Co-deletion of 1p/19q as Prognostic and Predictive Biomarker for Patients in West Bohemia with Anaplastic Oligodendroglioma

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Abstract. *Background: Anaplastic oligodendrogliomas (AO) are rare tumors. Two phase III clinical trials (RTOG 9402 and EORTC 26951) proved favorable effects of radiotherapy (RT) with chemotherapy (procarbazine, lomustine and vincristine; PCV) in patients with AO carrying chromosomal mutation of co-deletion1p/19q even if it was not the primary endpoint of these studies. We assessed 1p/19q co-deletion as a prognostic and predictive biomarker for our patients with AO. Materials and Methods: 1p/19q co-deletion was assessed by fluorescence in situ hybridization in tumor samples from 23 patients and correlated with progression-free (PFS) and overall (OS) survival for the entire cohort and for the subgroups of patients with different treatment (neurosurgery plus RT alone vs. RT plus PCV). Results: 1p/19q co-deletion was identified in 12 out of 23 tumors (52.2%). Patients with co-deletion had longer OS (587 vs. 132 weeks, p=0.012) and a trend for longer PFS (321 vs. 43 weeks, p=0.075). Patients with co-deletion treated with neurosurgery and RT plus PCV vs. neurosurgery and RT alone also had longer OS (706 vs. 423 weeks, p=0.008). There was no survival difference for patients without 1p/19q co-deletion in relation to treatment. Conclusion: The prognostic value of 1p/19q co-deletion in our patients with AO was verified. The strong positive predictive value of this biomarker for OS was also shown for patients with co-deletion treated with neurosurgery and RT plus PCV vs. neurosurgery and RT alone.*

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Anaplastic oligodendroglial tumors (oligodendrogliomas and oligoastrocytomas grade III; AO) are rare types of cancer that represent only 0.5-1.2% of all primary brain tumors (1, 2). The highest incidence of AO is between 45 and 50 years of age. The major symptoms are epileptic seizures, focal symptoms that affect the frontal and the temporal regions of the brain, or later the symptoms of intracranial hypertension. The standard therapy for AO comprises neurosurgery followed by radiotherapy (RT) and chemotherapy. RT is administered to a total dose of 54 to 60 Gy. Chemotherapy consists of a triple combination of procarbazine, lomustine and vincristine (PCV) or temozolomide (3, 4).

Oligodendrogliomas are known to respond better to RT and chemotherapy than other types of malignant primary brain tumors. Their sensitivity to RT was discovered as early as the 1980s (5), and the positive effect of chemotherapy, PCV and temozolomide, was found later (6-8). Research into molecular genetics of oligodendrogliomas offers new knowledge in the diagnosis and treatment of these tumors and has an impact on their management. The very frequent genetic aberration of oligodendroglial tumors is the co-deletion of chromosome 1p and 19q. This 1p/19q co-deletion means the loss of genetic material from the short arm of chromosome 1 (1p) and the long arm of chromosome 19 (19q) in the tumor and became the first biomarker in neuro-oncology discovered in 1994 (9). 1p/19q Co-deletion was found to be an important positive prognostic biomarker of this disease (4, 10-14).

Recently, the long-term results of two large independent phase III clinical trials, the Radiation Therapy Oncology Group (RTOG) 9402 and European Organization for Research and Treatment of Cancer (EORTC) 26961 trials, also demonstrated the strong predictive role of 1p/19q co-deletion for patients with AO treated with chemotherapy. Patients with tumors with1p/19q co-deletion that were

treated with RT and PCV had a significantly longer median overall survival (OS) than patients treated only with RT. There was no significant difference in median OS for patients without 1p/19q co-deletion that were treated either by RT alone or RT plus PCV (12, 13).

The aim of this study was to analyze the 1p/19q status in tumors of patients with AO treated in West Bohemia. We assessed the prognostic role of this biomarker for the entire patient cohort, as well as the ability to predict the better OS and PFS for patients treated with RT plus chemotherapy.

Patients and Methods

Patients. We performed a study of 23 patients with a diagnosis of WHO grade III oligodendroglioma, anaplastic oligodendroglioma (n=23; 13 males and 10 females; mean age=55.4 years) who were treated with the standard protocol at the Faculty Hospital Plzen, Czech Republic (neurosurgery plus RT alone, n=10; neurosurgery plus RT and PCV, n=13) (Table I).

