

A lower-dose, lower-toxicity cisplatin–etoposide regimen for childhood progressive low-grade glioma

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Received: 23 November 2009 / Accepted: 25 January 2010
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Abstract After successfully using cisplatin (30 mg/m²/day) and etoposide (150 mg/m²/day) in ten three-day courses for progressive low-grade gliomas, a subsequent protocol reduced the daily doses of cisplatin (to 25 mg) and etoposide (to 100 mg), with the objective of achieving the same response and three-year PFS rates with lower neurotoxicity and myelotoxicity. We treated 37 patients (median age 6 years); 23 had optochiasmatic tumours and nine were metastatic cases. Diagnoses were clinical in 13 cases and histological in 24, and comprised: pilocytic astrocytoma (17), ganglioglioma (3), pilomyxoid astrocytoma (2), and fibrillary astrocytoma (2). Treatment was prompted by radiological evidence of progression and/or clinical deterioration a median 18 months after the first diagnosis. After initial MRI staging, neurological and clinical

examinations were performed before each chemotherapy cycle, with MRI after the first three courses and every three months thereafter. After a median 48 months, a volume reduction was appreciable in 24 cases (65%) and response was maximum 12 months after starting treatment. The three-year EFS and OS rates were 65 and 97%, respectively. Clinical, neurological, or functional improvements were seen in 26/37 cases. No children had a WBC nadir below 2,000/mm³. Audiological toxicity caused damage in 4/34 cases. The previous protocol had achieved volume reductions in 70% of cases, causing audiological damage (data updated) in 11/31 ($P = 0.023$), with three-year PFS and OS rates of 70 and 100%, respectively. Lower doses of cisplatin/etoposide are still effective in progressive low-grade glioma, with less acute and persistent morbidity.

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Keywords Childhood low-grade glioma · Chemotherapy for brain tumours · Ototoxicity · Tumour response · Symptom amelioration

Introduction

For 20 years chemotherapy has been used in children with inoperable progressive low-grade glioma (LGG) or large symptomatic tumours with a view to delaying radiotherapy, especially in younger patients with large tumours or diencephalic syndrome [1–3]. Many schedules have been described, mainly including carboplatin, vincristine, etoposide, nitroso ureas, cisplatin, actinomycin-D, cyclophosphamide, procarbazine, 6-thioguanine [1–4], and, more recently, vinblastine [5] and imatinib [6].

Having obtained satisfactory results with a regimen of cisplatin (30 mg/m²/day) and etoposide (150 mg/m²/day) in ten three-day courses [7], we launched a new institutional protocol with lower daily doses of both drugs. The design of the protocol was a *non-inferiority* study whose primary objectives were to maintain the same rates of response and three-year progression-free survival with lower neurotoxicity (based on audiograms or other age-tailored acoustic tests) and myelotoxicity. We report the results obtained in this new series of patients.

Patients and methods

Eligibility

All children under 18 years of age with radiological or symptomatic evidence of inoperable progressive low-grade glioma were eligible for treatment irrespective of their age or the tumour's origin and dissemination. Histology of low-grade glioma classified according to WHO was required except in cases of optochiasmatic tumours in NF1, or when surgery was considered dangerous and the clinical and radiological signs clearly pointed to a low-grade glioma. Previous chemotherapy treatment, apart from steroids, was not allowed.

Chemotherapy schedule

Cisplatin was given as a 2-h infusion at 25 mg/m²/day on days 1–3, followed by etoposide infused in 30 min at a dose of 100 mg/m²/day, again on days 1–3; the drugs were preceded and followed by a 2-h hydration. In children under one year old or weighing less than 10 kg, the doses were adjusted to their weight. The interval between cycles lasted four weeks for the first four cycles, five weeks for the

next three cycles, and six weeks for the last three, aiming to cover a period of approximately 10–11 months with 10 cycles in all, giving total doses of 750 mg/m² cisplatin and 3,000 mg/m² etoposide.

The protocol was approved by our institution's ethical and scientific committee, and formal consent was obtained from the patients' parents.

The therapy was always administered on an outpatient basis, except for the first course, which was given during a hospital stay if the patient was fitted with a central venous catheter.

