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Sustained Response to Temozolomide Rechallenge after Hematological Toxicity in MGMT Methylated Glioblastoma

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1. Summary

1.1. Background: Glioblastoma Multiforme (GBM) is known to have a rapidly progressive and fatal clinical course. Methylation of the methylguanine DNA methyltransferase promoter (MGMT) has been associated with a more indolent clinical course and better response to the alkylating agent temozolomide. The standard of care treatment includes radiotherapy with concurrent temozolomide (75mg/m2) followed by adjuvant temozolomide for 6 months (150 mg/m2 at month one, followed by 200mg/m2 given for the remaining 5 months).

1.2. Case Report: Here we present a case of a 61-year-old woman with a large MGMT methylated GBM involving the corpus callosum that was not amenable to debulking surgery due to the location of her tumour, who had prolonged pancytopenia during chemo-radiotherapy but who had long-term disease control. She developed grade IV thrombocytopenia and grade IV neutropenia during the radiotherapy with concurrent temozolomide phase of treatment. She was successfully re-challenged with temozolomide on progression of her disease with excellent disease response, surpassing the median survival of patients with GBM by 35 months.

1.3. Conclusion: This case illustrates the heterogeneity of GBM as well as the challenges associated with managing temozolomide rechallenge in the setting of previous adverse reactions. Currently, there are limited treatment options in patients with GBM who have progressed through standard of care treatment, and this case highlights the importance of considering rechallenging with previous lines of treatment.

2. Background

Glioblastoma Multiforme (GBM) represents one of the most difficult to treat central nervous system (CNS) malignancies due to inherent aggressive growth patterns, limited treatment options and multiple mechanisms of drug resistance [1]. Certain tumor characteristics can affect the rate of disease progression including isocitrate dehydrogenase (IDH) mutations, ATRX status and methylation of methylguanine DNA methyltransferase promoter (MGMT) [2]. Irrespective of molecular subtype, radiotherapy with concomitant temozolomide chemotherapy followed by temozolomide has been the standard of care since 2005 [3]. This case describes a patient who was unable to complete chemo-radiotherapy due to prolonged neutropenia and thrombocytopenia, but who subsequently had excellent response and manageable toxicity upon temozolomide rechallenge.

3. Case Report

A 61-year-old woman presented to hospital with confusion, impaired ability to plan and altered right sided sensation. A magnetic resonance imaging (MRI) brain showed a peripherally enhancing, centrally necrotic mass, involving the left posterior frontal and anterior parietal lobes, with extension across the corpus callosum to the right parasagittal frontal region (Figure 1A). A biopsy showed GBM, IDH wild type, ATRX wild type, with 55% MGMT methylation. Due to the central position of the tumor, she did not undergo debulking surgery and began radiotherapy and concurrent temozolomide 75mg/m2 daily. She was admitted to hospital with febrile neutropenia on day 29. During this 33-day admission,

there was significant thrombocytopenia (Figure 2A); grade IV for 5 days, grade III for 10 days, and grade II for 4 days as well as neutropenia (Fig 2B); grade IV for 4 days and grade II for 13 days, before recovery of these toxicities (Figure 2A, B). These represent a 92% and 95% reduction in neutrophil and platelet counts from baseline respectively. A repeat MRI brain showed an increase in the extent of the centrally necrotic mass, involving the corpus callosum and bilateral parietal lobes. She did not undergo perfusion imaging. Despite intensive involvement of the multidisciplinary team (including Physiotherapy and Occupational Therapy), her overall condition continued to deteriorate to an ECOG performance status of 3. Therefore, a diagnosis of disease progression was made, and she was discharged to community palliative care for supportive care only.

