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CASE REPORT

Poor-risk high-grade gliomas in three survivors of childhood acute lymphoblastic leukaemia—an overview of causative factors and possible therapeutic options

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Abstract
Purpose Malignant high-grade gliomas are the most common secondary neoplasms in children cured of acute lymphoblastic leukaemia (ALL). Although many predisposing factors exist (including systemic or intrathecal chemotherapy, young age, brain infiltration and genetic predispositions), cranial irradiation appears to be the strongest one.
Methods Three cases of secondary high-grade gliomas (two multiform glioblastomas, grade IV; one anaplastic astrocytoma, grade III) developed in ALL survivors (F–M, 1:2) 3 to 6.3 years after stopping ALL therapy according to BFM-90 trial.
Results All tumours were supratentorial, contrast-enhancing, space-occupying, highly advanced and aggressive. Possible risk factors and current therapeutic options for paediatric ALL and malignant gliomas are reviewed and discussed.
Conclusions Prognosis in secondary malignant gliomas in children is poor (overall survival of 5, 10 and 19 months) despite intense therapy. Thus, protocols for paediatric ALL reduce prophylactic cranial irradiation in favour of intrathecal and intravenous high-dose MTX. Nevertheless, ALL survivors must undergo systematic, long-term surveillance for early detection of intracranial neoplasms.

Keywords Acute lymphoblastic leukaemia · Secondary neoplasia · High-grade glioma · Cranial radiotherapy complications · Intrathecal methotrexate · Children

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Introduction

Acute lymphoblastic leukaemia (ALL) is the most common malignancy in children. The modern treatment protocols for childhood ALL consist of intense chemotherapy (CHT) given to all patients and of central nervous system (CNS) radiotherapy (RTX) administered to selected patients according to their risk group assignment [6, 8, 25, 28]. This treatment has been shown to account for a significant improvement in overall survival rates; however, it may cause a number of serious early and long-term complications [2, 18, 20, 26, 29]. One of them is secondary neoplasia developing sometimes many years after the completion of the initial therapy for childhood ALL [1, 4, 13]. The secondary malignant CNS tumours have been reported to occur most frequently, followed by lymphomas and acute myeloblastic leukaemias [12, 21, 30]. Among the secondary CNS tumours, meningiomas and malignant astrocytic tumours (gliomas) have predominated in most studies [13, 16, 24, 30].

Several factors have been suggested to be responsible for the secondary brain tumours development. They include: brain RTX, intravenous (i.v.) or intrathecal (ith) CHT, young age of the patient at the time of ALL diagnosis, initial CNS

infiltration and some genetic predispositions. The strongest risk factor for the development of malignant brain tumours in ALL survivors seems to be cranial irradiation [1, 13, 16, 22, 24, 30]. To sustain a diagnosis of neoplasia induced by radiation, the tumour must occur within the irradiated field and after a latent period sufficient to exclude its having been present at the time of radiotherapy. The tumour should differ histologically from the original lesion and neurocutaneous syndromes predisposing to malignancy must be excluded.

Apart from brain RTX, also high-dose (5 g/m^2) methotrexate (MTX) given i.v. and MTX ith have been proved to be effective in preventing the CNS relapse in most children with ALL [6, 8, 15]. It is possible that the concurrent administration of ith MTX and cranial RTX may result in the induction of secondary CNS malignancies [26]. However, there is no evidence in man or experimental animals to indicate that ith MTX alone is carcinogenic or that it enhances the carcinogenic effect of radiation. The relationship between the young age at ALL diagnosis (<6 or <7 years) and increased risk of secondary CNS malignancies has been suggested in several clinical studies [13, 30].

The introduction of cranial RTX has provided efficient control of overt or subclinical meningeosis in ALL [6, 8, 28]. However, due to its long-term toxicity, the Berlin–Frankfurt–Munster (BFM) Study Group initiated several attempts in certain ALL risk subgroups to omit or reduce cranial RTX while using more CNS-directed CHT but without extended ith treatment during maintenance therapy [8, 15].

In the present paper, we report on three ALL survivors treated at our hospital because of secondary malignant high-grade gliomas. The possible risk factors as well as current therapeutic options for both paediatric ALL and malignant gliomas have been reviewed and discussed.

The diagnosis, risk group classification and therapy of ALL were conducted according to the BFM-90 protocol. The diagnosis and therapy of high-grade gliomas secondary to ALL were set according to the protocol of the Polish Solid Tumours Study Group. The histopathologic examinations were reviewed and confirmed in two separate institutions.

