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Original Investigation

The Correlation Between 1p/19q Codeletion, IDH1 Mutation, p53 Overexpression and Their Prognostic Roles in 41 Turkish Anaplastic Oligodendroglioma Patients

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ABSTRACT

AIM: To observe the correlation between 1p/19q codeletion, isocytate dehydrogenase-1 (IDH1) mutation and p53 protein overexpression and their prognostic value in Turkish anaplastic oligodendroglioma patients who were treated with adjuvant radiotherapy and temozolomide chemotherapy.

MATERIAL and METHODS: We retrospectively evaluated 41 patients who were diagnosed as anaplastic oligodendroglioma. Thirty-five patients received standard radiotherapy. Twenty-six patients received standard temozolomide chemotherapy concurrent to radiotherapy.

RESULTS: Chromosome 1p/19q codeletion was observed in 19 of 41 patients (46%) via Fluorescent In Situ Hybridisation (FISH) technique. Twenty-six patients (63%) showed positive immunoreaction with anti-IDH1 antibody. Six patients (15%) showed positive immunoreaction with anti-p53 antibody. A statistically significant correlation was determined between chromosome 1p/19q codeletion and IDH1 mutation ($p < 0.0001$). The patients who had tumors with chromosome 1p/19q codeletion and p53 overexpression were mutually exclusive. The mean estimated Progression Free Survival (PFS) of the patients who had tumors with chromosome 1p/19q codeletion and/or IDH1 mutation was determined to be significantly longer than that of the patients without these genetic changes, regardless of the treatment modality ($p = 0.006$, $p = 0.004$). PFS of the patients who received adjuvant chemotherapy and whose tumors had chromosome 1p/19q codeletion or IDH1 mutation was significantly longer than that of the patients without these genetic changes ($p = 0.001$, $p < 0.0001$).

CONCLUSION: Chromosome 1p/19q codeletion and/or IDH1 mutation are favorable prognostic factors in anaplastic oligodendroglioma patients, in terms of PFS.

KEYWORDS: Anaplastic oligodendroglioma, 1p/19q codeletion, IDH1 mutation, Temozolomide, Prognosis

INTRODUCTION

Oligodendroglioma is a rare tumor, accounting for about 2.5% of all primary brain tumors, and 5-6% of all gliomas (27). Anaplastic oligodendroglioma with chromosome 1p/19q codeletion is a chemosensitive tumor with better prognosis than their counterparts without deletion. Molecular cytogenetic trials have determined that the codeletion on

chromosome 1p/19q is an early genetic change which plays a significant role in the pathogenesis of oligodendroglioma, and is present more often in oligodendroglioma than any other primary brain tumor (2,5,8,9,11,14,16,17,19,21,28,32,33,35,37,41). Numerous clinical trials which have been performed since 1998 have proven the presence of the 1p/19q codeletion to be a favorable prognostic and predictive factor in



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anaplastic oligodendroglioma patients who received adjuvant chemotherapy, in addition to surgery and radiotherapy (5,8-10,14,25,35,41).

Isocitrate dehydrogenase-1 (IDH1), which is localised on chromosome 2q33.3, is a gene which encodes cytosolic nicotinamide adenine dinucleotide phosphate (NADP)(+) dependent isocitrate dehydrogenase in humans. It is an enzyme in the citric acid cycle, which catalyses the transformation of citrate to α -ketoglutarate (10,29). IDH1 is the main resource of NADPH, necessary for the regeneration of reduced cytosolic glutathione, which is the main cellular antioxidant (34). In previous studies, IDH1 mutations specific to gliomas have always been found to affect the arginine amino acid on codon 132, which encodes the isocitrate binding region (31). As a result of a mutation on this gene, IDH1 enzyme activity is inactivated and an oncometabolite called 2-hydroxyglutarate accumulates (1). Excessive 2-hydroxyglutarate accumulation plays a role in glioma pathogenesis and progression (7). Recent cytogenetic and immunohistochemical studies have shown that the IDH1 mutation is present in significantly higher rates in oligodendrogliomas exhibiting the 1p/19q codeletion and is a favorable prognostic marker in terms of progression free survival (PFS) and overall survival (13,24,26,36,39).