Evaluation of response

Initial staging included magnetic resonance imaging (MRI) of the brain and spine in all patients. When multiple sites of disease emerged at MRI, cytology of the spinal fluid was performed. Follow-up during the treatment was based on neurological and clinical assessments before each chemotherapy cycle, plus MRI of the tumour site after the first three cycles, then every three months thereafter for the first year. Tumour volume was calculated from T2-weighted and enhanced T1-weighted MRI scans. Thorough neurological and clinical assessments were repeated every four months for the first three years after completing the treatment, then every six months up to the fifth year, then yearly. In the event of neurofunctional impairment, specific tests (visual field and acuity, visual-evoked potentials (VEP)) were prescribed at the same time as the radiological evaluation. Visual field assessments and visual-evoked potentials were obtained at six-month intervals, wherever feasible, with audiometric evaluation (vocal, behavioural audiometry, auditory brainstem responses or acoustic oto-emission testing, depending on the patient's age) during the first five years after the glioma was diagnosed. Endocrinological tests were also performed routinely and repeated if a patient showed clinical signs of any endocrinological changes. Radiological response was assessed according to International Society of Paediatric Oncology criteria and protocols, i.e. complete response was defined as no evidence of disease, partial response meant a more than 50% radiographically evident size reduction, and stable disease meant no signs of tumour progression. We also considered objective response, i.e. a 25–50% size reduction in unequivocal residual tumour (the product of the two largest perpendicular diameters) [8]. All MRI were reviewed by one of the authors (PP). All patients were still being actively followed up at the time of this report.

Toxicity evaluation

Audiototoxicity was monitored in all patients during the treatment using full-tone audiometry, acoustic potentials,

or acoustic oto-emission testing (depending on their age) and then as explained in the previous paragraph after the treatment ended. When full-tone audiometry was feasible, the rules for stopping the treatment because of toxicity were those commonly adopted for medulloblastoma treated with a regimen containing platinum; audiometry was performed before every treatment course in children with NF1 and after two or three courses in the others. In the case of a loss of perception beyond 40 dB at 4,000–8,000 Hz, the cisplatin was to be replaced with carboplatin at a dose of 400 mg/m² on the first day of the next course. In the absence of standard criteria for stopping chemotherapy in the light of other ototoxicity tests, all other patients were assessed case by case.

Statistical analysis

Life tables were obtained for all patients. Overall and event-free survival rates were calculated according to the Kaplan–Meier method [9]. Class comparisons were drawn using the log-rank test.

Results

Patient accrual lasted from November 2001 to December 2007; 22 males and 15 females were enrolled; the median age was 72 months (range 6–198 months) at the time of their treatment. Median follow-up at the time of writing of this report was 48 months.

The main demographic features of this series are given in Table 1.

When chemotherapy was begun, all the children were suffering from radiologically evident progressive disease and/or worsening symptoms; the median time from the tumour's diagnosis to the start of the treatment was 18 months (range 1 month–10 years). Seven children had neurofibromatosis type 1 (NF1) and one other child had an unknown neurocutaneous syndrome with cervico-medullary glioma, spinal and subcutaneous lipomas and mental retardation; all the other patients had sporadic tumours.

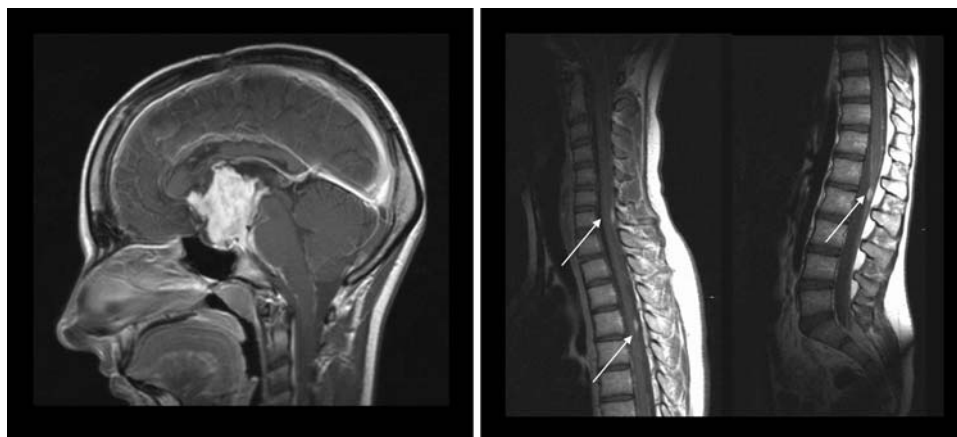
The tumour originated in the optochiasmatic–diencephalic region in 23 cases: 22 children had a Dodge 3 extension and one had a Dodge 1 tumour. Five children had tumours in the cervico–medullary region, five gliomas were mesencephalo–thalamic, two were multinodular with no clear primary site, one glioma occupied the whole spine, and one was temporal. In all, nine children presented with nodular metastases and one had a diagnosis of NF1. All patients with metastases had secondary nodules evident first in the brain, and subsequently confirmed by MRI in the spine, except for one girl who had sciatic