Patients' characteristics

Patient 1

A 2.8-year-old boy was treated for medium-risk-group (MRG) ALL (of pre-preB immunophenotype) with BFM-90 protocol between May 1993 and March 1996 (Table 1). At diagnosis, no CNS involvement was stated; however, 2 months after treatment initiation, the seizure after general anaesthesia was observed. The lumbar puncture revealed leukaemic meningitis with pleocytosis of 128/mm^3. Brain CT did not show any abnormalities at that time. The CNS involvement of ALL was diagnosed and thus the patient received both high-dose i.v. and ith MTX as well as ith cytarabine and prednisolone. In March 1994, the boy presented with rapid loss of consciousness, mydriasis and deep coma. The eye fundus examination showed no optic nerve oedema; however, the CT of the brain revealed leukaemic infiltration of left semioval centre, white matter and soft meninges. Therefore, the whole brain RTX with 24 Gy was brought forward immediately. Afterwards, he continued CHT which was stopped in March 1996. Soon after, he developed neurological complications comprising therapy-resistant symptomatic epilepsy, behavioural disorders and psychomotor retardation. Since June 2002, aggressive

Table 1 Clinico-pathological characteristics of acute lymphoblastic leukaemia and its therapy in three children presented in the study

ALL	Patient 1	Patient 2	Patient 3
Morphology immunophenotype	ALL L1-L2 preB-B	ALL L1-L2 common I	ALL L2 common I
Age at ALL diagnosis (years)	2.8	9.5	6.8
Treatment protocol	BFM-90	BFM-90	BFM-90
Risk group	MRG	MRG	MRG
Initial CNS infiltration	No	No	No
CNS infiltration during treatment	Yes	No	No
Brain RTX (dose)	Therapeutic (24 Gy)	Prophylactic (12 Gy)	Prophylactic (12 Gy)
MTX iv	Two doses of 5 g/m^2 Two doses of 1 g/m^2 (dose reduction due to ↓creatinine clearance)	Four doses of 5 g/m^2	Four doses of 5 g/m^2
MTX ith	16 doses of 12 mg	13 doses of 12 mg	13 doses of 12 mg
ARA-C ith	Four doses of 30 mg	No	No
Response to therapy	CR	CR	CR

ALL acute lymphoblastic leukaemia, *CNS* central nervous system, *MRG* medium-risk group, *CHT* chemotherapy, *RTX* radiotherapy, *MTX ith* methotrexate intrathecally, *MTX iv* methotrexate intravenously, *ARA-C ith* arabinoside intrathecally, *CR* complete remission

behaviour, increased frequency of epileptic seizures and symptoms of increased intracranial pressure have occurred. The MR examination showed extensive lesion located at the left temporo-parieto-occipital region (Fig. 1). In August 2002, the incomplete resection of the tumour was performed. The histological examination revealed astrocytoma anaplasticum (WHO grade III). The post-operative period was complicated by the *Salmonella* spp. abscess within the scar; thus, the adjuvant CHT was delayed. There was no response to CHT according to the Polish protocol for malignant gliomas (Tables 2 and 3)—after three cycles, the general condition of the child significantly deteriorated and the symptoms of increased intracranial pressure occurred again. The follow-up MR examination revealed extensive tumour progression involving lateral ventricles with herniation of ventricles under the falx cerebri. The intravenous CHT was discontinued and the palliative CHT with oral etoposide was introduced. The patient was under hospice care for 5 months and died from continual tumour progression.

Patient 2

A 9-year-old girl was diagnosed with ALL (immunophenotype common I) in July 1994. The patient was treated with CHT according to BFM-90 protocol for MRG ALL (Table 1). A prophylactic RTX of the whole brain with 12 Gy was performed. The patient completed treatment in 1997 and did well until July 2000, when rapid loss of consciousness, left limb paresis and seizures occurred. The CT of the brain revealed a fronto-parietal infiltration and pseudo-cystic mass of the right hemisphere accompanied by the intensive brain oedema. The MR examination suggested leukaemic origin of the lesion (Fig. 2). In August 2000, the patient underwent stereotactic biopsy of the tumour and the histological examination detected glioblastoma multiforme (WHO grade IV). In September 2000, a craniotomy and total resection of the tumour was performed. Subsequently, the patient received intense CHT according to different protocols for malignant gliomas as outlined in Tables 2 and 3. Nevertheless, the control MR performed in February 2001 showed local tumour recurrence; thus, the girl was administered brain RTX (52 Gy) and a different CHT scheme. There was a slight improvement in the control MR performed in June 2001, but the CHT had to be changed again because of the long-lasting thrombocytopenia episodes following RTX and CHT. Unfortunately, in October 2001, the progression of the tumour was detected in MR. Two cycles of a very intensive CHT ("8 in 1" protocol) did not appear effective so the

