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Effects of PCV chemotherapy on oligodendrogliomas and oligoastrocytomas

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Several reports published in the recent years have proven the efficacy of chemotherapy in recurrent forms of low- and high-grade oligodendrogliomas and oligoastrocytomas. The aim of this study was to evaluate the effects of the PCV chemotherapy regime (procarbazine, lomustine, vincristine) in oligodendrogliomas and mixed tumours, to compare treatment results in various groups of patients, to estimate progression-free survival and to identify prognostic factors for progression-free survival. We applied Macdonald' s criteria for assessing response of supratentorial gliomas to chemotherapy in second phase trials. Between the years 1999 and 2003 we performed an analysis of 29 patients. Median time to progression for all patients was 16 months. We observed the following results of chemotherapy without previous surgical treatment: complete response lasting 8 months in a patient after stereotactic biopsy (CR) – 1 (3.4%), partial response (50% tumour regression lasting 9 months) (PR) – 1 (3.4%) and minor response (MR) lasting 19, 26 and 16 months in 3 cases. 17 patients were found to have stable disease. In 7 cases disease progression (PD) was observed with a median time to progression of 5 months. We found no statistically significant differences between time to progression and age, sex, performance status measured in KPS, pathological diagnosis, tumour laterality within the brain hemispheres and central area and steroid therapy both in univariate and multivariate tests. The only statistically significant factor predicting the length of time to progression was the number of chemotherapeutical cycles. Non-certain statistical significance was achieved in case of previous teleradiotherapy and character of tumour. Chemotherapy was generally well tolerated. In 5 cases we observed myelotoxicity in grade 3; in 2 cases – in grade 4. Our results indicate that some oligodendrogliomas and mixed tumours may respond to PCV chemotherapy.

Ocena efektów chemioterapii według schematu PCV u pacjentów ze skąpodrzewiakami i skąpodrzewiakogwiaździakami

Badania opublikowane w ciągu ostatnich lat wskazują na skuteczność chemioterapii w nawrotowej postaci skąpodrzewiaków anaplastycznych, skąpodrzewiaków w niskim stopniu złośliwości i guzach mieszanych. Celem pracy była ocena skuteczności chemioterapii według standardowego schematu PCV (prokarbazyna, lomustyna – CCNU, winkrystyna) u pacjentów z rozpoznanym guzem mózgu o charakterze skąpodrzewiaka lub guza mieszanego skąpodrzewiako-gwiaździaka. Wykorzystano kryteria odpowiedzi na leczenie glejaków nadnamiotowych dla badań II fazy, ustalone przez Macdonalda. Analizie poddano grupę 29 pacjentów. Mediana czasu przeżycia wolnego od progresji dla wszystkich pacjentów wynosi 16 miesięcy. Biorąc pod uwagę efekty chemioterapii uzupełniającej PCV, nie uwzględniające efektów leczenia operacyjnego, całkowitą odpowiedź (CR) trwającą 8 miesięcy stwierdzono u 1 pacjentki po biopsji stereotaktycznej, u której guz uległ całkowitej regresji, częściową odpowiedź (PR) u 1 pacjenta z wynikiem czasu wolnego od progresji równym 9 miesięcy. Mniejszą odpowiedź (MR) z wynikami czasu wolnego od progresji 19, 26 i 16 miesięcy stwierdzono w trzech przypadkach, 17 pacjentów opisano jako stan stabilny (SD). W 7 pozostałych przypadkach zaobserwowano progresję choroby (PD) z wynikiem mediany czasu wolnego od progresji 5 miesięcy.

Wykorzystując testy analizy dla wielu zmiennych oraz analizę porównawczą dla dwóch zmiennych nie znaleziono statystycznie istotnej zależności pomiędzy wiekiem, płcią, jakością życia ocenioną w skali Karnofsky'ego, a rozpoznaniem histopatologicznym, półkulą mózgu, w której znajdował się guz, obecnością guza w obszarze środkowym, sterydoterapią. Istotnym statystycznie czynnikiem predykcyjnym, mającym wpływ na długość czasu wolnego od progresji, była liczba cykli chemioterapii, które chorzy ukończyli ($p=0,01$). Tendencję w kierunku statystycznej znamienności stwierdzono w odniesieniu do wcześniejszej radioterapii zewnętrznej ($p=0,02$ i log rank $p=0,22$) oraz w przypadku charakteru guza ($p=0,02$ i log-rank

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p=0,33). U 5 pacjentów (17,2%) stwierdzono objawy 3 stopnia i u dwóch pacjentek (6,9%) objawy 4 stopnia toksyczności hematologicznej, głównie w postaci leukopenii i trombocytopenii. Przedstawione badanie wskazuje, że niektóre skąpodrzewiaki i guzy mieszane mogą reagować na chemioterapię PCV.

