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Temozolomide in the treatment of malignant brain tumors in children

Elżbieta Korab-Chrzanowska[1], Stanisław Kwiatkowski[2]

Material and methods. A new alkylating cytostatic drug – Temozolomide (Temodal) – was administered to 13 children treated for malignant brain tumors between June 1999 and June 2002. The patients were followed up till November 2002. In two cases Temozolomide was employed preoperatively as the first-order agent aiming to reduce the tumor mass, while 11 patients received Temozolomide following the failure of previous standard therapy.
Results. Complete and almost complete regression was achieved in 2 cases. A short-term regression or stabilization of tumor size lasting 2-12 months was noted in 3 children. Five patients showed no therapeutic effect and further tumor progression occurred. In two patients the therapy was discontinued. In preoperative patients Temozolomide was successful in one patient.
Conclusions. Temozolomide was successful in 3 patients while in 3 children the disease stabilized for a period of 2-12 months.

Temozolomide w leczeniu złośliwych guzów mózgu u dzieci

Materiał i metody. U 13 dzieci leczonych z powodu złośliwych guzów mózgu w okresie od czerwca 1999 r do czerwca 2002 r zastosowano nowy cytostatyk, alkilujący temozolomide (Temodal). Kontrolę pacjentów po leczeniu prowadzono do listopada 2002 r W dwóch przypadkach temozolomide zastosowano przedoperacyjnie, celem zmniejszenia masy guza, podczas gdy 11 pacjentów otrzymało temozolomide z powodu niepowodzenia standardowej terapii.
Wyniki. Całkowitą i prawie całkowitą regresję otrzymano w 2 przypadkach. Krótkotrwałą regresję lub stabilizację masy guza, trwającą od 2 do 12 miesięcy, odnotowano u 3 dzieci. U 5 dzieci nie wykazano terapeutycznego efektu i wystąpiła progresja choroby. U 2 pacjentów leczenie przerwano. U pacjentów, u których Temozolomide zastosowano przedoperacyjnie, lek okazał się skuteczny u jednego.
Wnioski. Temozolomide wydaje się być skuteczny u 3 leczonych pacjentów. U 3 dzieci stabilizacja choroby utrzymała się przez okres 2-12 miesięcy.

Key words: malignant brain tumors in children, temozolomide
Słowa kluczowe: złośliwe guzy mózgu, dzieci, temozolomide

Introduction

Temozolomide (Temodal) is a new alkylating cytostatic agent, that has found its use in managing recurrent malignant brain *gliomas*, predominantly in adult patients [1-12]. The drug is administered orally as tablets at the dose of 150-200 mg/m^2/day over 5 days. The cycles are repeated every 28 days. Temozolomide is rapidly absorbed when administered orally and is spontaneously hydrolyzed at physiologic pH to its active metabolite 3-methyl-(triazen-1-yl) imidazole-4-carboximide (MTIC). The mechanism of action of MTIC is thought to be alkylation of the 06 position of guanine with additional alkylation at the N7 position. In preclinical studies, temozolomide has been shown to exert significant antitumor activity against a variety of human central nervous system tumor xenograft models [2-3, 5, 7, 9]. No accumulation occurs with multiple daily dosing. temozolomide achieves higher levels in human *astrocytoma*, as compared to the contralateral normal brain [3]. In clinical studies temozolomide has been shown to have 100% oral bioavailability and extensive tissue distribution including penetration of the blood-brain barrier [2-5, 7-12]. Dose-limiting toxicity appears as myelosuppression, consisting of grade 3 or 4 thrombocytopenia and/or neutropenia. Platelet and neutrophil count nadirs occur late in the cycle (usually between days 21 and 28) and recovery is rapid within 1-2 weeks. Temozolomide is reported to cause a relatively small number of adverse effects, mainly in the form of decreased blood count index [2-5, 8, 9, 12]. In a randomized multicenter phase II study temozolomide vs. Procarbazine, 42% adult patients suffered nausea, 35% vomiting and 30% fatigue [4]. These side effects are similar to other reports [3, 5, 11]. Reports indicate that temozolomide has been employed in children in a few

[1] Division of Radiotherapy
[2] Division of Pediatric Neurosurgery
University Children's Hospital of Cracow, Poland

centers and only fewer than 100 patients worldwide have received the drug, not only in relapsed brain *gliomas*, but also in *medulloblastomas* and PNET tumors [13, 18].

