%) cases, from 12 to 14 patients in 33 (40%) cases, and more than 14 patients in 34 cases (42%). Furthermore, only 12 (29%) out of the 41 selected studies were exclusively focused on newly-diagnosed patients. Twenty-seven (66%) of these studies were conducted in a single institution. A central review of histological types and neuro-imaging was only mentioned in four and six trials, respectively.

Results corresponding to 20% expected efficacy (at least 14 patients) were reported in only 15 series for medulloblastomas, 10 series for high-grade gliomas and brain stem gliomas, six for low- grade gliomas, and four series for ependymomas.

This review emphasises the need to analyse response rates separately according to newly-diagnosed (up-front window) or relapsing patients. Indeed, a comparison of response rates between newly-diagnosed versus relapsing patients can be done in three groups according to histology using the data found in the literature: medulloblastomas 62 versus 32% ($P<0.001$, Fisher's Exact test); low grade gliomas 30 versus 16% ($P< 0.05$); high grade gliomas 27 versus 11% ($P<0.05$).

Comparison between trials with or without a central review of radiological findings and/or pathology was not possible because of the rarity of studies with centrally reviewed data.

7. Dose intensity

Several clinical trials involving a variety of solid tumours have shown a correlation between dose intensity (i.e. the amount of drug delivered per unit of time) and both response rate and treatment results. The use of peripheral blood stem cell reduces the time of both neutropenia and platelet recovery following chemotherapy administration, allowing a dose intensification that cannot be achieved with growth factor support alone. Several trials have been published, but most often the number of patients is less than 10 in each tumour type. In the series of Jakacki and colleagues [53], 10 children with recurrence of newly-diagnosed brain tumours were treated with four sequential courses of high dose chemotherapy including VP16 (3.6 g/m^2), carboplatin, 1.95 g/m^2, cyclophosphamide (5–7 g/m^2) or carmustine (600 mg/m^2) and thiotepa (300–900 mg/m^2). After therapy was completed, three partial responses were observed, of whom only one was alive at time of publication (44 months). The benefit of this approach on survival has yet to be demonstrated.

8. High-dose chemotherapy

Using high-dose chemotherapy can improve the delivery of drugs that do not cross the blood–brain

Table 1
Conventional dose chemotherapy phase II trials

		Glioma low grade	Glioma high grade	Medulloblastoma	PNET	Ependymoma	Pineoblastoma	Brainstem	MGCT
Carboplatin		*n* of responders/total *n* of pts							
Allen and colleagues [13] 700 mg/m^2	R		0/6	6/14	0/2		1/1	1/8	10/10
Gaynon and colleagues [14] 560 mg/m^2	R		0/15	6/19		2/14		1/19	
Friedman and colleagues [15] 560 mg/m^2	R	1/13	2/19	2/26		2/17		1/23	
Aquino and colleagues [16] 560 mg/m^2	N	4/12							
Mastrangello and colleagues [17] 1.2 g/m^2	N			7/13			1/2		
Allen and colleagues [18] 600 mg/m^2	N								10/11
Iproplatin									
Friedman and colleagues [15] 270 mg/m^2	R	1/15	0/12	1/14		0/7		0/14	
Cisplatin									
Sexauer and colleagues [19] 120 mg/m^2	R	0/4	0/10	4/10		3/15		0/5	
Walker and colleagues [20] 120 mg/m^2	R	0/1	0/1	10/14	0/4	1/3		0/7	
Bertolone and colleagues [21] 120 mg/m^2	R	0/1	1/9	3/12	0/1	4/8	1/3		
Khan and colleagues [22] R 120 mg/m^2	R		2/16			3/6			0/1
Ifosfamide									
Chastagner and colleagues [23] 6 g/m^2	R		0/4	3/20	1/2	1/8			
Heideman and colleagues [24] 9 g/m^2	R	1/6	1/16	1/16		1/12	1/3	0/10	0/1
Cyclophosphamide									
Abrahamsen and colleagues [25] 2–5 g/m^2	R, N		0/11	4/4		1/1		0/4	
Moghrabi and colleagues [26] 2–5 g/m^2	R			9/10					
Lachance and colleagues [27] 2–5 g/m^2	R		2/13	8/9			1/2		1/1
Kadota and colleagues [28] 1.2 g/m^2	N	1/14							
Melphalan									
Friedman and colleagues [29] 45 mg/m^2	R		3/12						
PCNU									
Ragab and colleagues [30] 100 mg/m^2	R			0/5		0/10			
Allen and colleagues [31] 70–125 mg/m^2	R		3/12	0/5	0/3	1/1	0/2	3/17	
Thiotepa									
Heideman and colleagues [32] 65 mg/m^2	R	3/13	0/18	3/13		0/4		0/14	
Diaziquone									
Ettinger and colleagues [33] 45 mg/m^2	R		1/13	0/7	1/8	1/12	0/2	0/12	
Idarubicin									
Arndt and colleagues [34] 15 mg/m^2	R		3/19	1/20		0/13		0/13	

(continued)

Table 1 (*continued*)