Key words: oligodendrogliomas, chemotherapy, PCV
Słowa kluczowe: skąpodrzewiaki, chemioterapia, PCV

Introduction

Primary brain tumours comprise nearly 2% of all neoplasms. Every year over 3000 new cases of intracranial tumours are diagnosed in Poland and 17000 cases in United States [1-3]. Gliomas may be divided into several types, the most frequent being astrocytomas and oligodendrogliomas. Both of them may occur as tumours of low or high grade of malignancy. High-grade gliomas develop either as primary tumours or may transform from pre-existing low-grade forms [4].

Oligodendroglial tumours are a distinct clinical-pathologic entity, which cause a lot of interest due to their exceptional chemosensitivity. They are rare and represent between 5% and 20% of intracranial gliomas [5, 6].

Prognosis

The survival time of patients with oligodendrogliomas depends upon several factors, such as the grade of malignancy, age, performance status, extent of resection and postoperative radiation [6-8]. Recent studies have proved that allelic loss of chromosome arms 1p and 19q might be a marker of better prognosis and chemosensitivity [5]. Low-grade oligodendrogliomas have good prognosis [9, 10]. Recent reports present patients surviving over 16 years after diagnosis [11]. Median survival with low-grade mixed tumours is shorter than with oligodendrogliomas [8, 12]. Patients with anaplastic oligodendrogliomas survive longer than patients with other malignant gliomas, which may arise from tumour natural history or better reaction to treatment [9, 10].

Treatment of oligodendrogliomas

Surgery is the main treatment modality for intracranial gliomas, as in oligodendrogliomas, where resection is the standard initial mode of treatment. Surgery has cyto-reductive value, improves postoperative treatment (radiotherapy and chemotherapy), decreases steroid dosage, reduces symptoms and prolongs survival [5, 13-15]. In case of poorly differentiated tumours there is no evident data indicating that gross resection is more beneficial than subtotal [16].

Adjunctive radiation therapy is a necessity, although it may produce numerous complications [13]. Application of radiotherapy in low-grade oligodendroglioma has been questioned [17, 18].

Several recent reports present an analysis of the chemosensitivity of anaplastic oligodendrogliomas and oligoastrocytomas [5, 19-31].

In comparison with other types of gliomas, oligodendrogliomas respond to alkylating agents. The PCV (procarbazine+lomustine +vincristine) regimen has appeared to be effective in providing durable responses in anaplastic or aggressive oligodendrogliomas. The term "aggressive" stands for low or high-grade tumours, with rim enhancement and causing neurological symptoms [22]. In 1988 Cairncross and Macdonald have reported a series of recurrent oligodendrogliomas sensitive to the PCV regimen [20]. They have also demonstrated the chemosensitivity of anaplastic and aggressive oligodendroglioma to the PCV regimen [22].

In another paper Cairncross presents a nearly 75% response rate to the PCV regimen in patients with malignant oligodendroglioma [21]. In low–grade oligodendroglioma durable remissions with clinical improvement have been observed [4, 26, 28]. Fortin recommends chemotherapy as the initial postoperative mode of treatment in oligodendrogliomas. Radiotherapy should be reserved for anaplastic forms [5, 32], in case of which chemotherapy and then radiotherapy with at least a seven-day gap between are effective treatment modalities after the surgical procedure is completed [5]. It is common opinion that oligodendrogliomas are the only chemosensitive brain tumours and that in low-grade forms systemic therapy may be administered in conjunction with radiotherapy [13, 33]. The PCV regimen is not effective in the management of anaplastic astrocytomas [34]. Kapelle reports its administration in glioblastoma multiforme with quite good tolerance [35]. The results of temozolomide chemotherapy in recurrent forms of oligodendrogliomas and oligoastrocytomas appear to be promising [36-38].

Oligodendrogliomas respond to this treatment probably because they do not have 0^6-metylguanin-DNA-metyltransferase (MGMT), which is a repairing enzyme. Nitrosoureas alkylate DNA and this very damage may be repaired by methyltransferaze [39].

The PCV regimen

The standard PCV regimen consists of 3 chemotherapeutic agents administered altogether in 6 cycles with 8-week gaps:

CCNU: Lomustin 110 mg/m^2 orally day 1
PCB: Procarbazine/ 60mg/m^2 orally day 8-21
VCR: Vincristine 1.4 mg/m^2 iv <2 mg on day 8 and 29

Despite increased toxicity some clinicians prefer intensified PCV (I-PCV) administered every 6 weeks in higher doses [11, 13, 22, 40].

