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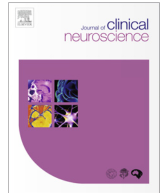

Clinical Study

Prognostic impact of molecular phenotype in patients with recurrent anaplastic glioma treated with prolonged administration of temozolomide

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ABSTRACT

We retrospectively investigated the prognostic impact of molecular phenotypes in patients with recurrent anaplastic glioma treated with prolonged administration of temozolomide (TMZ). Malignant gliomas have a dismal prognosis despite the available multimodal treatments. We reviewed 87 patients who were diagnosed with recurrent anaplastic gliomas between March 2004 and June 2010, and 58 were enrolled for analysis. In the cohort, 21 patients had anaplastic oligodendrogliomas, 18 anaplastic oligoastrocytomas and 19 anaplastic astrocytomas. All patients were initially treated with surgical resection or biopsy followed by involved-field radiotherapy. At recurrence, patients were treated with 150–200 mg/m^2 of TMZ on days 1–5 in 28 day cycles until disease progression. We evaluated the association of molecular phenotypes, including 1p19q deletion, O6-methylguanine DNA methyltransferase (MGMT) promoter methylation status, isocitrate dehydrogenase-1 (IDH1) mutation and other clinico-histopathological findings with treatment outcome. During the mean follow-up period of 34.6 months, 33 patients were still alive (56.9%). Median survival from recurrence was 39.7 months (95% confidence interval [CI] 22.7–56.7). Time to progression from administration of TMZ was 6.4 months (95% CI 5.0–7.8). Univariate analysis demonstrated that the presence of the IDH1 mutation was closely associated with treatment response (8.4 *versus* 3.8 months; $p = 0.015$). Oligodendroglial lineage, 1p19q deletion status and MGMT promoter methylation status were not independent variables for determining the TMZ treatment outcome. In recurrent anaplastic gliomas, TMZ treatment is an effective modality regardless of MGMT methylation status or histological type. The IDH1 mutation has the most powerful prognostic impact on overall patient survival.

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1. Introduction

Malignant gliomas have a dismal prognosis despite the available multimodal treatments and, therefore, they remain challenging to treat. The prognosis of anaplastic oligodendroglial tumors has been known to be closely associated with chromosome 1p19q codeletion, with better prognosis and higher chemosensitivity to procarbazine, 1-(2-chloroethyl)-3-cyclohexyl-L-nitrosourea, and vincristine (PCV) following radiotherapy. In contrast, the astrocytic subtype of anaplastic glioma is rarely 1p19q codeleted and is less responsive to PCV chemotherapy. As temozolomide (TMZ) has been widely accepted as a primary treatment for malignant gliomas, depending on O6-methylguanine DNA methyltransferase (MGMT) promoter methylation status, we have used chemotherapy with TMZ for recurrent anaplastic gliomas regardless of histological subtype.

Recently, a mutation affecting codon 132 of the isocitrate dehydrogenase 1 gene (IDH1), located on chromosome 2q33, was shown to be present in World Health Organization (WHO) Grade II–III gliomas and glioblastomas arising from lower grade gliomas [1–12]. Here, we retrospectively investigated the prognostic factors including histological subtype, 1p19q codeletion, MGMT promoter methylation status, and IDH1 mutation in recurrent anaplastic glioma patients who were treated with prolonged administration of TMZ.

2. Materials and methods

2.1. Patient characteristics

Of the 87 patients who were diagnosed with recurrent anaplastic gliomas at our institution between March 2004 and June 2010,

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Table 1
Characteristics of 58 patients with recurrent anaplastic gliomas

Variables	n (%)
Age, years	
<40	25 (43.1)
⩾40	33 (56.9)
Histological subtypes	
AO	21 (36.2)
AOA	19 (32.8)
AA	18 (31)
IDH1	
Wild type	24 (41.4)
Mutation	34 (58.6)
MGMT promoter	
Methylated	20 (34.5)
Unmethylated	38 (65.5)
1p deletion	
Yes	11 (19.0)
No	47 (81.0)
1p19q codeletion	
Yes	2 (3.4)
No	56 (96.6)

AA = anaplastic astrocytoma, AOA = anaplastic oligoastrocytoma, AO = anaplastic oligodendroglioma, IDH1 = isocitrate dehydrogenase 1, MGMT = O6-methylguanine DNA methyltransferase.

58 had tumor specimens available for tissue study and so were enrolled in this study. There were 36 men and 22 women with a mean age of 44.8 years (range: 18–73) of whom 21 had anaplastic oligodendrogliomas (AO), 18 anaplastic oligoastrocytomas (AOA) and 19 anaplastic astrocytomas (AA) according to the WHO Grade III classifications [13] (Table 1). All tumors were histologically reviewed by a single pathologist (Y.C.).

2.2. Treatment

All patients had previously been treated with surgical resection or biopsy followed by involved-field radiotherapy. Adjuvant PCV therapy was given following radiotherapy in 17 of 39 AO or AOA patients. At recurrence, patients were treated with 150–200 mg/m^2 of TMZ on days 1–5 in 28 day cycles. This study was approved by the Institutional Review Board of Samsung Medical Center (Seoul, Korea). The treatment was delivered until tumor progression or unacceptable toxicity was reached. Clinical information including age, sex, treatment, adverse effects and survival or disease progression was collected using clinical records and radiological investigation results.