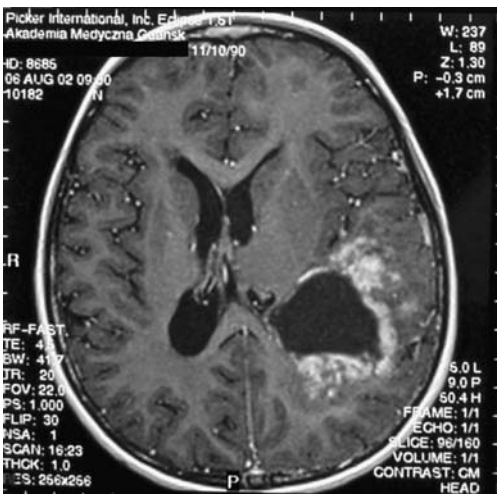

Fig. 1 MR of the brain—axial T1-weighted post-contrast image detecting a tumour in the temporo-parietal lobe (patient no. 1)

Table 2 Clinico-pathological characteristics of secondary gliomas in children cured of ALL

Secondary CNS tumour	Patient 1	Patient 2	Patient 3
Diagnosis date	VII 2002	VIII 2000	VI 2003
Interview (days)	45	7	14
Patient's age (years)	12	15.5	12.3
Genetic predispositions	No	No	No
Symptoms	Epilepsy, behavioural disorders, psychomotoric retardation, increased intracranial pressure	Loss of consciousness, left limb paresis, seizures	Right hemiparesis, central paresis of the right facial nerve
Localisation	Left temporo-parieto-occipital region	Right fronto-parietal region	Left parietal and frontal region
Histopathology	Anaplastic astrocytoma	Multiform glioblastoma	Multiform glioblastoma
Grade	III	IV	IV
CNS tumour therapy			
Neurosurgery	Incomplete tu resection	Complete tu resection	Stereotactic biopsy
CHT	Yes	Yes	Yes
RTX	No	52 Gy in 26 fractions	No
Response to therapy	No response PD after 4 months	No response PD after 5 months	No response PD after 2 months
Overall survival from diagnosis of CNS tumour	10 months	19 months	5 months

ALL acute lymphoblastic leukaemia, *CNS* central nervous system, *CHT* chemotherapy, *RTX* radiotherapy, *CTX* cyclophosphamide, *VP-16* etoposide, *PD* progressive disease

Table 3 Therapeutic protocols administered to children with secondary malignant gliomas

Protocol I	Carboplatin 500 mg/m^2/day iv; 1–2 days
	Etoposide 100 mg/m^2/day iv; 1–3 days
	Etoposide 60 mg/m^2/day iv; 21–25 days
	Vincristin 1.5 mg/m^2/day iv; 1 day
	Ifosfamide 900 mg/m^2/day iv; 21–25 days
	Cisplatin 20 mg/m^2/day iv; 21–25 days
Protocol I maintenance	Vincristin 1.5 mg/m^2/day iv; 1, 8, 15 days
	Lomustin 75 mg/m^2/day po; 15 days
	Cisplatin 75 mg/m^2/day iv; 15 days
Protocol II	Ifosfamide 3 g/m^2/day iv; 1–3, 21–23 days
	Etoposide 150 mg/m^2/day iv; 1–3, 21–23, 42–44, 63–65 days
	Doxorubicin 20 mg/m^2/day iv; 21–23, 63–65 days
"8in1"	Vincristin 1.5 mg/m^2/day iv
	Hydroxyurea 3 g/m^2/day iv
	Procarbazine 75 mg/m^2/day iv
	Lomustin 75 mg/m^2/day po
	Cisplatin 90 mg/m^2/day iv
	Cytosine arabinoside 300 mg/m^2/day iv
	Methylprednisolone 300 mg/m^2/day iv
	Dacarbasine 150 mg/m^2/day iv
Palliative CHT	Cyclofosfamide+Etoposide
	Etoposide

patient was given palliative oral CHT. After two doses of cytostatics, huge epistaxis occurred so CHT was cancelled in February 2002. The patient died a month later because of tumour progression not responding to any therapeutic options.