		Glioma low grade	Glioma high grade	Medulloblastoma	PNET	Ependymoma	Pineoblastoma	Brainstem	MGCT
Topotecan									
Blaney and colleagues [35] 5.5–7.5 mg/m^2	N, R	1/2	0/9	0/8		0/4		0/14	
Kadota and colleagues [36] 3–3.75 mg/m^2	R	0/11	0/13	0/12		0/17		0/19	
Etoposide									
Chamberlain and colleagues [37] 50 mg/m^2×21 d	R	5/14		6/7					
Methotrexate									
Mulne and colleagues [38] 45 mg/m^2/w	R	2/10	1/19	0/18		1/7		0/12	
CDDP + VCR									
Loeffler and colleagues [39] 100 mg/m^2 + 1.5 mg/m^2×4	N			10/12					
CDDP + CPM									
Kretshmar and colleagues [40] 100 mg/m^2 + 3 g/m^2	N							3/32	
CDDP + VP16									
Kovnar and colleagues [41] 90 mg/m^2 + 300 mg/m^2	N			10/11			2/2		
CPM + VCR									
Duffner and colleagues [42] 65 mg/kg + 1.3 mg/kg	N						1/11		
Friedman and colleagues [43] 2 g/m^2 + 2 mg/m^2	R			8/12					
CBDCA + VCR									
Packer and colleagues [44] 175 mg/m^2/w×4 + 1.5 mg/m^2/w×10	N	23/60							
CBDCA + VP16									
Gentet and colleagues [2] 0.8 g/m^2 + 500 mg/m^2	R			18/25					
Heideman and colleagues [45] 0.7 g/m^2 + 200 mg/m^2	N			8/16					0/2
VP16 + VCR									
Pons and colleagues [46] 150 mg/m^2 + 1.5 mg/m^2×7	N, R	1/20							
CBDCA + Tamoxifen									
Walter and colleagues [47] 40 mg/m^2 + AUC 6.5 mg/ml×mn	N	2/13							
CDDP + CCNU + VCR									
Packer and colleagues [48]	N			6/10					
MOPP									
Van Eys and colleagues [49]	R		4/13	4/19		1/4		3/16	
VCR + CDDP + CPM									
Mosijczuk and colleagues [50]	R			13/30					
8 in 1									
Chastagner and colleagues [51]	R, N		5/15	13/17	3/13	1/6	1/1		
Pendergrass and colleagues [52]	R, N		10/27	18/30	6/6	2/7			

R, relapse; N, newly-diagnosed; MGCT, malignant germ cell tumour; PNET, primitive neuroectodermic tumour; pts, patients; N, number; w, week; d, day; CDDP, cisplatin; VCR, vincristine; CPM, cyclophosphamide; VP16, etoposide; CBDCA, carboplatin; AUC, area under concentration curve.

barrier at conventional dosages and will achieve high concentrations within the tumour. The role of autografting is likely to be most effective in consolidation therapy for children with chemoresponsive tumours and minimal residual disease. Indications for chemotherapy dose intensification have yet to be established. It

remains to be seen whether this method will improve event-free survival (EFS). Alkylating agents appear the most appropriate class of drugs to be used in a high-dose setting. High dose chemotherapy phase II studies in children who have relapsed are difficult to conduct because of specific risk factors in this often previously heavily-treated population; therefore publications are scarce and generally put together patients with measurable disease and patients who receive high-dose chemotherapy as a consolidation. The results of phase II trials evaluating one or several drugs are reported in Table 2 [54–64]. It appears that more promising results are observed in medulloblastomas and malignant germ cell tumours, which are known to be sensitive to conventional chemotherapy dosages. Acute toxicity resulting from high dose chemotherapy regimens is comparable to that observed when treating tumours located elsewhere. It is, however, important to consider both the specific risk factors of high-dose chemotherapy in brain tumours and the potential late effects. Prior craniospinal irradiation, cerebral bleeding, swallowing disturbances are risk factors of engraftment delay, neurological complications, lungs infections and meningitis.

The overall mortality associated with the toxicity of high dose chemotherapy in childhood brain tumours varies from 5 to 20% in different series. It appears to be slightly higher than the rates observed for other cancers.

9. Concomitant chemotherapy and radiotherapy

In vivo preclinical experiments currently point out to the fact that cytotoxic agents may potentiate the therapeutic effect of radiotherapy by up to 2-fold without increasing the toxicity [65]. In an attempt to improve the effectiveness of external beam irradiation, topotecan was administered prior to each daily radiation treatment in a phase I study by the CCG in children with intrinsic pontine glioma [66]. The dose-limiting toxicity was haematological; no neurological severe adverse effects were observed. A phase II study was conducted on adults, using topotecan as a 21-day infusion with accelerated 3-dimensional conformal radiation therapy for patients with previously untreated glioblastoma [67]. An arrest of tumour progression was observed in 15 out of 20 patients with a median time to progression of 6

Table 2
High dose chemotherapy phase II trials[a]

		HG glioma	Medulloblastoma	Ependymoma	Brainstem	MGCT
Etoposide + thiotepa						
Finlay and colleagues [54]	R	0/14				
150 mg/m^2 + 900 mg/m^2						
Bouffet and colleagues [55]	N	2/8				
1500 mg/m^2 + 900 mg/m^2						
CPM + thiotepa						
Heideman and colleagues [56]	N	3/11				
6 g/m^2 + 900 mg/m^2						
Etoposide + thiotepa ± carboplatin						
Mason and colleagues [57]	R			0/7		
Modak and colleagues [58]	R					3/9
750–1500mg/m^2 + 900 mg/m^2 ± 1500 mg/m^2						
Melphalan (100 mg/m^2)						
Kalifa and colleagues [60]	N		13/16			
Busulfan + thiotepa						
Kalifa and colleagues [60]	R		21/28			
Grill and colleagues [61]	R			0/15		
Bouffet and colleagues [62]	N				0/25	
600 mg/m^2 + 900 mg/m^2						
Thiotepa + etoposide						
Baranzelli and colleagues [63]	R					3/6
900 mg/m^2 + 1500 mg/m^2						
Etoposide + thiotepa ± carmustine ± carboplatin						
Dunkel and colleagues [64]						
750–1500 mg/m^2 + 900 mg/m^2					0/16	
± 600 mg/m^2 ± 1500 mg/m^2	R, N					

