



Case Report

Temozolomide for Anaplastic Astrocytoma: A Case Report of Aplastic Anemia, Sustained Treatment Response, and Spontaneous Marrow Recovery

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Abstract

Introduction: Temozolomide is an alkylating agent used in the treatment of high-grade glioma. Rarely, it can induce an aplastic anemia that is usually rapidly fatal if the patient is unable to undergo a bone marrow transplant. This is the first case report of a temozolomide-induced aplastic anemia in an anaplastic astrocytoma patient, and of spontaneous complete marrow recovery with supportive care.

Presentation of Case: 21 year old Caucasian female presented with pancytopenia after 39 days of temozolomide at 75mg/m²/day concurrent with radiation. Hematologic nadir occurred and aplastic anemia was diagnosed 3 months after the first dose of temozolomide. She required multiple platelet and red cell transfusions in addition to granulocyte colony stimulating factor therapy. During this time, the patient also became pregnant and delivered a healthy baby. With supportive care, the patient's white cell count recovered after 6 months, red cell count after 1.5 years, and platelets after 3 years. Her tumour remains stable more than 4 years after temozolomide and radiation with no further treatment.

Conclusions: Aplastic anemia may occur with low-dose temozolomide. Spontaneous marrow recovery using only supportive care is possible following temozolomide-induced aplastic anemia.

Keywords: Temozolomide; Aplastic anemia; Anaplastic astrocytoma; Glioma

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Introduction

Anaplastic astrocytoma is a malignant, World Health Organization grade 3 brain tumour composed of astrocytic glial cells. A review of 1766 anaplastic astrocytoma patients diagnosed between 1990-2008 from the Surveillance, Epidemiology, and End Results (SEER) database identified a median overall survival of 15 months [1], although published estimates range from 1-6 years. Standard treatment includes maximal resection and involved-field radiation or clinical trial participation. The use of chemotherapy for anaplastic astrocytomas is based largely on high-grade glioma trials which involved a majority of glioblastoma multiforme patients [2]. Initial trials employed adjuvant procarbazine-lomustine-vincristine (PCV), but the regimen's poor tolerability has been a barrier to its use.

Temozolomide (TMZ), an oral alkylating agent, has been used instead based on its similar theoretical benefit and improved side effect profile compared to PCV [3, 4]. Though side effects are usually mild, TMZ has been associated with thrombocytopenia and other hematologic abnormalities. Rarely, TMZ is associated with aplastic anemia (AA) and it is even more uncommon for patients to regain normal bone marrow function following AA.

We report the case of a 21-year old female with anaplastic astrocytoma who experienced spontaneous marrow recovery and sustained treatment response following TMZ-associated aplastic anemia.

Case presentation

History and clinical course

Our patient was a 21 year-old Caucasian female who presented to hospital following a generalized seizure witnessed by her partner. She had experienced occasional seizures and increasing headache over the preceding 10 months but had not been assessed by a physician. An MRI showed a hypointense T1 and hyperintense T2 weighted, 6.5 x 5.4 x 3.6cm, minimally enhancing lesion with right lateral ventricle compression but no midline shift. Subtotal resection was completed 7 months following presentation. Pathology showed an anaplastic astrocytoma with MGMT promoter methylation, no loss of heterozygosity of 1p/19q, and no classic oligodendroglial features.

Six weeks after surgery, our patient underwent radiation with concurrent TMZ at 75mg/m²/day. During this phase, she received dapsone for *Pneumocystis jirovecii* prophylaxis and ciprofloxacin for leukopenia, but she declined anticonvulsant therapy. Thirty-nine days into her concurrent treatment, her platelet count fell to 88 x10⁹ cells/L and TMZ was discontinued. She completed radiation therapy with a total dose of 5940Gy in 33 fractions but was unable to restart TMZ due to persistently low blood counts. On the last day of radiation, her hemoglobin (Hgb) was 88g/L, white blood cell (WBC) count 0.7x10⁹ cells/L, absolute neutrophil count (ANC) 0.5x10⁹ cells/L, and platelet count (Plt) 49x10⁹ cells/L.

Despite multiple transfusions, her blood counts did not significantly recover. Ten days after the conclusion of radiation treatment, she was admitted to hospital for four days with febrile neutropenia then discharged with levofloxacin and dapsone. Most of her counts reached a nadir two weeks later

with WBC 0.5×10^9 cells/L, ANC 0.3×10^9 cells/L, Plt 6×10^9 cells/L, and Hgb 97g/L.

