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TEMOZOLAMIDE INDUCED PANCYTOPENIA: A RARE CASE SERIES OF 3 PATIENTS AND REVIEW OF LITERATURE

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ABSTRACT Temozolomide (TMZ) is an oral alkylating agent principally indicated for neurological malignancies including glioblastoma and astrocytoma. Most common side effects are mild to moderate and include fatigue, nausea, vomiting, thrombocytopenia and neutropenia. Severe or prolonged myelosuppression is seen uncommonly. We report a case series of 3 patients diagnosed with Glioblastoma, Recurrent Astrocytoma Grade 2 and 3 who had undergone craniotomy outside and came to our centre for further treatment with radiotherapy and concurrent temozolomide. In all cases Blood parameters were normal before treatment however patients developed significant pancytopenia afterwards. Treatment consisted of repeated platelet transfusions, intravenous antibiotics, antiviral and antifungal prophylaxis, and G-CSF. Post cessation of TMZ blood parameters started improving in patients. Temozolomide-induced pancytopenia is well documented in literature however handful cases are described in detail. Other potential causes were eliminated in our patient. Physicians should be aware of fatal toxicity while prescribing, frequent blood tests should be performed following TMZ treatment.

KEYWORDS : Astrocytoma, Glioblastoma Multiforme, Pancytopenia, Radiation Therapy, Temozolomide

INTRODUCTION

Diffuse gliomas are the most frequent primary brain tumors, and are graded 2 to 4, with grade 4 or glioblastoma being the most frequent and the most aggressive. The term 'lower-grade gliomas' was created to designate WHO grade 2 and 3 astrocytomas and oligodendrogliomas, as opposed to GB. Although these tumors altogether account for only a minority of diffuse gliomas (30–35%),[1,2] they represent an important cause of morbidity and mortality in young adults, the population primarily affected by these neoplasms.

Lower-grade gliomas form a biologically heterogeneous group of tumors. Histology alone is often insufficient to make accurate prognostic estimates and tumors belonging to the same WHO grade may display different malignant behavior, depending on their molecular profile. Diffuse astrocytomas (WHO grade 2) show an astrocytoma or oligoastrocytoma morphology on hematoxylin–eosin sections and display p53 overexpression and/or ATRX loss on immunohistochemistry.[3,4,5]

A recently reported phase III clinical trial demonstrated a significant benefit of combination therapy with temozolomide (TMZ) and radiation therapy (RT) compared with RT alone for patients with newly diagnosed glioblastoma (WHO grade 4 astrocytoma).[6] The study, conducted by the European Organisation for the Research and Treatment of Cancer (EORTC), used a regimen of concomitant daily TMZ and RT for six weeks, followed by six cycles of adjuvant monthly TMZ.[7]

TMZ, an oral alkylating agent, which has been in clinical use for over 20 years, is indicated in the treatment of several cancers, principally neurological malignancies such as glioblastoma and astrocytoma. It causes DNA methylation, subsequent DNA breakage and apoptosis of cancer cells. The most common side effects of TMZ are mild to moderate and include fatigue, nausea, vomiting, thrombocytopenia and neutropenia.[8]

Myelosuppression is the major dose-dependent toxicity, primarily affecting platelets and white blood cells. It is a non-cumulative and reversible effect, with bone marrow recovery usually occurring within 28 days. Severe or prolonged myelosuppression is a relatively uncommon adverse effect of TMZ. Major haematological adverse effects such as myelodysplastic syndrome, leukaemia, agranulocytosis and aplastic anaemia (AA) have also been reported.[8,9,10]

We wish to report a case series of 3 patients who were diagnosed with Recurrent Astrocytoma Grade 2 and 3, glioblastoma treated with surgical resection followed by concomitant TMZ + RT and developed pancytopenia. Patient consent has been obtained and approval for publication granted.