MGCT, malignant germ cell tumour; HG, high grade; R, relapse; N, newly diagnosed; CPM, cyclophosphamide.
[a] Results are number of responders/total number of patients.

months. One patient achieved an objective partial remission. Paclitaxel also demonstrated a radiopotentiation in preclinical studies and is now beginning to be used in clinical practice [68].

10. Localised administration of chemotherapy

No significant paediatric study experimenting with intraarterial chemotherapy and transient blood–brain barrier disruption has been reported. Such treatments do not appear to be safe or more effective in adult patients. Direct instillation of chemotherapy into the CSF or into the tumour mass through catheters has been occasionally attempted, with no significant results. There are no published phase II trials concerning intrathecal administration of chemotherapy. Chemotherapy-impregnated polymer implantation after debulking surgery is under study in adult patients.

11. Contribution of phase II to phase III trials

11.1. High-grade gliomas

The overall calculated response rate for children high-grade gliomas corresponding to our selected review of phase II trials is 12.8% (31/242), in accordance with the centrally reviewed response rate of 18% reported in the CCG 945 study [69]. This response rate differs significantly between newly-diagnosed (27%) and relapsed patients (11%) ($P<0.05$), but not according to whether platinum analogues are included in regimens (16% with analogues or 10% without) ($P=0.1$). Interestingly, the best cumulative response rate (36%) obtained in our review, represented by the '8 in 1' regimen, differs significantly from the response rate observed in the CCG 945 study (18%) using the same regimen, in which neuroimagings were centrally reviewed.

Currently, there is no evidence that the responses observed could be translated into an EFS increase [70]. The Children's Cancer Study Group (CCSG) has completed a trial that randomised children with high-grade cerebral gliomas to treatment either with local radiation therapy and concomitant vincristine, followed by eight cycles of CCNU and vincristine chemotherapy (the response rate of which for each agent has not been established in phase II trials), or with two cycles of eight-drugs-in-1-day chemotherapy followed by local radiation therapy and then eight more cycles of this regimen [69]. The overall 30% disease-free survival rate at 3 years between these groups is not statistically different. Interestingly, the cumulative response rate of 35% observed in phase II trials has not been reproduced in this phase III trial probably due to a neuroimaging central review that decreased the response rates [69]. New phase II studies with combination of drugs providing higher response rates are needed prior to conducting large-size phase III trials. Recently, temozolomide has been suggested as a valuable agent for high-grade gliomas in adults. The results of European and North American studies in paediatric high-grade gliomas are pending.

11.2. Low-grade gliomas

Management strategies for low-grade gliomas include surgery when possible, observation, irradiation, chemotherapy and a combination of these modalities. However, the late effects of radiation therapy for progressive inoperable tumours, above all for hypothalamus/optic pathway gliomas stimulated the use of chemotherapy with a view to delaying radiotherapy. Phase II trials produced objective response rates (calculated cumulative response rate = 24%, 30% in cases of newly-diagnosed patients versus 16% in cases of relapse, $P<0.05$), but also a high rate of stable diseases that allowed the need for radiation therapy in children under 5 years to be delayed or obviated. Dactinomycin and vincristine were extensively used in the 1980s in children with progressive diencephalic low-grade gliomas resulting in disease stabilisation in the majority of patients [71]. However, the objective response rates were less than 25% and evidence for the activity of each of these agents is lacking. Carboplatin alone was shown to result in partial responses for patients with newly-diagnosed low-grade gliomas and in stable diseases for patients with recurrent disease [15,16]. The largest phase II study for this disease has investigated the vincristine–carboplatin combination [44]. Due to the high response rate observed with this regimen, some North American and European groups have elected to use this combination as the standard arm of their current protocols. This experiment is unique in paediatric neuro-oncology and suggests that successful phase II studies can provide excellent framework for phase III trials. However, the success of this combination has its drawbacks and limits the possibility of comparing a treatment known to be highly effective with an experimental one. At least, it seems reasonable to consider, for these slowly growing tumours, that the effectiveness is represented by the best responses, whatever the number of courses, rather than the responses observed at two or four courses.

11.3. Brainstem gliomas

Despite the use of different chemotherapy modalities in several well-conducted phase II trials, the prognosis of malignant diffuse brainstem gliomas remains dismal. There are no encouraging survival data from the cooperative groups on the benefits of chemotherapy with a response rate lower than 10% (5% calculated cumula-

tive response rate in our selected phase II trials), whatever the drug used, and a median overall survival of 10 months. High-dose chemotherapy regimens followed by autologous bone marrow transplantation offered no benefit for 25 patients receiving busulphan and thiotepa [62] with a median progression-free survival (PFS) of 10 months and for 16 patients treated with thiotepa, vepeside and carboplatin with a median survival of 11.4 months from the time of high dose chemotherapy [64]. Brainstem glioma patients represent, according to their grim prognosis and their relative homogenicity, an ideal population to assess novel strategies in phase II trials.

