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REVIEW ARTICLE

Severe hematologic temozolomide-related toxicity and life-threatening infections

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Summary

Glioblastoma is the most frequent primary malignant brain tumor in adults. With the number of symptoms and signs, it belongs to diseases where a lot of treatment modalities are often applied. A standard treatment for patients with glioblastoma includes surgical resection followed by radiotherapy with concomitant and adjuvant temozolomide. Each type of treatment has its own toxicity. Temozolomide is an oral alkylating cytotoxic drug and like any other alkylating agent can induce side effects. Although temozolomide is generally a well tolerated drug, with rare severe toxic effects, sometimes certain toxicities can overcome the life risk of the underlying malignancy. By reviewing the literature, we have selected the cases with severe clinical presentation where some of them had a lethal outcome and we have chosen to present them in this article. In some patients with noticeable hematological toxic effects, as well as those with serious infections, attention must be paid to their treatment, as toxic effects can deepen and develop new toxicity, which all lead to a vicious circle without a favorable outcome. Preventive use of antiviral drugs should be considered before the treatment with temozolomide in patients with a positive history of viral infections such as Hepatitis B infection. In order to prevent rare but possible opportunistic infections, it is necessary to familiarize the patients with the treatment, toxicity and rare opportunistic infections. These infections can be triggered by various factors from the nearest environment, including both domestic and wild animals and pets.

Key words: *glioblastoma, hematologic toxicity, infections, temozolomide, toxicity*

Introduction

Glioblastoma (GB) (Figure 1) is the most frequent primary malignant brain tumor in adults [1]. Typical symptoms of this intracranial neoplasm include headaches, seizures, personality changes, neurocognitive symptoms, nausea and vomiting [2]. In 2016, WHO classification of CNS tumors used molecular parameters in addition to histology to define a certain number of tumor entities. According to 2016 CNS WHO, glioblastomas are classified into: a) glioblastoma, IDH-wildtype, b) glioblastoma, IDH-mutant, and c) glioblastoma, NOS, a diagnosis where full IDH tumor evaluation cannot be performed [3]. There is a remark that primary and secondary GB develop in patients of different age groups and have a different sex distribution, and also may have significantly different clinical outcome [4]. The current standard therapy of GB is maximal surgical resection followed by postoperative radiation therapy with concomitant and adjuvant temozolomide (TZM).

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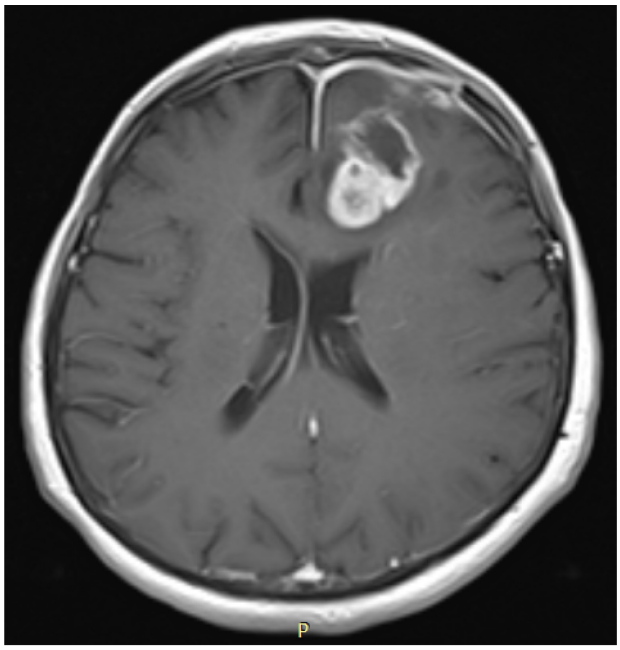

Figure 1. Contrast-enhanced T1-weighted postoperative MRI showing left frontal residual glioblastoma.

