Immunohistochemical Analysis of p18INK4C and p14ARF Protein Expression in 117 Oligodendrogliomas
Correlation With Tumor Grade and Clinical Outcome

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Objective.—To investigate immunopexpression of 2 cyclin-dependent kinase inhibitors, p18INK4C (p18) and p14ARF (p14), in oligodendrogliomas and to evaluate the possible association with tumor grade and clinical outcome.

Design.—One hundred seventeen specially selected cases of cerebral oligodendrogliomas were studied retrospectively. Tumor specimens were immunohistochemically examined with antibodies to p18INK4C (118.2) and p14ARF (FL-132) proteins. A computerized color image analyzer was used to count immunostained nuclei.

Results.—p18 nuclear immunopexpression was found in 57 (49%) of the oligodendrogliomas we studied. p18 immunoreactivity exhibited a clear tendency to elevate with increasing tumor grade, and the mean p18 labeling index was 9.7% for low-grade (World Health Organization [WHO] grade II) and 19.2% for high-grade (WHO III) tumors. p14-immunopositive nuclei were found in 87 (74%) tumors, and p14 immunoreactivity showed no correlation with oligodendroglioma histological malignancy. Survival times were significantly reduced for p18-positive tumors, and risk of death was independently associated with p18 expression (hazard ratio = 2.48; P = .01). There was no difference in survival times in patients with or without p14 immunoreactivity.

Conclusions.—p18 protein expression is closely associated with malignant oligodendrogliomas and worse clinical outcome. It seems unlikely that p14 immunohistochemistry will be of value in assessing individual prognosis for these tumors.

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According to traditional opinion, oligodendrogliomas are relatively rare neoplasms that constitute approximately 2% to 5% of all primary brain tumors and 4% to 15% of gliomas.1,2 However, using expanded histologic criteria, researchers have recently established that oligodendrogliomas may represent 25% to 35% of all glial neoplasms.3,4 A precise diagnostic definition of this entity is very important clinically, because in contrast to astrocytomas, oligodendrogliomas have been demonstrated to be highly chemosensitive tumors.5 Therefore, the correct identification of a glial tumor as an oligodendroglioma is a very significant step in guiding further therapy. Moreover, recent cytogenetic studies have identified that some specific chromosomal aberrations may be strongly associated with the oligodendroglioma prognosis and treatment response.6,11 Rapid and reproducible cytogenetic techniques for investigating archival oligodendroglioma specimens have been described previously.10 Nevertheless, the search for and verification of immunohistochemical markers that might be closely related to prognostically significant cytogenetic aberrations appear to be useful for diagnostic neuropathology.

Deletions of chromosome arms 1p and 19q have been found in approximately 50% to 80% of oligodendrogliomas, regardless of the tumor grade.7,11 Therefore, it has been proposed that these chromosomal aberrations appear to be initial events for oligodendroglioma tumorigenesis. That is, the findings mentioned above suggest the presence of tumor suppressor genes in the deleted regions of chromosomes 1 and 19. For chromosome 1, the putative location of allelic loss spans a large region between 1p13 and 1pter. The p18INK4C gene is located on the 1p32 locus; therefore, it is an appropriate candidate to be involved in oligodendroglioma oncogenesis. The p18 gene encodes the cell-cycle regulatory protein that belongs to the family of cyclin-dependent kinase (CDK) inhibitors. It inhibits CDK4 and CDK6 and prevents hyperphosphorylation of pRb, thereby suppressing cell-cycle progression.12 However, only a small fraction of oligodendroglial neoplasms has been found to carry the p18INK4C gene alteration.13,14 To our knowledge, data concerning p18 protein status in oligodendroglial neoplasms have not been presented to date.

The next common and prognostically significant chromosomal aberration in oligodendrogliomas is allelic loss on 9p21 with frequent deletion of the CDKN2A gene locus. The latter has been found to be altered in 21% to 42% of tumors examined, preferentially in anaplastic oligodendrogliomas.6,9 As recently discovered, the CDKN2A locus encodes for 2 gene products, p16INK4A and p14ARF. Both these proteins appear to function as negative cell-cycle regulators.