2.3. IDH1 sequence analysis

Genomic DNA was extracted from 10 mm thick sections of 10% neutral formalin-fixed, paraffin-embedded (FFPE) tumor tissue blocks using the QIAamp DNA Mini Kit (Qiagen, Germantown, MD, USA). The complete coding sequence of exon 4 of the IDH1 gene, including codon 132, was obtained by overlapping polymerase chain reaction (PCR) amplification. PCR was performed in 20 mL volumes containing 100 ng of template DNA, 10 mL of PCR buffer, 0.25 mM of deoxynucleotide triphosphates (dNTP), 10 pmol primers, and 1.25 units of Taq DNA polymerase (iNtRON Biotechnology, Seoul, Korea). PCR products were electrophoresed on 2% agarose gels and were purified with a QIAquick PCR purification kit (Qiagen). Bidirectional sequencing was performed using the BigDye Terminator v1.1 kit (Applied Biosystems, Foster City, CA, USA) on an ABI 3130xl genetic analyzer (Applied Biosystems). Sequencher (version 4.10.1; Gene Codes Corporation, Ann Arbor, MI, USA) was used along with manual chromatogram reviews for sequence analysis. Confirmatory resequencing from replicate PCR amplification reactions was performed for all sequences that were ambiguous or deviated from wild type so that all abnormal sequences were confirmed at least in quadruplicate (Fig. 1).

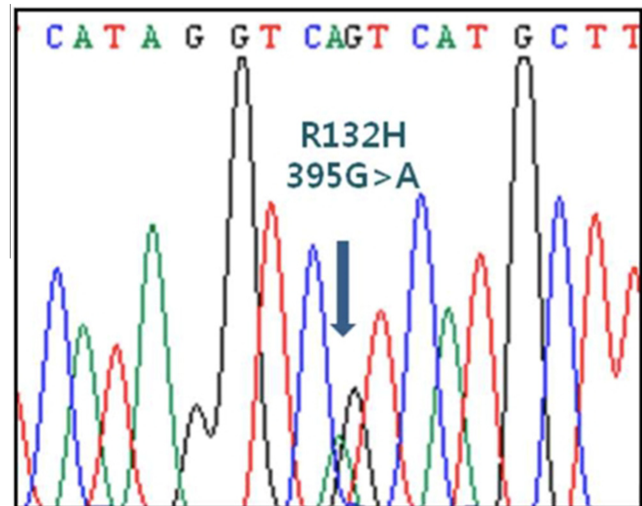

Fig. 1. Chromaview snapshot of isocitrate dehydrogenase 1 gene wild type and mutant sequences (R132H and R132S, respectively) in tumor tissue sample G48 where the guanine base (black) at position 395 has been replaced with an adenine (green) in a point mutation.

2.4. MGMT promoter methylation analysis by quantitative real-time methylation-specific PCR

DNA extracted from FFPE tissues was treated with sodium bisulfite using the EZ DNA methylation kit (Zymo Research, Irvine, CA, USA). Quantitative methylation-specific PCR assays were performed in an ABI 7900HT Fast Real-time PCR system (Applied Biosystems). Primer pairs used were as follows: MGMT forward CGTTTCGA CGTTCGTAGGT, and reverse AAAACTCCGCACTCTTCCG with the TaqMan probe 6FAM-AACGACCCAAACACTCACCAAATCGC-BBQ; ACTB forward TGGTGATGGAGGAGGTTTAGTAAGT, and reverse ACCAATAAAACCTACTCCTCCCTTAA with the TaqMan probe 6FAM-ACCACCACCCAACACACAATAACAAACACABBQ. The housekeeping β-actin gene (ACTB) was used for normalization of the methylation-independent control reaction. For relative quantification, the amounts of methylated DNA (percentage of methylated reference; PMR) at an MGMT promoter region were normalized to the methylation value of the calibrator, which was defined as 100%. Universal methylated DNA (Qiagen) was used as the calibrator. The PMR was defined as 100 × 2^([sampleACTB{ct} − sample MGMT{ct}]/[2[calibratorACTB{ct} − [calibratorMGMT{ct}]). The cut off value for discrimination between methylation levels was 12 and samples with PMR of 12 were considered to be methylated, whereas those with PMR < 12 were considered unmethylated [14,15].

2.5. Multiplex ligation probe amplification (MLPA) for 1p19q deletion

Deletion status of chromosome arm 1p19q was tested using the MLPA probe mix (Salsa MS-MLPA Kit ME011 MMR; MRC-Holland, Amsterdam, The Netherlands) which includes three probes specific for 1p19q. The resultant PCR fragments were separated by capillary gel electrophoresis (ABI Prism; Applied Biosystems). Methylation status was quantified using GeneMarker software (version 1.5; SoftGenetics, State College, PA, USA). To compensate for the differences in the PCR efficiency for the individual samples, the peak

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