Aim

The aim of this study was to evaluate the effects of PCV chemotherapy (procarbazine, lomustine, vincristine) in oligodendrogliomas and mixed tumours, to compare the results in various groups of patients, to estimate progression-free survival and identify the factors prognostic for progression-free survival (e.g.: patient age, patient sex, performance, tumour laterality, histopathologic diagnosis, surgery, radiation therapy).

Material and methods

The study was initiated in July 1999. Of the 35 patients who had been entered for analysis until January the 1st 2003, 6 patients (who had not completed cycle 2, or with whom contact had been lost) were excluded from the analysis. Altogether we analysed the cases of 29 patients (aged 26 – 67 years, median 38) (Table I) with histologically confirmed oligodendrogliomas or mixed oligoastrocytomas. In all cases the performance status was good (a minimum of 70 points acc. to the Karnofsky scale); there was no history of previous chemotherapy nor of any neurological or psychiatric disorders, blood cell count parameters were stable: white blood count >3.000; platelets >100.000/mm^3; haemoglobin >10 g/dl.

Table I. Clinical characteristics

Parameter		No of patients N=29	%
Age (years)			
Range	26-67		
Median	38		
Sex	Male	15	51.7%
	Female	14	48.3%
KPS			
Range	70-100		
Median	90		
	KPS = 80-100	25	86.2%
	KPS< 80	4	13.8%
Previous treatment	Teleradiotherapy	12	41.4%
	Brachytherapy	6	20.7%
	Surgery in reccurence	6	20.7%
	Gross resection	4	13.8%
	Subtotal resection	14	48.3%
	Biopsy	16	55.2%
Histopathology	Oligodendroglioma II°	14	48.3%
	Oligoastrocytoma II°	4	13.8%
	Oligodendroglioma III°	8	27.6%
	Oligoastrocytoma III°	3	10.3%

Neurological deficits as dominant symptoms were observed in 14 cases (48.3%), epilepsy in 23 cases (79.3%). The histological diagnoses were as follows: 14 oligodendrogliomas (48.3%), 8 anaplastic oligodendrogliomas (27.6%), 4 oligoastrocytomas (13.8%) and 3 anaplastic oligoastrocytomas. 14 (48.3%) patients had completed all 6 cycles, 2 (6.9%) patients had completed 2 and 4 cycles only due to myelotoxicity, 3 (10.3%) patients died before the 4th cycle.

In 9 cases (31%) PCV chemotherapy was the single initial therapeutic modality after stereotactic biopsy, in another 8 cases (27,6%) it was administered after surgery as neoadjuvant chemotherapy without previous radiotherapy.

We evaluated the clinical and radiological status (MRI, CT) after every other clinical cycle, while the SPECT scans were obtained before the 1st and after the 4th and 6th cycle.

Criteria of response to chemical treatment

Evaluation of response was based on performance, neurological and clinical status and radiological findings (enhanced CT or MRI scans). Response was graded according to Macdonald's criteria for phase II studies of supratentorial gliomas based on largest perpendicular area of enhancement of the tumour [23, 41-44]:

CR: Complete response – no tumour in enhanced scans, no steroids, neurologically stable or improved.
PR: Partial response – >50% decrease in tumour size, stable or reduced dose of steroids, neurologically stable or improved
MR: Minor response – 25%-50% decrease in tumour size, stable or reduced dose of steroids
SD: Stable disease – no change or <25% change in tumour size, stable or reduced dose of steroids, neurologically stable, improved or deteriorated
PD: Progressive disease – >25% increase in tumour size or new enhancement area, stable or increased dose of steroids, stable or deteriorated neurological status.

Statistical analysis

Time to progression was counted from the start of chemotherapy to the day of progression or death. Progression-free survival was estimated acc. to the Kaplan-Meier method. Univariate analyses were performed using the log-rank test and multivariate analyses using Cox's proportional hazard model. We assumed $p \leq 0.05$ to be statistically significant [45].

Results

The shortest observed time to progression was 3 months, the longest – 26 months, median time to progression for all patients was16 months (Figure 1). As for effects of chemotherapy without previous surgical treatment the following results were achieved: complete response lasting 8 months after stereotactic biopsy (CR) – 1 (3.4%) (Figures 8, 9) partial response (50% tumour regression lasting 9 months) (PR) – 1 (3.4%). Minor response (MR) lasting 19, 26 and 16 months – 3 (10.2%). 17 patients (incl. 3 who had received chemotherapy after gross-total resection without radiological evidence of tumour before and after chemotherapy and with stable neurological status) were qualified as stable disease. In 7 cases disease progression (PD) was observed with median time to progression of 5 months (Table II, Figure 2).