The p53 gene is localised on chromosome 17p13.1. This gene encodes a tumor suppressor protein called p53 (42). The p53 gene mutation plays an important role in gliogenesis and malignant transformation of human gliomas (6). Chromosome 17p loss and p53 mutation are rarer in oligodendroglial tumors, compared with astrocytic tumors (19,33,42). Studies have shown a negative correlation between chromosome 1p/19q codeletion and p53 protein expression in oligodendroglial tumors. Chromosome 1p/19q codeletion and p53 mutation have been found mutually exclusive in some clinical trials (15,20,33). The absence of chromosome 1p/19q codeletion and presence of p53 overexpression have been stated to be negative prognostic and predictive factors in oligodendroglial tumors (18).

There is a limited number of studies which have observed chromosome 1p/19q codeletion, IDH1 mutation and p53 protein overexpression at the same time, in anaplastic oligodendroglioma patients who received adjuvant temozolomide chemotherapy (26,40,44).

The aim of our study was to analyze the correlation between 1p/19q codeletion, IDH1 mutation and p53 protein overexpression and to determine their prognostic and predictive roles in anaplastic oligodendroglioma patients who received adjuvant temozolomide chemotherapy, in addition to surgery and radiotherapy.

■ MATERIAL and METHODS

Clinical Material

In our study, we retrospectively evaluated 41 patients who were diagnosed as anaplastic oligodendroglioma in Istanbul University, Istanbul Medical Faculty, Pathology Department, between 2004 and 2011. Twelve of the cases were determined

to be patients with recurrent tumors. We accessed the clinical data, including patient age at diagnosis, sex, operation status, treatment modalities of 36 of 41 patients which have been included in our study. Prognostic statistical analysis was performed on the data obtained from those patients. PFS, defined as the period from primary diagnosis to first progression of the disease, was collected from the patient files. The study was approved by the Ethics Committee of Istanbul University, Istanbul Medical Faculty Hospital.

Treatment

Standard treatment consisted of surgery and postoperative radiotherapy, with or without adjuvant temozolomide chemotherapy. Maximal tumor bulk resection while preserving the key eloquent cortex was the principle goal during surgery. Preoperative functional magnetic resonance image (MRI) and intraoperative awake brain mapping were used when necessary. Extent of resection was assessed on the postoperative enhanced MRI within 24 hours and graded as total or subtotal resection. Thirty-five of the patients received 54-60 Gray adjuvant radiotherapy for 35 days. One patient did not receive radiotherapy due to the tumor localization. Twenty-six patients received 75 mg/m²/day adjuvant temozolomide chemotherapy concurrent to radiotherapy. These patients received 200 mg/m² temozolomide for 5 days post radiotherapy and continued receiving 200 mg/m² temozolomide once a month for 6 months. Ten patients did not receive chemotherapy.

Assessment of chromosome 1p/19q deletion

Chromosome 1p/19q statuses of the patients was assessed on paraffin-embedded blocks of the tumor samples of the patients with the Fluorescent In Situ Hybridisation (FISH) technique. In each case, hematoxylin-eosin slides were reevaluated, and the tumor areas with the most prominent anaplastic features, with no necrosis or hemorrhage were selected. Two 4 μ m thick sections were obtained from the paraffin embedded tumor blocks. In the FISH technique, for the assessment of chromosome 1p status, a dual colored FISH probe which contains a mixture of a ~435 kb SpectrumOrange-labeled 1p36 probe and a ~618 kb SpectrumGreen-labeled 1q25 probe premixed in hybridization buffer (The Vysis LSI 1p36 SpectrumOrange/1q25 SpectrumGreen Probe, Vysis Abbott Laboratories, Abbott Park, IL, USA); for the assessment of chromosome 19q status, a dual colored FISH probe which contains a mixture of a ~380 kb SpectrumOrange-labeled 19q13 probe and a ~502 kb SpectrumGreen-labeled 19p13 probe premixed in hybridization buffer (The Vysis LSI 19q13 SpectrumOrange/19p13 SpectrumGreen Probe, Vysis Abbott Laboratories, Abbott Park, IL, USA) were used. For the interpretation of chromosome 1p and 19q deletion, a FISH protocol including deparaffinization, pre-hybridization and hybridization steps was used.

