Treatment-related Acute Myeloid Leukaemia After Temozolomide for Glioblastoma Multiforme

Dear Editor,

Temozolomide (TMZ) is an orally administered analogue of dacarbazine and is considered as a second-generation alkylating agent with antineoplastic activity. It exerts its effect primarily via deoxyribonucleic acid (DNA) methylation at the O6 and N7 positions of guanine leading to DNA replication inhibition. It received accelerated approval by the United States (US) Food and Drug Administration (FDA) in 1999 for the treatment of refractory anaplastic astrocytoma in adults. Subsequently it has been approved by the FDA in 2005 for treatment of newly diagnosed glioblastoma multiforme (GBM), initially in combination with radiotherapy, then as maintenance treatment.[1] In Singapore, TMZ has been approved for use by the Health Sciences Authority (HSA) since November 2001.

Under World Health Organization's (WHO) classification, there are 2 main types of therapy-related myeloid neoplasms (t-MNs): alkylating agent/radiation-related and topoisomerase II inhibitor-related acute myeloid leukaemia (AML).[2] These conditions arise following the use of cytotoxic chemotherapy and/or radiation therapy. For the alkylating agent-related ones, it frequently presents as myelodysplastic syndrome (MDS) initially. It may then evolve into AML. This group of secondary MDS and AML commonly has complex cytogenetics and unbalanced translocations or deletions involving primarily chromosomes 5 and/or 7.

There were a few reports of TMZ-associated MDS/AML and all of these patients described had either received other cytotoxic agents in addition to TMZ and radiation, or their AMLs were preceded by a period of marrow failure in the form of MDS.[3-8] We present a case of AML at initial presentation following the use of TMZ and radiation for GBM.

Case Report

The patient was a 56-year-old Chinese female who was diagnosed with GBM (WHO grade 4) involving the left occipital and insular regions at the end of January 2008 after complaining of headache. The diagnosis was based on brain biopsy performed. She had no significant past medical history of note and no family history of malignancy. She was initially given dexamethasone. She subsequently underwent intensity-modulated radiation therapy of 60 Gy for 30 fractions from 27 February 2008 to 9 April 2008. She was given TMZ 75 mg/m^2/day concurrently with the radiation therapy. Subsequently, she was given TMZ 150 mg/m^2/day for 5 days every month from 20 May 2008. She received a total of 8 cycles of TMZ and her last dose was from 22 December 2008 to 26 December 2008. She was also on tapering dose of dexamethasone till September 2008. Her full blood counts prior to initiation of TMZ were unremarkable with haemoglobin of 13.0 g/dL, white blood cell (WBC) of 8.6 x 10^9/L and platelet of 219 x 10^9 L.

Magnetic resonance imaging (MRI) brain assessment of the GBM conducted in early November 2008 demonstrated partial response with decrease in size of the occipital lesion while the insular lesion was stable. She tolerated TMZ well and only experienced grade 2 haematologic toxicity affecting solely the haemoglobin level (haemoglobin was 9.5 g/dL) (common toxicity criteria) since early December 2008.

She first developed grade 3 haematological toxicity (common toxicity criteria) on 13 January 2009. Her full blood counts then showed haemoglobin of 6.3 g/dL, WBC count of 1.9 x 10^9/L (with absolute neutrophil count of 0.83x 10^9/L) and platelet of 70 x 10^9 L. Initial impression was likely TMZ-related myelospurression and her upcoming cycle of TMZ was held off. TMZ was stopped since then. Her counts continued to be low, requiring weekly blood and platelet transfusions. She also received 2 doses of filgastrim for her severe neutropenia on 20 and 21 January 2009. Her full blood counts on 29 January 2009 showed haemoglobin of 8.2 g/dL, WBC count of 1.52 x 10^9/L (neutrophil count of 0.47 x 10^9/L) and platelet of 36 x 10^9 L. In view of such severe and prolonged cytopenias, referral to the haematology department was made. Bone marrow evaluation (including bone marrow aspirate and trephine, and tests for flow cytometry and karyotype profile) was conducted on 30 January 2009. In summary, there were features compatible with AML (blast cells of 23% demonstrated in bone marrow aspirate) with background of myelodysplatic syndrome (Fig. 1) and complex cytogenetics (Fig. 2).

The patient received induction chemotherapy that included 3 days of idarubicin (12 mg/m^2/day by slow bolus on days 1, 2 and 3) and 7 days of cytarabine (100 mg/m^2/day by continuous infusion) (3 + 7) in February 2009.