11.4. Medulloblastomas

The cumulative response rate of 37% is, following germ cell tumours, the highest response rate obtained in brain tumours. However, it differs significantly according to whether platinum analogues are included in regimens (48%) or not (27%) and between newly-diagnosed (62%) and relapsed ($P<0.001$) patients (32%). The second most active agent seems to be cyclophosphamide which was tested in less than ten patients in each reported study. It is remarkable that none of the agents (CCNU and vincristine) which have demonstrated a survival advantage for metastatic patients in the CCG and the International Society of Paediatric Oncology (SIOP) 1 trials (CCG, SIOP 1 trials) have ever been properly tested in phase II trials. The results of a regional trial headquartered at Children's Hospital in Philadelphia using vincristine during radiation therapy and a combination of CCNU, cisplatin, and vincristine after radiation therapy showed a 5-year disease-free survival rate higher than 85% in children with high-risk disease [72]. These results have recently been confirmed in the CCG 9892 study, using the same protocol, but with a reduced dose of craniospinal radiation (23.4 Gy) in children with non-disseminated medulloblastoma [73]. A study by SIOP, on patients treated with preirradiation chemotherapy (procarbazine, methotrexate and vincristine, none of them correctly tested in phase II trials) for non-disseminated medulloblastoma brought no evidence that the addition of chemotherapy was beneficial [7]. Furthermore, the worst 5-year EFS ($41\% \pm 8\%$) was observed in children who received preradiation chemotherapy followed by reduced-dose craniospinal irradiation. These last two results emphasise the need for a rigorous clinical background concerning agents incorporated in large phase III trials which might be selected on indisputable phase II trials such as cisplatin.

11.5. Ependymomas

The calculated cumulative response rate according to our selection of phase II trials is 10%, which is in keeping with the lack of efficacy of adjuvant chemotherapy used in the only randomised trial CCG-942 study [74]. In this study, the 10-year response rate is 40% for patients receiving CCNU and vincristine and 35% in patients not receiving chemotherapy. However, no pilot study tested the role of adjuvant chemotherapy with the most active agents, which seem to be platinum analogues with a disappointing 20% response rate in the only informative study which reported on 15 patients. However, no information has yet been reported on the response rate to chemotherapy in an upfront window setting. Several cooperative studies are currently under way, which might provide useful information. Despite interesting preclinical data, high-dose chemotherapy has given disappointing results in ependymomas. The role of chemotherapy is still limited in this disease, but phase II data are required before reaching the conclusion that ependymoma is definitely a chemoresistant disease.

11.6. Children less than 3 years of age

The primary reason for placing young children on a chemotherapy regimen is to delay or avoid radiotherapy. While no phase II trials have been specifically conducted in this age group, several studies have been performed using different multidrug regimens. In most of them (nitrogen mustard, oncovin, prednisone, procarbazine MOPP), eight drugs-in-1-day, dactinomycin–vincristine), evidence for the activity of each of these agents is poor or even non-existent. However, this approach has afforded a 2-year radiotherapy delay in 75% of the cases in low-grade gliomas [44] and a 3-year-progression free survival of 40% in average-risk medulloblastomas [59]. In the latter study, for patients who relapsed, the possibility of curative treatment with high-dose busulphan-thiotepa followed by irradiation limited to the involved areas (i.e. posterior fossa for local relapse and craniospinal axis for metastatic disease) was assessed. At 5 years, the event-free survival of the 21 patients who suffered an isolated local relapse and who were treated according to this salvage treatment is 80%, but only two of the nine metastatic relapsed patients are alive.

The role of prolonged (up to 18 months in the case of low-grade gliomas) low-dose chemotherapy, or more intensive chemotherapy (in the case of medulloblastoma and PNET) is under study. The duration of regimens including agents such as etoposide and carboplatin would be randomised to decrease the risk of occurrence of secondary acute leukaemia.

12. How to improve the contributions of phase II trials

12.1. Cooperative groups

Due to the heterogeneity of brain tumours, the number of patients assessable by histology is limited. Experience gained over the past 20 years has provided

evidence that phase II methodology should take histological diagnosis into account to assess the response rate to a drug. This can be achieved either in disease-orientated phase II studies or in stratified studies recruiting different histological groups up to a statistically predefined number. This suggests that monocentric studies have become unsuitable and participation in cooperative investigational studies will be critical to improve the quality of information and reducing the duration of investigation for each agent or combination tested. North American groups have recently developed such a strategy and the phase II study of temozolomide with six stratifications (medulloblastomas, ependymomas, high-grade gliomas, low-grade glioma, brainstem gliomas and other brain tumours) is an excellent example.

12.2. In vivo *preclinical background*

Fundamental investigation of primary brain tumours has partly depended on the use of animal models. The most desirable model is one that is both histologically representative of the tumour and biologically comparable to its human equivalent, which is obviously hard to obtain. New chemotherapeutic drugs would first be tested *in vivo* in animal tumour systems to identify antitumour activity on the basis of response rates and increased life span in treated animals compared with a control group. Laboratory results suggesting an activity against paediatric brain tumours have been successful in supporting the development of clinical trials with melphalan and busulphan in medulloblastomas and PNET [75–80]. Preclinical studies of irinotecan have supported its clinical evaluation in medulloblastoma, and suggest that its activity is schedule-dependent [78]. Current phase II studies are assessing both the response rate and optimal schedule of this agent. Such an approach could avoid treating many children in phase II trials with a drug known to be inoperative in xenografted human brain tumours. New strategies such as concomitant radio- and chemotherapy aiming at obtaining a radiopotentiation and an increase in therapeutic index, while decreasing radiotherapy doses can also be tested in animal models. Radiopotentiation has already been demonstrated *in vivo*, using topotecan on two xenografted human glioblastomas [79].