Immunopexpression of p18INK4C and p14ARF—Korshunov & Golanov
The p16 tumor suppressor gene exerts growth control by inhibition of CDK4 and CDK6. Loss of p16 gene expression and protein down-regulation have been disclosed in various human gliomas, including oligodendrogliomas. According to previous reports, p16 immunoexpression was frequently decreased in anaplastic oligodendrogliomas, and lack of protein immunoreactivity strongly correlated with poor survival for these tumors.16,17

The p14ARF gene product is a protein with a molecular weight of approximately 14 kd, and it is encoded by exon 1b of the CDKN2A gene. In addition to inhibiting cell-cycle progression in G1, p14 protein also realizes inhibitory effects at the G2/M phase. The MDM2-mediated degradation of p53 protein is controlled by p14 protein, which neutralizes MDM2 and thereby stabilizes p53.

Recent reports strongly suggest an important role of p14ARF gene mutations in the biology of various human malignancies, including astrocytic neoplasms.18-21 Recently, Watanabe et al22 revealed a relatively high frequency of promoter hypermethylation and homozygous deletion of the p14ARF gene locus in a series of 49 oligodendrogliomas. To our knowledge, data on p14ARF protein status in these tumors have not been reported to date.

In the present study, biopsy samples of 117 oligodendrogliomas were examined immunohistochemically to evaluate a possible association between expression of p18INK4C and p14ARF proteins and patient survival. We have already found a strong significance of DNA topoisomerase II-α (Ki-S1) and p27/Kip-1 protein (p27) protein immunoreactivity for oligodendroglioma prognosis,23 therefore these markers were also included in the analysis.

MATERIALS AND METHODS

One hundred seventeen adult patients with newly diagnosed pure cerebral oligodendrogial tumors, consecutively treated at the Burdenko Neurosurgical Institute (Moscow, Russia) between January 1, 1989 and January 1, 1999, were studied retrospectively. This group represents an expanded patient sample from our previous studies.23,24 Twenty-four patients were younger than 30 years, 67 patients were between 30 and 50 years, and 26 patients were older than 50 years; mean age was 42 years. The study group included 60 men and 57 women.

Patients had undergone gross total (70 cases) and subtotal (47 cases) tumor resections, as confirmed by postoperative contrast computed tomographic scans or magnetic resonance imaging. One hundred two patients had received postoperative external beam irradiation with 55 to 61 Gy. Additionally, 53 patients had received chemotherapy (43 previously irradiated and 10 nonirradiated).

Follow-up data were received for at least 24 months after surgery, ending January 1, 2001. Progression-free survival and overall survival were estimated separately. Data regarding death, recurrence, or last contact were evaluated at the end of the study. Progression-free survival and overall survival were estimated with the Kaplan-Meier method. The comparisons among various patient subgroups were performed by the log-rank test. Multivariate analysis for survival was performed using the Cox proportional hazards model. The chi-square test was performed to determine whether the relations were statistically significant. Nonparametric Spearman rank correlation coefficients were used to assess the degree of linear association between pairs of variables. Survival analyses from the date of operation were estimated with the Kaplan-Meier method. For numerically continuous variables, the cutoff point which best subdivided patients into distinct survival groups was made according to Segal.26 The comparisons among various patient subgroups were performed by the log-rank test. Multivariate analysis for survival was performed using the Cox proportional hazard models. Probability (P) values less than .05 were considered significant. A significant correlation between 2 parameters was taken at the 95% confidence interval.