To determine the chromosome 1p/19q status, the orange subtelomeric (determining) and green paracentromeric (reference) signals in 200 collateral cells were counted and photomicrographically documented by an experienced molecular pathologist. The ratio of orange/green signals less than 0.70 was considered to be a deletion. In cases which were difficult

to assess, the number of cells whose signals were counted were increased to 300.

Assessment of IDH1 mutation

IDH1 mutation was assessed immunohistochemically by using mutant IDH1 protein specific anti-IDH1 antibody (anti-human IDH1 R132H astrocytoma, oligodendroglioma tumor cell marker mouse monoclonal antibody clone H09, Dianova GmbH Warbugstrasse 45 D-20354 Hamburg, Germany). Positive control tissues were included in all experiments to ensure the quality of staining. Nuclear and cytoplasmic stainings in tumor cells was regarded as positive immunostaining.

Assessment of p53 protein overexpression

p53 protein overexpression was assessed immunohistochemically by using p53 Ab-8, Mouse monoclonal antibody clone DO-7+BP53-12. Thermo Fisher Scientific Inc. 81 Wyman Street Waltham, MA, 02454, USA). Positive control tissues were included in all experiments to ensure the quality of staining. A nuclear staining which is observed more than 10% of the tumor cells was regarded as positive immunos-

taining. The immunohistochemical analyses were interpreted by two experienced pathologists (Figure 1A-D).

Biostatistical analysis

The biostatistical analysis of our study was implemented using the Statistical Package for Social Sciences 21.0 program. For recurrence and survival analysis, Kaplan Meier survival analysis, for all other categorical variables chi-square test, for the assessment of the factors which affect time to progression, cox regression analysis was used. p value ≤ 0.05 was granted to be statistically significant.

RESULTS

We assessed the tumor samples of 41 patients who were diagnosed as anaplastic oligodendroglioma between 2004-2011 in our pathology department. Twelve patients' tumors have been diagnosed as anaplastic oligodendroglioma before, in other centers. We assessed their recurrent tumors. The ages of the patients at time of diagnosis ranged between 12 and 63 years. The main age of the patients at the time of diagnosis

