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Managing Side Effects of Cytotoxic Chemotherapy in Patients With High Grade Gliomas

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Cytotoxic chemotherapy has been a mainstay of cancer treatment since the 1940s. In the recent era of emergent targeted therapies and immunotherapies, many cytotoxic chemotherapy agents including temozolomide are still one of main weapons for the treatment of high grade gliomas. However, cytotoxic chemotherapy often causes side effects. Proper management of chemotherapy-induced toxicity can have a significant impact on a patient's quality of life and clinical outcomes. Many supportive care advances have transformed our ability to give full doses of chemotherapy, which is important for achieving their full efficacy. Prevention and treatment strategies have been developed for many chemotherapy-related toxicities. This review focused on managing gastrointestinal toxicity, chemotherapy-induced nausea and vomiting, and hematologic toxicities such as thrombocytopenia during cytotoxic chemotherapy treatment in high-grade brain tumors.

Keywords Chemotherapy; Brain tumor; Adverse drug event.

INTRODUCTION

Recent advances in effective anticancer treatments have improved the survival rates of patients suffering from cancers. In the current era of targeted therapies and immunotherapies for many types of cancers, cytotoxic chemotherapies still represent a crucial therapeutic weapon in many cancers, including brain tumors. Many cytotoxic chemotherapeutic agents, including temozolomide, are still one of the main treatment options in the current guidelines for anaplastic gliomas and glioblastomas [1,2]. Chemotherapy, especially cytotoxic chemotherapy, affects cancer cells more than normal cells. Cytotoxic chemotherapy also affects all other cells in the body to a greater or lesser extent. The cells most affected by the cytotoxic effects of chemotherapy are tumor cells; however, other cells that share characteristics with fast cell division, such as hair follicles, bone marrow, gastrointestinal cells, and genital cells also affected by cytotoxic chemotherapy. Therefore, these kinds of cytotoxic chemotherapies have many toxicities. Many patients often face the serious negative side effects of life-saving treatments during and after therapy in brain tumors.

For example, RTOG 9802 phase III randomized trial was one of the landmark trials demonstrating the role of procarbazine, lomustine, and vincristine (PCV) adjuvant chemotherapy in low-grade brain tumors [3]. In this RTOG 9802 trial, the median age was as young as 40, and the Karnofrsky performance score of the patients in the trial was more than 70% of patients was over 90, suggesting that relatively young patients with good general conditions participated. As a result, overall survival (OS) after radiotherapy (RT)+PCV was significantly increased. The patients treated with PCV after RT experienced a substantially higher incidence of adverse events (specifically neutropenia, gastrointestinal toxicities, and fatigue) than RT alone. These results suggest that the PCV regimen is difficult to apply to elderly patients. As this trial was studied about 20 years ago, it may be challenging to reflect on current clinical practice because current supportive care is different from what it used to be. EORTC 26951 trial enrolled relatively older patients compared to the RTOG 9802 study. EORTC 26951 trial consisted of RT followed by six cycles of PCV. The results

demonstrated significantly improved median progression-free survival (PFS) and OS in adult patients with newly diagnosed anaplastic oligodendrogliomas and oligoastrocytomas. A total of 368 patients were enrolled. For a median follow-up period of 140 months, OS in the RT/PCV group was significantly longer. However, in this EORTC 26951 trial, more than 70% of patients in the RT followed by PCV arm did not complete the planned six cycles of treatment [4]. In RTOG 9402, a similar trial to EORTC 26951 trial, there was also a high rate of study treatment discontinuation [4,5]. In that trial, the most frequent and severe toxicities were myelosuppression, cognitive or mood change, peripheral or autonomic neuropathy, and vomiting. And PCV chemotherapy regimen was stopped for toxicity in 20% of participating patients. Glioblastoma is the most common primary malignancy of the central nervous system in adults. Chemoradiation therapy with temozolomide is the current standard of care for glioblastoma after a phase III clinical trial conducted by Stupp et al. [6]. The study showed that adding six cycles of adjuvant temozolomide to post-surgical treatment and concurrent chemoradiotherapy significantly improved the survival outcome of newly diagnosed glioblastoma. Temozolomide is an oral alkylated cytotoxic drug that can cause side effects like any other alkylating agent. Although the toxicity profile of temozolomide was usually better than that of the PCV chemotherapy regimen, early discontinuation of concomitant temozolomide was observed in 13% of patients during treatment [6,7].