13. Future prospects

New drugs are currently under development or investigation, which aim at targeting a specific mechanism in tumour cells. For example, O-6 Alkylguanine-DNA-alkyltransferase is a DNA repair protein which may be involved in the resistance of medulloblastoma and gliomas to nitrosourea. Pretreatment using drugs such as O-6 Benzylguanine can deplete the intracellular content of O-6 Alkylguanine-DNA-alkyltransferase and may therefore increase the activity of nitrosourea [80]. Other agents are emerging, such as tyrosine kinase inhibitors or angiogenesis inhibitors. These new drugs are likely to play a major role in the future medical management of childhood brain tumours. They will be tested in phase II studies and the quality of these investigations is essential to accurately determine the potential benefit in each specific subgroup of tumours. The parallel development of biological investigations is a prerequisite for phase II studies conducted with these novel therapies. We are at the beginning of a new era and the success of investigations of novel therapies is highly dependent on the accuracy of the biological background both for testing a new drug and ensuring the quality of the clinical study. We are at the end of an era, and a phase II study in paediatric brain tumours should no longer be an investigation conducted without clearly-delineated statistical endpoints, a clear definition of the group of tumours assessed, and central radiology and central pathology reviewing.

14. Conclusions

Although guidelines for conducting clinical trials for brain tumours are firmly established, these requirements need to be emphasised because the rarity of some brain tumours give rise to composite reports that are a summary of patients treated at different times. Only very few drugs have been investigated with adequate neuroimaging techniques in a significant number of patients. Most of the previous phase III trials were conducted with multi-drug chemotherapy regimens containing drugs that were not tested as single agents and when they were, adequate neuro-imaging was not available. We have learnt some fundamental principles from phase II trials: (1) the histological type is of major importance for chemosensitivity and its corollary, good response rates in germinomas and medulloblastomas, while only rare responses are observed for high grade and brain stem gliomas; (2) better response rates are achieved in newly-diagnosed rather than in relapsed patients, and this encourages up-front window studies; (3) platinum-derivatives and alkylating agents offer the best response rates; (4) responses could be observed after several months in low-grade gliomas, whereas the need for radiation therapy may be deferred or obviated when the disease is stable; (5) encouraging results are being obtained with dose intensity and prolonged low-dose strategies which warrant assessment in large cooperative groups.

