Toxicities and associated factors in patients receiving temozolomide-containing regimens: a 12-year analysis of hospital data

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Abstract

Background: Although temozolomide has been extensively used to treat various tumors, there is a lack of large-cohort studies on temozolomide's toxicity profile.

Objective: To analyze the toxicity profiles and associated factors in patients treated with temozolomide-containing regimens.

Setting: The Union Hospital of Tongji Medical College, Huazhong University of Science and Technology.

Methods: A retrospective analysis of the clinical data of patients treated with temozolomide-containing regimens from January 2008 to December 2019. Univariate chi-square test and multivariate logistic regression analysis were employed to identify factors associated with the occurrence of toxicities.

Main outcome measure: The rate of toxicity occurrence and the characteristics of the toxicities.

Results: Among the 1,057 patients received temozolomide-containing regimens, 922 patients were included in our analyses. Of the 922 patients, 484 patients (52.5%) experienced toxicities. Univariate analysis revealed that radiotherapy, chemotherapy cycle, chemotherapy regimen, and clinical stage were significantly associated with the toxicity during temozolomide treatment ($P < 0.05$). The chemotherapy regimen, chemotherapy cycle, and clinical stage were significantly associated with the overall occurrence of toxicities ($P < 0.05$). A chemotherapy regimen, chemotherapy cycle, and clinical stage were associated with the hematological system's toxicities, whereas gender, age, clinical diagnosis, and clinical stage were related to gastrointestinal toxicities ($P < 0.05$). Clinical diagnosis, chemotherapy regimen, and age were associated with liver toxicity ($P < 0.05$).

Conclusion: Toxicities are common among patients receiving temozolomide-containing regimens. Clinicians should be aware of factors associated with toxicities to minimize the impact of the toxicity.

Keywords

Temozolomide; toxicity; hematological system; gastrointestinal system; liver toxicity

Introduction

Temozolomide is an imidazotetrazine derivative and a second-generation alkylating agent with antitumor effects. Orally administered temozolomide capsules are fully absorbed and well distributed in tissues; hence, the drug crosses the blood-brain barrier resulting in predictable adverse reactions [1]. Temozolomide's toxic profile and side effects are relatively mild and tolerable in patients receiving six or more cycles of treatment [2]. Temozolomide has been

associated with anemia, lymphopenia, neutropenia, and severe thrombocytopenia [2]. In clinical practice, temozolomide has been extensively used to treat glioma, non-small cell lung cancer, leukemia, melanoma, lymphoma, and certain solid tumors. Among other chemotherapeutics, temozolomide provides the most potent antitumor effects in glioblastoma [3]. In China, temozolomide has been on the market for nearly 20 years. Due to its sound curative effects in glioma patients, temozolomide has become the first-line treatment for malignant brain tumors [4, 5].

Temozolomide's efficacy and therapeutic regimen have been extensively studied in various tumors [6-10]. However, there is a lack of large-cohort studies on the toxicity profile of temozolomide. In this study, we retrospectively analyzed clinical data in patients treated with temozolomide in our hospital during the past 12 years. The in-depth analysis of the temozolomide-related toxicities can guide the clinical use of temozolomide to prevent toxicities.

Aim of the study

The study aimed to identify toxicities in patients treated with temozolomide containing therapeutic regimens and analyze factors associated with these toxicities.

Ethics approval

This study was approved by the Ethics Committee of Union Hospital of Tongji Medical College of Huazhong University of Science and Technology (reference number: 2019-S893).

Methods

Study design

This retrospective study analyzed the toxicity profiles of cancer patients treated with temozolomide-containing regimens from January 1, 2008, to December 31, 2019, at the Union Hospital of Tongji Medical College of Huazhong University of Science and Technology. The hospital is a 5,000 - bed comprehensive university teaching hospital in Wuhan, a megacity in China. The exclusion criteria were 1) patients with poor treatment adherence (irregular use, discontinuation or change of medication), which might have affected the evaluation of temozolomide's safety and efficacy, and 2) patients with incomplete data.