She continued to attend outpatient clinics and significantly improved in both symptom burden and performance status, despite chronic issues with short term memory loss and ataxia. Surveillance MRI scans continued to improve with significantly less enhancing disease (Figure 1B-D). Unfortunately, she had disease progression 29 months after diagnosis, with a marked increase in the size of the mass. Retreatment with temozolomide with shorter interval blood testing, due to her previous cytopenias, was recommended. Due to concerns about possible adverse events, she opted to continue surveillance imaging. She was readmitted to hospital at month 37 post diagnosis with deteriorating confusion, headaches, lethargy, ataxia with falls, and was requiring the assistance of two people to carry out her activities of daily living. An MRI showed further progression of the mass within the corpus callosum, and leptomeningeal enhancement (Figure 1E). She agreed to a reduced dose of temozolomide, 100mg/m2 day 1-5 every 28 days and had tapering steroid doses to help with symptom control. Despite having ongoing issues with confusion, she tolerated temozolomide well, having no issue with cytopenias (Figure 2C, D). Following this 6-day admission with extensive input from the multidisciplinary team, she was discharged home. Surveillance imaging at month 45 post diagnosis, after completion of 6 months of temozolomide showed a significant reduction in the size and extent of the tumor (Figure 1F), indicating an excellent treatment response. On clinical exam, her ataxia had much improved, and she was able to mobilize independently, with no admissions to hospital during this 6-month period. She had disease progression at month 47 and was commenced on bevacizumab before dying 50 months after her diagnosis.

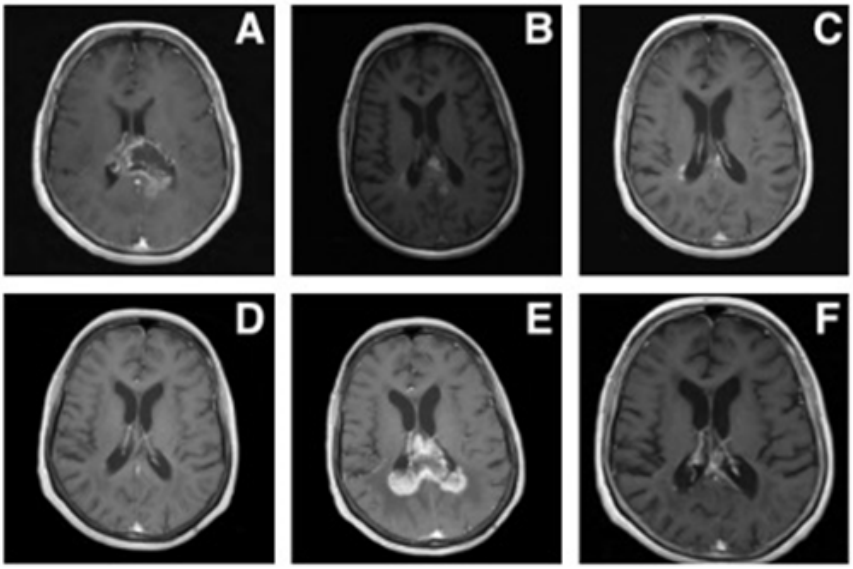

Figure 1: MRI brain imaging performed throughout the case. 1A: MRI brain on first presentation to hospital. 1B-D: Surveillance MRI brain imaging performed at 10 months, 16 months, and 24 months post diagnosis respectively, showing decreasing tumor burden. 1E: MRI brain at month 37, showing significant progression of disease. 1F: MRI brain at month 45 post diagnosis (after Temozolomide rechallenge) showing significant radiological response.

