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ORIGINAL ARTICLE

Temozolomide-related infections: review of the literature

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Summary

Temozolomide (TMZ) is an alkylating, antineoplastic agent which is being used to treat cases of refractory anaplastic astrocytoma, newly-diagnosed glioblastoma multiforme and metastatic melanoma. TMZ causes lymphopenia and T-cell dysfunction in most of the patients. Related to this toxicity several opportunistic infections have been reported in the literature, but were not well characterized. To further investigate this topic, relevant English language studies were identified through Medline. There were 36 previously reported cases of infection related to TMZ. The median age of the cases was 55 years (range 33-73). The most frequently experienced infections were mucocutaneous candidiasis (n=11; 28.2%), herpes zoster (n=5; 12.8%), herpes simplex virus (n=4; 10.2%), cytomegalovirus (CMV) (n=5; 12.8%), pneumocystis carinii pneumonia (PCP) (n=3; 7.6%), hepatitis B virus (HBV) (n=2; 5.1%) and others (n=9; 23%). Mortality rates were 28.5% (n=4/14) in patients with reported outcome.

In this survey, about one third of the TMZ-related severe infections resulted in death. Patients treated with TMZ are at increased risk for opportunistic viral and bacterial infection. Therefore, close monitoring of patients receiving TMZ for opportunistic infections should be carried out.

Key words: anaplastic astrocytoma, glioblastoma multiforme, infections, metastatic melanoma, temozolomide

Introduction

TMZ is an alkylating, antineoplastic agent used to treat cases of refractory anaplastic astrocytoma, newly-diagnosed glioblastoma multiforme and metastatic melanoma. TMZ is an oral compound that is a prodrug of the alkylating agent and is spontaneously converted to 5-(3-methyltriazen-1yl)imidazole-4-carboxamide (MTIC) under physiologic conditions. The drug shows 100% oral bioavailability [1,2]. A complication of TMZ is lymphopenia, with CD4+ T cells being preferentially affected. This selective T-cell depletion was associated with clinically significant opportunistic infections like Pneumocystis carinii, Aspergillus pneumoniae, Herpes simplex etc. [2]. These changes may be accompanied by an increase in serious infections. Reactivation of chronic HBV infection is one of the reported serious viral infections [3]. Some fatal infections other than HBV have also been reported after TMZ treatment, such as CMV and cryptococcus [4,5].

The true incidence and consequences of infections related to TMZ treatment are not well defined. The difference in incidence and outcome of infections among the patient groups is wide and is possibly dependent on the intensity and duration of T-cell-mediated immune suppression. This study analyzed the patient main characteristics who experienced TMZ-related infections and their outcomes, as reported in the literature. Evaluated were also the types and frequency of infections.

Methods

To investigate this topic, relevant English language studies were identified through Medline. For our search we used the generic name temozolomide and the word infection and found 46 articles till December 2010. The references from the identified articles were reviewed for additional sources. We identified 39 cases of previously reported TMZ-related infections. The parameters regis-

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tered and analysed were patient diagnosis, age, gender, type and treatment of infections and outcome.

Results

We identified 39 cases of infections related to TMZ treatment. Twenty-one patients who received TMZ had melanoma (53.8%), 14 had brain cancer (glioblastoma multiforme, anaplastic astrocytoma and primary CNS lymphoma; 35.8%), and 4 had neuroendocrine tumors (10%). The median age of the cases was 55 years (range 33-73). Patient characteristics, infection types and outcomes of infections are shown in Table 1.

The infections most frequently encountered were mucocutaneous candidiasis (n=11; 28%), herpes zoster (n=5; 12.8%), herpes simplex virus (n=4; 10.2%), CMV (n=5; 12.8%), PCP (n=3; 7.6%), HBV (n=2; 5.1%) and others (n=9; 23%).

The outcome of 25 patients who had experienced infections related to TMZ could not be determined. The remaining 4 out of 14 patients died of infectious complications. Of the patients with CMV infection, 2 (40%) died and with HBV and Cryptococcal infections, 1 (50%) and 1 (50%) died, respectively. In the examined cases it was unclear whether the patients had received PCP prophylaxis. Frequencies and outcomes of the infections are shown in Table 2.

Discussion

TMZ, an oral alkylating agent that readily crosses the blood-brain barrier, is being used in the treatment of glioblastoma multiforme and recurrent anaplastic astrocytoma. Relatively recently it is also used in malignant melanomas, metastatic neuroendocrine tumors and in some cases with brain metastases. It is a generally well-tolerated agent, its main toxicities being nausea, vomit-

Table 2. Temozolomide-related infections, frequencies, and outcomes

Microorganisms	*Outcome (Dead/Alive)*	*Frequency n (%)*
Mucocutaneous candidiasis	unknown/unknown	11 (28.2)
Herpes zoster	unknown/1	5 (12.8)
Cytomegalovirus	2/3	5 (12.8)
Herpes simplex virus	unknown/unknown	4 (10.2)
Pneumocystis carinii pneumonia	unknown/2	3 (7.6)
Hepatitis B virus	1/1	2 (5.1)
Cryptococcus	1/1	2 (5.1)
Salmonella and serratia	0/1	1 (2.5)
Listeria	0/1	1 (2.5)
Strongyloides	0/1	1 (2.5)
Mycobacterium tuberculosis	0/1	1 (2.5)
Aspergillus terreus	0/1	1 (2.5)
Aspergillus pneumoniae	unknown/unknown	1 (2.5)
Bordetella bronchiseptica	0/1	1 (2.5)
Total	4/14	39 (100)

