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Original Research

Expression-based intrinsic glioma subtypes are prognostic in low-grade gliomas of the EORTC22033-26033 clinical trial

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Abstract ***Introduction:*** The European Organisation for Research and Treatment of Cancer (EORTC) 22033-26033 clinical trial (NCT00182819) investigated whether initial temozolomide (TMZ) chemotherapy confers survival advantage compared with radiotherapy (RT) in low-grade glioma (LGG) patients. In this study, we performed gene expression profiling on tissues from this trial to identify markers associated with progression-free survival (PFS) and treatment response.

Methods: Gene expression profiling, performed on 195 samples, was used to assign tumours to one of six intrinsic glioma subtypes (IGSs; molecularly similar tumours as previously defined using unsupervised expression analysis) and to determine the composition of immune infiltrate. DNA copy number changes were determined using OncoScan arrays.

Results: We confirm that IGSs are prognostic in the EORTC22033-26033 clinical trial. Specific genetic changes segregate in distinct IGSs: most samples assigned to IGS-9 have *IDH*-mutations and 1p19q codeletion, samples assigned to IGS-17 have *IDH*-mutations without 1p19q codeletion and samples assigned to other intrinsic subtypes often are *IDH*-wildtype. A trend towards benefit from RT was observed for samples assigned to IGS-9 (hazard ratio [HR] for TMZ is 1.90, P = 0.065) but not for samples assigned to IGS-17 (HR 0.87, P = 0.62). We did not identify genes significantly associated with PFS within intrinsic subtypes, although follow-up time is limited. We also show that LGGs and glioblastomas differ in their immune infiltrate, which suggests that LGGs are less amenable to checkpoint inhibitor–type immune therapies. Gene expression analysis also allows identification of relatively rare subtypes. Indeed, one patient with a pilocytic astrocytoma was identified.

Conclusion: IGSs are prognostic for PFS in EORTC22033-26033 clinical trial samples.

1. Introduction

Low-grade or low-grade II gliomas (LGGs) are a heterogeneous set of primary brain tumours that mainly occur in the fourth and fifth decade of life [1,2]. The incidence is relatively low (<one per 100,000 persons/year), and as they are slow-growing tumours, patients have a relatively favourable prognosis, especially compared with gliomas of higher grade. Nevertheless, LGGs have the tendency to evolve into gliomas of higher grade, and most patients will ultimately die from the disease [3,4]. Based on their histological appearance, three subtypes of LGG can be distinguished: oligodendrogliomas, astrocytomas and mixed oligoastrocytomas. The current World Health Organisation (WHO) classification has incorporated molecular markers (1p19q codeletion, and mutations in the *IDH1/2* and *ATRX* genes) to delineate astrocytomas and oligodendrogliomas, but no longer considers oligoastrocytomas as a separate entity as they cannot molecularly be distinguished from other entities [2,5].

Treatment options for LGG patients include surgery, radiotherapy (RT) and chemotherapy (or combinations thereof), or a watchful waiting strategy can be adopted [4,6]. Nevertheless, the optimal management of patients with an LGG has remained controversial, and only relatively few randomised phase III clinical trials have been performed. Earlier trials focussing on the effect of RT showed no effect of RT dosing on overall survival, and in a separate trial, there was no effect of early versus delayed RT after surgery on overall survival [7–9]. Data from two large randomised clinical trials recently reported on the efficacy of chemotherapy in LGGs. First, the Radiation Therapy Oncology Group (RTOG) 9802 clinical trial, examining the role of the addition of procarbazine, lomustine (CCNU) and vincristine (PCV) chemotherapy after RT showed improved survival of this regimen when compared with RT only [10]. Second, the European Organisation for Research and Treatment of Cancer (EORTC) 22033-26033 clinical trial examined the role of RT versus temozolomide (TMZ) chemotherapy and found no difference between the two on progression-free survival (PFS) or in quality of life [11,12]. Because of the limited follow-up time, data on overall survival are not available.

Interestingly, correlative molecular marker analysis in the EORTC22033-26033 study identified a subpopulation of patients who benefit from RT: Within the group of patients harbouring tumours with an IDH mutation and in which the 1p and 19q chromosomal arms were not codeleted ('molecular astrocytomas'), an improved PFS was noted when they were treated with RT. No such benefit was observed within the group of IDH-mutated, 1p19q-codeleted tumours ('molecular oligodendrogliomas') [11]. We have previously shown that gene expression profiling and subsequent molecular subtyping based on the gene expression profile (intrinsic glioma subtypes) can identify prognostic subgroups and identify genes and subtypes that are associated with