Two weeks after that, she was admitted to hospital with another episode of febrile neutropenia complicated by *Clostridium difficile* colitis and Plt 2×10^9 cells/L. During this stay, she received vancomycin and started G-CSF. Her astrocytoma remained stable. She had no other medical conditions and was not taking any medications other than G-CSF. Vitamin B12, folate, and ferritin levels were not drawn; mean corpuscular volume and mean corpuscular haemoglobin concentration were within normal limits, but her blood smears showed 1+ abnormal cells. An attempt at Fanconi anemia testing failed due to inadequate cells.

A bone marrow biopsy performed 3 months following the start of her concurrent chemoradiation showed marrow cellularity <5%, iron stores increased with no sideroblasts, and no evidence of neoplasm, blasts, or atypical cells. Hematology was therefore consulted about an allogeneic bone marrow transplant. A sibling match was identified and a date for transplantation was arranged.

After a 3-week stay, she was discharged home but received pegfilgrastim 6mg every 2-3 weeks with regular outpatient transfusions of irradiated packed red blood cells and platelets. Ultimately, her bone marrow transplant was cancelled due to financial concerns regarding pre-transplant dental work.

Three months later (six months following TMZ Day 1), our patient was able to maintain an ANC over 1×10^9 cells/L with once-monthly pegfilgrastim, and her RBC transfusion requirements decreased to 1 unit biweekly. A year after that, she was able to discontinue RBC transfusions but continued to require multiple units of platelets weekly for

another 1.5 years despite use of tranexamic acid. She developed iron overload from the multiple transfusions and was partially compliant with desferasirox therapy started in October 2009. It was held for about a year from November 2009 during her pregnancy; she delivered a healthy baby in August 2010. In May 2011 she attempted phlebotomy but tolerated it poorly, so continued on desferasirox only.

About 3 years after her first platelet transfusion (33 months following TMZ Day 1), our patient began to have transfusion reactions. Her platelets reached a nadir of 5×10^9 cells/L despite a normal WBC and Hgb, so she was given a single dose of IVIg to rule out autoimmune causes. Subsequently, her platelet count began to improve and she was able to discontinue transfusions. By November 2012, she became compliant with the desferasirox and her ferritin fell from 2329 to 1191. Nearly five years after her diagnosis (4 years after chemoradiation) and with no additional treatment, her tumour remains stable and her hematologic abnormalities have resolved aside from slightly low platelets (86×10^9 cells/L in March 2013).

Discussion

Hematological abnormalities secondary to TMZ are thought to be caused by its alkylating effects. In addition, bone marrow precursors may have a reduced ability to repair TMZ damage because of their relatively low levels of O6-methylguanine-DNA methyltransferase (MGMT), a DNA repair enzyme that removes methyl groups from guanine moieties [4].

While severe cytopenias are uncommon, a 10-year review of the United States' Food and Drug Administration (FDA)'s MedWatch adverse event database found 39 temozolomide-associated reports

of aplastic anemia, and multiple others of pancytopenia or marrow aplasia. Eleven aplastic anemia incidents were thought to be responsible for patient demise [5].

Concurrent medications were not described in the FDA report, but some medications commonly used with temozolomide in brain cancer can also affect blood counts. Examples include trimethoprim-sulfamethoxazole, dapsone, and anticonvulsants. Our patient received dapsone during her temozolomide treatment. However, dapsone-induced aplastic anemia has been reported only rarely in the literature. Of the published cases, the clinical onset is 2–12 weeks, and the outcome is usually fatal [6, 7].

In comparison to the present case, previously published reports describe patients with glioblastoma, which has an inherently poorer prognosis (see Tab 1). Regardless, most patients who develop aplastic anemia do not experience hematologic recovery and receive only supportive care [8-11]. Of those who do recover, some are spontaneous but partial [12] while others require a bone marrow transplant [13, 14]. Our patient received G-CSF and transfusions to maintain her counts until full marrow recovery occurred nearly 3 years after her first dose of temozolomide. Marrow recovery time is not well-established, but timeframes from 1 week to 6 months have been proposed [13, 15]. No significant impact of MGMT promoter methylation on recovery time has been identified [16].