Table II. Results of PCV chemotherapy

Response	N	%	MTP months
CR	1	3.4	-
PR	1	3.4	-
MR	3	10.3	-
SD	17	58.6	32.0
PD	7	24.1	5.0

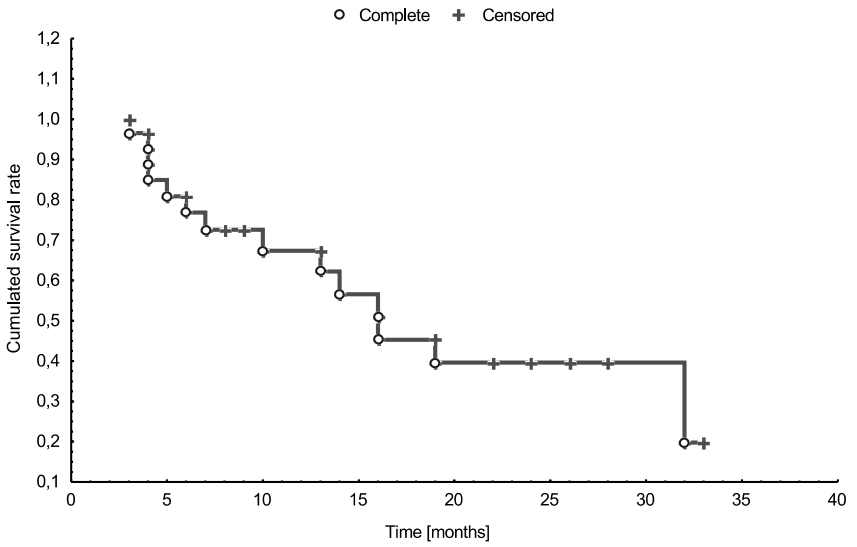

Figure 1. Kaplan-Meier cumulated progression-free survival rate. Median time to progression (16 months)

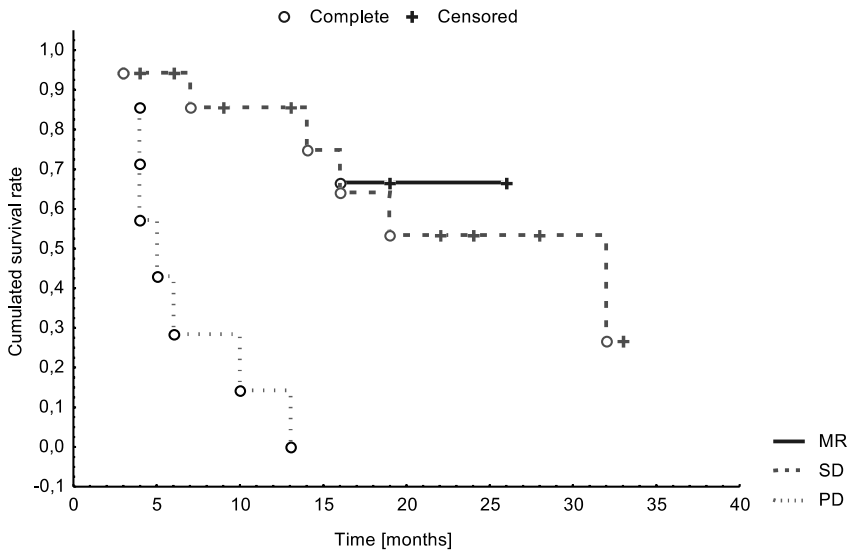

Figure 2. Kaplan-Meier progression-free survival rate in relation to response

Results of chemotherapy in relation to histopathological diagnosis

(Table III, Figure 3).

Table III. Results of chemotherapy in relation to histopathologic diagnosis

Response	N	%	MTP months
OII	14	48.3	32
OIII	8	27.6	16
OAII	4	13.8	7
OAIII	3	10.3	19

Median time to progression was 32 months in oligodendrogliomas, 16 months in anaplastic oligodendrogliomas, 7 months in mixed tumours and 19 months in anaplastic mixed tumours.

