ABSTRACT

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Postmortem study of organ-specific toxicity in glioblastoma patients treated with a combination of temozolomide, irinotecan and bevacizumab.

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PURPOSE: Systemic chemotherapy including monotherapy with temozolomide (TMZ) or bevacizumab (BEV); two-drug combinations, such as irinotecan (IRI) and BEV, TMZ and BEV and a three-drug combination with TMZ, IRI and BEV (TIB) have been used in treating patients with progressive high-grade gliomas including glioblastoma (GBM). Most patients tolerated these regimens well with known side effects of hypertension, proteinuria, and reversible clinical myelosuppression (CM). However, organ- or system- specific toxicities from chemotherapy agents have never been examined by postmortem study. This is the largest cohort used to address this issue in glioma patients.

METHODS: Postmortem tissues (from all major systems and organs) were prospectively collected and examined by standard institution autopsy and neuropathological procedures from 76 subjects, including gliomas (N = 68, 44/M, and 24/F) and brain metastases (N = 8, 5/M, and 3/F) between 2009 and 2019. Standard hematoxylin and eosin (H&E) were performed on all major organs including brain specimens. Electronic microscopic (EM) study was carried out on 14 selected subject's kidney samples per standard EM protocol. Medical records were reviewed with adverse events (AEs) analyzed and graded according to the Common Terminology Criteria for Adverse Events (CTCAE), version 4.03. A swimmer plot was utilized to visualize the timelines of patient history by treatment group. The binary logistic regression models were performed to explore any associations between treatment strategies and incident myelosuppression.

RESULTS: Twenty-four glioma subjects were treated with TIB [median: 5.5 (range: 1-25) cycles] at tumor recurrence. Exposure to IRI significantly increased the frequency of CM (p = 0.05). No unexpected adverse events clinically, or

permanent end-organ damage during postmortem examination was identified in glioma subjects who had received standard or prolonged duration of BEV, TMZ or TIB regimen-based chemotherapies except rare events of bone marrow suppression. The most common causes of death (COD) were tumor progression (63.2%, N = 43) followed by aspiration pneumonia (48.5%, N = 33) in glioma subjects. No COD was attributed to acute toxicity from TIB. The study also demonstrated that postmortem kidney specimen is unsuitable for studying renal ultrastructural pathological changes due to autolysis.

CONCLUSION: There is no organ or system toxicity by postmortem examinations among glioma subjects who received BEV, TMZ or TIB regimen-based chemotherapies regardless of durations except for occasional bone marrow suppression and reversible myelosuppression clinically. IRI, but not the extended use of TMZ, significantly increased CM in recurrent glioma patients. COD most commonly resulted from glioma tumor progression with infiltration to brain stem and aspiration pneumonia.

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