TZM, a covalent DNA-binding agent, is one of imidazotetrazinone derivates. After oral administration, TZM is completely absorbed, then it spontaneously converts into an active metabolite and, lastly, penetrates into all tissues, including the brain parenchyma [5]. TZM is generally a well tolerated drug, usually with mild side effects. Some severe and fatal infections have been reported in several case reports. Myelosuppression is considered a dose limiting toxic effect, but severe hematological adverse events have also been reported during or after treatment of TZM.

Methods

To investigate the toxicity profile of TZM, we performed a systematic electronic search on PubMed/Medline using the keywords "glioblastoma", "temozolomide" and "toxicity", "severe toxicity" or "hematological toxicity", "myelosuppression", "aplastic anemia" and "glioblastoma", "temozolomide" and "infections", and "severe infections" or "brain infections". Additional searches were carried out from the references of important articles on the main topic. The literature search was conducted up till May 2017.

Temozolomide-related severe hematological toxicity

One of the main features of the treatment with TZM is that myelosuppression is relatively unusual, and most studies show an overall incidence of 5-8% for grade 3 or 4 myelotoxicity [6]. According to the results of the trial that included a concomitant treatment with radiation therapy plus TZM, Stupp et al. documented grade 3 or 4 of hematological toxicity in 7% of the patients, and in 14% of the patients during adjuvant TZM therapy [1]. In the retrospective study that included 69 patients who underwent surgery and postoperative radiotherapy with TZM, Becker-Schiebe and colleagues reported severe anemia in 5.8%, leucopenia in 7.2% and thrombocytopenia in 8.6 % of the patients [7]. Gerber et al. reported severe thrombocytopenia in 15-20% of the patients treated with concomitant radiation therapy and TZM [8]. Grade 3-4 thrombocytopenia occurred in 25% of the women and 14% of the men, and grade 3-4 neutropenia and anemia were noticed in 10 and 8% of the patients, respectively [8]. Some studies developed clinical risk factors for myelotoxicity in patients with GB treated with concurrent TZM and radiotherapy or adjuvant TZM. Armstrong et al. developed clinical risk factors for each gender [6]. For males, risk factors comprise body surface area ≥2m^2, not using steroids, taking bowel medicines. For women, risk factors were no prior chemotherapy, baseline creatinine ≥ 1mg/dl, baseline platelet count <270,000/mm^3, BSA <2m^2, using analgesics, and not on medication for gastroesophageal reflux disease [6]. There are results indicating that female gender and O^6-methylguanine-DNA-methyltransferase (MGMT) methylation seemed to be risk factors for grade 4 hematological toxicity [7]. However, methylation of MGMT promoter blocks protein transcription by impairing the cell's DNA repair mechanism and making the malignant cells more susceptible to the cytotoxic effects of alkylating agents [9].

In addition to myelosuppression, other toxic effects have been reported, such as myelodysplastic syndrome, acute myeloid leukemia or aplastic anemia. Villano et al. reported a case of profound pancytopenia after the fourth cycle of TZM (previously treated with concurent radiotherapy and TZM), and after repeated bone marrow biopsy, a diagnosis of aplastic anemia was established [10]. A 45-year-old male patient received aerolysed pentamidine at the beginning and at the end of chemoradiotherapy for prophylaxis of *Pneumocystis carinii*. Also, other medications that the patient used were ondansetron, prochlorperazine, ranitidine, dexamethasone, phenytoin, carbamazepine and gabapentin [10]. After conducting the treatment, including T cell-depleted allogenic stem-cell transplantation, the patient developed cytomegalovirus viremia, followed by transverse myelitis and paraplegia [10].