Patient 3

A 6-year-old-boy was diagnosed with ALL common I in December 1997. The CNS prophylaxis included i.v. and ith MTX as well as cranial RTX with a dose of 12 Gy given between August and September 1998. The patient entered complete remission and completed the maintenance therapy in March 2000. No neurological symptoms were observed for 3 years following therapy. In June 2003, the boy presented with right hemiparesis and central paresis of the right facial nerve. MR scan of the brain showed multifocal lesion in the left hemisphere with a large mass located in the parietal lobe. The secondary brain tumour was suggested and the stereotactic biopsy of the tumour was done in July 2003. The microscopic examination revealed glioblastoma multiforme (WHO grade IV). No response to intensive CHT for malignant gliomas was observed—the patient developed new neurologic symptoms (sensorimotor aphasia, headaches, nausea and periodic somnolence) and worsening of the right hemiparesis. The progression of disease was confirmed in control brain MR in October 2003. The palliative oral CHT was administered, but soon after the patient demonstrated generalised seizures, symptoms of increased intracranial pressure and dyspnoea of central origin. The patient was disqualified from further treatment and referred to the palliative care unit. He died of disease progression 2 months later (Fig. 3).

Discussion

Secondary brain tumours after ALL

Malignant tumours of the CNS have been reported to develop six to 30 times more frequently in childhood ALL survivors than in non-cancer control populations [1, 4, 12, 13]. The 15-year cumulative risk of secondary malignant brain tumours was reported to be 0.5–2.0% in most published papers [30], even in children treated with repeated CHT and RTX and stem cell transplantation [4]. However, it should be remembered that the cumulative risk of malignant secondary brain neoplasms increases with time reaching 4.91% at 30 years from therapy discontinuation [12].

Among secondary brain tumours occurring in ALL survivors, the high-grade neoplasms of glial origin predominate, including glioblastomas and malignant astrocytomas; however, in some studies, brain sarcomas and meningiomas have been diagnosed more frequently [4, 13, 24]. Among 5,006 children with B-precursor or T-ALL enrolled in five ALL-BFM multicenter trials, Löning et al. [13] stated 13 secondary neoplasms of the CNS including 11 high-grade gliomas (four glioblastomas, four astrocytomas and three primitive neuroectodermal tumours) and only two cases of meningioma. Walter et al. [30], in their cohort of 1,612 patients with childhood ALL, found 22 cases of secondary brain tumours, including ten high-grade gliomas, one low-grade glioma and 11 meningiomas. The authors noticed that gliomas occurred at a median latency of 9.1 years in contrast to meningiomas that developed later (19 years) [30]. In the study of Loning et al. [13], the median time from initiation of ALL treatment to diagnosis of the secondary CNS tumour was 7.9 years (range 4–13 years).

Among the patients treated for ALL in our institution, we have stated three cases of secondary brain tumours that we present herein. All these three patients were diagnosed with malignant high-grade gliomas from 3 to 6.3 years after termination of therapy for ALL and from 5.6 to 9.1 years after ALL diagnosis.

Risk factors

There are several factors suggested to be responsible for the occurrence of secondary brain tumours in the survivors of