Mutation detection. Deletion of 1p and 19q in tumor tissue samples were primarily assessed with fluorescence *in situ* hybridization (FISH) with locus-specific probes (10 μl mixture) LSI 1p36/1q25 or LSI 19q13/19p13 (Vysis/Abbott, Downers Grove, IL, USA). A positive result for 1p/19q co-deletion was assessed as the loss of 1p36 or 19q13 signal in more than 50% of nuclei.

Statistical analysis. OS was defined as the time between the diagnosis and death or last follow-up; PFS was defined as the time between the diagnosis and recurrence or last follow-up. Kaplan–Meier survival curves were plotted and the survival distributions were compared with the use of the Wilcoxon test. Reported *p*-values are two-sided; *p*-values of less than 0.05 were considered to indicate statistical significance.

Table I. *Patients' demographics and clinical characteristics.*

Characteristic	
Gender	
Male	13
Female	10
Age, years	
Median	55.4
Range	25-72
mRS	
Median	3.35
Range	0-6
Postoperative treatment	
RT alone	10
RT + PCV	13

mRS, Modified Rankin Scale; RT, radiotherapy; PCV, procarbazine, lomustine and vincristine.

Table II. *Results for progression-free survival and overall survival differences in patients with anaplastic oligodendroglioma in relation to 1p/19q co-deletion.*

Variable	N	Median (±SD), weeks	*p*-Value*
Overall survival			
1p/19q co-deleted	12	587 (±61.3)	0.012
1p/19q negative	11	132 (±71)	
Progression-free survival			
1p/19q Co-deleted	12	321 (±152.8)	0.075
1p/19q Co-deletion-negative	11	43 (±55)	

*Wilcoxon test.

Results

1p/19q Co-deletion was detected in 12 out of 23 patient tumor samples (52.2%). Patients with tumors with co-deletion had a significantly longer median OS than patients without 1p/19q co-deletion (587±61.3 *vs*. 132±71 weeks, respectively, $p=0.012$) (Table II and Figure 1A). There was also the trend for better median PFS in patients with tumors with co-deletion than in those without (321±152.8 *vs*. 43±55 weeks, respectively, $p=0.075$) (Table II and Figure 1B).

In the subgroup of patients with tumors with co-deletion of 1p/19q (n=12), the median OS was significantly longer in those treated with neurosurgery plus RT and PCV (n=7) in comparison to patients that were treated with neurosurgery followed by RT alone (n=5) (706±15.7 *vs*. 423±292.5 weeks, respectively, $p=0.008$) (Table III and Figure 2A). On the other hand, there was no significant difference in median PFS in the subgroup of patients treated with neurosurgery plus RT and PCV *vs*. those treated with neurosurgery plus RT alone (374±124.5 *vs*. 321±129.5 weeks, respectively, $p=0.626$) (Table III and Figure 2B).

In contrast to the previous results, in the subgroup of patients without 1p/19q co-deletion (n=11), the median OS was not significantly different in those treated with neurosurgery plus RT and PCV (n=6) in comparison to those treated with neurosurgery followed by RT alone (n=5) (182±86.3 *vs*. 53±32.8 weeks, respectively, $p=0.223$) (Table III and Figure 3A); there was also no significant difference in the median PFS (43±92.5 *vs*. 26±7.7 weeks respectively, $p=0.523$) (Table III and Figure 3B).

Discussion

The molecular genetic characteristic of oligodendroglial tumors is frequent co-deletion of chromosome 1p and 19q. This genetic aberration was identified in 1994 and became the first biomarker in neuro-oncology (9). The mechanism of 1p/19q co-deletion is the unbalanced translocation t(1;19)(q10;p10) (15). Recently, the presence of mutations in two important tumor-suppressor genes, capicua (Drosophila)