References

1. Pollack IF. Brain tumours in children. *N Engl J Med* 1994, **331**, 1500–1507.

2. Gentet JC, Doz F, Bouffet E, *et al*. Carboplatine and VP16 in medulloblastoma: a phase II study of the French Society of Pediatric Oncology. *Med Pediatr Oncol* 1994, **23**, 422–427.
3. Norruddin L, Yates A, Becker L, Burger PC, Davis R. Outcome for children with centrally reviewed lowgrade gliomas, treated with chemeotherapy with or without irradiation: the malignant glioma study CCG-945. *J Pediatr Hematol Oncol* 1999, **21**, 319 (abstr).
4. Paulus W, Peiffer J. Intratumoral histologic heterogeneity of gliomas. A quantitative study. *Cancer* 1989, **64**, 442–447.
5. Halperin EG, Bentel G, Heinz ER, Burger PC. Radiation therapy treatment planning in supratentorial glioblastoma multiforme: an analysis based on post mortem topographic anatomy with CT correlations. *Int J Radiat Oncol Biol Phys* 1989, **17**, 1347–1350.
6. Tishler DM, Weinberg KI, Sender LS, Nolta JA, Raffel C. Multidrug resistance gene expression in pediatric primitive neuroectodermal tumors of the central nervous system. *J Neurosurg* 1992, **76**, 507–512.
7. Bailey CC, Gnekow A, Wellek S, *et al*. Prospective randomised trial of chemotherapy given before radiotherapy in childhood medulloblastoma. International Society of Paediatric Oncology and the german Society of Paediatric Oncology. *Med Pediatr Oncol* 1995, **25**, 166–178.
8. Bouffet E, Doz F, Demaille MC, *et al*. Improving survival in recurrent medulloblastoma: earlier detection, better treatment or still in impasse? *Br J Cancer* 1998, **77**, 1321–1326.
9. Gnekow AK. Recommendations of the Brain Tumor Subcommittee for the reporting of trials. SIOP Brain Tumor Subcommittee. International Society of Pediatric Oncology. *Med Pediatr Oncol* 1995, **24**, 104–108.
10. Fouladi M, Gajjar A, Boyett JM, *et al*. Comparison of lumbar and shunt cerebrospinal fluid specimens for cytologic detection of leptomenigeal disease in pediatric patients with brain tumors. *J Clin Oncol* 1999, **17**, 1825–1828.
11. Watling CJ, Lee DH, Macdonald DR, Cairncross JG. Corticosteroid-induced magnetic resonance imaging changes in patients with recurrent malignant glioma. *J Clin Oncol* 1994, **12**, 1886–1889.
12. Gehan EA. The determination of the number of patients required in a preliminary and a follow-up trial of a new chemotherapeutic agent. *J Chron Dis* 1961, **13**, 346–353.
13. Allen JC, Walker RW, Luks E, Jennings M, Barfoot S, Tan C. Carboplatin and recurrent childhood brain tumors. *J Clin Oncol* 1987, **5**, 459–463.
14. Gaynon PS, Ettinger LJ, Baum ES, Siegel SE, Krailo MD, Hammond GD. Carboplatin in childhood brain tumors: a Children's Cancer Study Group phase II trial. *Cancer* 1990, **66**, 2465–2469.
15. Friedman HS, Krischer JP, Burger PC. Treatment of children with progressive of recurrent brain tumors with carboplatin or iproplatin: a Pediatric Oncology Group randomized phase II study. *J Clin Oncol* 1992, **10**, 249–256.
16. Aquino VM, Fort DW, Kamen BA, *et al*. Carboplatin for the treatment of children with newly diagnosed optic chiasm gliomas: a phase II study. *J Neurooncol* 1999, **41**, 255–259.
17. Mastrangello R, Larosella A, Riccardi R, *et al*. Carboplatin in childhood medulloblastoma/PNET: feasability of an in vivo sensitivity test in an 'up front' study. *Med Pediatr Oncol* 1995, **24**, 188–196.
18. Allen JC, DaRasso RC, Donahue B, Nirenberg A. A phase II preirradiation carboplatin in newly diagnosed germinoma of the central nervous system. *Cancer* 1994, **74**, 940–944.
19. Sexauer CL, Kahn A, Burger PC, *et al*. Cisplatin in recurrent pediatric brain tumors. *Cancer* 1985, **56**, 1497–1501.
20. Walker RW, Allen JC. Cisplatin in the treatment of recurrent childhood primary brain tumors. *J Clin Oncol* 1988, **6**, 62–66.
21. Bertolone SJ, Baum ES, Krivit W, Hammond GD. A phase II study of cisplatin therapy in recurrent childhood brain tumors. A report from the Childrens Cancer Study Group. *J Neurooncol* 1989, **7**, 5–11.
22. Khan AB, D'Souza BJ, Wharam MD, *et al*. Cisplatin therapy in recurrent childhood brain tumors. *Cancer Treat Rep* 1982, **12**, 2013–2020.
23. Chastagner P, Sommelet-Olive D, Kalifa C, *et al*. Phase II study of ifosfamide in childhood brain tumors: a report by the French Society Of Pediatric oncology. *Med Pediatr Oncol* 1993, **21**, 49–53.
24. Heideman RL, Douglass EC, Langston JA, *et al*. A phase II of every other day high-dose ifosfamide in pediatric brain tumors: a pediatric oncology group study. *J Neurooncol* 1995, **25**, 77–84.
25. Abrahamsen TG, Lange BJ, Packer RJ, *et al*. A phase I and II trial of dose-intensified cyclophosphamide and GM-CSF in pediatric malignant tumors. *J Pediatr Hematol Oncol* 1995, **17**, 134–139.
26. Moghrabi A, Fuchs H, Brown M, *et al*. Cyclophosphamide in combination with sargramostim for treatment of recurrent medulloblastoma. *Med Pediatr Oncol* 1995, **25**, 190–196.
27. Lachance DH, Oette D, Schold SC, *et al*. Dose escalation of cyclophosphamide with sargramostim in the treatment of central nervous system neoplasms. *Med Pediatr Oncol* 1995, **24**, 241–247.
28. Kadota RP, Kun LE, Langston JW, *et al*. Cyclophosphamide for the treatment of progressive low grade astrocytoma: a pediatric oncology group phase II study. *J Pediatr Hematol Oncol* 1999, **21**, 198–202.
29. Friedman HS, Schold SC, Mahaley S, *et al*. Phase II treatment of medulloblastoma and pineoblastome with melphalan: Clinical therapy based on experimental models of human medulloblastoma. *J Clin Oncol* 1989, **7**, 904–911.
30. Ragab AH, Burger PC, Badnitsky S, Krischer J, Van Eys J. PCNU in the treatment of recurrent medulloblastoma and ependymoma A POG study. *J Neurooncol* 1986, **3**, 341–342.
31. Allen JC, Hancock C, Walker R, Tan C. PCNU and recurrent childhood brain tumors. *J Neurooncol* 1987, **5**, 241–244.
32. Heideman RL, Packer RJ, Reaman GH, *et al*. A phase II evaluation of thiotepa in pediatric central nervous system malignancies. *Cancer* 1993, **72**, 271–275.
33. Ettinger LJ, Ru N, Krailo M, Ruccione KS, Krivit W, Hammond GD. A phase II study of diaziquone in children with recurrent or progressive primary brain tumors: a report from the childrens cancer study group. *J Clin Oncol* 1990, **9**, 69–76.
34. Arndt CAS, Krailo MD, Steinherz L, Scheithauer B, Liu-Mares W, Reaman GH. A phase II clinical trial of idarubicin administered to children with relapsed brain tumors. *Cancer* 1998, **83**, 813–816.
35. Blaney SM, Phillips PC, Packer RJ, *et al*. Phase II evaluation of topotecan for peditric cental nervous system tumors. *Cancer* 1996, **78**, 527–531.
36. Kadota RP, Stewart CF, Horn M, *et al*. Topotecan for the treatment of recurrent or progressive central nervous system tumors—a pediatric oncology group phase II study. *J Neurooncol* 1999, **43**, 43–47.
37. Chamberlain MC, Grafe MR. Recurrent chiasmatic-hypothalamic glioma treated with oral etoposide. *J Clin Oncol* 1995, **13**, 2072–2076.
38. Mulne AF, Ducore JM, Elterman RD, *et al*. Oral methotrexate for recurrent brain tumors in children: a Pediatric Oncology Group study. *J Pediatr Hematol Oncol* 2000, **22**, 41–44.
39. Loeffler JF, Kretshmar CS, Sallan SE, *et al*. Pre-irradiation chemotherapy for infants and poor prognosis children with medulloblastoma. *Int J Radiat Oncol Biol Phys* 1988, **15**, 177–181.
40. Kretshmar CS, Tarbell NJ, Barnes PD, Krisher JP, Burger PC, Kun LE. Pre-irradiation chemotherapy and hyperfractionated radiation therapy 66 Gy for children with brain stem tumors. *Cancer* 1993, **72**, 1404–1413.