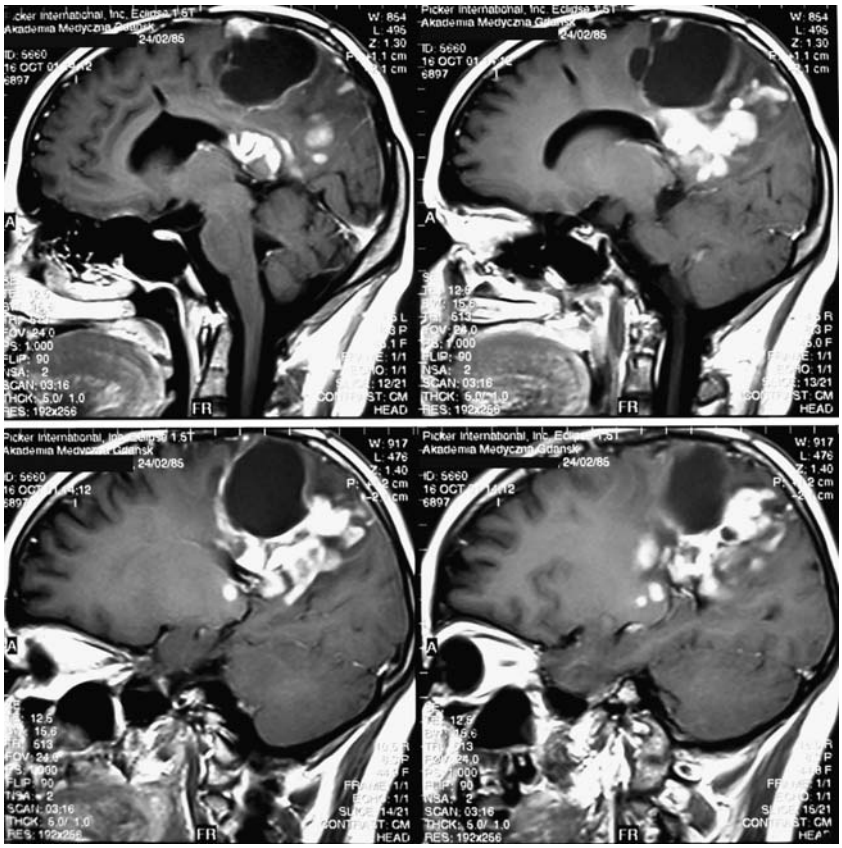

Fig. 2 MR of the brain—sagittal T1 post-contrast enhancement, showing partially cystic and solid tumour located in the fronto-parietal region of the right hemisphere (patient no. 2)

childhood ALL. They include genetic predisposition, clinical features of primary malignancy (ALL type and risk group, patient's age at diagnosis, leukaemic involvement of CNS) and therapy (especially prophylaxis against CNS ALL).

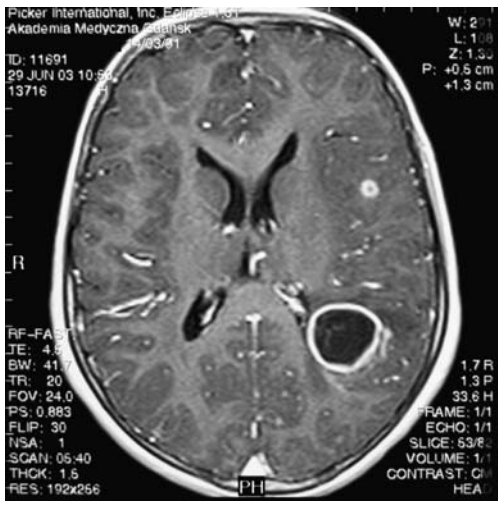

Fig. 3 Brain MR—axial T1 post-contrast examination, demonstrating cystic tumour in the temporo-parietal lobe and a small focus in the left temporal lobe (patient no. 3)

Genetic predisposition

Genetic predisposition for secondary brain tumours includes the presence of inborn cancer-prone syndromes and genetic polymorphisms of a thiopurine *S*-methyltransferase, an enzyme crucial for the inactivation of 6-mercaptopurine [9, 10, 11]. In our series of patients, the presence of genetic syndromes predisposing to neoplastic disease was clinically excluded; however, the activity of *S*-methyltransferase was not examined in any of them.

Young age at ALL diagnosis

A clear relationship between young age at ALL diagnosis and increased risk of high-grade glioma occurrence has been revealed in the multicenter studies of L. Löning et al. [13] and A. Walter et al. [30]. The cumulative probability that these patients would develop a CNS tumour was 1.5% after 15 years, compared to the risk of only 0.1% in patients 7 years of age or older [13]. Moreover, brain tumours were the most common secondary neoplasms in children below the age of 7 years at diagnosis of ALL. In our series of patients, two of three children were younger than 7 years at the time of ALL diagnosis, which may have played some role in the oncogenic process.

CNS prophylaxis in children with ALL

CNS prophylaxis in children with ALL is a very important component of the treatment protocol. It includes cranial RTX, ith CHT and high-dose i.v. CHT. Since these treatment modalities are introduced, the cumulative incidence of CNS leukaemia has been significantly reduced [6, 8, 17, 28]. However, this treatment (especially cranial RTX) may cause a number of serious complications detectable in radiologic examinations, particularly in the brain MR [29]. In physical examination, post-radiation damage results in learning disabilities, growth retardation, intellectual dysfunction, seizures and secondary neoplasia [20, 26, 29].