Prognostic factors

Both in multivariate and univariate analysis we found no statistically significant correlation between progression free survival and age (p=0.3), sex (p=0.54), performance status (p=0.76), histopathological diagnosis (p=0.16), brain hemisphere with tumour location (p=0.72), presence of the tumour in central area of brain (p=0.13), steroid therapy (p=0.12) and application of chemotherapy as the sole treatment after stereotactic biopsy (p=0.82). Median time to progression for patients less than 40 years of age was 19 months, while for patients with KPS <80 points it was only 5 months. Statistical significance was achieved in case of radiation therapy (p=0.02) applied previously in patients referred for chemotherapy. However, due to a certain lack of complete observations median time to progression could have not been counted in group of non-irradiated

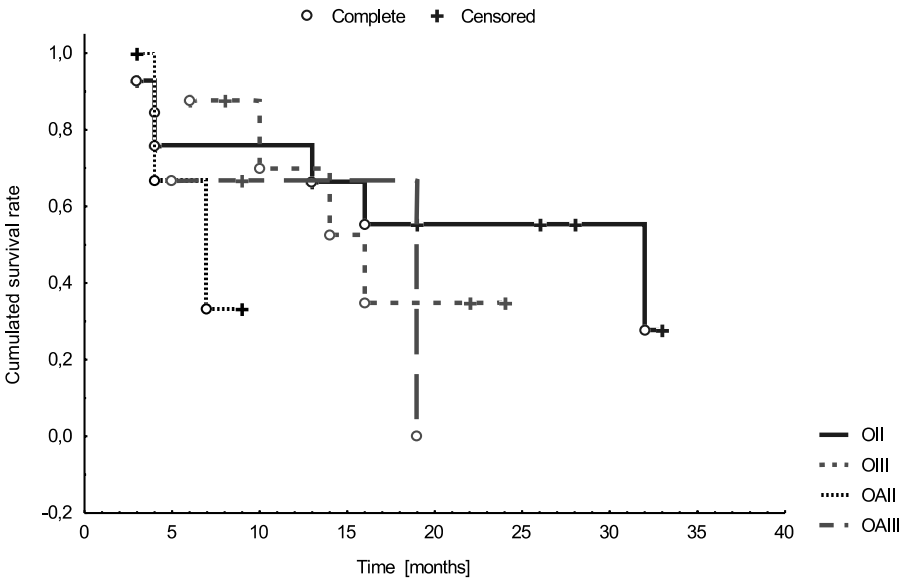

Figure 3. Kaplan-Meier progression-free survival rate in relation to histopatologic diagnosis

patients, while in the group of irradiated patients it was 14 months – shorter than in the entire examined group (Figure 4).

It is likely that gross total removal has significant influence on progression free survival. However, neither the median nor any statistical significance could have been estimated due to the small number of cases (Figure 6).

Tumour characteristic – primary or recurrent – achieved statistical significance (p=0.02) acc. to a multivariate analysis using Cox's proportional hazard model. Median time to progression for primary tumours was 16 months in the entire group, while for patients with recurrent tumours it was shorter – only 14 months. However, this was not found to be statistically significant in the univariate analysis using the log-rank test (p=0.33) (Figure 5).

The one statistically significant factor affecting the length of time to progression was the number of administered cycles of chemotherapy (p=0.01) (Figure 7). Uncertain statistical significance was achieved in relation to such factors as previous teleradiotherapy and recurrent character of the tumour, which shortened the time to progression.

Toxicity

Generally chemotherapy was well tolerated. In 5 patients (17.2%) we observed grade 3, and in 2 patients (6.9%) – grade 4 haematological toxicity (leucopoenia and thrombocytopoenia). In a number of patients we observed

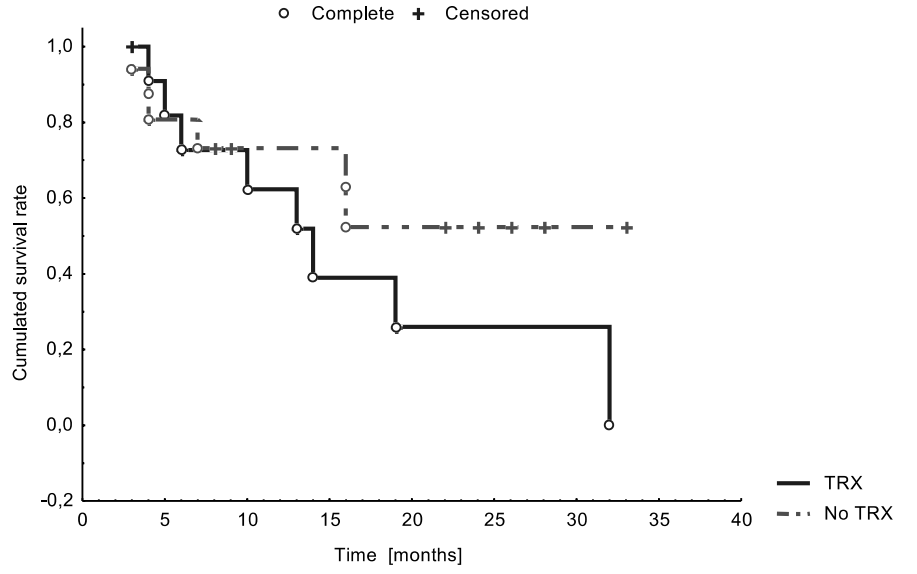

Figure 4. Kaplan-Meier progression free survival in relation to previous irradiation