41. Kovnar EH, Kellie SJ, Horowitz ME, *et al*. Preirradiation cisplatin and etoposide in the treatment of high-risk medulloblastoma and other malignant embryonal tumors of the central nervous system: a phase II study. *J Clin Oncol* 1990, **8**, 330–336.
42. Duffner PK, Cohen ME, Sanford RA, *et al*. Lack of efficacy of postoperative chemotherapy and delayed radiation in very young children with pineoblastoma. *Med Pediatr Oncol* 1995, **25**, 38–44.
43. Friedman HS, Mahaley MS, Schold SC, *et al*. Efficacy of vincristine and cyclophosphamide in the therapy of recurrent medulloblastoma. *Neurosurgery* 1986, **3**, 335–340.
44. Packer RJ, Ater J, Allen JC, *et al*. Carboplatin and vincristine chemotherapy for children with newly-diagnosed progressive low grade gliomas. *J Neurosurg* 1997, **86**, 747–754.
45. Heideman RL, Kovnar EH, Kellie SJ, *et al*. Preirradiation chemotherapy with carboplatin and etoposide in newly diagnosed embryonal pediatric CNS tumors. *J Clin Oncol* 1995, **13**, 2247–2254.
46. Pons M, de Los A, Finlay JL, Walker RW, Puccetti D, Packer RJ, McElwain M. Chemotherapy with vincristine and etoposide in children with low-grade gliomas. *J Neurooncol* 1992, **14**, 151–158.
47. Walter AW, Gajjar A, Reardon DA, *et al*. Tamoxifen and carboplatin for children with low-grade gliomas: a pilot study at St. Jude Children's Research Hospital. *J Pediatr Hematol Oncol* 2000, **22**, 247–251.
48. Packer RJ, Siegel KR, Sutton LN, *et al*. Efficacy of adjuvant chemotherapy for patients with poor-risk medulloblastoma: a preliminary report. *Ann Neurol* 1988, **24**, 503–508.
49. Van Eys J, Baram TZ, Cangir A, Bruner JM, Martinez-Prieto J. Salvage chemotherapy for recurrent primary brain tumors in children. *J Pediatr* 1988, **113**, 601–606.
50. Mosijzuck AD, Nigro MA, Thomas PRM, *et al*. Preradiation chemotherapy in advanced medulloblastoma. A pediatric oncology group study. *Cancer* 1993, **72**, 2755–2762.
51. Chastagner P, Olive D, Philip T, *et al*. Efficacité du protocole '8 drogues en un jour' dans les tumeurs cérébrales de l'enfant. *Arch Fr Pediatr* 1988, **45**, 249–254.
52. Pendergrass TW, Milstein JM, Geyer JR, *et al*. Eight drugs in one day chemotherapy for brain tumors: experience in 107 children and rationale for preradiation chemotherapy. *J Clin Oncol* 1987, **5**, 121–131.
53. Jakacki RI, Jamison C, Heifetz SA, Caldemeyer K, Hanna M, Sender L. Feasability of sequential high dose chemotherapy and peripheral blood stem cell support for pediatric central nervous system malignancies. *Med Pediatr Oncol* 1997, **29**, 553–559.
54. Finlay JL, Goldman S, Wong MC. Pilot study of high-dose thiotepa and etoposide with autologous bone marrow rescue in children and young adults with recurrent CNS tumors. The Children's Cancer Group. *J Clin Oncol* 1996, **14**, 2495–2503.
55. Bouffet E, Mottolese C, Jouvet A. Etoposide and thiotepa followed by ABMT in children and young adults with high grade gliomas. *Eur J Cancer* 1997, **33**, 91–95.
56. Heideman RL, Douglass EC, Krance RA. High-dose chemotherapy and autologous bone marrow rescue followed by interstitial and external-beam radiotherapy in newly-diagnosed pediatric malignant gliomas. *J Clin Oncol* 1993, **11**, 1458–1465.
57. Mason WP, Goldman S, Yates AJ, *et al*. Survival following intensive chemotherapy with bone marrow reconstitution for children with recurrent ependymoma. *J Neurooncol* 1998, **37**, 135–143.
58. Modak S, Gardner S, Dunkel I, *et al*. High dose chemotherapy with autologous stem cell rescue in patients with recurrent CNS germ cell tumors. Presented at Childhood Cancer into the 21st Century: an International Conference to mark the 20th Anniversary of the UKCCSG, 23–25 April 1997, Birmingham, UK.
59. Kalifa C, Valteau D, Pizzer B, Vassal G, Grill J, Hartmann O. High-dose chemotherapy in childhood brain tumours. *Child's Nerv Syst* 1999, **15**, 498–505.
60. Valteau-Couanet D, Grill J, Schoepfer C, *et al*. High-dose chemotherapy in childhood brain tumours. *Med Pediatr Oncol* 1999, **33**, 201.
61. Grill J, Kalifa C, Doz F, *et al*. A high-dose busulfan thiotepa combination followed by autologous bone marrow transplantation in childhood recurrent ependymoma. *Pediatr Neurosurg* 1996, **25**, 7–12.