The relationship between temozolomide dose and the incidence of aplastic anemia is not clear. While myelosuppression usually occurs 21 to 28 days after the first dose of temozolomide [16], some patients do not experience difficulty until several adjuvant cycles have been given [11, 15],

and others never experience dose-limiting hematologic toxicity. MGMT-promoter methylated tumours [17], certain MGMT polymorphisms [18], and female sex have been associated with pancytopenia. In men, no corticosteroid use, or body surface area (BSA) greater than 2m^2 , and in women, no prior chemotherapy, baseline serum creatinine greater than 1mg/dL , baseline platelets $<270,000/\text{mm}^3$, or BSA less than 2m^2 have also been associated with early myelosuppression [19].

Our patient, and others whose counts recovered following marrow failure, appeared to fare well without pursuing further cancer treatment. It is tempting to consider a relationship between temozolomide response severe enough to require bone marrow transplant with overall outcomes. The literature is cautionary regarding the use of transplant or transfusion to allow more aggressive dosing of temozolomide: many of the patients who developed aplastic anemia following a temozolomide regimen died despite supportive transfusions, from development of sepsis [9-11] or cancer progression [20]. In addition, while alternative dosing regimens have been explored, evidence currently indicates that cumulative dose and duration of exposure may offer equivalent tumour impact and improved hematological tolerability compared to using fewer high doses of temozolomide.

A bone marrow transplant was planned for our patient after 3 months without marrow recovery. However, it was not performed. With supportive care only, it was 6 months before our patient's neutrophil count remained above 1×10^9 cells/L, 16 months before RBC transfusions could be discontinued and just over 33 months before platelet transfusions were no longer needed.

Table 1 AA: anaplastic astrocytoma; Abx: antibiotics; BMT: bone marrow transplant; chg: changed to carbamazepine; d: days; D/C: discontinued; Epo: epoetin alfa; G-CSF: granulocyte colony stimulating factor; GBM: glioblastoma multiforme; Meds: medication changes; NR: not reported; Plt: platelet transfusion; RBC: red blood cell transfusion; RT: radiation therapy; SCT: stem cell transplant boost.

Case report	Age	Sex	Primary Diagnosis	Time to Nadir	Temozolomide Received	Concurrent Medications	Treatment								Outcome	
							Meds	Plt	RBC	G-CSF	Epo	Abx	BMT	SCT		
Morris et al 2009	16	f	GBM	24 days	24d x 90mg/m ² + RT	NR		x	x	x				x	x	Doing well 37 months post-temo
Present case	21	f	AA	11 weeks	39d x 75mg/m ² + RT	ciprofloxacin, dapsone		x	x	x			x			Doing well 4 years post-temo
Jalali et al 2007	30	f	GBM	10 weeks	42d x 75mg/m ² + RT	phenytoin, trimethoprim-sulfamethoxazole		x	x	x			x			Rapidly deteriorated; died of sepsis
Comez et al 2010	31	f	GBM	12 weeks	3 cycles x 5d x 150mg/m ² + RT	phenytoin	Chg	x	x	x						Rapidly deteriorated; died of sepsis
Villano et al 2006	45	m	GBM	19 weeks	42d x 75mg/m ² + RT, then 3 cycles x 5d of 200mg/m ² , then 5d x 150mg/m ²	acetaminophen, carbamazepine, gabapentin, dexamethasone, ondansetron, aerosolised pentamidine, phenytoin, prochlorperazine, ranitidine	D/C all	x	x	x	x	x	x	x		Opportunistic infections Day 60 post-BMT; died 2 months later
Ko-pecky et al 2010	61	f	GBM	48 days	23d x 75mg/m ² + RT	citalopram		x	x	x			x			No recovery after 28 days in hospital; died 4 days later from sepsis
Oh et al 2010	63	f	GBM	18 days	18d x 75mg/m ² + RT	amlodipine, levothyroxine, lisinopril, omeprazole, ranitidine		x	x	x	x	x				WBC recovery to 4.1x10 ⁹ /L but needed Plt & RBC transfusions; discharged to hospice
George et al 2009	65	f	GBM	9 weeks	49d x 75mg/m ² + RT, then 5d x 200mg/m ²	None		x	x							No recovery- discharged to hospice
Doyle et al 2005	NR	NR	GBM	46 days	NR x 75mg/m ² + RT	dexamethasone, trimethoprim-sulfamethoxazole	NR									NR
	NR	NR	GBM	38 days												

Conclusions

Cases of temozolomide-associated aplastic anemia have been previously documented in glioblastoma multiforme patients, and full recoveries have involved a bone marrow transplant. Our patient had anaplastic astrocytoma, and her recovery timeframe is longer than described in previous reports. However, it demonstrates that complete hematological recovery and stable treatment response are possible following temozolomide-induced aplastic anemia using only supportive care.

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