Table 1. Patient characteristics, causes of infections and results

First author [Ref. no.]	*Patient age/sex*	*Diagnosis*	*Infections*	*Outcome*
Grewal et al. [3]	65/F	GBM	HBV	Died
Chheda MG et al. [10]	50/M	GBM	HBV	Cure
Jesus et al. [5]	68/F	Gliosarcoma	CMV	Died
Choi et al. [4]	73/M	GBM	Cryptococcus	Died
	33/M	Anaplastic astrocytoma	Cryptococcus	Cure
Georgescu et al. [14]	38/M	Anaplastic astrocytoma	Salmonella and serratia	Cure
Ganiere et al. [15]	55/M	GBM	Listeria	Cure
Aregawi et al. [9]	51/F	GBM	Strongyloides	Cure
Yaman et al. [11]	55/F	GBM	CMV	Cure
Schwarzberg et al. [8]	70/M	NT	CMV	Died
	37/M	NT	VZV	Cure
	55/F	NT	PCP	Cure
	42/F	NT	PCP	Cure
Paiva Jr et al. [16]	59/F	GBM	M. Tuberculosis	Cure
Damek DM et al. [17]	1 patient	GBM	Aspergillus terreus	Cure
Su YB et al. [1]	1 patient	Melanoma	PCP	Unknown
	1 patient	Melanoma	Aspergillus pneumonia	Unknown
	4 patients	Melanoma	HZV	Unknown
	4 patients	Melanoma	HSV	Unknown
	11 patients	Melanoma	Mucocutaneous candidiasis	Unknown
Maije et al.[19]	57/F	GBM	CMV	Cure
	59/M	Primary CNS high grade B-cell lymphoma	CMV	Cure
Ridelman-Sidi et al.[20]	56/M	GBM	Bordetella bronchiseptica	Cure

M: male, F: female, GBM: glioblastoma multiforme, CMV: cytomegalovirus, PCP: pneumocystis carinii pneumonia, HBV: hepatitis B virus, VZV: varicella zoster virus, NT: neuroendocrine tumor, CNS: central nervous system, HZV: herpes zoster virus, HSV: herpes simplex virus

ing, anorexia and thrombocytopenia. While considered less toxic than historical chemotherapy for glioblastoma, such as with older nitrosoureas, its use may cause clinically significant opportunistic infections such as pneumocystis carinii, aspergillus pneumoniae, herpes simplex etc.[2].

Its use is associated with lymphopenia, specifically CD4+ lymphocyte depletion [1,2]. Some authors found that TMZ caused lymphopenia in 60% of the cases without inducing generalized suppression of bone marrow function and median time to lymphopenia was 101 days [1,6]. When TMZ is given in high doses, its complications are more severe. Spence et al. used high dose TMZ (5,500 mg over 2 days) in a patient which resulted in severe pancytopenia lasting for 4 weeks while the patient experienced life threatening neutropenic fever [7].

Prolonged exposure to TMZ is associated with severe lymphopenia and opportunistic infections [8]. Treatment of opportunistic infections, like PCP, is generally effective when infection is detected and treated early [9,10]. The European Organization for Research and Treatment of Cancer (EORTC) study recommends routine pneumocystis pneumonia prophylaxis [11]. The most lethal infections after TMZ treatment were CMV and HBV infections in our survey.

The possibility that the concomitant use of steroids with TMZ to prevent peritumoral edema in CNS tumors might have played a role in the development of infections cannot be excluded, but the results of recent studies suggest that selective CD4+ lymphopenia is itself associated with TMZ use [1,8].

It is estimated that more than 1.5 million HBsAg carriers reside in the United States. Treatment of hematologic malignancies with chemotherapy and corticosteroids includes a high risk (>60%) of HBV reactivation. Reactivation is also associated with pregnancy and liver transplantation or may occur spontaneously. In addition to morbidity from hepatitis, viral reactivation may disrupt cancer treatment, resulting in decreased overall survival. Data supports the use of antiviral agents for HBsAg carriers during chemotherapy. It may be recommended that hepatitis screening and viral prophylaxis be considered when they are clinically appropriate in patients receiving TMZ [12].

The other important condition associated with TMZ administration is hypersensitivity pneumonitis [13]. Clinicians should be also aware of this condition because its clinical presentation is similar to PCP and other opportunistic infections in the lung.

Moreover, Ridola et al.[18] reported 4 cases of infection in pediatric patients receiving TMZ but we did not investigate this study due to the particular features of a pediatric age group.

In conclusion, patients receiving TMZ must be monitored closely for myelosuppression, and specifically for lymphopenia. Physicians should be aware of possible opportunistic infections, especially viral ones, due to increased mortality rate (about 3/10) as found in this survey. Prophylactic therapy for PCP is recommended. Patients who are candidates to receive TMZ may be screened for hepatitis B and C infections.

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