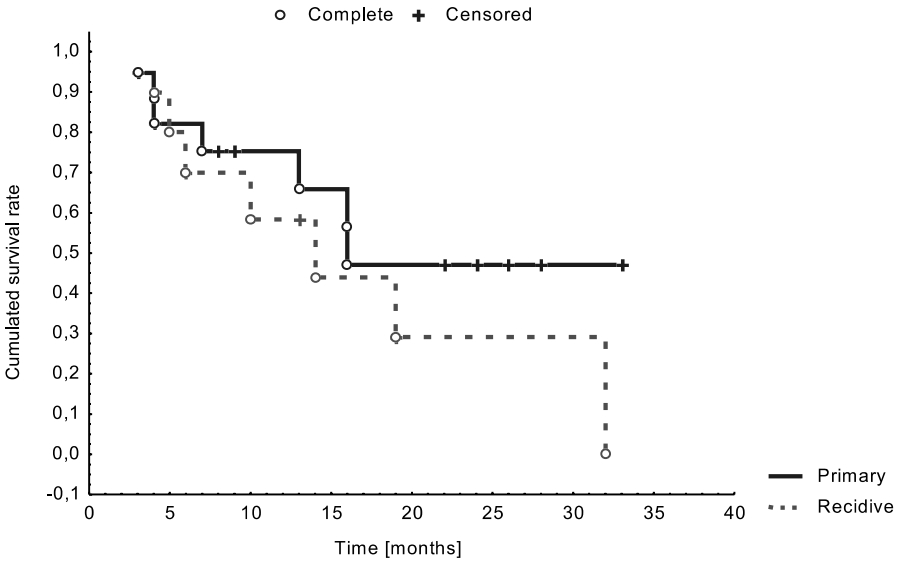

Figure 5. Kaplan-Meier progression free-survival rate in relation to character of the tumour

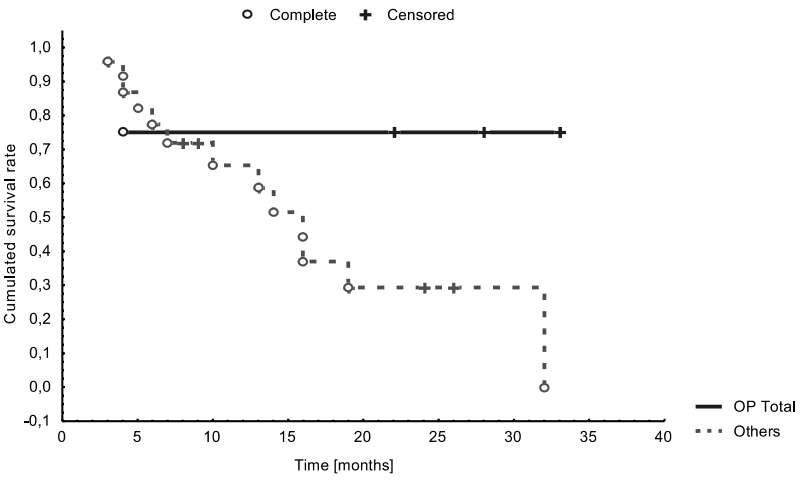

Figure 6. Kaplan-Meier progression-free survival rate after gross-total surgery

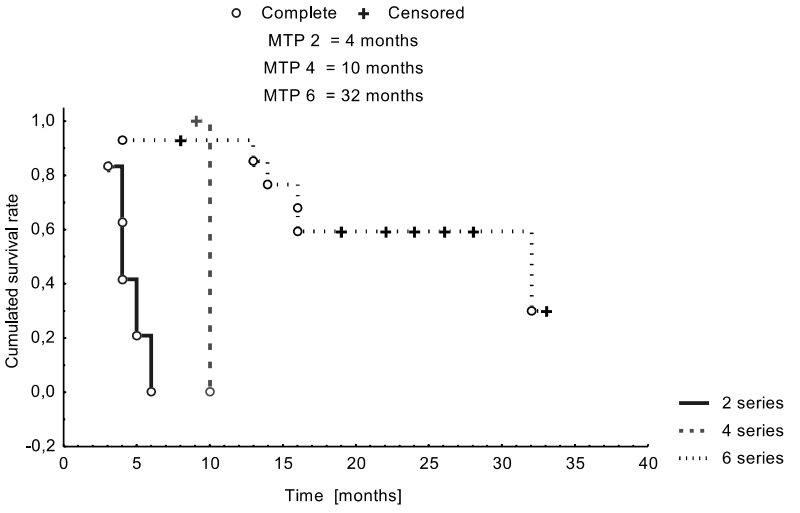

Figure 7. Kaplan-Meier progression-free survival rate after 2nd, 4th, 6th cycle of chemotherapy

discrete symptoms of myelotoxicity, but after haematological normalization chemotherapy was continued. In 2 cases chemotherapy had to be discontinued due to grade 4 toxicity. In 1 case we observed an eczematic reaction to Natulan, in another case there was transient transaminaze elevation.