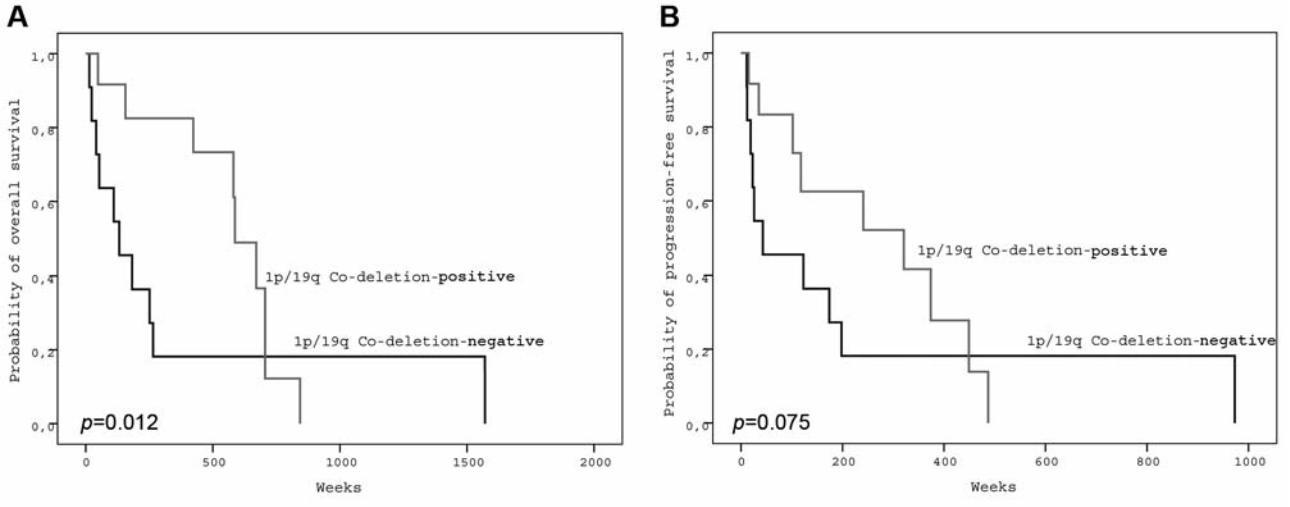

Figure 1. *Overall (A) and progression-free (B) survival of patients with anaplastic oligodendroglioma in relation to 1p/19q co-deletion status.*

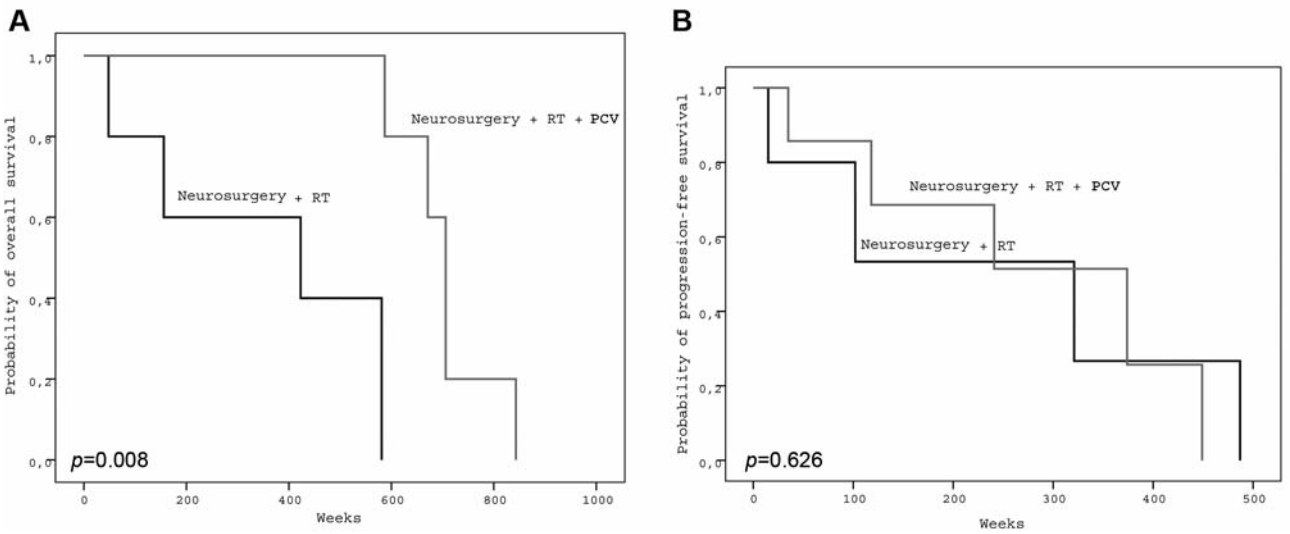

Figure 2. *Overall (A) and progression-free (B) survival of patients with anaplastic oligodendroglioma and 1p/19q co-deletion in relation to the treatment protocol [neurosurgery plus radiotherapy (RT) vs. neurosurgery plus RT and procarbazine, lomustine and vincristine (PCV)].*

homolog (*CIC*) located on 19q13.2, and far upstream element-binding protein (*FUBP1*) on the 1p chromosome, was discovered in the majority of oligodendrogliomas with 1p/19q co-deletion (16, 17). Mutations in these genes are probably involved in the formation and progression of oligodendrogliomas. However, their true significance in neoplastic diseases remains to be verified.