Table 1 Main demographic features of the series

Patient	Sex	Age	Histology	NF1	Site	Meta
1	m	7.06		y	Opto-chiasmatic	n
2	m	7.00		y	Multi-nodular	y
3	m	10.08		y	Opto-chiasmatic	n
4	f	3.09	Fibrillary	n	Mesencephalo-thalamic	n
5	f	1.06		y	Opto-chiasmatic	n
6	f	9.03	Pilocytic	n	Cervico-medullary	n
7	m	6.07		n	Opto-chiasmatic	n
8	m	0.07		n	Opto-chiasmatic	n
9	m	7.00	Fibrillary	n	Opto-chiasmatic	n
10	f	13.00		n	Opto-chiasmatic	n
11	m	6.00		n	Opto-chiasmatic	n
12	m	0.06		n	Opto-chiasmatic	y
13	f	14.00	Pilocytic	n	Temporal	n
14	f	0.05	Pilomixoid	n	Opto-chiasmatic	y
15	f	12.00	Ganglioglioma	n	Mesencephalo-thalamic	n
16	m	2.00		n	Cervico-medullary	n
17	m	0.06		n	Opto-chiasmatic	y
18	m	6.00		y	Opto-chiasmatic	n
19	f	11.00	Pilocytic	n	Mesencephalo-thalamic	n
20	m	2.00	Ganglioglioma	n	Multi-nodular	y
21	m	6.00	Pilocytic	y	Opto-chiasmatic	n
22	m	7.00	Pilocytic	n	Opto-chiasmatic	n
23	m	1.10	Pilocytic	n	Opto-chiasmatic	n
24	f	6.00	Pilocytic	n	Opto-chiasmatic	y
25	m	12.06	Pilocytic	n	Opto-chiasmatic	n
26	m	7.10	Ganglioglioma	n	Cervico-medullary	n
27	f	6.05	Pilocytic	n	Opto-chiasmatic	n
28	m	6.00	Pilocytic	n	Opto-chiasmatic	y
29	m	13.02	Pilocytic	n	Mesencephalo-thalamic	n
30	m	2.06	Pilocytic	n	Mesencephalo-thalamic	y
31	m	7.00	Pilocytic	n	Cervico-medullary	n
32	f	6.00	Pilocytic	n	Opto-chiasmatic	y
33	m	1.04	Pilocytic	n	Pan-medullary	n
34	f	7.10	Pilocytic	n	Opto-chiasmatic	n
35	f	4.02	Pilomixoid	n	Cervico-medullary	n
36	f	1.00	Pilocytic	n	Opto-chiasmatic	n
37	f	4.01		y	Opto-chiasmatic	n

y, yes; n, no

nerve pain prompting spinal MRI (Fig. 1). Liquoral seeding was never documented by cephalo–spinal cytology. Twenty-four children underwent surgery (partial tumour resections in 18 cases and biopsies in six), enabling a histological diagnosis in all cases. The

Fig. 1 Chiasmatic/metastatic tumour

centrally reviewed (FG) histological diagnoses were: pilocytic astrocytoma in 17 cases, pilomyxoid astrocytoma in two, ganglioglioma in three, and fibrillary astrocytoma in two. The diagnoses were concordant in 22/24 cases, and two tumours previously diagnosed as grade 3 astrocytoma were downgraded to pilocytic astrocytoma. The other 13 children were diagnosed on clinical grounds alone: 12 had optochiasmatic tumours and one was a 23-month-old child with a cervico–medullary tumour who had a recent history of rapid loss of limb strength and gait competence and was sent urgently for primary adjuvant treatment after a multidisciplinary discussion concluded that a low-grade glioma was highly likely. The signs and symptoms prompting these diagnoses were eyesight deficiencies in 23 cases, pyramidal deficiencies in 15, diencephalic syndrome in four, cranial nerve palsy in two, monolateral proptosis in one and intractable seizures in one. Other functional alterations were early puberty in three cases and panhypopituitarism in three, obesity in one, and isolated growth hormone deficiency in one; one child developed diabetes insipidus after surgery.