RESULTS

Pathologic and Immunohistochemical Findings

By light microscopy, all 117 tumors examined presented the histopathologic appearance typical for pure oligodendrogliomas. Fifty-four tumors were defined as low grade (WHO II) and the remaining 63 as high grade or anaplastic (WHO III). The latter were recognized by an increasing cell density, brisk mitotic activity, and an obligatory presence of microvascular proliferation with various degrees of spread. Forty (63%) of 63 high-grade tumors contained necrotic foci with and without pseudopalisading. p18-immunopositive nuclei were found in 57 (49%) tumors (Figure 1, A). In a small cell fraction, slight cyttoplasmic staining was observed. There were no p18-stained nuclei in adjacent nontumoral brain tissue. According to the immunostaining score, tumors were classified as follows (Table 1): (1) negative, 60 tumors (35 low grade and 25 high grade); (2) weakly positive, 23 tumors with p18 LIs from 3% to 20% (11 low grade and 12 high grade); and (3) strongly positive, 34 tumors with p18 LIs greater than 20% (8 low grade and 26 high grade). Mean p18 LIs were 9.7% for low-grade and 19.2% for high-grade tumors (significant difference; \( \chi^2; P < .0001 \)).
The results of univariate survival analyses revealed that both the progression-free (Table 3) and overall (Table 4) survival times were significantly reduced for high-grade tumors, for Ki-S1 LI greater than 10%, for p27 LI less than 20%, and for p18-positive tumors (Figure 2). For low-grade tumors, survival rates were significantly reduced for p27 LI less than 20%, whereas high-grade oligodendrogliomas with Ki-S1 LI greater than 10% and p18 positivity (Figure 3) revealed significantly shortened survival times.

We found no difference in survival times in patients with or without p14 immunoreactivity (log-rank; \( P = .3 \)). Additionally, we found no differences when tumors with strong p14 expression were compared with those with weak expression or immunonegativity (log-rank; \( P = .4 \)).

Multivariate analysis using the Cox hazard model for entire cohort of patients revealed that risk of tumor progression was independently associated with high-grade tumors (hazard ratio = 2.32; \( P = .02 \)), with Ki-S1 LI greater than 10% (hazard ratio = 2.72; \( P = .01 \)), and with p27 LI less than 20% (hazard ratio = 3.32; \( P = .0001 \)), whereas risk of death was independently associated with high-grade tumors (hazard ratio = 3.29; \( P = .0009 \)), with Ki-S1 LI greater than 10% (hazard ratio = 4.02; \( P = .0005 \)), and with p18 positivity (hazard ratio = 2.48; \( P = .01 \)).

**COMMENT**

At the present time, the prognosis of oligodendroglial neoplasms is an open issue. There is also no widely ac-

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**Table 1. Distribution of Various Patterns of p18INK4C Immunoreactivity in Relation to Oligodendroglioma Grade**

<table>
<thead>
<tr>
<th>Tumor Grade</th>
<th>p18INK4C Immunoreactivity, No. (%)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Low (n = 54)</td>
<td>Negative 35 (65)</td>
<td>Weakly Positive 11 (20)</td>
</tr>
<tr>
<td>High (n = 63)</td>
<td>25 (40)</td>
<td>12 (19)</td>
</tr>
<tr>
<td>( P ) value</td>
<td>&lt;.0001</td>
<td>Not significant</td>
</tr>
</tbody>
</table>

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**Table 2. Distribution of Various Patterns of p14ARF Immunoreactivity in Relation to Oligodendroglioma Grade**

<table>
<thead>
<tr>
<th>Tumor Grade</th>
<th>p14ARF Immunoreactivity, No. (%)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Low (n = 54)</td>
<td>Negative 13 (24)</td>
<td>Weakly Positive 24 (44)</td>
</tr>
<tr>
<td>High (n = 63)</td>
<td>17 (27)</td>
<td>25 (40)</td>
</tr>
<tr>
<td>( P ) value</td>
<td>Not significant</td>
<td>Not significant</td>
</tr>
</tbody>
</table>

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**Figure 1. Photomicrographs showing various patterns of p18INK4C (A) and p14ARF (B) immunoreexpression in the 1 oligodendroglioma sample (LSAB immunostaining, original magnification ×400).**

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p14-immunopositive nuclei were found in 87 (74%) tumors. A predominantly granular p14ARF staining pattern was noted (Figure 1, B). Single glial cells with p14 positivity were also found within nervous tissue beyond the tumor margin. According to the immunostaining score, tumors were classified as follows (Table 2): (1) negative, 30 tumors (13 low grade and 17 high grade); (2) weakly positive, 49 tumors with p14 LIs from 8% to 30% (24 low grade and 25 high grade); and (3) strongly positive, 38 tumors with p14 LIs greater than 30% (17 low grade and 21 high grade). Mean p14 LIs were 35.2% for low-grade and 35.4% for high-grade tumors (difference not significant; \( \chi^2; P = .6 \)).