Proper management of chemotherapy-induced toxicities can significantly impact patients' quality of life and outcomes. If toxicities were severe, they might lead to emergency room visits, hospital admissions, dose reduction, and potentially even discontinuation of chemotherapy which might be important for survival outcomes. Therefore, it is essential to stay up to date on how to treat chemotherapy-induced adverse events. Many prevention and treatment strategies have been developed for chemotherapy-related adverse events. Reporting adverse events is essential in clinical trials to ensure patient safety and understand the toxicity profile of the treatment. Therefore, the method of collecting this information must be accurate and reliable. The standard approach for documenting symptomatic adverse events in cancer clinical trials is by investigators using the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE). CTCAE has been used widely to report toxicity in real-world practice as well as clinical trials.

This review focused on gastrointestinal toxicity, chemotherapy-induced nausea and vomiting (CINV), and hematologic toxicities such as thrombocytopenia during cytotoxic chemotherapy treatment in high-grade brain tumors. We also summarized recent advances in side effect management strategies for chemotherapy. Additionally, we reviewed novel treatment agents for chemotherapy side effect management.

GASTROINTESTINAL TOXICITIES: DIARRHEA

Diarrhea is one of the common adverse events of chemotherapy. Diarrhea related to chemotherapy develops relatively early during treatment and resolves over time. The true extent of clinically relevant chemotherapy-induced diarrhea is unknown. Prevalence and severity vary widely [8]. The possibility that diarrhea might occur related to chemotherapy is different for each anticancer drug regimen, and it is reported to be around 10% and at most 40% or more [9,10]. The incidence of diarrhea is most closely related to the type of drug. Most commonly seen with fluoropyrimidines and irinotecan. Some of these patients also suffer from neutropenia, and it is unclear whether infections associated with neutropenia contribute to diarrhea and mortality, but chemotherapy-induced diarrhea remains a significant complication. Chemotherapy-induced diarrhea can significantly impact the quality of life, leading to adjustments in chemotherapy dosing, resulting in suboptimal treatment. Diarrhea can significantly impact performance status and ability to perform daily activities. The severity of diarrhea is often defined by a CTCAE. The most important decision is whether the patient can be managed on an outpatient basis or hospitalization for fluid resuscitation is necessary. This decision usually depends on the grade of adverse events. Patients with grade 3–4 diarrhea typically need to be hospitalized immediately unless the patient is well enough hydrated, has not yet taken antidiarrheal drugs, and could be reviewed daily. Patients with chemotherapy-related diarrhea can also have acute kidney injury, electrolyte abnormalities (hyponatremia), and other infections. Patients with acute grade 3–4 diarrhea admitted to the hospital require urgent stool culture for microscopy and *Clostridium difficile* testing. Laboratory findings should be tested for complete blood count, urea and electrolytes, liver function, glucose, thyroid function, and C-reactive proteins. If the patient has hypotension or tachycardia, acid-base balance and lactate levels should also be measured. An abdominal X-ray should be taken, and the frequency of defecation and the type of stool passed should be charted [11].

A detailed evaluation of the patient should be encouraged. The existence of fever and hydration status, stool consistency, stool volume, and duration of diarrhea are important factors in assessing diarrhea. In addition, in order to properly diagnose and manage diarrhea, patients should be asked about factors that may exacerbate diarrhea. Chemotherapy dosing and regimens might also affect the incidence of chemothera-

py-related diarrhea. A regimen containing bolus 5-FU appears to be associated with a higher incidence of diarrhea than the infusion regimen. Capecitabine, the oral form of 5-FU, has the lowest toxicity of diarrhea. The schedule of irinotecan administration also affects the incidence of chemotherapy-related diarrhea. The 3-weekly irinotecan regimen was associated with more severe irinotecan-induced diarrhea than the weekly dosing schedule. The mechanism of diarrhea during chemotherapy is not fully understood yet. However, it is thought that gastrointestinal epithelial damage leads to secretory diarrhea and increased intraluminal osmotic concentration leads to osmotic diarrhea or a change in gastrointestinal motility [11].