Co-deletion of 1p/19q appears almost exclusively in oligodendroglial tumors (80% to 90% of grade II oligodendrogliomas and 50% to 70% of AO) (18, 19). This chromosomal mutation in oligodendrogliomas can be used in clinical practice as an important diagnostic, prognostic, as well as predictive biomarker. From the diagnostic point of view, the presence of 1p/19q co-deletion supports the diagnosis of oligodendroglioma, especially in cases where the histological findings are not clear. Some other tumor types may also mimic oligodendrogliomas, such as dysembryoplastic neuroepithelial tumors, neurocytomas, clear cell ependymomas and small cell anaplastic astrocytomas. These tumors usually do not have 1p/19q co-deletion and this biomarker is a useful diagnostic aid in these clinical cases (10).

The presence of 1p/19q co-deletion has a role as an important positive prognostic biomarker of the disease.

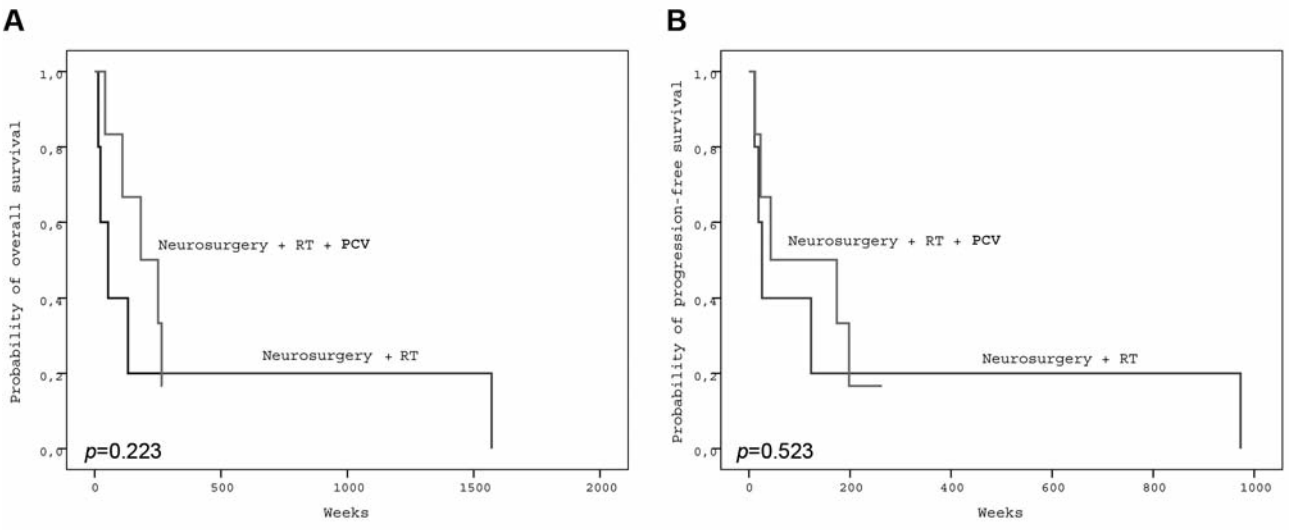

Figure 3. *Overall (A) and progression-free (B) survival of patients with anaplastic oligodendrogliomas without 1p/19q co-deletion in relation to the treatment protocol [neurosurgery plus radiotherapy (RT) vs. neurosurgery plus RT and procarbazine, lomustine and vincristine (PCV)].*

Table III. *Results for progression-free (PFS) and overall (OS) survival differences in patients with anaplastic oligodendroglioma treated with neurosurgery plus radiotherapy (NRT) or with neurosurgery plus radiotherapy and procarbazine, lomustine and vincristine (NRT-PCV) in relation to 1p/19q co-deletion.*

1p/19q Co-deletion status	Median OS (±SD), weeks	*p*-Value*	Median PFS (±SD), weeks	*p*-Value*
Co-deletion (n=12)				
NRT-PCV (n=7)	706±15.7	0.008	374±124.5	0.626
NRT (n=5)	423±292.5		321±129.5	
Without co-deletion (n=11)				
NRT-PCV (n=6)	182±86.3	0.223	43±92.5	0.523
NRT (n=5)	53±32.8		26±7.7	

*Wilcoxon test.