Case Presentation

Case 1

A 34 year old woman, known case of (k/c/o) Astrocytoma Grade 2, with past history of Generalised tonic clonic seizures since 1 year for which Magnetic resonance imaging (MRI) done on 28th march ,2023 demonstrated 5.5x4.1x4.5 cm left insular space occupying lesion (SOL) at anterior temporal pole. On the 26th july 2023, a craniotomy and resection of the left frontotemporal tumour was performed. Histology demonstrated Astrocytoma (World Health Organisation grade 2) which was p53 mutated, isocitrate dehydrogenase (IDH1)-wild type , ATRX expression lost. She presented at our centre on 17th august 2023 for further treatment, Patient was advised post operative MRI Brain. On 24th august, 2023 MRI findings showed 5.8x3.8x4.6cm residual temporal mass lesion. Patient examination on next visit was done, general condition was good. Patient was oriented to time, place and person with no sensory motor deficit. Treatment plan of Adjuvant RT 55.8Gy/31 # with concentrated TMZ 100mg with weekly follow-up was established.

Prior to this current illness patient had also underwent resection of benign right breast lump excision 4 years back. On 29th august,2023 patient was commenced with RT + concentrated TMZ, baseline hematology parameters were within normal limits. Next three weekly follow–up went uneventful then patient hemogram started showing decreasing trend as illustrated in Table 1. Patient completed her treatment on dated 11th october, 2023.

Grading of hematologic toxicity was based on the NCI Common Terminology Criteria for Adverse Events version 5.0. Grade 3 (severe) and grade 4 (life-threatening) hematologic toxicities were noted as follows: hemoglobin (grade 3, <8 g/dl–6.5 g/dl; and grade 4, life threatening early intervention needed); neutrophils (grade 3,

<1000/mm^3–500/mm^3; and grade 4, <500/mm^3); and platelets (grade 3, <50,000/mm^3–25,000/mm^3; and grade 4, <25,000/mm^3).[11]

Hemogram done on dated 15th october, 2023 revealed Hb-9.8g/dl, TLC-2000, plt 50000. On 19th October 2023, patient presented in emergency with c/o left molar gum bleeding, hemogram revealed pancytopenia with Hb-8.1g/dl, TLC 450, Plt 5000. Patient was admitted, kept in isolation, Injectable Neukine was given stat, was transfused with 4 unit Random Donor Platelets (RDP) however subsequent hemogram depicted Hb 6.9g/dl, TLC 250, Plt 5000 so 1 unit Packed Cell Volume (PCV) was transfused and 4 unit RDP were given which showed Hb- 8.6g/dl, TLC 560, Plt 5000. Her blood count was within normal range for B12, folic acid, thyroid function tests, reticulocyte, direct coombs, infection markers, lactate dehydrogenase (LDH), liver function tests and coagulation tests were in the normal range. She had never received cotrimoxazole (trimethoprim and sulphamethoxazole) prophylaxis. Patient improved symptomatically and maintained on intravenous antibiotics, antiviral and antifungal prophylaxis, and granulocyte colony stimulating factor (G-CSF), hemogram improved with Hb-8.1g/dl, TLC 4180, however plt remained consistent 5000. Patient was discharged uneventfully with due advise and kept on weekly follow-up with hemogram reports. Post medication cessation day 24 patient came on follow-up with improved hemogram dated 4th November 2023 with Hb-8.3g/dl, TLC 2540/mcl, Platelet 26,000/mcl.

Case 2

A 67 year old male, known case of k/c/o Diabetes and Hypertension since 12 years. Patient past history states 4th july 2022 he presented at outside hospital with c/o left upper and lower limb weakness for which he was advised MRI that revealed right parietal mass, PET SCAN showed 3.5x3.2x4.1cm right parietotemporal mass with FDG uptake (suv 5.03) along with bulky submandibular gland and multiple cervical lymphnodes. Patient underwent surgical resection on dated 14th july 2022 which went uneventful. Histopathology reported outside stated Glioblastoma grade 4, submandibular lesion was also evaluated revealing pleomorphic adenoma. On 23rd july 2022 Patient was referred at our centre for further treatment so Adjuvant RT 59.4Gy/28# with concurrent TMZ 100mg was planned, patient received planned treatment with uneventful history as illustrated in Table 2.1.

On 2nd November,2022 follow-up MRI revealed residual lesion measuring 3.1x3.2x2.8cm around post operative site then patient was commenced on Tab.TMZ 250mg/6# monthly. After 5th cycle dated 17th march 2023, Hemogram parameters started showed decreasing trend as illustrated in following Table 2.2. 6th cycle TMZ was given under observation on dated 19th april 2023 with supportive transfusion with 3 unit PCV, his blood count was within normal range for B12, folic acid, thyroid function tests, reticulocyte, direct coombs, infection markers, lactate dehydrogenase (LDH), liver function tests and coagulation tests were in the normal range. He had never received cotrimoxazole (trimethoprim and sulphamethoxazole) prophylaxis. On day 6th, patient was discharged in satisfactory condition with advised follow-up. Post medication cessation dated 23rd may 2023 hemogram showed improvement with Hb-11g/dl, TLC-4000, Plt-90000.