Irinotecan has been used in recurrent glioblastoma with bevacizumab [12]. The gastrointestinal toxicity of irinotecan, unlike the toxicity of other chemotherapeutic agents, is associated with early-onset and late diarrhea. Early-onset is defined as diarrhea that occurs during or within 24 hours of irinotecan administration, and delayed onset is defined as diarrhea that occurs 24 hours or more after irinotecan administration. The mechanism of acute diarrhea during irinotecan is that irinotecan is also a selective and reversible inhibitor of acetylcholinesterase. Although the main symptom is diarrhea, patients may experience other cholinergic effects such as sweating, hypersalivation, flushing, rhinitis, and abdominal cramps. Atropine works as a competitive antagonist at anticholinergic receptors. Atropine 0.25−1 mg administration just before the irinotecan therapy has been demonstrated to be a relatively safe and effective treatment in irinotecan-related acute diarrhea. Currently, if necessary, atropine is routinely used in patients treated with irinotecan, and the incidence of severe cholinergic symptoms interfering with treatment is very low. Delayed onset diarrhea related to irinotecan treatment is usually more severe, longer-lasting, and significantly impacts cancer treatment. About 60%−87% of patients treated with irinotecan experience delayed-onset diarrhea [13]. As the primary treatment of choice, loperamide is usually administered. The initial dose of loperamide is 4 mg, and then the dose of 2 mg is adjusted every 2−4 hours while observing the patient's symptoms. Patient education is essential as the patients usually take medications at home [11].

CHEMOTHERAPY-INDUCED NAUSEA AND VOMITING

Nausea and vomiting remain one of the most worrying side effects in patients receiving cancer treatment. Nausea and vomiting used to be among the most debilitating side effects of chemotherapy. Nausea and vomiting caused by chemotherapy can significantly impact a patient's quality of life and may reduce their compliance with further chemotherapy. It can also cause dehydration, metabolic imbalances, diminished self-care, and functional capacity, nutrient depletion, loss of appetite, poor general condition of the patient, and withdrawal from potentially useful chemotherapeutic treatments. The development of novel, more effective antiemetic drugs has provided relief from nausea and vomiting, and many patients no longer experience nausea or vomiting at all. Up to 60%−90% of the patients who received chemotherapy did not experience nausea and vomiting with the development of new antiemetic regimens, including neurokinin-1 receptor antagonists [14,15]. However, CINV remain a challenging side effect in patients with brain tumors, despite guideline-based antiemetics with selective serotonin receptor antagonists. In addition, physicians often underestimate nausea due to the lack of accurate measurements of subjective results that the patient can only report. As in most settings, nausea has been reported to be more frequent and challenging to control than vomiting in patients with brain tumors.

CINV frequency depends primarily on the emetogenic potential of the specific chemotherapy agents. Several classifications have been developed to define the emetogenicity of anticancer agents. They generally divide chemotherapy regimens into four levels according to the percentage of patients who experience acute emesis when the patients do not receive antiemetic prophylaxis. The PCV regimen is classified as a moderate emetic risk agent as this regimen is predicted to cause acute emesis in 30% to 90% of patients if the patients did not receive antiemetic prophylaxis. Temozolomide is also classified as a moderate emetic risk agent. There are several guidelines to control nausea and vomiting related to chemotherapy developed by the National Comprehensive Cancer Network (NCCN) [16], Multinational Association of Supportive Care in Cancer (MASCC) [17], and American Society of Clinical Oncology (ASCO) [18]. Most of the content between guidelines is similar, although there are some differences [19]. It is commonly categorized as acute, delayed, predictive, refractory, and breakthrough. Acute onset nausea or vomiting usually occurs within 24 hours of administration of the chemotherapeutic agent and usually resolves within the first 24 hours. The intensity of acute vomiting generally peaks 5−6 hours after chemotherapy. Delayed CINV develops more than 24 hours after chemotherapy and is usually associated with highly emetic chemotherapy such as cisplatin, carboplatin, cyclophosphamide, and anthracyclines. Breakthrough CINV refers to nausea or vomiting that occurs despite optimal prophylactic antiemetic treatment and requires rescue with other antiemetics. Refractory CINV refers to nausea or vomiting during the next treatment cycle if antiemetic prophylaxis is ineffective in the previous cycle. Anticipatory CINV describes nausea and vomiting before chemotherapy treatment as a conditional response

to the development of CINV in the previous cycle of chemotherapy. Anticipatory CINV rarely responds to standard antiemetic regimens.