GB treated with TZM is not the only high grade brain tumor where hematological toxic-

ity occurs. Lam et al. reported aplastic anemia in 21-year-old female patient with anaplastic astrocytoma with MGMT promoter methylation, who was treated with concurrent chemoradiotherapy, and diagnosed with aplastic anemia about 3 months after the first dose of TZM (75mg/m^2/day concurrent with radiation). She received dapsone for Pneumocystis jirovecii pneumonia (PJP) prophylaxis and ciprofloxacin for leukopenia, but she did not use anticonvulsant therapy [11]. There are other cases of aplastic anemia reported related with the therapy with TZM [12-17]. Exposure to other drugs may be a cause of myelosuppression and aplastic anemia. Some of the drugs individually can cause toxic effects or cumulative toxicity in interaction with other drugs. Epileptic seizures are one of the symptoms of malignant gliomas and usually require anticonvulsant drugs. Anticonvulsants, like valproate, can cause direct bone marrow suppression leading to aplastic anemia or peripheral cytopenia affecting one or more cell lines [18]. In a retrospective case-control study conducted by Handoko et al., the results indicated that the use of antiepileptic drugs, like carbamazepine and valproic acid, was associated with increased risk of aplastic anemia [19]. Some patients receive a prophylactic antibiotic, like trimethoprim-sulfamethoxazole, which is recognized as a potential risk factor for the development of aplastic anemia [20].

It should be noted that elderly patients under the Stupp protocol may experience serious adverse effects, including hematological and other toxicities. According to the study by Sijben et al., who reviewed toxicity values in patients aged 65 years or older with GB, 8 patients (42%) in the chemoradiotherapy group experienced grade 3 or 4 toxicity, unlike the group where only radiotherapy was applied, and where there was no toxicity of such grades [21].

Severe temozolomide-related infections

Myelotoxicity itself is a risk factor for the appearance of severe and lethal infections. As already mentioned, patients with hematological and solid tumor diseases are at increased risk for bacterial infections and pneumonia caused by *Pneumocystis jirovecii* [22]. Due to the nature of the primary disease (GB) and its symptoms, many patients require different doses of corticosteroids. There is data indicating that the use of corticosteroids in oncologic patients, including those with primary brain tumors, is associated with the risk of pneumocystis jirovecii pneumonia (PJP) [23-25]. Sarasúa and colleagues reported a case of a 69-year-old patient who developed fever with progressive respiratory failure after 4 weeks of using TZM. PJP was confirmed in bronchoalveolar lavage [26]. Hayashi et al. reported three cases with fatal pneumonia that was highly suspected to be pneumocystis carinii pneumonia (PCP) based on a serological diagnosis (marked elevation of serum KL-6 and b-D-glucan levels). They displayed severe respiratory failure requiring mechanical ventilation. All three patients were treated with TZM after surgery for malignant glioma, although two patients had GB, and one patient had anaplastic astrocytoma [27]. Other reports indicated that patients who received a standard-dose of TZM therapy were at risk of PCP [28].

There are also reports dealing with the toxicity of TZM to the pulmonary parenchyma and drug-induced interstitial pneumonia, which can be fatal [29,30].

It should be borne in mind that during chemotherapy many viral infections can lead to death, as well as to the possible viral reactivation. Grewal et al. reported a case of 65-year-old female with GB, treated with maximum resection, radiotherapy with concomitant TZM and 3 cycles of adjuvant TZM. The patient received corticosteroid therapy which was discontinued a week after the operation. This patient had a positive history of hepatitis B. She was hospitalized during her 3 cycles of adjuvant TZM due to progressive encephalopathy. Hepatitis B core antigen and hepatitis B surface antigen were positive. The patient was treated with antiviral drugs, but after two weeks she died. Although the patient was taking an antiepileptic drug, and such drugs alone can cause hepatotoxic effects, the authors suggested that the death of the patient was the result of hepatitis B reactivation caused by the use of TZM [31]. Similarly, Ohno et al. described the case of a 61-year-old patient with hepatitis B reactivation, after concomitant postoperative treatment with radiotherapy and TZM. The patient was not receiving corticosteroid therapy during chemoradiotherapy but had recorded grade 4 lymphopenia [32].