Material and methods

Temozolomide therapy was commenced at the University Children's Hospital of Cracow in June 1999. The treatment program included 13 patients (7 girls and 6 boys) aged 3-19 years (mean age 10.6 years). In cases of *pineoblastoma* specimens for histopathology were obtained by a stereotactic biopsy, while in the remaining patients specimens were collected intraoperatively, during open neurosurgical procedures. Table I presents the patients and their histopathological diagnoses.

Table I. Histopathological findings in children with brain tumors

Histopathology	No. of patients
Medulloblastoma	3
Pineoblastoma	1
Glioblastoma multiforme	3
Anaplastic astrocytoma	3
Fibrillary astrocytoma with single *cellular atypia foci*	2
Brainstem *glioma*	1

Temozolomide was administered orally every 28 days for 5 days at the dose of 150-200 mg/m^2, depending on blood cell count values and previous chemotherapy. In the group with no effect after standard treatment (2 children) or with relapsed disease (9 patients) no more than 6 cycles were given. In the group with preoperative chemotherapy (2 children), 3 courses of chemotherapy were prescribed. In the case of progression of the disease the treatment was discontinued.

Patients

Medulloblastoma

Temozolomide was employed in 3 children: a 9-year old boy treated 6 months earlier because of his T2M1 disease according to Chang, a 6-year old girl with a T3AM1 tumor and a 10-year old boy with advanced T3AM1 disease. All the children had been previously subjected to chemotherapy and total CNS irradiation therapy with an increased dose applied to the tumor site. The patients relapsed within 6 months to 4 years after the completion of treatment. All the children had disseminated disease. They presented with severe pain involving the lumbosacral segment of the spine.

Pineoblastoma

A 15-year old girl with *pineoblastoma*: one year after the completion of chemotherapy and irradiation therapy, CT and MRI revealed persistent residual tumor mass.

Malignant brain *gliomas*

Relapses at the tumor site were detected in 5 children. No total regression after standard treatment was observed in two patients. Two (a 14-year old girl and a boy) had grade III (WHO) malignant *astrocytomas*. Both patients had been previously treated surgically and subjected to irradiation therapy. The girl manifested tumor regrowth at the original site one year after radiotherapy completion. The patient was reoperated and according to the operator the tumor mass was completely resected. The 14-year old boy with a malignant brainstem *astrocytoma* had undergone a non-radical tumor excision and subsequently irradiation therapy. Two months after radiotherapy, tumor regrowth occurred. The third patient was a 19-year old girl with *glioblastoma multiforme* presented with massive tumor regrowth one year after radiotherapy completion. The patient was reoperated and according to the operator, macroscopically the mass was completely resected. Another patient was a 10-year old boy treated surgically and irradiated in our center due to a grade III (WHO) malignant brain *glioma*. Seven years later tumor regrowth was detected at the tumor site and a radical surgery as attested by the operator followed. Intraoperative histopathology revealed a *glioblastoma multiforme* type tumor.

Three children were diagnosed with brainstem *gliomas,* including two with histologically confirmed brainstem *fibrillary astrocytomas* with isolated *atypia foci*. These included a 6-year old boy previously subjected to chemotherapy and radiotherapy in another center and a 14-year old girl treated with irradiation therapy alone. Less than one year after treatment completion, the boy manifested massive tumor regrowth. The patient was reoperated and tumor mass situated in the central and superior pons was partially resected. In the case of the second patient, apart from a brainstem tumor, she also revealed neoplastic cells within the spinal canal. Following irradiation therapy involving the entire central nervous system with an increased dose applied to the tumor site, the child presented with complete regression within the spinal canal and partial regression of brainstem mass.

The third patient was a 7-year old boy with diffuse brainstem *glioma*. The tumor was partially resected with residual brainstem malignancy after irradiation therapy.

Preoperative temozolomide administration

The drug was employed in two girls. One of them was a 3-year old patient with a CT and MRI-confirmed extensive brainstem tumor suggestive of a markedly malignant *glioma*. The other patient was a 12-year old girl with a CT and MRI-confirmed malignant brainstem *glioma*.

Results of temozolomide chemotherapy

In the group of patients in whom standard therapy had failed, total and almost total tumor regression following temozolomide chemotherapy was achieved in two children, namely in a girl with *pineoblastoma* and in another female patient with brainstem *fibrillary astrocytoma* with *cellular atypia*. Any evaluation of this outcome is difficult, since post-radiotherapy residual lesions may undergo a slow, long-term remission. In seven children temozolomide failed to prevent further tumor progression. In two patients the therapy was discontinued. This group included a boy with diffuse brainstem *glioma* who developed grade IV WHO bone marrow aplasia after the first cycle, and a 19-year old girl with relapsed *glioblastoma multiforme*, who died in a regional hospital due to subarachnoid hemorrhage. In the two children in whom temozolomide was administered preoperatively, a therapeutic effect was achieved in one patient. The girl was operated on and intraoperative histopathology revealed a *glioblastoma multiforme*-like malignancy with numerous post-chemotherapy necrotic foci. Table II.

