Corticosteroids compromise survival in glioblastoma.


Abstract

Glioblastoma is the most common and most aggressive primary brain tumour. Standard of care consists of surgical resection followed by radiotherapy and concomitant and maintenance temozolomide (temozolomide/radiotherapy→temozolomide). Corticosteroids are commonly used perioperatively to control cerebral oedema and are frequently continued throughout subsequent treatment, notably radiotherapy, for amelioration of side effects. The effects of corticosteroids such as dexamethasone on cell growth in glioma models and on patient survival have remained controversial. We performed a retrospective analysis of glioblastoma patient cohorts to determine the prognostic role of steroid administration. A disease-relevant mouse model of glioblastoma was used to characterize the effects of dexamethasone on tumour cell proliferation and death, and to identify gene signatures associated with these effects. A murine anti-VEGFA antibody was used in parallel as an alternative for oedema control. We applied the dexamethasone-induced gene signature to The Cancer Genome Atlas glioblastoma dataset to explore the association of dexamethasone exposure with outcome. Mouse experiments were used to validate the effects of dexamethasone on survival in vivo. Retrospective clinical analyses identified corticosteroid use during radiotherapy as an independent indicator of shorter survival in three independent patient cohorts. A dexamethasone-associated gene expression signature correlated with shorter survival in The Cancer Genome Atlas patient dataset. In glioma-bearing mice, dexamethasone pretreatment decreased tumour cell proliferation without affecting tumour cell viability, but reduced survival when combined with radiotherapy. Conversely, anti-VEGFA antibody decreased proliferation and increased tumour cell death, but did not affect survival when combined with radiotherapy. Clinical and mouse experimental data suggest that corticosteroids may decrease the effectiveness of treatment and shorten survival in glioblastoma. Dexamethasone-induced anti-proliferative effects may confer protection from radiotherapy- and chemotherapy-induced genotoxic stress. This study highlights the importance of identifying alternative agents such as vascular endothelial growth factor antagonists for managing oedema in glioblastoma patients. Beyond the established adverse effect profile of protracted corticosteroid use, this analysis substantiates the request for prudent and restricted use of corticosteroids in glioblastoma.

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KEYWORDS: CNS tumour: surgical treatment; astrocytoma; genetics; glioma; neurooncology
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