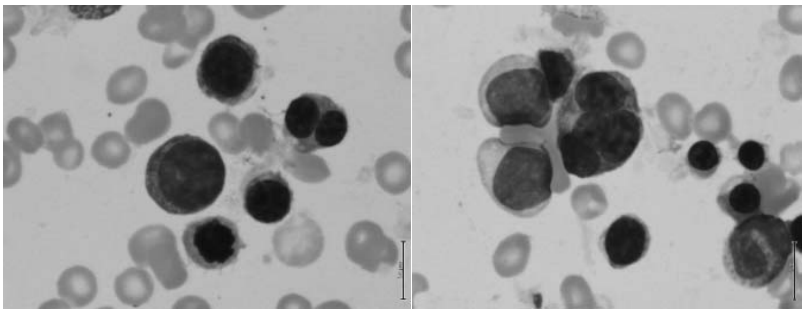

Fig. 1. Two bone marrow aspirate slides of the patient demonstrating myeloid blasts and dyserythropoiesis. (May-Grunwald-Giemsa stain, x 1000).

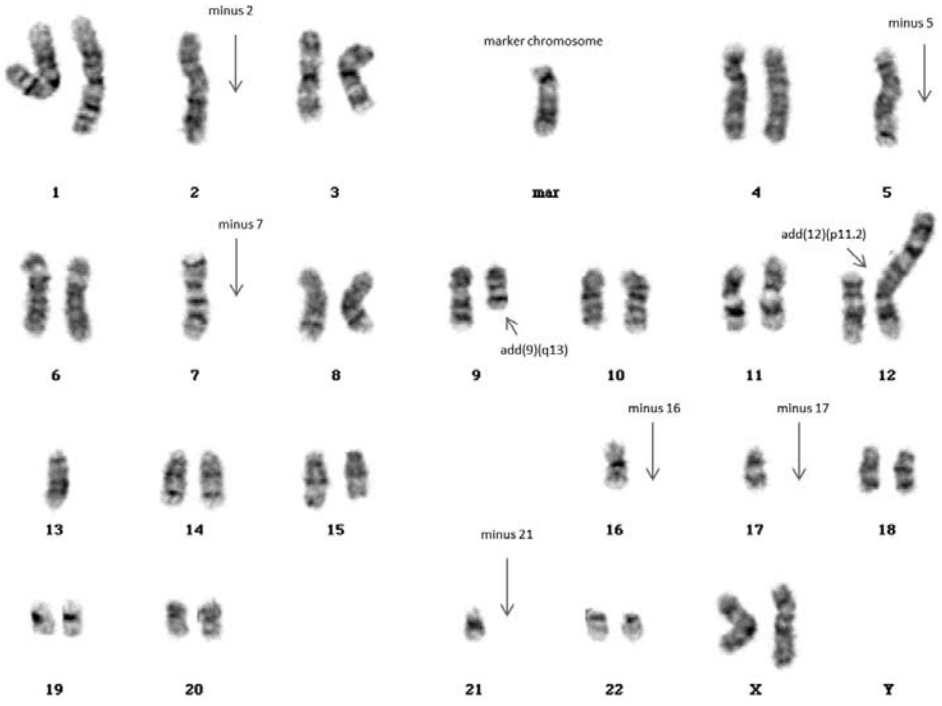

Fig. 2. Karyogram of the patient demonstrating a hypodiploid cell with numerical and structural abnormalities, specifically monosomies 5 and 7 were observed. (NB: Cytogenetic analysis was done on bone marrow cells directly after 40 minutes of incubation in a colcemid-containing hypotonic solution, and after short-term cultivation for 24 hours using RPMI 1640 culture medium. Twenty cells were analysed, chromosomal abnormalities were described according to ISCN 2009.)

Post-induction bone marrow evaluation revealed persistence of approximately 5% of blasts and she received a further cycle of 2 days of idarubicin (12 mg/m^2/day by slow bolus on days 1 and 2) and 5 days of cytarabine (100 mg/m^2/day by continuous infusion) (2 + 5) in March 2009. This was initially meant to be consolidation chemotherapy but the cytarabine was shortened from 7 to 5 days when her GBM showed progression on MRI. No further intensive chemotherapy was given after that as her cytopenia had resolved. With the treatment intent of her AML switched to palliative due to limited treatment options available for her progressive GBM, no further bone marrow investigations were done to confirm her response to the second cycle of idarubicin and cytarabine.