Table II. Outcome of temozolomide therapy in children with malignant brain tumors

Histopathology	Sex	Age	Cause of Temodal treatment	No of Temodal cycles	Duration of symptom stabilization	Outcome
Glioblastoma multiforme	F	19 years	Tumor relapse	I	Symptom-free	Death because of subarachnoid hemorrhage
	M	10 years		II	1,5 month	Progression Death
Anaplastic astrocytoma	M	14 years		II	No effect	Progression Death
	F	14 years		II	1 month	Progression Death
Fibrillare astrocytoma with *cellular atypia*	M	6 years		II	No effect	Progression Death
Medulloblastoma	M	9 years	Tumor relapse	III	2 months	Progression Death
	M	10 years		IV	6 months	Progression Death
	F	6 years		VI	12 months	Progression Death
Brainstem *glioma*	M	7 years	No total tumor regression after standard treatment	I		Lost to the study
Fibrillare astrocytoma with *cellular atypia*	F	14 years		VI	Symptom-free	Regression Alive near 3 years
Pineoblastoma	F	15 years		VI	Symptom-free	Total regression Alive 2,5 years
Anaplastic astrocytoma	F	12 years	Neoadjuvant treatment	II	No effect	Progression
Glioblastoma multiforme	F	3 years		III	Regression of symptoms	Tumor shrinkage

Discussion

Data originating from clinical temozolomide trials suggest that the drug evokes a relatively small number of adverse effects and is particularly well tolerated by children when administered orally [3, 4, 6, 11-18]. Unfortunately, communications of temozolomide employed in relapsed brain malignancies in children are still scarce, and the analyzed groups of patients are small [13-18]. Data on temozolomide therapy originate mostly from adult centers. A multicenter, randomized clinical trial carried out in large groups of adult patients has demonstrated that temozolomide is more effective in treating relapsed *glioblastoma multiforme* than Procarbazine. The 6-month overall survival in the temozolomide group was 60%, while in the Procarbazine patients the corresponding value was 44% only [4]. In his clinical study of 48 adult patients with recurrent *anaplastic oligodendrogliomas*, who had been previously treated with irradiation therapy and PCV chemotherapy (Procarbazine, Lomustine and Vincristine), Chinot employed temozolomide and demonstrated a complete response in 16.7% patients, a partial response in 27.1% and a stable disease in 39.6% [12]. Also the quality of life improves in patients on temozolomide, and the time lapse before disease progression occurs is prolonged. This has been demonstrated by the largest to-date clinical trial carried out in 525 adult patients with relapsed malignant *gliomas* [5]. Other clinical studies have pointed to a low therapeutic effectiveness of temozolomide in the treatment of malignant brain *gliomas*, but with a clear improvement in the quality of life [6, 10, 11].

In the investigated group of 11 children with relapsed malignant brain tumors or after standard therapy failures, temozolomide seems to be successful in two patients (18%). Once again it is difficult to evaluate this outcome, since both patients who were administered temozolomide had persistent residual tumor mass fragments following standard radiotherapy. Possibly the reaction to temozolomide therapy is found in a slow tumor mass regression following irradiation therapy. A doubtlessly positive palliative effect has been achieved in three children with *medulloblastoma*, who demonstrated resolution of such symptoms as headache, nausea, vomiting, balance disturbances and severe sacrolumbar pain, observed already after the first cycle of therapy. For the period of 2-12 months these patients were in a very good general state and asymptomatic. The drug inhibited the neoplastic process for this time and the patients were able to function without any symptoms of the disease. Other patients showed a brief clinical improvement following temozolomide therapy, yet the drug did not

prevent further progress of the disease. Nevertheless, aware of the fact that the investigated group of patients consisted of individuals without any chances for a cure, we believe that the use of temozolomide in order to achieve even brief remissions allowing the children to be pain-free and capable of normal functioning was justified. No temozolomide -associated toxicity was noted in two children. Four children showed mild bone marrow toxicity of grade II (WHO). Five patients manifested grade III bone marrow aplasia (WHO), while one showed grade IV aplasia and treatment was discontinued. A 19-year old patient died due to a subarachnoid hemorrhage showing no histopathological signs of bone marrow aplasia.