A "Temozolomide Safety Reassessment Research Card" was designed to collect demographic data, medication status, and toxicity occurrence. Additional information gathered included Karnofsky Performance Status Scale (KPS scale), body-mass index (BMI), drug manufacturer, radiotherapy, chemotherapy cycle, chemotherapy regimen, clinical diagnosis, and clinical tumor stage. Data were retrieved from the hospital electronic health records (EHR).

Chemotherapy regimens were divided into five categories: (1) concurrent chemoradiotherapy with adjuvant chemotherapy (usually six cycles of adjuvant chemotherapy with temozolomide alone); (2) mono-chemotherapy (only temozolomide); (3) combined chemotherapy with two drugs (temozolomide combined with capecitabine, cisplatin, irinotecan, apatinib, bevacizumab, recombinant human endostatin, gemcitabine, methotrexate, or rituximab); (4) complex chemotherapy regimen, including multidrug chemotherapy involving three or more drugs and concurrent chemoradiotherapy followed by combined chemotherapy; (5) adjuvant chemotherapy after radiotherapy. In this analysis, the chemotherapy cycle was regarded as the total cycle number with clear examination results during the patient's hospitalization. Usually, temozolomide was used for five days in a cycle, and each cycle lasted for 28 days. However, in concurrent chemoradiotherapy, temozolomide was employed for 42 consecutive

days, and this was regarded as one chemotherapy cycle due to the continuous use of temozolomide in concurrent chemoradiotherapy.

The severity of toxicities was assessed based on the Common Terminology Criteria for Adverse Events (CTCAE) v4.0 [11]. The CTCAE displays Grades 1 through 5 with unique clinical descriptions of severity for each adverse event. Grade 1- mild: asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated. Grade 2 - moderate: minimal, local, or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL). Grade 3 - severe or medically significant but not immediately life-threatening: hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL. Grade 4 - life-threatening consequences; urgent intervention indicated. Grade 5 - death related to an adverse event.

Statistical analysis

Data were recorded using Microsoft Excel®, and SPSS 25.0 was used for statistical analyses. Normally distributed data were expressed as means ± standard deviation (SD), whereas categorical data were expressed as percentages. The chi-square test was used to compare groups, and the influencing factors were analyzed by multivariate logistic regression analysis. Significant factors in univariate analysis were used in multivariate logistic regression analysis. *P*-values < 0.05 were considered statistically significant.

Results

Characteristics of patients and analysis of toxicities

A total of 1,057 patients were treated with temozolomide-containing regimens within the analysis period, and 922 met the inclusion and exclusion criteria. Among the 922 patients, 558

were males, and the average age was 45.25 years (ranged from 1 to 93 years). Toxicities were reported in 484 of the 922 patients, with an overall toxicity rate of 52.5% (Table 1).

[*insert Table 1 here*]

A total of 787 toxic cases were recorded in patients treated with temozolomide-containing regimens. The most common cases involved the hematological system (34.9%, 275/787), followed by the gastrointestinal system (24.8%, 195/787) (Supplemental Table 1). When cases were analyzed based on chemotherapy regimens, the concurrent chemoradiotherapy with adjuvant chemotherapy accounted the most, 55.3% (435/787), followed by temozolomide mono-therapy (17%, 134/787) (Table 2).

[*insert Table 2 here*]

Among the 922 patients who were treated with temozolomide, 183 patients concurrently received other chemotherapeutic agents. The toxicity occurrence based on the concurrent drugs used in more than ten patients is listed in Table 3. The most common combination drug used was capecitabine (31.7%, 58/183), followed by cisplatin (23.5%, 43/183).