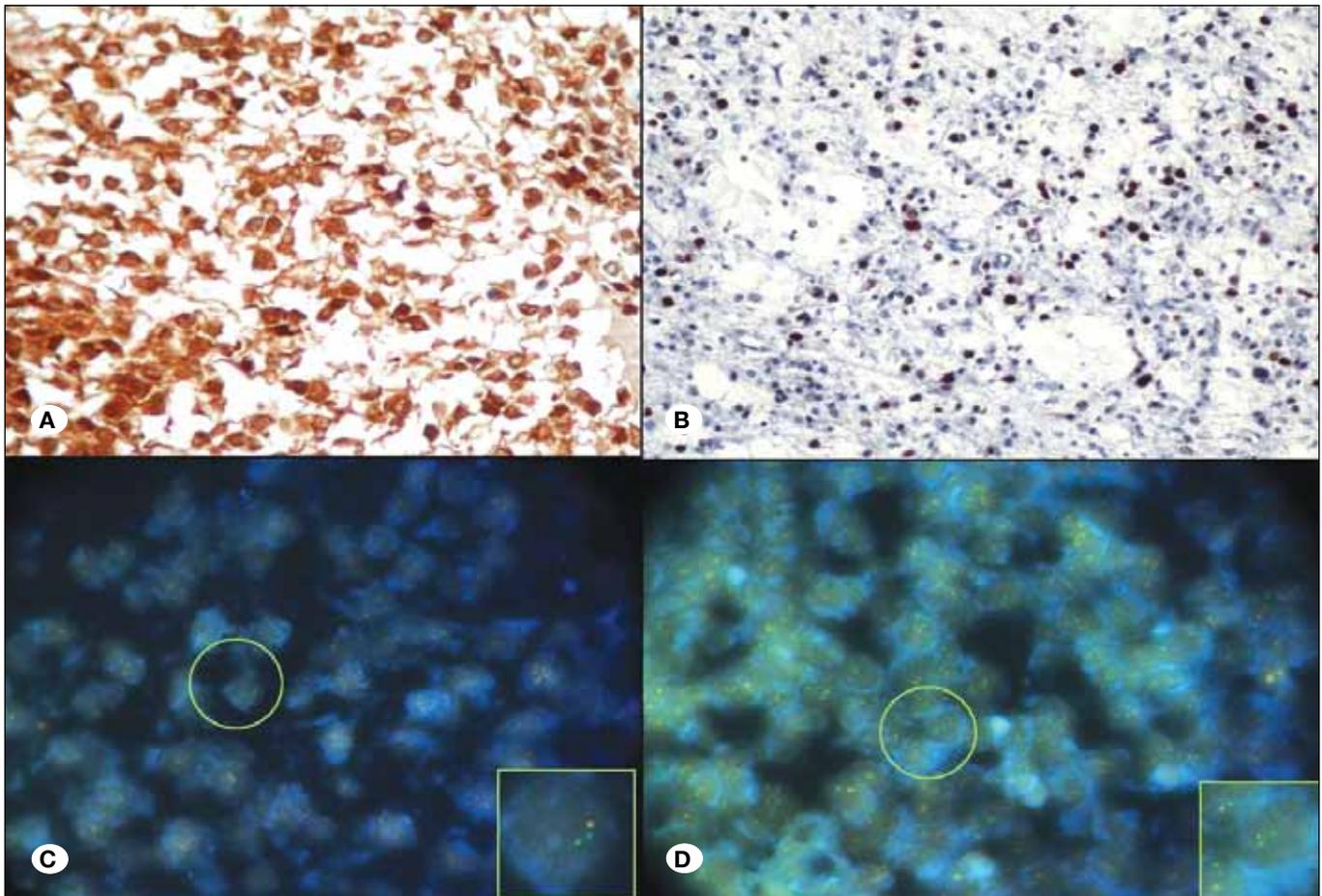


Figure 1: **A)** Anaplastic oligodendroglioma with positive immunoreaction with anti-IDH1 antibody, (anti-IDH1 antibody, X400). **B)** Anaplastic oligodendroglioma with positive immunoreaction with anti-p53 antibody, (anti-p53 antibody, X400). **C)** Detection of chromosome 1p deletion by FISH in anaplastic oligodendroglioma, (FISH, chromosome 1p probe, X1000). **D)** Detection of chromosome 19q deletion by FISH in anaplastic oligodendroglioma, (FISH, chromosome 19q probe, X1000).

was 41.7 years. Twenty one of 41 patients were female. Male/female ratio was 0.95. Seventeen of the patients' tumors were located at parietal region. Fifteen patients had frontally, 8 patients had temporally, and 1 patient had occipitally located tumors. Twenty-nine patients (71%) underwent total tumor resection. The mean clinical follow-up of the patients was 70.4 months. We observed recurrent anaplastic oligodendroglioma in 28 patients. The mean PFS of the patients was 59.2 months (Table I). Nine patients died from anaplastic oligodendroglioma during the follow-up time.

Chromosome 1p/19q codeletion

We observed chromosome 1p deletion in 23 of 41 patients (56%). Nineteen patients (46%) had chromosome 19q deletion. We could not get any signals on chromosome 19q on tumor sample of one patient in spite of two times repetition. Nineteen patients (46%) had chromosome 1p/19q codeletion. Three patients (7%) had chromosome 1p deletion, but did not have chromosome 19q deletion.