After chemotherapy, radiology revealed tumour reductions in 24/37 cases, meeting the criteria for partial remission in 17 of these and of complete remission in one. To date, the maximum response was recorded a median 12 months (range 2–31 months) after starting the treatment. Table 2 shows how the main signs and symptoms evolved during and after the treatment. As for sight impairments, 17/23 children with optochiasmatic tumours could be assessed adequately with consistent tests at the start and end of the chemotherapy, as explained above: seven improved and the other ten were stable; of the six remaining patients, three could only undergo behavioural sight evaluation at the beginning of their course of chemotherapy, and were judged to have improved during and after treatment, whereas two were blind after surgery and one only underwent an instrumental assessment at the end of the treatment because of non-compliance.

Table 2 Main signs and symptoms evolving during and after treatment

Sight deficits 23	Improvement 7, stable others
Diencephalic syndrome 4	Improvement 4
Proptosis 1	Improvement 1
Pyramidal deficits 15	Improvement 12 Stable 1 Worse 2
Cran.nerves palsy 2	Improvement 2
Seizures 1	Improvement 1
As a total, of 37	Improvement 26 Stable 9 Worse 2

Three-year progression-free survival (PFS) and overall survival (OS) were 65.5 ± 8.5 and $97 \pm 3\%$, respectively, for all patients (Fig. 2); five-year PFS and OS were 60 ± 9.6 and $86.4 \pm 8\%$, respectively. For the purposes of this report, we updated the follow-up on all 28 patients in our first reported series who had not been pre-treated, whose median follow-up was 113 months: their three-year PFS was $86 \pm 7\%$ and their OS $96 \pm 3.5\%$ (P ns); their five-year PFS and OS were 74.5 ± 8.3 and $96 \pm 3.5\%$, respectively. If we compare only the patients without metastatic deposits in the two series, the three-year PFS rates are $85 \pm 7\%$ for the first series and $75 \pm 9\%$ for the second (P ns), and the three-year OS are 96.3 ± 4 and $96.3 \pm 3\%$.

So far, 13 children have had adverse events, occurring a median 26 months after starting the treatment. Tumours progressed in 12 children and one (the child with mental retardation and an unidentified neurocutaneous syndrome) died of *ab ingestis pneumonia* while on the treatment. Another four children died 39, 49, 61, and 62 months after starting the treatment, two because of tumour bleeding after re-surgery, one of a glioblastoma developing 44 months after irradiation for fibrillary astrocytoma

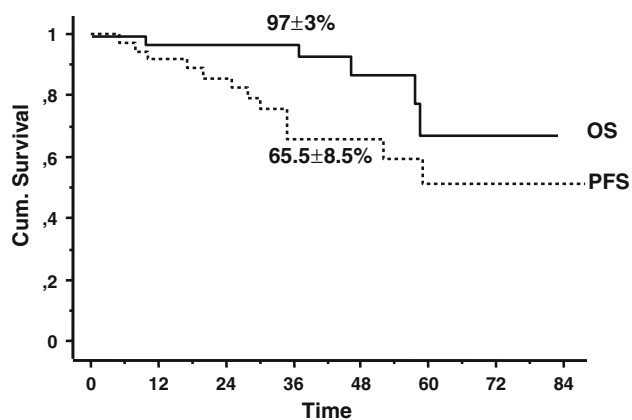


Fig. 2 Fig 1 PFS and OS for the whole series

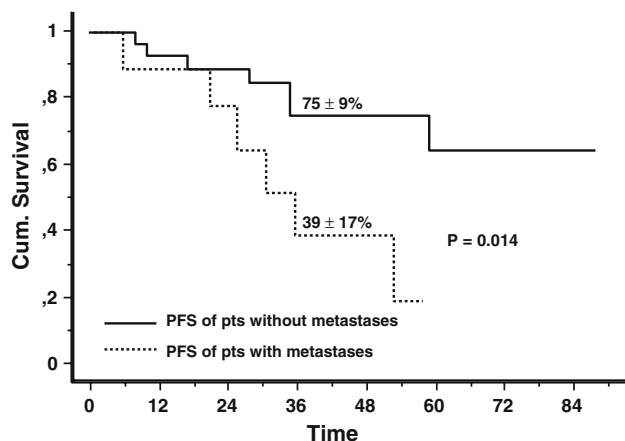


Fig. 3 PFS for cases with/without metastases

progression, and one while on radiotherapy for rapid tumour progression; one other child developed a glioblastoma 14 months after radiotherapy for a progressive fibrillary astrocytoma. Tumour progression was local in nine patients and in metastatic nodules in three, all of whom had already presented with metastases at the time of their diagnosis.