[*insert Table 3 here*]

Among the 922 patients analyzed, 285 (30.9%) were classified as clinical stages 1-2, and 637 (69.1%) as stages 3-4. The occurrence of toxicities in patients with different clinical diagnoses and at different stages is listed in Table 4. In patients at clinical stages of 1 and 2, patients with glioma (n = 192) experienced the highest rate of toxicities (47.9%, 92/192), followed by patients with lymphoma (46.7%, 7/15). This pattern was also observed in patients at clinical stages 3 and 4, patients with glioma (n = 368) had the highest rate of toxicities (77.7%, 286/368), followed by patients with lymphoma (67.9%, 19/28). The rates of toxicity occurrence were higher in stages 3-4 than stages 1-2 regardless of cancer types. Due to the large gap in the

number of toxicity occurrence of different severities, no statistically significant factors affecting toxicity severity are identified.

[*insert Table 4 here*]

The case toxicity severities were assessed using the CTCAE rating scale. A total of 726 cases (92.2%) were rated at grades 1-2, and 61 (7.8%) were rated grade 3 or above. Within the grades 1-2 categories, the hematological system accounted for 249 cases (34.3%, 249/726), followed by the gastrointestinal system (25.9%, 188/726). Within the grades 3 or above category, the hematological system accounted for the most, 26 cases (42.6%, 26/61), followed by the other type (37.7%, 23/61) (Table 5).

[*insert Table 5 here*]

Factors affecting the toxicity occurrence of temozolomide-containing regimens

Univariate analysis indicates that radiotherapy, chemotherapy cycle, chemotherapy regimen, and clinical stage were significant factors affecting the toxicity occurrence ($P < 0.05$) (Table 1). Among the 92 patients, 616 had BMI recorded in EHR. Univariate analysis revealed that BMI was not associated with the overall toxicity occurrence ($P = 0.082$) (Supplemental Table 2).

The variables that showed statistical significance in univariate analysis were used as independent variables in logistic multivariate regression analysis. The overall toxicity and toxicities in the hematological system, gastrointestinal system, and liver were used as dependent variables. A chemotherapy regimen, chemotherapy cycle, and clinical stage were identified as factors significantly affecting the overall occurrence of toxicity ($P<0.05$) (Table 6).

[*insert Table 6 here*]

A chemotherapy regimen, chemotherapy cycle, and clinical stage were identified as factors significantly affecting the occurrence of toxicities in the hematological system ($P<0.05$)

(Supplemental 3). Gender, age, clinical diagnosis, and clinical stage were factors significantly associated with toxicity in the gastrointestinal system (P<0.05) (Supplemental Table 4). Clinical diagnosis, chemotherapy regimen, and age were factors significantly affecting the occurrence of toxicity in the liver (P<0.05) (Supplemental Table 5).

Discussion

This retrospective analysis reveals that in patients receiving temozolomide-containing regimens, the toxicity occurrence rate is high, around 50%. A chemotherapy regimen, chemotherapy cycle, and clinical stage are significant factors affecting the overall toxicity occurrence. Factors affecting the toxicity occurrence varies among organ systems.

Evaluation of toxicity occured in the combination therapy

When combined with the orally-administered chemotherapeutic agent capecitabine, the toxicity rate in temozolomide-treated patients is 25.9% (15/58), lower than that of patients receiving temozolomide mono-chemotherapy (38.2%, 73/191). However, why the combination of temozolomide with capecitabine has a favorable safety profile remains unclear. The combination of temozolomide with injectable chemotherapeutics increases the toxicity rate occurrence except for the combination with bevacizumab, which exhibits a comparable rate to temozolomide mono-chemotherapy.