However, her cytopenia recurred at the end of June 2009 and was deemed to be due to relapse of her AML. She received 1 cycle of decitabine (20 mg/m^2 for 5 days) in mid-August 2009 with little haematological response. In mid-September 2009, she developed headache with new onset of expressive dysphasia. Computed tomography (CT) brain demonstrated several new foci of lesions suspicious of intratumoral haemorrhage. Patient was given blood product support and palliative treatment. She passed away at the end of September 2009.

Discussion

Prior to the use of TMZ, nitrosoureas have been widely used for the treatment of gliomas. However, nitrosoureas is more myelotoxic than TMZ and prolonged use of nitrosoureas is not feasible given the progressive significant myelosuppression and toxicity that will ensue. TMZ, on the other hand, is much well tolerated. Concurrent radiation therapy with TMZ treatment for glioblastoma resulted in grade 3 or 4 haematological toxicity in approximately 7%

of patients only.[1] This opens up the possibility of prolonged use of TMZ in patients with gliomas who have responded to its treatment. Having established that, treatment of gliomas with TMZ is still non-curative, similar to nitrosoureas.

Mustafa et al reported a small case series of prolonged TMZ use of at least 5 years with minimal long-term toxicity.[9] There are also reports of severe haematological toxicities such as pancytopenia, t-MDS and leukaemias following the use of TMZ.[3-8] The time of exposure prior to the development of such toxicities can be as short as weeks. However, most of the patients described had been exposed to the other alkylating agents, of which the contribution to leukemogenesis cannot be excluded. The only form of chemotherapy that our patient received prior to her AML diagnosis was TMZ and hence this provides the most direct evidence of the role of TMZ in the development of secondary AML. All the AML cases described so far evolved from MDS (majority of which took a few months and only one reported progression to AML 1 week after diagnosis of MDS). Our patient presented with AML (WHO 2008 definition)[2] at the point of diagnosis which is unusual. We could not verify from past published reports if this is attributed to the revised WHO 2008 definition of AML which classifies all myeloid neoplasms with at least 20% as AML, rather than 30% in the past. The duration of the first onset of significant cytopenias to the evaluation of her bone marrow was only slightly more than 2 weeks. The presence of highly complex cytogenetic abnormalities that include deletion of chromosomes 5 and 7 in our patient were suggestive of alkylating agent/radiation-related AML.

While clinically significant haematological toxicity is not common with TMZ as first described by Stupp et al,[1] such toxicity may potentially emerge as an important side effect as it is now a common practice for many physicians to extend the treatment of TMZ for patients with non-progressive disease. This extension may be up to 12 to 36 months, much longer than the duration of TMZ exposure described originally (up to 628-day cycle of adjuvant TMZ). Apart from a phase 2 trial on continuous use of TMZ for recurrent malignant gliomas that demonstrated severe haematological toxicity was uncommon,[10] data regarding the efficacy and toxicity of protracted course of TMZ are, however, lacking. The optimal duration of TMZ therapy for patients who have good response has yet to be established. Our patient's GBM was responding to TMZ and her treatment was extended to 8 cycles. Unfortunately the development of therapy-related AML (t-AML) necessitated the cessation of TMZ. The progression of the GBM after 3 months of stopping TMZ subsequently became the limiting factor for further aggressive treatment of her t-AML. Given that such toxicity may be life threatening to those at risk, reports of clinical and genetic factors in predicting this risk would be worth exploring further.

Till the end of April 2013, there had been 383 patients who were treated with TMZ in our institution. To the authors' best knowledge, this was the only case of TMZ-associated MDS/AML. Although the true incidence of TMZ-related MDS/AML could not be calculated based on these data, it seems the occurrence of such complication is uncommon. Therefore, TMZ is still likely the most suitable treatment option for patients with GBM. The paucity of TMZ-associated MDS/AML may be partly due to the poor prognosis of patients with malignant gliomas.

Optimal treatment for patients with t-MDS/AML has not been established and many factors including the patient's age, performance status, concurrent medical conditions and status of the primary malignancy play a pivotal role in deciding the management approaches for these patients. Intensive chemotherapy followed by allogenic stem cell transplantation may be the only curative option for eligible patients but is often not a suitable option for patients with malignant gliomas due to the poor prognosis of the latter. t-MDS/AML also confer an unfavourable prognosis which often cannot be cured by intensive chemotherapy alone and is associated with a median overall survival of only 6 months.[11,12]

Conclusion

Clinicians should be aware of the potentially serious haematological side effects of t-MDS/AML with the use of TMZ. Although this adverse effect is rare and is outweighed by the benefits of TMZ, t-MDS/AML may worsen the overall prognosis of the patient and may occur after only short courses of TMZ.

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