Case 3

A 52 year old female, k/c/o Hypertension, diagnosed case of Recurrent right temporal Astrocytoma. Patient past history states she is operated case of right temperoparietal Astrocytoma Grade 2 in 2010. In 2019 she developed slurred speech for which multiplanar MRI was done, findings of altered signal intensity show multiple areas of gradient blooming, post operative cystic cavity with haemorrhage and residual mass lesion suggestive of recurrence were found. Patient underwent craniotomy dated 18th septemer 2019. Histopathology report stated Astrocytoma Grade 3, patient came to our centre then for further treatment where plan of adjuvant RT 59.4Gy/33# + TMZ 100mg was made. Patient hemogram profile shows decreasing trend as illustrated in Table 3.

Table 1: **Lab Trend Case 1 Throughout Treatment**

PARAMETERS	Before treatment 29/08/23	After 1st cycle 5/09/23	After 2nd cycle 12/09/23	After 3rd cycle 19/09/23	After 4th cycle 26/09/23	After 5th cycle 4/10/23	After 6th cycle 9/10/23
Hemoglobin	11.9	12.7	12.6	12.3	11.9	11.4	10.1
RBC count	4.38	4.63	4.61	4.52	4.19	4.06	3.72
TLC	6030	5530	5050	4450	3040	2920	2450
Platelet	187000	164000	150000	129000	80000	75000	55000

Note: Reference Range Hb- 11.5 To 16.5 g/dl, Rbc - 4.2 To 5.4 million cells/mcl, Tlc – 4000 To 11,000/mcl, Plt-150,000 To 450,000/mcl

Table 2.1:LAB TREND CASE 2 THROUGHOUT TREATMENT TMZ 100mg

PARAMETERS	Before Treatment 8/7/22	After 1st cycle 18/8/22	After 2nd cycle 26/8/22	After 3rd cycle 2/9/22	After 4th cycle 9/9/22	After 5th cycle 16/9/22	After 6th cycle 23/9/22
Hemoglobin	13.5	12.2	12.1	11.5	11.4	11.2	11.1
RBC count	4.27	3.89	3.80	3.71	3.55	3.47	3.44
TLC	10710	10500	7800	7200	6200	5200	4950
Platelet	182000	175000	173000	172000	162000	150000	150000

Note: Reference Range Hb- 11.5 To 16.5 g/dl, Rbc - 4.2 To 5.4 million cells/mcl, Tlc – 4000 To 11,000/mcl, Plt-150,000 To 450,000/mcl

Table 2.2: Lab Trend Case 2 Throughout Treatment

PARAMETERS	Before Treatment 23/10/22	After 1st cycle 4/11/22	After 2nd cycle 12/12/22	After 3rd cycle 13/01/23	After 4th cycle 15/02/23	After 5th cycle 17/03/23	On 6th cycle 19/04/23
Hemoglobin	13.5	12.3	10.9	10.4	9.3	9.1	7.2
RBC count	4.27	4.12	3.49	3.22	2.94	2.89	2.26
TLC	10200	9089	8590	7780	6990	4160	3710
Platelet	150000	150000	145000	133000	120000	92000	66000

TMZ 250mg Note: Reference Range Hb- 11.5 To 16.5 g/dl, Rbc - 4.2 To 5.4 million cells/mcl, Tlc – 4000 To 11,000/mcl , Plt-150,000 To 450,000/mcl

Table 3: Lab Trend Case 3 Throughout Treatment

PARAMETERS	Before Treatment 18/10/19	After 1st cycle 21/10/19	After 2nd cycle 28/10/19	After 3rd cycle 05/11/19	After 4th cycle 11/11/19	After 5th cycle 20/11/19
Hemoglobin	12.8	11.9	11.6	11.2	10.9	9.8
RBC count	4.26	3.32	2.88	2.86	2.83	2.81
TLC	8090	7200	6600	4300	3700	3600
Platelet	240000	228000	174000	148000	119000	18000