Evaluation of factors associated with temozolomide-containing therapies

A chemotherapy regimen and chemotherapy cycle are significant factors affecting the overall toxicity occurrence. The risk of toxicity in complex chemotherapy regimens and concurrent chemoradiotherapy with adjuvant chemotherapy is 4.06 and 3.37 times higher than that of temozolomide mono-chemotherapy. Notably, patients receiving more treatment cycles exhibit a

significantly higher rate of toxicity occurrence. In patients receiving temozolomide for eight cycles or above, the risk is 4.04 times higher than patients receiving one treatment cycle ($P < 0.05$). The risk of toxicity in patients at clinical stages 1-2 is only 0.56 times higher than that of patients at stages 3-4 ($P < 0.001$). Interestingly, the factors affecting the toxicity occurrence varies among different organ systems.

A chemotherapy regimen, chemotherapy cycle, and clinical stage are significant factors affecting the hematological system's toxicity. In patients undergoing concurrent chemoradiotherapy with adjuvant chemotherapy, adjuvant chemotherapy after radiotherapy, and complex chemotherapy, the risk of toxicity is 6.42, 5.31, and 4.79 times higher, respectively, than patients receiving mono-chemotherapy ($P < 0.05$). A study on the risks of toxicity in patients receiving temozolomide-containing regimens for glioma treatment also indicates a higher risk of concurrent chemoradiotherapy with adjuvant chemotherapy than mono-chemotherapy [12]. The number of chemotherapy cycles is also associated with the risk of toxicity. Importantly, patients receiving temozolomide for eight cycles or above exhibit a six times higher toxicity rate than patients receiving one cycle ($P < 0.05$). Gender is not a significant factor associated with the risk of hematological toxicity occurrence in our analysis. This is different from a retrospective analysis of 680 patients with malignant glioma, which reveals that temozolomide's hematological toxicity is higher in women than in men [13]. This discrepancy could be attributed to the fact that we included all cancer patients treated with temozolomide, not just glioma patients. The risk of hematological toxicities in patients at clinical stages 1-2 is only 0.64 times higher than that in patients at stages 3-4 ($P < 0.05$).

Clinical diagnosis, clinical stage, gender, and age are significant factors affecting the gastrointestinal system's toxicity occurrence. In lung cancer patients, the risk of the

gastrointestinal system toxicity is 6.2 times higher than that in patients with neuroendocrine tumors ($P < 0.01$). The risk of gastrointestinal toxicity in patients at clinical stages 1-2 is only 0.59 times higher than that in patients at stages 3-4 ($P < 0.05$). Our analysis is consistent with another study, which indicates that the risk of gastrointestinal toxicity is 1.88 times higher in women than in men ($P < 0.01$) [12].

Clinical diagnosis, chemotherapy regimen, and age are significant factors contributing to treatment-related liver dysfunction. The risk of abnormal liver function in lymphoma patients is 6.01 times higher than that in patients with neuroendocrine tumors ($P < 0.05$). The risk of liver toxicity in patients undergoing concurrent chemoradiotherapy with adjuvant chemotherapy, complex chemotherapy, and combined chemotherapy is 6.75, 4.33, and 3.37 times higher, respectively, compared with the risk in patients receiving temozolomide mono-chemotherapy ($P < 0.05$). The risk of liver dysfunction in patients under 18 is only 0.09 times higher than that in patients aged over 59 ($P < 0.05$). Notably, out of 56 patients aged under 18, only one patient (1.79%) exhibited liver toxicity instead of the 15.1% overall incidence of treatment-related liver dysfunction.

Our study analyzed patients who received temozolomide-containing regimens over 12 years using data from real-world clinical practice. The findings may help clinicians better design temozolomide-containing chemotherapies and monitor at-risk patients to develop treatment-related toxicities. The study has the following limitations 1) the analysis is a single-center study, and 2) the study is retrospective in nature. We did not assess the clinical outcome of the patients.

Conclusion

In patients treated with temozolomide-containing regimens, toxicities present commonly in the

hematological and gastrointestinal systems and the liver. Clinicians should pay particular attention to the significant factors associated with the toxicity occurrence, such as the chemotherapy regimen, chemotherapy cycle, and the patient's clinical stage.

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Conflicts of interest

All authors declare that they have no conflict of interests.

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