Discussion

The presented results have been obtained in the course of a phase II study, in which the use of the chemotherapeutical agent had been assessed on the basis of clinical and therapeutical criteria of response. The efficacy of the agent is expressed as the percentage of objective responses (i.e. complete or partial responses) [14, 46]. In the presented study the small number of patients and the short observation time are an evident drawback, as they would be in the case of other similar phase II trials.

The efficacy of PCV chemotherapy has not yet been reported in Polish literature

In papers reporting the role of chemotherapy on central nervous system tumours one can find no direct relation between tumour response and progression-free survival or overall survival. Several other factors can influence survival – previous surgery, radiation therapy or steroid therapy. These factors may affect the interpretation of the results of radiological examinations.

Response criteria should include radiological scans, neurological status assessment and steroid doses [13, 41, 43]. However, the most important mark of efficacy is time to progression. There exists no direct correlation between the category of response and time to progression [41]. In patients who had undergone brachytherapy or teleradiotherapy the effects of these modalities may be observed during chemotherapy. Radiotherapy can decrease permeability of brain vessels, which may be interpreted as tumour regression in enhanced CT or MRI scans [13].

In 17 cases (58.6%) the PCV regimen was applied as neoadjuvant chemotherapy, after stereotactic biopsy (9 cases – 31%) or tumour resection (8 cases – 27.6%), but before radiation therapy. In 12 patients (41.4%) PCV chemotherapy was administered as adjuvant treatment, after surgery and radiation (9 cases – 32%) or stereotactic biopsy and radiation (3 cases- 10.3%).

Four patients, who had undergone gross total removal, had no radiological or neurological evidence of tumour before chemotherapy. In 1 case progression of disease was observed, in 3 other cases stable disease was assessed, i.e. the effects of combined surgical and chemical treatment were good and could have been interpreted as complete response.

We presume that chemotherapy may control tumour growth and slow down its progression, as well as provide symptom relief. In one isolated case we observed a new tumour area in SPECT, but without enhancement in CT scans. It could have been considered to be disease progression but acc. to the classical criteria of response to chemical treatment only radiological scans are considered eligible.

We have observed that low-grade mixed tumours have a poorer response than low-grade oligodendrogliomas. Median progression-free survival for oligodendrogliomas (OII – 32 months) is longer than for oligoastrocytomas (OAII – 7 months). Several reports indicate that oligodendrogliomas respond better to chemotherapy than oligoastrocytomas [5, 22, 24]. Complete response was observed in 1 patient with anaplastic oligodendroglioma (Figures 8, 9). Minor response was achieved in 2 patients after surgical treatment and in 1 patient after stereotactic biopsy. In some patients we observed delayed radiological response after clinical improvement. Decreases in frequency of epileptic seizures and neurological deficit

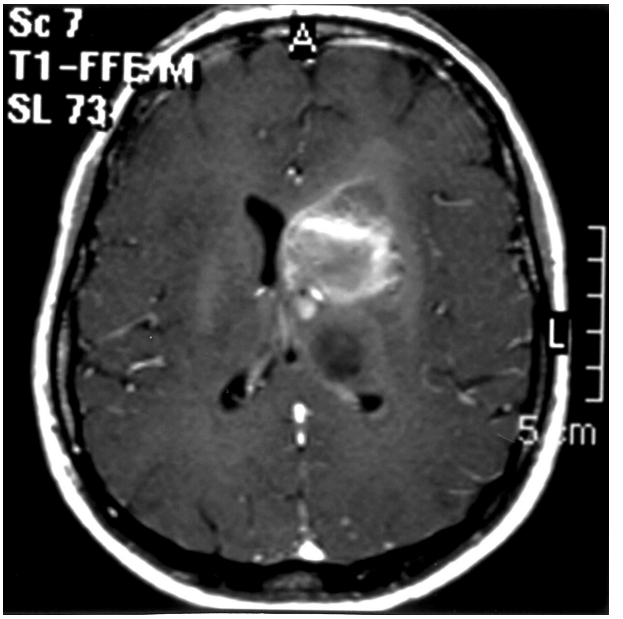

Figure 8. 40-years old female after stereotactic biopsy with anaplastic oligodendroglioma before chemotherapy