Cranial RTX

The cranial or craniospinal RTX is undoubtedly a strong risk factor for the development of secondary CNS malignancies in patients with ALL [1, 13, 21, 24, 30]. However, the exact mechanism of the radiation in tumorigenic effects has not been well known in humans and experimental animal models. Löning et al. [13] proved that the overall cumulative risk of secondary brain neoplasms at 15 years was significantly higher in patients after cranial RTX than in non-irradiated children (3.5% vs. 1.2%). In the presented series of patients, all children underwent brain RTX—in two of them it was prophylactic cranial RTX with 12 Gy and in one (patient n.a.1) the dose was therapeutic (24 Gy). The latter patient demonstrated additional risk factor for secondary brain tumour development as he experienced leukaemic infiltration of the brain during ALL therapy and thus required a higher dose of cranial RTX. In his case, this fact may be of particular significance as most reported radiation-associated gliomas have occurred after higher doses of radiation (usually more than 3,000 rad) [21, 30]. On the contrary, in a Saint Jude Children's Research Hospital study of 361 patients whose therapy excluded cranial irradiation, none developed brain tumours [21, 30].

Intrathecal and intravenous high-dose MTX

It has been stated by Relling et al. [21] that also ith MTX might increase the incidence of brain tumours, especially when administered concomitantly with RTX [19, 21]. P. Rosso et al. [23] suggested that there may be a synergistic action of RTX and prolonged exposure to ith MTX given before RTX and thereafter for years. Also, high-dose MTX given i.v. was shown to be responsible for the development of leukoencephalopathy in children treated for ALL [20]. It should be underlined, however, that there is no single evidence that MTX alone may contribute to tumorigenesis or that it enhances the carcinogenic effect of RTX. The use of intrathecal CHT was not found to increase the risk of developing secondary brain tumour in a clinical study of AW Walter et al. [30]. In fact, the intrathecal MTX alone or in combination with RTX is highly effective in preventing initial CNS relapse and thus constitutes an important element of ALL therapy [8, 15].

Clinical attempts to reduce cranial RTX

Because cranial RTX appears to be the strongest risk factor in patients with ALL [21, 30], various clinical trials, including successive BFM protocols, have tried to substitute cranial irradiation with systemic and/or intrathecal CHT without increasing the risk of CNS relapse of leukaemia [6, 28]. Several clinical studies have also evaluated the use of reduced intensity conditioning for allogeneic hematopoietic stem cell transplantation in children with ALL [14].

Secondary CNS tumours—need for early detection and therapeutic options

Although the results of these studies are promising, it is obvious that the ALL survivors are surveyed for intracranial neoplasms for many years after the end of their therapy. Since our patients developed secondary brain tumours 3–6.3 years after ALL discontinuation, we would advise frequent MR/CT imaging in this period of time. In our oncologic centre, this is a routine practice. Early detection of this severe complication and immediate introduction of multimodal therapy (neurosurgery, CHT, RTX, high-dose CHT with hematopoietic stem cell transplantation in selected cases) is essential; however, these do not warrant improved outcome [13]. The prognosis in primary and even more in secondary malignant gliomas is extremely poor, although many authors agree that children with these neoplasms fare much better than their adult counterparts [5]. In our series of patients with secondary high-grade gliomas, only one child (patient n.a.2) was feasible to complete tumour resection, and in two others only diagnostic biopsies could be performed because of very extensive brain involvement. The overall survival of the patient n.a.2 was the longest (19 months) compared with 10 and 5 months in the children who experienced incomplete tumour excision and stereotactic biopsy only.

In a study of Stewart et al. [27], analysing data on 3,004 high-grade glioma patients from 12 randomised controlled trials, CHT was shown to prolong the survival significantly, independently of patients' age, sex, histology, performance status or extent of resection. Modern treatment strategies for high-grade gliomas suggest supplementing the tumour excision with RTX combined with temozolomide or bevacizumab with irinotecan [3, 7]. Unfortunately, we were

not able to observe any objective response to CHT in our patients and they progressed from 2 to 5 months after the therapy was started. Radiotherapy was feasible only in patient 2, who was irradiated immediately after the recurrence of the previously resected tumour was detected in CT.

Conclusion

Although the presented review of the literature points some possible risk factors for secondary brain tumours, the analysis of our patients' medical histories could not identify any of them as a definite risk factor. All patients were treated with the same protocol including CHT with i.v. MTX, ith MTX and brain RTX.

Early detection and complete resection of the secondary high-grade gliomas, supplemented with CHT and RTX, are indispensable; however, they do not warrant much improved prognosis. In our material, none of the patients were diagnosed at a pre-symptomatic stage and the outcome was poor in all cases despite intense therapy.

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