CINV, especially acute CINV, is primarily associated with the release of multiple emetogenic neurotransmitters such as serotonin type 3, neurokinin 1, and dopamine. Drugs that control these neurotransmitters help treat acute CINV. The backbone drugs of CINV treatment are serotonin receptor antagonists, neurokinin-1 receptor antagonists, and dexamethasone [14]. Olanzapine is an atypical antipsychotic agent widely used to treat schizophrenia and other psychiatric disorders. This drug is also helpful as an antiemetic agent due to its mechanisms as an antagonist of multiple receptors involved in CINV, including dopamine, serotonin, histamine, and acetylcholine. Some patients receiving oral anticancer agents of low/minimal emetogenicity may experience nausea and vomiting. These patients should be escalated to the next higher level of antiemetic therapy in future cycles of anticancer agents. Breakthrough nausea or emesis presents a difficult situation. Generally, it is much easier to prevent nausea and vomiting than treat it, which is why many guidelines recommend prophylactic antiemetic regimens. In the case of breakthrough CINV, the general treatment principle is to add one agent from a different class of drug to the current regimen. Changing from the current neurokinin-1–containing regimen to an olanzapine-containing regimen or switching to another serotonin receptor antagonist or neurokinin-1 receptor antagonist could be helpful. The efficacy of olanzapine (10 mg/day oral for three days) as a treatment for breakthrough emesis was compared with metoclopramide in the phase III trial. Olanzapine was significantly superior to metoclopramide in the control of breakthrough CINV in the trial [20].

Several oral chemotherapy agents, including temozolomide, have the potential for emesis and are categorized as moderate emetogenic agents. However, most prior antiemetics trials have been conducted in patients receiving intravenous chemotherapy. There is a lack of evidence-based guidance regarding effective antiemetics for multi-day oral chemotherapy regimens. More trials studying antiemetic treatment for oral chemotherapy were needed. Single-agent serotonin antagonists are usually recommended as antiemetics for oral anticancer agents. Additionally, the trials establishing antiemetic guidelines for general cancer populations often exclude brain tumor patients due to brain lesions and steroid use [21].

One phase II study evaluated palonosetron to prevent CINV in glioblastoma treated with temozolomide [22]. They conducted a small phase II single-arm study in patients with brain tumors taking steroids 2–8 mg/day. They administered long-acting palonosetron 0.25 mg intravenously before oral adjuvant temozolomide (150–200 mg/m^2/day for five days) every four weeks. They reported that 91% of patients did not vomit or use rescue medication during the study period (days 1–7). However, the study only evaluated the first week of temozolomide administration. In another phase II trial assessing steroid-sparing regimen, they compared ondansetron alone with adding neurokinin-1 receptor antagonist (aprepitant) in patients receiving adjuvant temozolomide [23]. Aprepitant plus ondansetron may increase the acute-complete response rate but was not statistically significant. Adding a 5-day aprepitant to ondansetron was not superior to ondansetron alone in preventing CINV. However, the delayed complete response, defined as no vomiting or nausea rescue medication needed on days 2–7 following temozolomide, was only about 55%. In quality-of-life analysis, there were no statistical differences between the two groups. Further improvement in antiemetic therapy for concomitant chemoradiotherapy with temozolomide is warranted.

CHEMOTHERAPY-INDUCED THROMBOCYTOPENIA

As mentioned earlier, the standard treatment for patients with newly diagnosed glioblastoma includes surgery followed by radiation therapy with temozolomide and six cycles of additional maintenance temozolomide [6]. Thrombocytopenia represents one of the main toxicities of this regimen. In the landmark trial, grade 3–4 thrombocytopenia, the most common hematologic toxicity, was noted in 3% of patients during concomitant temozolomide and RT and 11% during adjuvant temozolomide treatment. Temozolomide is an imidazole tetrazine derivative, a second-generation alkylating agent with antitumor effects. Myelotoxicity was the dose-limiting toxicity of temozolomide in an earlier phase I trial [24]. Generally, 15%–20% of newly diagnosed patients receiving temozolomide developed severe and potentially irreversible thrombocytopenia, although there are some differences in incidences between studies [25]. The risk of severe myelosuppression is relatively low and acceptable but not negligible. Chemotherapy-induced thrombocytopenia could lead to hemorrhage, with increased risk in patients treated with corticosteroids. In addition, thrombocytopenia usually requires dose reduction, further delay in the course of scheduled chemotherapy, or discontinuation of treatment, which may jeopardize OS. One study showed that a decrease in platelet count during concurrent treatment with RT and temozolomide was significantly correlated with prolongation of survival [26]. However, further research must confirm this relationship and clarify the underlying mechanism. Although the underlying comorbidities can cause thrombocytopenia, it often results from myelosuppressive cytotoxic chemotherapy. Anticancer

drugs can cause thrombocytopenia via various mechanisms. Various chemotherapeutic agents affect the production pathways of megakaryocytes and platelets at various stages. The only treatment option for thrombocytopenia has been a platelet transfusion. However, this provides a temporary amelioration of thrombocytopenia.