When p18 and p14 scoring and tumor grade were compared (Tables 1 and 2), p14 immunoreactivity showed no correlation with oligodendroglioma histologic malignancy. In contrast, p18 immunoreactivity exhibited a clear tendency to elevate with increasing tumor grade (Spearman test; \( r = 0.78; P = .0001 \)).

All oligodendrogliomas exhibited nuclear Ki-S1 expression; the mean Ki-S1 LI was significantly prominent for high-grade tumors, 9.3% versus 3.1% for low-grade tumors (\( \chi^2; P < .0001 \)).

All tumors exhibited nuclear accumulation of p27/Kip-1; the mean p27 LI was significantly higher for low-grade oligodendrogliomas, 48.3% versus 23.1% for high-grade tumors (\( \chi^2; P < .0001 \)).

Correlation analysis revealed a statistically significant covariation between increasing Ki-S1 and decreasing p27 counts (Spearman test; \( r = 0.63; P = .008 \)), and between elevated counts of both Ki-S1 and p18 (Spearman test; \( r = 0.61; P = .01 \)). We were unable to show other significant associations between immunohistochemical variables.

**Correlation Between Pathologic Variables and Patient Outcomes**

Five-year survival rates for low- and high-grade oligodendrogliomas were found to be significantly different: 56% versus 9% for progression-free survival and 93% versus 27% for overall survival (log-rank; \( P < .0001 \)).

The correlation between increasing Ki-S1 and decreasing p27 expression was characterized by a statistically significant trend (Spearman test; \( r = 0.63; P = .008 \)), and between Ki-S1 and p27 (Spearman test; \( r = 0.61; P = .01 \)). We were unable to show other significant associations between immunohistochemical variables.

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*Immunoreexpression of p18INK4C and p14ARF—Korshunov & Golanov*
The present study confirmed earlier data,23 established to be an indicator for poor oligodendroglioma outcome and specific chromosomal aberrations has been recently concordance with the data on investigation of this protein in the previously reported experimental study.40 The data obtained revealed that p18 reactivity is significantly related to high-grade oligodendrogliomas and worse outcome for the whole group and for anaplastic tumors. Hence, in contrast to p16 and p27, p18INK4C protein is not functioning as a tumor suppressor gene product in oligodendrogliomas.

A clear association between oligodendroglioma clinical outcome and specific chromosomal aberrations has been established.27±36 Only single reports were unable to show such associations.37,38 Additionally, down-regulation of p16 and p27 CDK inhibitors has been recently established to be an indicator for poor oligodendroglioma prognosis.16,17,39 The present study confirmed earlier data,23 in that strong prognostic value for the Ki-S1 and p27 counts was shown once again.

Table 3. Statistical Correlation Between Each Parameter Studied and Overall Survival in Univariate Analysis (Log-Rank Test)*

<table>
<thead>
<tr>
<th>Prognostic Factor</th>
<th>Total</th>
<th>Low Grade</th>
<th>High Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (&lt;30 y vs 30–50 y vs &gt;50 y)</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Sex (male vs female)</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Location (frontal vs nonfrontal)</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Postoperative KPS (&lt;70 vs &gt;70)</td>
<td>P = .0001</td>
<td>. . .</td>
<td>. . .</td>
</tr>
<tr>
<td>Radiotherapy (present vs absent)</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Chemotherapy (present vs absent)</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Tumor grade (low grade vs high grade)</td>
<td>P = .0001</td>
<td>. . .</td>
<td>. . .</td>
</tr>
<tr>
<td>p18INK4C expression (present vs absent)</td>
<td>P = .003</td>
<td>NS</td>
<td>P = .001</td>
</tr>
<tr>
<td>p14ARF expression (present vs absent)</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Ki-S1 LI (&lt;10% vs &gt;10%)†</td>
<td>P = .0001</td>
<td>NS</td>
<td>P = .0001</td>
</tr>
<tr>
<td>p27 LI (&lt;20% vs &gt;20%)</td>
<td>P = .004</td>
<td>P = .0001</td>
<td>NS</td>
</tr>
</tbody>
</table>

* KPS indicates Karnofsky performance score; LI, label index; and NS, not significant.
† Less than 5% versus >5% for low-grade tumors.