Retrospective and prospective studies found significantly better survival outcome for patients with oligodendroglioma with 1p/19q co-deletion than for those without (4, 10-14, 20).

Co-deletion of 1p/19q was found to have substantial clinical significance as a strong predictive biomarker for patients with anaplastic oligodendroglial tumors. Its detection predicts longer survival with PCV and RT in comparison to RT alone, as recently shown by the long-term follow-up of two important phase III randomized clinical trials, RTOG 9402 and EORTC 26951 (12, 13). These trials are producing substantial results and leading to a paradigm shift in disease treatment (11-14). In the RTOG 9402 study, the median OS for patients with anaplastic oligodendroglial tumors without 1p/19q co-deletion was similar in both groups receiving PCV plus RT or RT alone (2.6 and 2.7 years, respectively) (12). On the other hand in patients with 1p/19q co-deletion, the OS was significantly longer in the PCV plus RT arm than in the RT-alone arm (14.7 *vs.* 7.3 years, respectively, $p=0.03$) (12). Similar results were found in the EORTC 26951 trial (13). After more than 10 years' follow-up, the median OS in patients with anaplastic oligodendroglial tumors and without 1p/19q co-deletion was similar in the group receiving PCV plus RT and that receiving RT alone (25 and 21 months, respectively, $p=0.19$). However, the median OS was not reached for patients with co-deletion in the PCV plus RT arm, whereas it was just 9.3 years in patients primarily receiving RT alone (13). The positive effect of combined oncological treatment (PCV plus RT) in patients with 1p/19q co-deletion was present in both clinical studies, irrespective of which type of therapy was started first. Both studies demonstrated that neither radiotherapy nor chemotherapy alone is sufficient in AO treatment.

There are also other molecular biomarkers that could be used to better determine the prognosis for patients with oligodendrogliomas such as mutations in the genes for isocitrate dehydrogenase 1 and 2 (*IDH1/2*). A high frequency of mutations in the *IDH1* and *IDH2* (up to 69%-94%) was found in patients with oligodendroglioma (21, 22). The presence of the *IDH1/2* mutations is a significant positive prognostic biomarker for patients with various types of glioma (22–25). The alteration of certain other well-known pro-oncogenes and tumor-suppressor genes in patients with AO was identified, such as mutations in phosphatidylinositiol 3-kinase (*PI3K*), amplification of epidermal growth factor receptor (*EGFR*) or loss of the phosphatase and tensin homolog (*PTEN*) tumor suppressor. These alterations are associated with the poorer prognosis of AO (26, 27).

In our study, we found 1p/19q co-deletion to be a strong prognostic biomarker for OS for all patients with AO, irrespectively of their treatment regimen. Moreover, the predictive value of 1p/19q co-deletion was demonstrated for the subgroup of patients treated with the combination of neurosurgery and RT plus PCV *vs*. those treated with neurosurgery and RT alone. Our results are in concordance with the results from the recently published long-term follow-up of two phase III clinical trials RTOG 9402 and EORTC 26951. Although the follow-up of our patients is sufficient to prove the positive prognostic value of 1p/19q co-deletion in relation to combined therapy with PCV, the major weakness of this work remains the relatively small number of patients and the retrospective study design. The small number of patients in our study is mainly because of the rare incidence of anaplastic gliomas.

In our future work, we will expand the assessment of other molecular biomarkers in our patient cohort such as mutations in *IDH1/2* or the PI3K signaling pathway and we will correlate these alteration with 1p/19q co-deletion and patient clinical characteristics and outcome.

Conclusion

The importance of 1p/19q co-deletion in anaplastic oligodendrogliomas as a diagnostic, prognostic and predictive biomarker was shown and its presence should be also tested in all low-grade gliomas. Patients with anaplastic oligodendrogliomas who have tumors with 1p/19q co-deletion should be treated intensively with combined RT and chemotherapy (PCV).

Conflicts of Interests

The Authors declare that they have no conflict of interests regarding the publication of this article.

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