Cases of infection or reactivation of cytomegalovirus (CMV) are published. After 45 days from the beginning of concomitant radiotherapy with TZM, a 57-year-old female patient developed gastrointestinal CMV disease presented with colitis with diarrhea, rectal bleeding and colonic ulcers. She also developed lymphopenia. Three days after antiviral therapy, the patient had an episode of meningitis caused by *Escherichia coli*, and the authors were of the opinion that it was likely due to the presence of ventriculo-peritoneal shunt [33]. There is a publication about CMV reactivation in patients with gliomatosis cerebri who developed

pneumonia presented with cough, fever, and severe lymphopenia 1 month after chemoradiotherapy with TZM [34].

Parasite infestation are also documented in patients treated with radiotherapy and TZM. A 51-year-old female patient with GB and oligodendroglial component was treated postoperatively with radiotherapy and TZM. The patient received corticosteroid therapy. Among other things, the patient developed a respiratory failure and bronchoalveolar lavage demonstrate larvae of *Strongyloides stercolaris* with positive Strongyloides serum IgG. Also, this patient had cutaneous *Strongyloides stercoralis* infestation. Further in the course of disease, a brain MRI scan showed multiple infarcts in the brain indicating strongyloidiasis-induced vasculitis. During a comprehensive hospital treatment the patient had bacterial, viral and fungal infections [35].

Fungal skin infections are not rare, but invasive skin infections can lead to sepsis and sometimes death in immunocompromised patients. Ikeda et al. described the case of a 67-year-old woman with cutaneous invasive aspergillosis who had received long-term TZM and corticosteroid therapy for GB. In addition to induration, erythema and purulent content, large inter or intramuscular abscesses were described on the front abdominal wall. Noticeable was the fact the patient had lymphopenia [36].

It should be considered that some microorganisms which cause diseases in domestic animals and pets, can potentially cause serious illnesses in humans with immunodeficiency. The first reported case of *Bordetella bronchiseptica* infection in a patient receiving TZM was in 2011, and it was reported by Redelman-Sidi et al. A 56-year-old man was diagnosed with *B. bronchiseptica* infection possibly acquired from an infected kitten [37]. This and similar unusual microorganisms can be lethal [38].

In practice, bacterial, fungal and viral brain infections associated with the use of TZM can occur. Brain infections have great significance because of the possible rapid lethal outcome, and also because of the suspension of chemotherapy and radiotherapy which can indirectly lead to a rapid malignant disease relapse. A patient who received radiation therapy with concurrent and adjuvant TZM was diagnosed with brain abscess (gram positive cocci) and herpes simplex virus (HSV) 1 encephalitis [39]. In addition to all the systemic signs and symptoms of infection, brain abscesses sometimes can mimic tumor progression [40]. Ganière and colleagues reported the case of a patient with GB who underwent tumor resection and received neoadjuvant TZM (100mg/m^2 daily for 3 weeks, repeated every 4 weeks), which was given during 3-4 cycles before radiotherapy. After 3 cycles of TZM, the patient began a treatment with radiation therapy and concomitant dexamethasone 2mg daily. In the fifth week of radiotherapy the patient developed fever and headaches, and brain MRI showed an abscess. A biopsy was taken and from the culture of the lesion *Listeria monocytogenes* was isolated. In the further course of the disease, a biopsy of the scrotum was performed and diagnosis of Kaposi sarcoma with expression of CD 34 and Human herpes virus 8 was established. In the same patient, a bronchoalveolar lavage was performed which revealed an infection with *Pneumocystis jirovecii*. At that time the patient

Table 1. Characteristics of 9 patients who suffered brain infections related to temozolomide therapy