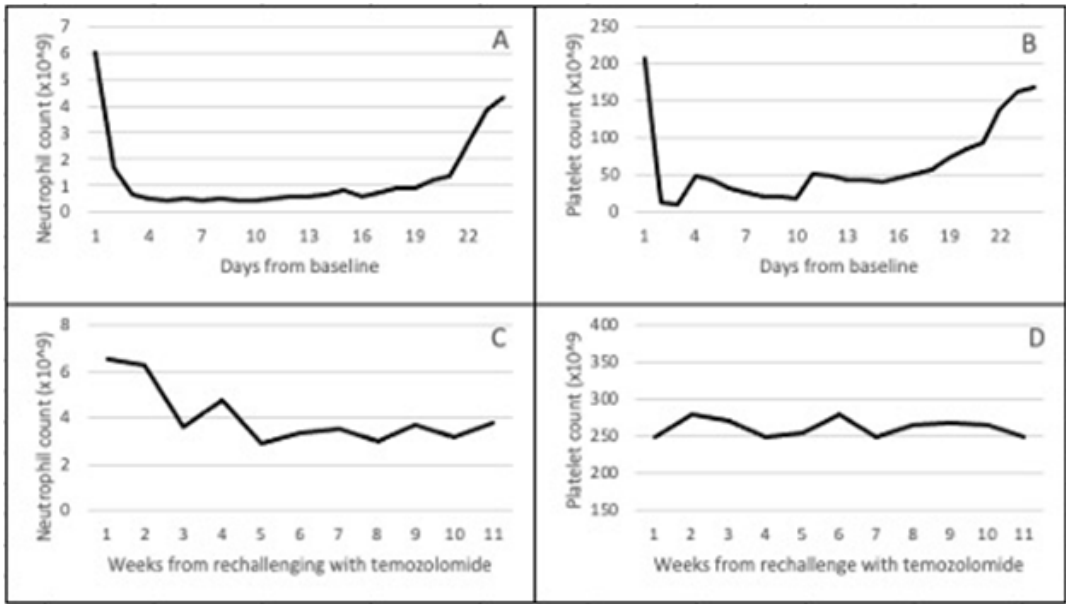

Figure 2: Neutrophil and platelet counts during treatment. 2A, B: Neutrophil and platelet counts from commencement of concurrent temozolomide and radiation until the end of hospital admission with febrile neutropenia. Figure 2C, D. Neutrophil and platelet counts during rechallenging with temozolomide

4. Discussion

For patients with newly diagnosed GBM, 6 weeks of concurrent temozolomide with radiation, followed by 6 months of temozolomide is associated with a median 2-year overall survival (OS) rate of 26% compared with 10.4% with radiation alone [3]. GBM is very heterogeneous, and a small group of patients have long term disease control. A meta-analysis has subsequently shown that OS is increased in patients with methylated MGMT [4]. Neutropenia and thrombocytopenia are common toxicities from temozolomide. Of note, a decrease in neutrophil count of more than 40% from baseline has been linked to improved survival and hence can be a positive prognostic indicator [5]. However, high grade hematological toxicity can occur in up to 25% patients and extreme cytopenias as depicted in this case (92% and 95% decrease in neutrophil and platelet count respectively) present significant challenges for temozolomide retreatment [6]. In this case, the adverse hematological effects did not recur, potentially as no radiotherapy was given, due to selected dosing schedule or other factors. The patient made a profound improvement radiologically and clinically, indicating that rechallenging, despite the risks, is a reasonable approach for selected patients.

The dosing of chemotherapy is always an individual decision. Alternative dosing schedules of temozolomide have been used to varying degrees of success – specifically either a dose-dense or metronomic schedule. A randomized phase II study comparing both options showed that continuous dosing with metronomic temozolomide was associated with fewer grade III and IV hematologic adverse events [7,8]. The 1-year survival rate was 80% versus 69% for dose-dense temozolomide and metronomic temozolomide respectively [8]. The extent of methylation of MGMT can also impact on temozolomide response and hence overall survival. Methylation of MGMT promoter is found in 95% of long-term survivors with GBM [9]. In this case, a patient with 55% MGMT methylation had an overall survival of 50 months. There is ongoing research to determine percentage methylation of MGMT cutoffs for treatment decisions and trial design, with some studies defining this as greater than 12.5% [10].

5. Conclusion

The dosing of chemotherapy can vary and in cases associated with significant toxicities this is often advised by consultant medical oncologists. This case illustrates the heterogeneity of GBM and that rechallenge with temozolomide is safe and effective even after profound toxicity. This highlights the importance of consideration of previous lines of chemotherapy, which is of special importance in cases of GBM where treatment options are limited.

6. Declarations

6.1. Funding: No funding was obtained for this research.

6.2. Conflicts of Interest/Competing Interests: The author(s) declare(s) that there is no conflict of interest'.

6.3. Data Availability (data transparency): Data sharing is not applicable to this article as no datasets were generated or analysed during the current study.

6.4. Author's Contributions: OF wrote the main manuscript. CM prepared figure 1, OF prepared figure 2. OF, PM and CM reviewed and edited the manuscript.

6.5. Ethics Approval/Consent: Consent was obtained from the patients legal next of kin for the use of the case including radiology, bloods and clinical course.

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