Table 4. Statistical Correlation Between Each Parameter Studied and Overall Survival in Univariate Analysis (Log-Rank Test)*

<table>
<thead>
<tr>
<th>Prognostic Factor</th>
<th>Total</th>
<th>Low Grade</th>
<th>High Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (&lt;30 y vs 30–50 y vs &gt;50 y)</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Sex (male vs female)</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Location (frontal vs nonfrontal)</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Postoperative KPS (&lt;70 vs &gt;70)</td>
<td>P = .013</td>
<td>P = .018</td>
<td>P = .002</td>
</tr>
<tr>
<td>Radiotherapy (present vs absent)</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Chemotherapy (present vs absent)</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Tumor grade (low grade vs high grade)</td>
<td>P = .00001</td>
<td>. . .</td>
<td>. . .</td>
</tr>
<tr>
<td>p18INK4C expression (present vs absent)</td>
<td>P = .001</td>
<td>NS</td>
<td>P = .0008</td>
</tr>
<tr>
<td>p14ARF expression (present vs absent)</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Ki-S1 LI (&lt;10% vs &gt;10%)†</td>
<td>P = .0001</td>
<td>NS</td>
<td>P = .00001</td>
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<tr>
<td>p27 LI (&lt;20% vs &gt;20%)</td>
<td>P = .006</td>
<td>P = .0003</td>
<td>NS</td>
</tr>
</tbody>
</table>

* KPS indicates Karnofsky performance score; LI, label index; and NS, not significant.
† Less than 5% versus >5% for low-grade tumors.

Accepted consensus about histologic parameters for identification of oligodendroglioma grade and prediction of patient outcome. Nevertheless, some recently published studies revealed a significant association between oligodendroglioma clinical course and the WHO tumor grade.2 It has also been pointed out that among the histologic factors for oligodendroglioma grading, endothelial (microvascular) hyperplasia and/or proliferation may be estimated as a strongly objective and reproducible pattern because the other criteria, such as “high” cellularity or “brisk” mitotic activity, appear to be more subjective and less reliable.4,6,24

Numerous studies have revealed significant correlation between tumor growth fraction measured by Ki-67/MIB-1 or DNA topoisomerase II-α immunolabeling and oligodendroglioma prognosis.27–30 Only single reports were unable to show such associations.37,38 Additionally, down-regulation of p16 and p27 CDK inhibitors has been recently established to be an indicator for poor oligodendroglioma prognosis.16,17,39 The present study confirmed earlier data,23 in that strong prognostic value for the Ki-S1 and p27 counts was shown once again.

A clear association between oligodendroglioma clinical outcome and specific chromosomal aberrations has been established.27±36 The allelic loss of 1p and 19q is prognostically favorable, and these changes are strongly associated with high chemosensitivity of oligodendrogial neoplasms, especially within the category of malignant tumors. On the other hand, anaplastic oligodendrogliomas with CDKN2A homozygous deletion were characterized to be chemoresistant tumors with worse outcome.

We made an attempt to evaluate the prognostic significance of p18INK4C and p14ARF protein immunoreactivity in oligodendrogliomas, because the down-regulation of both these CDK inhibitors might theoretically be claimed as a possible marker for the above-mentioned chromosomal aberrations. Patients in our sample had undergone various combined treatments, and the 5-year rate of overall survival (60%) was very similar to that reported previously.2,6,26,32,36

About 50% of the tumors examined exhibited the various grades of p18 protein immunoreexpression. A predominately nuclear staining pattern was observed, and this is in concordance with the data on investigation of this protein in the previously reported experimental study.40 The data obtained revealed that p18 reactivity is significantly related to high-grade oligodendrogliomas and worse outcome for the whole group and for anaplastic tumors. Therefore, it seems unlikely that p18 protein down-regulation in oligodendroglioma cells is related directly to loss.
Figure 2. Graph displaying progression-free (A) and overall (B) Kaplan-Meier survival curves for various p18 expression patterns for the whole oligodendroglioma group.

of 1p. Moreover, some previous studies have found detectable levels of p18 mRNA transcripts, revealed by reverse transcriptase-polymerase chain reaction in all tumors examined. These findings allow us to fully exclude a possibility of p18INK4C transcriptional silencing caused by gene promoter hypermethylation. Therefore, loss of p18 protein at the level of translation, its binding, or proteasome-mediated degradation might be responsible for p18 down-regulation in oligodendrogliomas.