IDH1 mutation

Twenty-six patients (63%) showed positive immunoreaction with mutant protein spesific anti-IDH1 antibody.

p53 protein overexpression

Six patients (15%) showed positive immunoreaction with anti-p53 antibody.

Statistical Analysis

We accessed the clinical data of 36 of 41 patients. The prognostic statistical analysis were performed on the data obtained from those patients.

Correlation between chromosome 1p/19q codeletion, IDH1 mutation and p53 protein overexpression

Ninety percent of patients (17 of 19) who had tumors with chromosome 1p/19q codeletion showed positive immunoreaction with anti-IDH1 antibody (p<0.0001, Chi-square, log rank). Two of 3 patients who had tumors with chromosome 1p, but not 19q deletion showed positive immunoreaction with anti-IDH1 antibody. In our study, the patients who had tumors with chromosome 1p/19q codeletion and p53 overexpression were mutually exclusive (p=0.01, Chi-square, log rank). Twelve percent of patients (3 of 26) with IDH1 mutation showed p53 protein expression, whereas 20% of patients (3 of 15) without IDH1 mutation showed p53 protein expression.

Factors associated with Progression Free Survival (PFS)

The mean estimated PFS of the patients who had tumors with chromosome 1p/19q codeletion was 73.4 ± 13 months, (p=0.004, Kaplan-Meier, log rank). The mean estimated PFS of the patients who had tumors with IDH1 mutation was 73.2±12.5 months, (p=0.004, Kaplan-Meier, log rank). The mean estimated PFS of the patients who had tumors with 1p/19q codeletion together with IDH1 mutation was 75.9±13.6 months, (p=0.006, Kaplan-Meier, log rank)(Figure 2).

The mean estimated PFS of the patients who received adjuvant temozolomide chemotherapy in addition to radiotherapy, and whose tumors had chromosome 1p/19q codeletion was 64.3±15 months, while that of the patients without 1p/19q codeletion was 18.3±5.2 months (p=0.001,

Table I: General Characteristics of the Patients in Our Study

Variable	Anaplastic oligodendroglioma patients (n=41)
Mean age at diagnosis (years)	41.7
Sex	
Female	21
Male	20
Extent of tumor resection	
Total	29
Subtotal	9
Radiotherapy	
Yes	35
No	1
Temozolomide chemotherapy	
Yes	26
No	10
Chromosome 1p deletion	
Yes	23
No	18
Chromosome 19q deletion	
Yes	19
No	21
Chromosome 1p/19q codeletion	
Yes	19
No	18
IDH1 mutation	
Yes	26
No	15
p53 protein overexpression	
Yes	6
No	35
Mean follow up time (months)	70.4
Mean PFS (months)	59.2

Kaplan-Meier, log rank)(Figure 3A). The mean estimated PFS of the patients whose tumors had IDH1 mutation and who received temozolomide chemotherapy was 68.9±14.5 months while that of the patients without IDH1 mutation was 12.2±2.5 months ($p<0.0001$, Kaplan-Meier, log rank)(Figure 3B). In our study, the number of the patients whose tumors showed p53 expression was not sufficient enough to perform the statistical survival analysis.