Note: Reference Range Hb- 11.5 To 16.5 g/dl, Rbc - 4.2 To 5.4 million cells/mcl, Tlc – 4000 To 11,000/mcl , Plt-150,000 To 450,000/mcl Post 5th cycle TMZ, patient was admitted and 4 unit RDP were transfused. The hospital stay remained uneventful, She had never received cotrimoxazole (trimethoprim and sulphamethoxazole) her blood count was within normal range for B12, folic acid, thyroid function tests, reticulocyte, direct coombs, infection markers, lactate dehydrogenase (LDH), liver function tests and coagulation tests were in the normal range, patient hemogram showed improvement with hb-11.2g/dl, TLC-3700/mcl and plt -47000/mcl. Post cessation of TMZ, patient hemogram improved on dated 12/12/2019 with Hb-12g/dl, TLC-4200, Plt- 80000/mcl. Patient was then started on Bevacizumab 10mg/kg every 2 weeks.

DISCUSSION

Grade 2 astrocytomas, occur in almost 1 out of 200,000 people per year with a peak incidence between 30 and 35 years [19-22]. In our case 1, patient was 34 year old consistent with age mentioned in the literature. Since 2016, neuro-pathologists confered genetic parameters to differentiate them from oligodendrogliomas[23]. Due to their slow growth, they determine cortical adaptor mechanisms leading to a functional and morphologic brain reorganization; as a consequence, tumor onset is usually characterized by seizures in the absence of other neurological deficits.[24,25] Grade 2 astrocytomas are prognostically differentiated depending on the presence or absence of IDH 1 and 2

mutations, which, when occurring, correlate to a favorable outcome.

Additionally, the IDH-wild type patient's prognosis worsens in presence of pTERT-mutations and EGFR amplification.[26] The treatment of lower-grade astrocytomas is established according to several stratification features (anaplastic gliomas, patients aged over 40 years and subtotal removal). In presence of at least one of those risk factors, the suggested treatment is multimodal, consisting of post-surgical RT followed by chemotherapy with either TMZ or a combination of procarbazine, lomustine and vincristine.[27] Glioblastoma is the most common primary tumors that arise within the brain parenchyma, accounts for approximately 20-30% cases with peak incidence at 40-60 years. In our case 2 and 3, patients age were 67 and 52 years consistent with age mentioned in literature. It is more common in males, male-to-female 1.5:1. In our scenario, we encountered 2 cases with M:F ratio 1:1. The survival is approximately 10 to 12 months. It showed a 37% relative reduction in the risk of death and a clinically meaningful median survival of 14.6 months for patients treated with RT + TMZ as compared with those who received RT alone. The most common presentation are headache, seizures , memory loss and behavioral changes. These findings are associated with increased pressure due to rapid growth of the tumor. The deep-seated infiltrative masses can also cause cognitive difficulties or personality change.[6]

TMZ, an oral alkylating agent, has demonstrated antitumor activity as a single agent in the treatment of recurrent glioma. The conventional schedule is a daily dose of 150 to 200 mg per square meter of body surface area for 5 days of every 28-day cycle. Daily therapy at a dose of 75 mg per daily dose of 150 to 200 mg per square meter of body surface area (BSA) for 5 days of every 28 day cycle up to seven weeks is safe; this level of exposure to TMZ depletes the DNA-repair enzyme O^6-methylguanine- DNA methyltransferase (MGMT). This effect may be important because low levels of MGMT in tumor tissue are associated with longer survival among patients with Glioblastoma who are receiving nitrosourea-based adjuvant chemotherapy.[6]

Stupp et al. study demonstrates that the addition of chemotherapy to radiotherapy significantly prolongs survival among patients, with a median increase in survival of 2.5 months or a relative reduction in the risk of death of 37 percent. However most patients experienced some form of myelotoxicity after TMZ treatment. Lymphopenia was most common and occurred in 81.2%, followed by anemia in 44.7% of patients. Thrombocytopenia and neutropenia were observed in 26.5% and 18.9% of patients, respectively.[6]