Radiation-free survival for the 32 surviving children was $94 \pm 4.3\%$ at both three and five years.

Children with metastatic disease had a significantly lower three-year PFS, i.e. $39 \pm 17\%$ as opposed to $75 \pm 9\%$ in those without metastases ($P = 0.0149$; Fig. 3).

In univariate analysis, age under 12 months or over five years, NF1, gender, tumour originating in the optic chiasmatic region, and debulking surgery as opposed to biopsy had no statistical effect on PFS or OS. It is worth emphasizing, however, that only one of the seven children with NF1 has relapsed so far and this child had ubiquitous tumour deposits at diagnosis. On pooling our first and second series, the three-year PFS for 15 children with NF1 was $93 \pm 6\%$ and their OS was 100%.

Toxicity

The leukocyte nadir was always above $2.0 \times 10^9/l$ after the first course of treatment and was, consequently, not checked again between courses. No infections were documented. None of the children had to stop the treatment because of toxicity.

Audiological toxicity was evaluated according to the Brock grading system [10] after completing all the planned treatment in 34 children: grade 1 audiological damage was documented in one child, grade 0 in two, and acoustic potential deficiencies in one. For both the patients graded as 0, this meant a 20 dB loss at 4,000 Hz. In our first series, damage had been recorded in 11/31 cases, classified as grade 1 in six, grade 2 in three and grade 0 in two ($P = 0.023$); the toxicity in the two patients graded as 0 meant a 20 dB loss at 8,000 Hz in both cases.

All patients were assessed by a psychiatrist at diagnosis and tailored rehabilitation was provided, as appropriate. Endocrine tests were included in the diagnostic work-up and in the subsequent follow-up.

Discussion

In previous reports on the efficacy of chemotherapy in preventing the progression or inducing the regression of paediatric low-grade gliomas, many authors describe institutional, national, or international trials using different drug combinations given to cases inoperable because of the site, diffusion, or the clinical aggressiveness of the disease (i.e. rapid recurrence after surgery), or when radiotherapy was considered too harmful in view of the tumour's extent and the patient's young age [1–4].

Given that most children presenting with the above-described features have tumours arising in visual pathways, causing more or less severe eyesight deficiencies, we were concerned to find that, although good results were achieved in terms of tumour response and PFS in our first reported series treated with cisplatin and etoposide, 28% of these children developed hearing impairments [7]. Another issue was the potentially cumulative toxicity of etoposide, especially in patients with neurofibromatosis.

Hence this second trial using substantially reduced doses of cisplatin (17% less) and etoposide (34% less).

We recorded much the same results, in terms of three-year PFS and OS, as in the earlier series of patients: the tumour (evaluated using the same criteria in the two series) shrank in 20/28 patients in the first series and in 24/37 in the second, confirming a very similar response. The time to maximum response differed substantially between the two series, however, being a median 8 months for the first and 12 months for the second, prompting us to suggest that

cumulative quantities of cisplatin (around 700–750 mg/m²) and etoposide (around 3,000–3,600 mg/m²) are needed to obtain the maximum response with this regimen. We also deduce that higher cumulative doses are responsible for greater toxicity, but fail to improve or extend tumour response. Unlike our earlier series [7], no prognostic significance emerged from our second series for patients below one year old or over five years old. A possible explanation of this discrepancy might lie in the different numbers after subgroup stratification, i.e. there were more over five-year-olds and fewer under one-year-olds in our second series.

It is also worth mentioning that our second series included an unusually large proportion of patients with metastases—over 24% of all the consecutively treated children—whereas the rates reported in the literature are under 10%, even in these modern times of MRI [11, 12]. The PFS rate was significantly lower for the subgroup of metastatic patients, despite 7/9 of them responding to the treatment. This emphasizes the need to find a different approach, possibly including other drugs, if genetics succeed in revealing a particular profile for tumours with this pattern of presentation, as recently demonstrated for pilocytic astrocytoma originating at other sites [13].