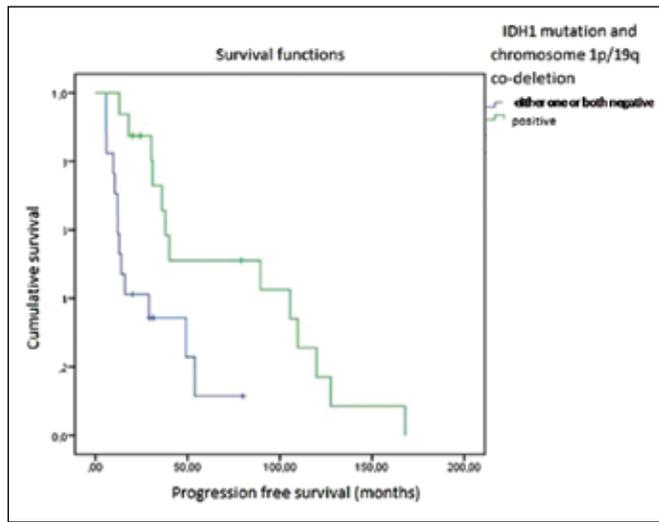


Figure 2: The mean estimated PFS of the patients who had tumors with 1p/19q codeletion together with IDH1 mutation was 75.9 months. This period was statistically significant longer than that of the patients with chromosome 1p/19q codeletion without IDH1 mutation, IDH1 mutation without chromosome 1p/19q codeletion, and of the patients with neither chromosome 1p/19q codeletion nor IDH1 mutation (29 months), ($p=0.006$, Kaplan-Meier, log rank).

DISCUSSION

Previously, the gold standard method in diagnosis and grading of gliomas was based on the histopathological features of the tumors (hypercellularity, mitosis, necrosis and vascular endothelial proliferation). In order to provide a better prediction and therapy management, a need for a more advanced and objective classification has emerged and the number of studies revealing the genetic changes in gliomas have been rapidly increasing (22).

Anaplastic oligodendroglioma is a chemosensitive tumor. Chromosome 1p/19q codeletion is a predictive factor in response to chemotherapy and is a positive prognostic factor by means of survival. This fact was proven first in 1998, by Cairncross et al., and was supported by numerous studies which have taken place in the following years (4,14,25,30).

European Organisation for Research and Treatment of Cancer (EORTC) and Radiation Therapy Oncology Group (RTOG) studies, which have been conducted for over 40 years on glioma patients, are randomised, multi-centered phase III studies, including patients with long term follow-up. In a report of Kouwenhoven et al. on EORTC 26951 study, it is concluded that chromosome 1p/19q codeletion is the most powerful molecular prognostic marker in anaplastic oligodendroglioma patients (23). In RTOG 9402 study, the patients who had tumors with 1p/19q codeletion and received Procarbazine, Lomustine, and Vincristine (PCV) chemotherapy in addition to radiotherapy had significantly longer overall survival than the patients who had tumors without 1p/19q codeletion (3). In a study of van den Bent et al., which represents the long term follow-up of EORTC 26951, the anaplastic oligodendroglioma patients who had tumors with chromosome 1p/19q codeletion and treated with six cycles adjuvant PCV chemotherapy, received statistically significant more benefit from the chemotherapy regimen (38).