Thrombopoietin receptor agonists (TPO-RAs) increase platelet production through interactions with the thrombopoietin receptor on megakaryocytes [27]. In normal hematopoiesis, the liver produces thrombopoietin, which stimulates megakaryocytes to proliferate, differentiate, and produce platelets. Romiplostim activates the thrombopoietin receptor and stimulates Janus kinase 2 and signal transducers and activators of transcription 5 pathways [28]. This leads to megakaryocyte proliferation and differentiation. The chemical structure of romiplostim is composed of the Fc portion of IgG1, to which two thrombopoietin peptides consisting of 14 amino acids are coupled through glycine bridges at the C-terminal of each γ heavy chain.

TPO-RA studies in cancer are mainly retrospective or phase II trials [29]. In these trials, romiplostim and eltrombopag showed potential benefits in patients experiencing severe thrombocytopenia. In patients receiving chemotherapy for solid tumors, TPO-RAs may improve platelet counts and the ability to prescribe scheduled anti-cancer treatments. Two trials compared a TPO-RA with a placebo in individuals with solid tumors receiving chemotherapy [30,31]. No difference was observed in all-cause mortality. There is not enough evidence to determine whether TPO-RAs reduce the number of patients with at least one bleeding episode of any severity. One study showed that patients treated with gemcitabine who received eltrombopag or placebo prophylaxis starting at cycle two found higher nadir platelet counts in the eltrombopag group [31]. Another study with 183 patients receiving carboplatin/paclitaxel regimens for solid tumors to eltrombopag or placebo. The study exhibited higher post-nadir platelet counts in the eltrombopag groups [30]. But the evidence was insufficient to determine whether these drugs reduced bleeding or the need for platelet transfusions.

Planum trial was conducted to determine the efficacy of the thrombopoietin receptor agonist romiplostim for preventing temozolomide-induced thrombocytopenia in newly diagnosed glioblastoma [32]. In an open-label phase II study of romiplostim in patients with glioblastoma receiving temozolomide, 60% of patients had a good response, and only 20% had no response. No serious adverse events with romiplostim have been reported. Unexpectedly, one pulmonary embolism was observed, and no major bleeding was noted. Furthermore, no detrimental effects of romiplostim on PFS or OS have been demonstrated. But the trial was a small (only 20 patients) phase II open-label, single-arm trial. Further randomized phase III trial is warranted to confirm that romiplostim helps reduce platelet transfusions and hemorrhagic complications and improves outcomes in patients with chemotherapy-induced thrombocytopenia by allowing chemotherapy to be completed. The rate of thrombotic complications in patients who received romiplostim has been reported between 5%−15% in other studies with various cancer types [33,34]. Most of the events were venous thromboembolism, and only a small number of arterial events were reported. It is still unclear whether TPO-RAs increase thrombosis in patients with cancer since no comparison group was included in most of the studies. Recently, a phase III study of avatrombopag versus placebo in patients with cancer who experienced grade 3−4 thrombocytopenia was terminated due to no benefit [35]. NCCN provides recent guideline for the management of chemotherapy-induced thrombocytopenia [36].

CONCLUSIONS

In conclusion, many supportive care advances have transformed our ability to give full doses of chemotherapy, which is important for achieving their full efficacy. Significant unmet needs remain in the assessment and treatment of patients. It is also important to recognize the potential risk of developing delayed toxicity, whose actual incidence might be underestimated due to poor survival in brain tumor patients. Future research will elucidate identifying the genetic profile associated with these serious adverse events. Proper management of chemotherapy-related toxicities improves patient quality of life during and after treatment and ultimately improves clinical outcomes.

Ethics Statement

Not applicable

Availability of Data and Material

Data sharing not applicable to this article as no datasets were generated or analyzed during the study.

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Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

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