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Clinical Investigation

Comprehensive Molecular Analysis in NRG Oncology/RTOG 9813: A Phase III Study of Radiation and Temozolomide Versus Radiation and BCNU/CCNU in Anaplastic Astrocytoma

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Abstract

Purpose

There is a need to better understand the molecular features that characterize grade 3 astrocytomas and their significance in predicting clinical outcomes. The aim of this study was to determine the significance of the 2021 WHO-defined molecular subgroups, along with *MGMT* promoter methylation, and other alterations in xxxx.

Methods and Materials

Mutation status was determined by immunohistochemistry and/or next-generation sequencing. Copy number alterations and *MGMT* methylation were determined by Affymetrix Oncoscan and/or Illumina 450K arrays. Progression-free survival and overall survival were estimated using the Kaplan-Meier method and tested using the log-rank test. Multivariable analyses used Cox proportional hazards models.

Results

Application of the 2021 WHO-defined criteria resulted in the reclassification of 26/79 (33%) patients to grade 4 astrocytoma, *IDH*-mutant or glioblastoma. When looking at newly assigned molecular grade, grade 3 patients experienced longer survival outcomes compared to grade 4 patients. As individual biomarkers, *IDH1/2* mutations, *MGMT* promoter methylation, and *ATRX* mutations were each associated with longer survival, while *TERT* promoter mutations, *EGFR* amplification, and gain of chromosome 7/loss of 10 (Chr+7/-10) were associated with shorter survival. Similar survival outcomes were observed for *MGMT* methylated patients treated with radiotherapy (RT) and temozolomide (TMZ) or RT and BCNU/CCNU, and *MGMT* unmethylated patients treated with RT and TMZ. Additionally, *IDH*-mutant patients seemed to respond well to the addition of TMZ.

Conclusions

This study demonstrated the importance of classifying patients according to the 2021 WHO-defined criteria. The majority of *IDH*-wildtype anaplastic astrocytomas (grade 3) were reclassified as glioblastoma (grade 4). These analyses also shed light on the efficacy of TMZ in certain molecular subgroups, where the addition of TMZ to RT appeared to benefit patients regardless of *MGMT* methylation status.

Introduction

xxxx was a phase III study of radiotherapy (RT) and temozolomide (TMZ) versus RT and nitrosurea (BCNU/CCNU) therapy in patients with grade 3 (anaplastic) astrocytomas. Astrocytomas are inherently heterogeneous and clinically remain a challenge to manage due to the lack of predictive biomarkers guiding treatment options. The primary report from xxxx did not show a significant difference in survival between the two treatment arms; however, TMZ was shown to be better tolerated[1]. *IDH1* mutation status, captured by immunohistochemistry, was also reported as an important prognostic biomarker associated with longer survival outcomes[1]. Our study builds upon the initial report by incorporating comprehensive molecular and genomic profiling data.

In 2021, the World Health Organization (WHO) published new guidelines for the classification of CNS tumors, including updates to adult-type gliomas[2]. While the molecular features that define oligodendroglioma remained the same (*IDH1/2* mutation and 1p/19q co-deletion), major revisions were made to the classification of astrocytic tumors. All *IDH1/2*-mutant (*IDH*-mut) astrocytic tumors are now designated astrocytoma, *IDH*-mut, and the presence of *CDKN2A/B* homozygous deletion, microvascular proliferation, or necrosis results in a diagnosis of grade 4. For *IDH1/2*-wildtype (*IDH*-wt) astrocytic tumors, independent of histologic markers, the presence of any of the 3 genetic features [*TERT* promoter mutation, combined gain of chromosome 7 and loss of chromosome 10 (Chr+7/-10), and *EGFR* amplification] leads to a diagnosis of glioblastoma[2]. Other genes commonly altered in adult gliomas, but not incorporated in the official classification include *ATRX, CIC, FUBP1*, and *TP53*[2,3]. The significance of *MGMT* as a

prognostic and predictive biomarker of TMZ is well-established in glioblastoma[4]; however, recent reports suggest *MGMT* may also add value for lower grade gliomas[5-8].

Recently, we have learned that many patients initially diagnosed as histological grade 3 astrocytoma display molecular features of and behave clinically like glioblastoma[9,10]. Thus, this provides a unique opportunity to evaluate the updated 2021 WHO classification in addition to *MGMT* promoter methylation in a clinical trial of histological grade 3 astrocytomas. Here we assessed the prognostic and/or treatment-specific significance of the WHO-defined molecular subgroups, as well as *MGMT* promoter methylation, and other established gene alterations, including those within *ATRX, CIC, FUBP1*, and *TP53* in xxxx.

Section snippets

Tumor Biospecimens

Prior to trial enrollment pathology was centrally reviewed and patients were eligible if diagnosed with grade 3 anaplastic astrocytoma or oligoastrocytoma. All sites obtained institutional review board approval and patients signed informed consents prior to trial enrollment. Formalin-fixed paraffin embedded tumor tissues were collected via either 1 mm core punches or unstained slides. After neuropathology review, representative areas (>70% tumor) were selected for DNA isolation. …

Molecular Evaluations

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WHO Classification

Formalin-fixed paraffin embedded tumor biospecimens were available for 116 of the 196 patients enrolled in xxxx. *IDH1/2* mutation status was obtained on 111/116 patients, of which 61 (55%) were *IDH*-mut and 50 (45%) were *IDH*-wt. Of the 75/116 patients with copy number data available, 71 (95%) were 1p/19q non-co-deleted (non-co-del), 8 (11%) were found to have Chr+7/-10, 12 (16%) were *EGFR* amplified, and 9 (12%) were *CDKN2A/B* homozygous deleted. Ninety-one patients had *TERT* promoter data and 18 …

Discussion

The application of the 2021 WHO-defined criteria within a phase III trial of histological grade 3 astrocytomas resulted in the reclassification of 26 patients to grade 4 astrocytoma, *IDH*-mut or glioblastoma (Fig. 1). Specifically, 8% (4/48) of *IDH*-mut astrocytomas contained *CDKN2A/B* homozygous deletion, corroborating what other groups have reported[15]. While *CDKN2A/B* homozygous deletion has been shown to be associated with worse survival outcomes[16], an

association was difficult to interpret in …

Conclusions

The present study demonstrates the importance of using the 2021-WHO criteria to classify patients diagnosed with histological grade 3 astrocytoma. Additionally, results from these analyses shed light on the efficacy of TMZ in *IDH*-mut gliomas and suggest there may be a subset of *MGMT* unmethylated patients that benefit from the addition of alkylating therapy. Clearly, however, there remains a great need to develop more effective therapies for *IDH*-wt/*MGMT* unmethylated patients. …

Conflicts of Interest

Drs Aldape, Ashby, Becker, Chakravarti, Fleming, Hunter, Kavanagh, McElroy, Pugh, Robins and Schultz have nothing to declare. Dr Bahary declares during the past 36 months NRG Vice Chair for Canadian affairs, NRG membership committee. Dr Chang declares during the past 36 months member of AstraZeneca Scientific Advisory Board. Dr Mehta declares during the past 36 months Consulting fees for Kazia Therapeutics, Novocure, Zap, Xoft, Karyopharm, Sapience, Board of Directors; stock options …

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Clinical Trial

NCT00004259 …

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Data Availability

Data will be made available in accordance with NRG Oncology data sharing policies. ...

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