Of two children subjected to preoperative temozolomide chemotherapy, partial tumor regression was achieved in one.

Our results are similar to data from pediatric centers where temozolomide was employed in children. Unfortunately, such reports are still too scarce and predominantly of a preliminary character.

Conclusions

- In view of its oral route of administration, temozolomide is a well tolerated form of chemotherapy in children.
- In 3 children with *medulloblastoma* stabilization of the disease was achieved, for a period of 2 to 12 months and allowed the patients to be pain-free and to function normally.
- The paper sums up the observations of 13 patients. The issue of temozolomide effectivness in children with malignant brain tumors reguires futher studies in a more numerous group of patients.

Elżbieta Korab-Chrzanowska MD, PhD
Division of Radiotherapy
University Children's Hospital of Cracow
265 Wielicka St., 30-663 Cracow, Poland
e-mail: ElKorChrzanowska@poczta.onet.pl

References

1. Newlands ES, Blackledge GRP, Slack JA et al. Phase I trial of temozolomide. *Br J Cancer* 1992; 65: 287-91.
2. O'Reilly SM, Newlands ES, Glaser MG et al. Temozolomide: a new oral cytotoxic chemotherapeutic agent with promising activity against primary brain tumours. *Eur J Cancer* 1993; 29A: 940-2.
3. Yung WKA, Prados MD, Yaya-Tur R et al. Multicenter Phase II Trial of temozolomide in patients with anaplastic *astrocytoma* or anaplastic *oligoastrocytoma* at first relapse. *J Clin Oncol* 1999; 17: 2762-71.
4. Yung WKA, Albright RE, Olson J et al. A phase II study of temozolomide vs. Procarbazine in patients with *glioblastoma multiforme* at first relapse. *Br J Cancer* 2000; 83: 588-93.
5. Yung WKA Temozolomide in malignant *gliomas*. *Semin Oncol* 2000; 27: suppl 6, 27-34.
6. Efstathiou J, Panapoulos C, Samantas E et al. Phase II study of temozolomide in patients with relapsing high grade *glioma* and poor performance status. *Med Oncol* 2000; 17; 106-10.
7. Prados MD Future directions in the treatment of malignant *gliomas* with temozolomide. *Semin Oncol* 2000; 27: suppl 6, 41-46.
8. Friedman H.S. Temozolomide in early stages of newly diagnosed malignant *glioma* and neoplastic meningitis. *Semin Oncol* 2000; 27: suppl 6, 35-40.
9. Friedman HS, Kerby T, Calvert H. Temozolomide and treatment of malignant *glioma*. *Clin Cancer Res* 2000; 6: 2585-97.
10. OsobaD, Brada M, Yung WKA et al. Health releted guality of life in patients with anaplastic *astrocytoma* during treatment with temozolomide. *Eur J Cancer* 2000; 36: 1788-95.
11. Brada M, Hoang-Xuan K, Rampling R et al Multicenter phase II trial of temozolomide in patients with *glioblastoma* multiforme at first relapse. *Ann Oncol* 2001; 12: 149-50.
12. Chinot O-L, Honore S, Dufour H. Safety and efficacy of temozolomide in patients with recurrent anaplastic *oligodendrogliomas* after standard radiotherapy and chemotherapy. *J Clin Oncol* 2001; 19: 2449-55.
13. Nicholson HSA, Ames MM, Krailo M et al. Phase I and pharmacokinetics study of temozolomide (Temodal) in children and adolescentes. A report from the Children's Cancer Group (CCG). *Proc ASCO* 1995; 14A: 1439 abstract.
14. Ouintana J, Zuleta A. Use of Temozolamide in high risk of relapses brain tumor in children- Luis Calvo Mackenna Hospital Santiago- Chile. *Med Pediat Oncol* 2002; 39: 336 abstract.
15. Cefalo G, Ruggiero A, Abate ME et al. High response rate to temozolomide in heavily preteated children and young adults with *medulloblastoma*. *Med Pediat Oncol* 2002; 39: 336 abstact.
16. Epelman S, Melargano R, Arancibia A et al. Phase II study of temozolomide in children and adolescents with brain tumor. *Med Pediat Oncol* 2002; 39: 337 abstract.
17. Verschuur AC, Grill J, Vassal G et al. Temozolomide in pediatric high grade *glioma*: The Institut Gustave Roussy experience. *Med Pediat Oncol* 2002; 39: 338 abstract.
18. Donfrancesco A, De Sio L, Castellano G et al. Phase II of temozolomide in resistant or relapsed pediatric solid tumor. *Med Pediat Oncol* 2002; 39: 337 abstract.

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