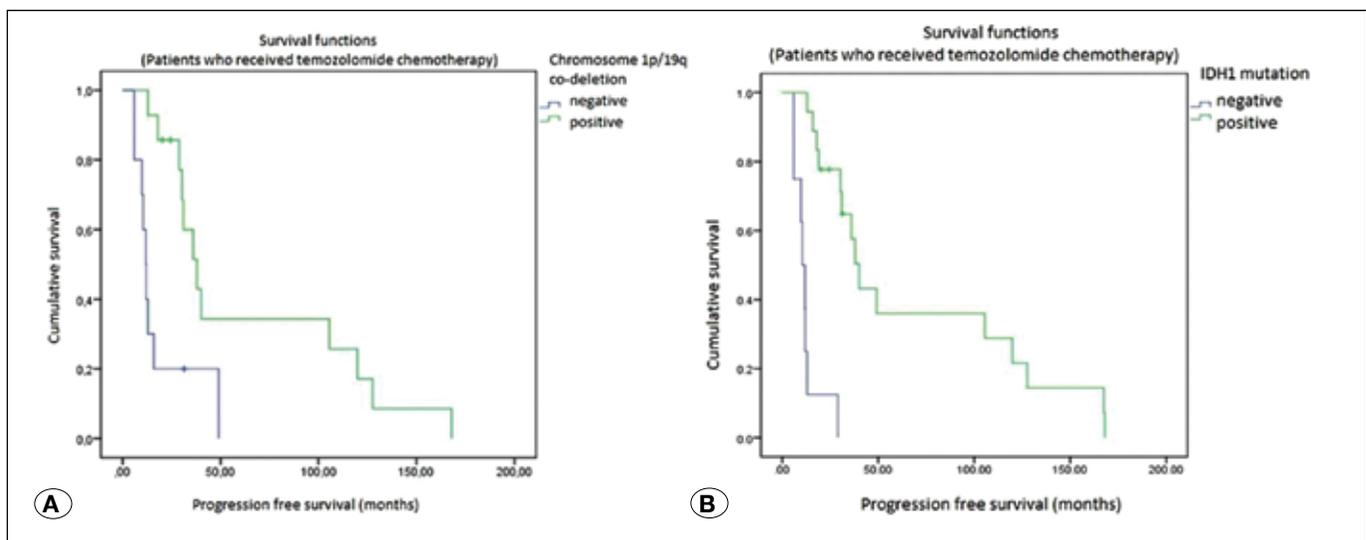


Figure 3: A) The mean estimated PFS of the patients with and without 1p/19q codeletion, who received adjuvant temozolomide chemotherapy in addition to radiotherapy was 64.3 vs 18.3 months respectively, ($p=0.001$, Kaplan-Meier, log rank). **B)** The mean estimated PFS of the patients with and without IDH1 mutation, who received adjuvant temozolomide chemotherapy in addition to radiotherapy was 68.9 vs 12.2 months respectively, ($p=0.001$, Kaplan-Meier, log rank).

Gorlia et al., in a prognostic analysis of the EORTC 26951 study, stated that both chromosome 1p/19q codeletion and IDH1 mutation are favorable prognostic factors in terms of overall survival (OS) and PFS in anaplastic oligodendroglioma patients. They concluded that the detection of chromosome 1p/19q codeletion together with IDH1 mutation should be used in routine practice to determine the prognosis in anaplastic oligodendroglioma patients (12).

Other recently performed cytogenetic and immunohistochemical studies have also determined that the IDH1 mutation which was shown to be in correlation with the 1p/19q codeletion is also a favorable prognostic marker for anaplastic oligodendroglioma patients who received adjuvant chemotherapy (24,26,36,39).

In our study, we aimed to show the prognostic role of these genetic changes in Turkish anaplastic oligodendroglioma patients who received adjuvant temozolomide chemotherapy.

The role of genetic changes on prognosis

As a result of our study, parallel with the previous studies, we found a correlation between the number of the cases with 1p/19q codeletion and IDH1 mutation ($p < 0.0001$). As a result of our study, chromosome 1p/19q codeletion and/or IDH1 mutation are determined to be statistically significant favorable prognostic factors in anaplastic oligodendroglioma patients, in terms of PFS ($p = 0.004$, $p = 0.006$).

The role of the genetic changes in response to temozolomide chemotherapy

In our study, the mean estimated PFS of the patients who received adjuvant temozolomide chemotherapy in addition to radiotherapy, and whose tumors had chromosome 1p/19q codeletion was significantly longer than the patients without 1p/19q codeletion ($p = 0.004$). The mean estimated PFS of the patients whose tumors had IDH1 mutation and received adjuvant temozolomide chemotherapy was significantly longer than the patients without IDH1 mutation ($p < 0.0001$). Although we accessed statistically significant results, due to the retrospective nature of our study, the number of patients was not sufficient enough to determine the predictive role of these genetic changes for the benefit from temozolomide chemotherapy. Like our study, all of the previous studies which have been performed up to date could not determine the predictive role of IDH1 mutation on chemotherapy in anaplastic oligodendroglioma patients (7,12,39-41,43).

CONCLUSION

Chromosome 1p/19q codeletion and/or IDH1 mutation are determined to be statistically significant favorable prognostic factors in anaplastic oligodendroglioma patients, in terms of PFS. In order to determine the IDH1 mutation's predictive role for the benefit from chemotherapy in anaplastic oligodendroglioma patients, prospective studies with sufficient number of patients are needed to be performed in the future.

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