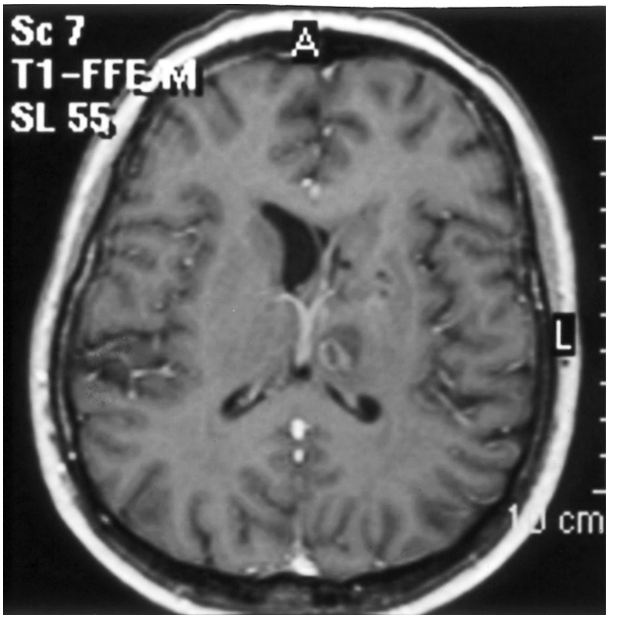

Figure 9. The same patient after chemotherapy. Complete response

improvement were observed after the second or fourth cycle of chemotherapy, but radiological regression much later. These observations confirm that oligodendrogliomas may react to chemical treatment with a certain delay.

Some clinicians administer PCV regimen prior to irradiation thus allowing to evaluate the effects of chemotherapy on the residual tumour. The objective response ratio is higher in those recurrent oligodendrogliomas in which radioterapy had not been applied [31]. Acc. to Glass this regimen is more effective as an initial mode of treatment before radiation therapy [23]. Theoretically, radiation decreases the permeability of the blood-brain barrier, thus also affecting its penetration by oncolytic drugs [31]. Kyritsis suggests the induction of new mutations, which may lead to the development of forms more aggressive and resistant to treatment [25].

19 patients (65.5%) had primary tumours; in 10 other patients chemotherapy was employed when recurrence was observed. Disease progression was observed in 40% of recurrent tumours and 16% of primary ones. Complete response and partial response was observed only in primary tumours. The character of the tumour affected the duration of progression-free survival; in case of recurrent tumours it was shorter – only 14 months. Cairncross had reported better response in recurrent anaplastic oligodendrogliomas than in primary ones [20, 21], while Kyritisis had observed worse results in primary anaplastic tumours [25]. Van den Bent had achieved similar results in both groups [40].

Oligodendrogliomas and oligoastrocytomas require surgical treatment. Chemotherapy and radiotherapy are only adjunctive forms of treatment [4, 5, 16]. In 36% patients after radiotherapy symptoms of dementia and brain necrosis occur, while 20% patients after chemotherapy report hepatotoxic and hematotoxic side effects [19]. Surgical treatment is safer – new neurological deficits are observed only in 6% of patients [19].

Chemotherapy administered to patients with relatively lengthy survival in the presence of residual disease allows delaying radiation therapy, which is potentially detrimental [4]. Low-grade oligodendrogliomas and oligoastrocytomas show no progressive growth with stable neurological status for several years [11]. The range of surgical resection has an important impact on the time to progression [7]. In the reported studies tumour resection affected time to progression, although not significantly. Acc. to several reports the effect of gross-total resection is obvious in low-grade tumours [7, 10, 47]. Fortin has not reported any differences as to the effects of chemotherapy in patients after gross total resection, subtotal resection or biopsy [5]. Surgical treatment has a decompressing effect and decreases the amount of acquired genetic anomalies leading to deceleration of anaplastic progression and delay of recurrence. It provides better penetration of chemotherapeutic agents.

In case of low-grade oligodendrogliomas chemotherapy may improve the neurological status and lengthen time to progression [4, 26, 28]. In our studies median time to progression in low-grade oligodendrogliomas was the longest – 32 months, although in most of the cases stable disease was observed. Complete response was observed in one patient with anaplastic oligodendroglioma located in the central area of the brain. Chemotherapy has an effect in anaplastic and aggressive oligodendrogliomas [21, 22].

Conclusions

1. Our results indicate that some oligodendrogliomas or oligoastrocytmas may respond to PCV chemotherapy.
2. According to our study results the only statistically significant factor predicting the length of survival until progression was the number of cycles of chemotherapy. Uncertain statistical significance was achieved by previous teleradiotherapy and by the character of tumour.

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