62. Bouffet E, Raquin MA, Doz F, *et al*. Radiotherapy followed by high dose busulfan and thiotepa: a prospective assessment of high dose chemotherapy in children with diffuse pontine gliomas. *Cancer* 2000, **88**, 685–692.
63. Baranzelli MC, Pichon F, Patte C, *et al*. High-dose etoposide and thiotepa for recurrent intracranial germ cell tumours. *Med Pediatr Oncol* 1998, **31**, 256 P2.
64. Dunkel IJ, Garvin JH, Goldman S, *et al*. High-dose chemotherapy with autologous bone marrow rescue for children with diffuse pontine brain stem tumors. *J Neurooncol* 1998, **37**, 67–73.
65. Chastagner P, Taghian A, Marchal C, Hoffstetter S, Merlin JL, Duprez A. Effect of combined radiotherapy and topotecan on four human tumor xenografts. In Mornex F, Mazeron ?, Droz JP, Marty M, eds. *Concomitant Chemoradiation: Current Status and Future*. Paris, Helsevier, 2000, 39–55.
66. Nedle MN, Mehlta M, Krailo M, Geyer JR, Reaman GH. Phase I study of topotecan as a radiosensitizer prior to daily involved field irradiation in children with intrinsic pontine glioma. A Children's Cancer Group Study. *Proc Am Soc Clin Oncol* 1999, **18**, 2152.
67. Grabenbauer GG, Buchfelder M, Schrell U, Fahlbusch R, Sauer R, Staab HJ. Topotecan (TPT) as a 21-day infusion (CIV) with accelerated 3-D conformal radiation therapy (RT) for patients with previously untreated glioblastoma. *Proc Am Soc Clin Oncol* 1999, **18**, 142a.
68. Gannett DE, Hill D, Hamilton AJ, Stea B. Paclitaxel as a radiosensitizer combined with fractionated stereotactic chemotherapy in the treatment of recurrent medulloblastoma. *Am J Clin Oncol* 1997, **20**, 233–236.
69. Finlay JL, Geyer JR, Turski PA, *et al*. Pre-irradiation chemotherapy in children with high-grade astrocytoma: tumor response to two cycles of the '8-drugs-in-1-day' regimen. A Childrens Cancer Group study, CCG-945. *J Neurooncol* 1994, **21**, 255–A65.
70. Chastagner P, Kalifa C, Mechinaud-Lacroix F. Pilot study of combined BCNU, cisplatin and VP16 for the treatment of newly-diagnosed high grade glioma in children. *Med Pediatr Oncol* 1995, **25**, 258.
71. Packer RJ, Sutton LN, Bilaniuk LT, *et al*. Treatment of chiasmatic/hypothalamic gliomas of childhood with chemotherapy: an update. *Ann Neurol* 1988, **23**, 79–85.
72. Packer RJ, Sutton LN, Elterman R, *et al*. Outcome for children with medulloblastomas treated with radiation and cisplatin, CCNU, and vincristine chemotherapy. *J Neurosurg* 1994, **81**, 690–698.
73. Packer RJ, Goldwein J, Nicholson HS, *et al*. Treatment of children with medulloblastoma withreduced-dose craniospinal radiation therapy and adjuvant chemotherapy: a Children's Cancer Group study. *J Clin Oncol* 1999, **17**, 2127–2136.
74. Evans AE, Anderson JR, Lefkowitz-Boudreaux IB, Finlay JL. Adjuvant chemotherapy of childhood posterior fossa ependymoma: cranio-spinal irradiation with or without adjuvant CCNU, vincristine and prednisone: a Childrens Cancer Group study. *Med Pediatr Oncol* 1996, **27**, 8–14.
75. Friedman HS, Schold SC, Bigner DD. Chemotherapy of subcutaneous and intracranial human medulloblastoma xenografts in athymic nude mice. *Cancer Res* 1988, **46**, 224–228.
76. Boland I, Vassal G, Morizet J, *et al*. Busulphan is active against neuroblastoma and medulloblastoma xenografts in athymic mice at clinically achievable plasma drug concentrations. *Br J Cancer* 1999, **79**, 787–792.

77. White L, Sterling-Levis K, Fisher R, Tobias V. Response of brain tumors to chemotherapy, evaluated in a clinically relevant xenograft model. *J Neurooncol* 1995, **25**, 39–47.
78. Vassal G, Pondarre C, Boland I, *et al*. Preclinical development of camptothecin derivatives and clinical trials in pediatric oncology. *Biochimie* 1998, **80**, 271–280.
79. Chastagner P, Merlin JL, Marchal C, *et al*. Role of dose and schedule of topotecan and radiotherapy in xenografted human glioblastoma multiforme (GBM). *Proc Am Assoc Cancer Res* 1999, **40**, 588.
80. Friedman HS, Dolan ME, Moschel RC, *et al*. Enhancement of nitrosourea activity in medulloblastoma and glioblastoma multiforme. *J Natl Cancer Inst* 1992, **84**, 1926–1931.