Report	*Sex*	*Age (years)*	*Cancer*	*Microorganism*	*LYP*	*Steroids*	*Diagnostics*
Riel-Romero et al. 2003 [44]	M	15	Brainstem glioma	HSV 1	NK	Yes	CSF, PCR
Ganière et al. 2006 [41]	M	55	GB	L. monocytogenes	Yes	Yes	Biopsy, culture
Choi et al. 2008 [43]	M	73	GB	C. neoformans	NK	Yes	CSF, cultures
Choi et al. 2008 [43]	M	33	AA	C. neoformans	NK	Yes	CSF, cultures
Damek et al. 2008. [40]	F	60	GB	A. terreus	Yes	Yes	Biopsy, culture
Okada et al. 2013 [40]	M	33	AA	HSV	NK	Yes	CSF, PCR
Tsai et al. 2014 [39]	M	59	GB	Gram positive cocci, HSV 1	Yes	Yes	Culture, CSF, PCR
Christman et al. 2014 [45]	F	57	GB	HSV 1	NK	Yes	CSF, PCR
Bertero et al. 2015 [42]	M	68	Gliomatosis cerebri	Nocardia Sp.	Yes	Yes	Histology, culture

M: male, F: female, GB: glioblastoma, AA: anaplastic astrocytoma, HSV: Herpes simplex virus, LYP: lymphopenia, NK: not known, CSF: cerebrospinal fluid, PCR: polymerase chain reaction. L.monocytogenes: Listeria monocytogenes, C.neoformans: Cryptococcus neoformans, A.terreus: Aspergilus terreus. Nocardia sp.: Nocardia species.

had profound lymphopenia [41]. The information previously listed above, as well as some other cerebral infections are shown in Table 1 [39-46].

Kizilarslanoglu et al. analyzed some of the reported cases of infections related to TZM till December 2010. They identified 39 cases of infections in coherence with the use of TZM, although 53.8% had melanoma, 35.8% had brain cancer and 10% had neuroendocrine tumors. According to their survey, about one third of the TZM-related severe infections resulted in death [47]. In the retrospective study by Peponi et al., 98% of the patients received concurrent TZM and 81% received adjuvant TZM. Of the patients, 4.4% experienced grade 3/4 non hematological toxicity [48]. Although the authors systematically presented a review of hematological toxicity as of May 2012, Scaringi and colleagues noted that doctors should be aware of the increased incidence of lymphopenia at dose-dense TZM protocols, and consider prophylactic use of antibiotics to prevent opportunistic infections [49]. Ohmagari et al. revealed in their study that steroids appeared to be the dominant risk factors for invasive aspergilosis in patients with brain tumors [50].

Conclusion

According to the existing literature, lymphopenia is seen as a frequent hematological manifestation in the use of TZM and is often associated with opportunistic infections, as well as with the use of steroids. Steroids are often necessary drugs in the treatment of brain edema and many other medical conditions. Anti-epileptics are of utmost importance for the prevention of seizures, and thus they reduce the risk of patient injuries and improve the quality of life. It should be kept in mind that only rarely patients don't rarely have comorbidities and that different drug combinations can contribute to direct and indirect hematological toxicity. Sometimes, chemotherapeutics and other drugs interfere with liver function, which can lead to indirect hematological toxicity. In myelosuppression, one infection can lead to another and drugs for the treatment of infections can deepen the state of myelosuppression, which leads to vicious circle. From all this, it can be concluded that a special and personalized approach may be needed and a special selection of medications for the treatment of complications during oncological treatment. Although prevention for Pneumocystis jiroveci pneumonia does exist, there are no official recommendations for the prevention of other opportunistic infections. Patients with a positive history of hepatitis may be candidates for the use of antiviral therapy before the onset of chemoradiotherapy, but again paying attention to possible interactions and side effects. A detailed medical history should not be ignored. Not only physicians, but also patients should be aware and informed of the possible rare opportunistic infections, which can be triggered by various factors from the nearest environment, including both domestic and wild animals and pets.

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Conflict of interests

The authors declare no conflict of interests.

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