The strong association of p18 positivity with high-grade oligodendrogliomas that we observed is in line with the data previously published by Husemann et al, who found that p18 mRNA levels are significantly greater in anaplastic tumors. Husemann et al explained this phenomenon by the existence of a close relationship between p18 up-regulation and elevated oligodendroglioma growth fraction. Indeed, as it has been established by the experimental study, the level of p18 mRNA expression is regulated in a cycle-dependent manner with a maximum of mRNA concentration in S-phase.

Our data allow us to suppose that the detectable levels of p18 protein are immunohistochemically recognized mainly within the proliferating pool of oligodendroglioma cells. Theoretically, this presumption could be partly supported by the previously published experimental data that p18 level was found to be dramatically increased in proliferating cells of embryonic brain and consequently falling to very low levels in the adult nervous system. Absence of p18 expression in glial cells beyond the tumor margin, observed in our study as a close correlation between elevated tumor growth fraction and p18 positivity, also argues in favor of our suggestion.

In the meantime, it is very difficult to estimate whether p18 immunoreactivity is a reliable and weighty indicator of oligodendroglioma clinical course. In our opinion, at present p18 immunoreactivity has not shown an essential prognostic advantage over growth fraction measurements. Therefore, the real value of p18 expression for oligodendroglioma prognosis requires further investigation. Another important point is the specificity of p18 protein down-regulation for oligodendrogliomas, and comparative studies with the other types of glial tumors should be performed.

Alteration of the p14ARF gene has been found to be a
frequent event in the biology of astrocytic gliomas.\textsuperscript{18–21} Nakamura et al\textsuperscript{20} additionally revealed a strong tendency toward down-regulation of p14ARF protein immunoreactivity during progression from low-grade astrocytoma to glioblastoma. Recently, Watanabe et al\textsuperscript{22} established the presence of various alterations of p14ARF gene in 13 (27\%) of 49 oligodendrogliomas, of which 6 were WHO grade II and 7 were WHO grade III. Promoter hypermethylation of the p14ARF gene was detected in both tumor grades, whereas homozygous deletion of the gene locus was revealed in anaplastic oligodendrogliomas only.

In the present study, p14-immunostained nuclei were found in 74\% of the tumors examined. A predominantly granular staining pattern was observed, which was in accordance with the data on p14ARF protein in tumor cell lines.\textsuperscript{44} There was no association of aberrant expression of p14 protein with the oligodendroglioma grade. Since the frequency of p14ARF gene alteration in oligodendrogliomas (27\%) is very similar to the rate of p14-negative tumors (26\%), the p14 protein down-regulation caused by inactivation of the corresponding gene may be suggested.

We were unable to establish an appreciable correlation between p14 immunoreactivity and oligodendroglioma outcome. Therefore, it may be claimed that regardless of the undisputed importance of p14ARF gene alteration for oligodendroglioma tumorigenesis, the distinct role of p14ARF protein down-regulation in the biologic behavior of these neoplasms remains to be defined.

In summary, we came to the following conclusions: (1) p18 protein expression is closely associated with high-grade oligodendrogliomas and worse outcome. However, the distinct prognostic role of p18 reactivity appears to be an open issue, especially for determining survival from histologically low-grade tumors. (2) p14 protein down-regulation showed no differences in the various oligodendroglioma grades, and it seems unlikely that p14 immunohistochemistry will be of value in assessing individual prognosis for these tumors. (3) As noted in our previous article, Ki-S1 and p27 LIIs appear to be more reliable markers for prediction of oligodendroglioma clinical outcome. (4) The search for suppressor genes (and gene products) that might be related to the specific chromosomal aberrations within the chemosensitive oligodendroglioma cohort needs to be continued. Application of the oligonucle-
otide microarrays technique may also be useful for this purpose.45

References


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