In our experience, the two children with fibrillary astrocytoma fared very badly, their tumour evolving into glioblastoma. According to the recent literature, grade 1 and grade 2 astrocytoma are clearly distinguishable at the molecular level in children [14, 15] and in adults, so a tumour's evolution from fibrillary astrocytoma to glioblastoma may be related to radiotherapy or it may be spontaneous, as is more often the case in adults [16–18]. In our two fibrillary astrocytoma cases the IDH1 mutation, that correlates with adult low-grade glioma evolution into glioblastoma, was not found.

The rapid disease progression and death of a third patient with a pilocytic astrocytoma of the visual pathway (presenting with huge metastases already at diagnosis) was rather unexpected, although there are reports of similar evolution in the literature and the recent histopathological stratification of pilocytic astrocytoma can clarify such cases with a particularly poor outcome [19].

In addition to the radiological response, we also considered the signs and symptoms prompting our patients' diagnosis, which improved in 70% of cases. As Gutmann also pointed out, given the slow growth rate and infiltrative nature of low-grade glioma in children, a reduction in overall tumour volume cannot be the only endpoint of clinical trials on these diseases [20]. Changes in clinical variables may be very difficult to assess [4] because, for example, of the lack of standardized methods of ophthalmological evaluation, the patients' young age, and the difficulties of conducting complex endocrinological and/or

neurofunctional tests at peripheral treatment centres. As paediatric oncologists, we are obliged to face a number of issues relating to the final outcome of our patients with low-grade glioma, who may be referred for diagnosis under emergency conditions with life-threatening disease in cases of diencephalic syndrome, or with slow-growing disease, as is more often the case of patients with NF1 [21]. This latter subset of patients is, per se, at risk of developing subsequent tumours, including juvenile chronic myelomonocytic leukaemia [22]. We are therefore very cautious, on the one hand, about when and how to treat these children, being aware that they have a long life ahead of them and risk suffering from side-effects; on the other hand, when we do decide to start treating them, it is best to adopt an effective and possibly definitive strategy, based on disease control at three years documented in over 90% of our patients. Children with NF1 warrant close haematological follow-up even though secondary leukaemia after epipodophyllotoxins has not been associated with any genetic predisposition, including germline NF1 mutations. We also substantially lowered the cumulative dose of etoposide, adopted a “moderate” dosage with a low correlated risk of secondary leukaemia, as defined by the NCI in their analysis [23], but still risky when coupled with platinum compounds [24].

In most patients whose disease is diagnosed at over one year of age, a low-grade glioma is more like a chronic condition than a true tumour with a definite beginning and end of the time when it is a threat to life, so we are also obliged to prevent our treatments from harming our patients. We have, in fact, demonstrated that a good response rate can be maintained with a cisplatin/etoposide regimen, achieving a satisfactory PFS, and the dosage of these drugs (by comparison with the original cisplatin/etoposide schedule) can be safely reduced together with the related risk of ototoxicity in a significant number of patients. We are also confident that our treatment did not cause any significant cognitive impairment in our patients, as already demonstrated in 18 patients in our former series with chiasmatic-hypothalamic tumours [25].

In conclusion, we can confirm that the cisplatin/etoposide regimen is equally effective at lower cumulative doses, which coincide with a lower haematological and audiological toxicity. This regimen should be intensified for metastatic tumours, however, and it is not indicated for the fibrillary histotype.

If some concerns remain for the risk correlated with cumulative doses of these drugs and their potential toxic effects that are not reduced to zero, we have also to remember that over 90% of survivors were never irradiated at five years of observation, thus escaping from the very well known neuro-cognitive, endocrine, and oncogenic additive risks of this adjuvant treatment.

Apart from this and other effective chemotherapy regimens, however, new radiotherapeutic and neurosurgical techniques have now become a reality for the treatment of these tumours (albeit only at referral centres for the time being) and paediatric neuro-oncologists need to be aware of these new possibilities and always discuss their cases in a multidisciplinary setting in order to give patients every chance of suitable treatment [26–28].

Acknowledgements This paper was presented in part at the ISPNO, 13th International Symposium on Pediatric Neuro-Oncology: June 29–July 2, 2008 Chicago, USA. This paper was partly financed by the AIRC (Associazione Italiana per la Ricerca sul Cancro) and Associazione Bianca Garavaglia (Busto Arsizio, Varese).

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