The mechanisms underlying myelotoxicity are still poorly defined and focus generally on identification of risk factors from retrospective patient cohorts or as part of clinical trials. In most clinical trials, women have a much higher risk of developing TMZ -induced myelotoxicity than men.[7,28] Risk stratification done by Armstrong TS et al.[28] stated men with a Body Surface Area (BSA)$\geq 2\ m^2$ and age > 40 years had a higher risk on myelotoxicity. Meanwhile, for women, BSA $< 2\ m^2$ and age 31–40 years were independent risk factors. In our case1, 31 year old female with recurrent glioma history started on concurrent TMZ and RT, developed Grade 4 platelet hematotoxicity assessed as per CTCAE v5 [11] having ADR score of +4 as per the Naranjo algorithm designed for adverse drug reactions described by CA Naranjo et al.[29] stating TMZ as possible cause for pancytopenia. Both case 2 and case 3 also showed ADR score +4 with similar hematological findings. In all cases, patient seems to have no likely causative factors for the development of pancytopenia other than TMZ. There was no family history, exposure to environmental factors or possible medication causes. Post cessation of TMZ hemogram in all cases showed improvement so bone marrow planned in the respective cases was not performed.

Vera K et al.[30] conducted study on dose dependent TMZ acceptable dosage among 70 patients who had primary central nervous system tumors.

Table 4: Case Reports Of Temozolamide Induced Pancytopenia

Name Of The Study	Age	Gender	Diagnosis	Medication	Time Course Of Pancytopenia Development	Treatment Given
Bozkurt K et al.[12]	54	F	GBM	RT+TMZ	After 6 cycles	Blood products, GCSF, and Antibiotics
Nagane M et al.[13]	51	F	GBM	RT+TMZ	After 4 cycles	Platelet transfusion. GCSF(lenograstim 100 lg sc daily), Prophylactic antibiotics (levofloxacin 600 mg/day)
Altinoz MA. et al.[14]	46	F	GBM	RT+TMZ	After 5th weekt	Prophylactic treatment with antiviral, antifungal GCSF, blood products and filgristim
Ariel Gru A. et al.[15]	39	M	Anaplastic transformation in Oligodendroglioma WHO grade II	RT+TMZ	After 2 months	Platelet transfusion,PRBCs, G-CSF
Stepanovic A et al.[16]	62	F	GBM	RT+TMZ	After 5 weeks	Blood products, GCSF, PRBC, ceftazidime and filgrastim
Koehler A et al.[17]	58	F	GBM	RT+TMZ	Day 23	Blood Products, GCSF, Prophylactic antibiotics, filgrastim, avastin and optune device
Scaringi C et al.[18]	67	M	GBM	RT+TMZ	Day 21	Prophylactic antibiotics, Platlet transfusion, PRBC, erythropoeitin and G-CSF

Patients were divided in four groups to receive TMZ at daily doses of 200 (7 patients), 250 (13 patients), 300 (38 patients) and 350 mg/m^2/day (12 patients) and given total of 23, 72, 192 and 83 cycles were at daily doses of 200, 250, 300 and 350 mg/m^2, respectively. Grade 3–4 thrombocytopenia was observed in 0/7, 1/13, 5/38 and 4/12 patients whereas neutropenia was observed in 1/7, 0/13, 3/38 and 4/12 patients. Similar findings were observed in case 2 with increase in dose of TMZ from 100 to 250 mg patient developed pancytopenia in due course.

A systemic review of literature demonstrates many case reports stating TMZ induced pancytopenia. All seven cases more are illustrated in detail in Table 4.

To our opinion the only strategy to limit this toxicity is to strictly follow the rules given by the manufacturer and to interrupt the medication at the time points recommended. To our experience it would not have been possible to identify those patients with an unfavourable result before RT, thus alteration of the fractionation protocol,, reduction of the dose of TMZ or to terminate prematurely or even not to apply TMZ concomitantly to radiotherapy do not appear to be reasonable possibilities.

CONCLUSION

TMZ is an oral alkylating agent which is first-line therapy for the treatment of glioblastoma and Astrocytomas. Although it is considered a comparatively safe drug with a favorable side-effect profile, numerous cases of pancytopenia or aplastic anemia and myelosuppression have been reported while using TMZ. However it is imperative to rule out other causes in patients due to concomitant use of other medications and RT. Literature suggests many reported cases of TMZ induced pancytopenia since no optimal treatment for the same

is well established. Patients should be duly advised for fatal complications regarding the usage of TMZ, evaluated repeatedly with hematology parameters for early detection and treatment.

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