Published in final edited form as:

J Neurooncol. 2014 October ; 120(1): 111–115. doi:10.1007/s11060-014-1523-1.

Analyzing Temozolomide Medication Errors: Potentially Fatal

Nathalie Letarte, B. Pharm, MSc, Michael P. Gabay, Pharm D, Linda R. Bressler, Pharm D, Katie E. Long, Pharm D, Joan M. Stachnik, Pharm D, and J. Lee Villano, M.D., Ph.D

Centre hospitalier de l'Université de Montreal (NL); University of Illinois at Chicago (MPG, LRB, JMS); University of Kentucky, Lexington (KEL, JLV)

Abstract

Background—The EORTC-NCIC regimen for glioblastoma requires different dosing of temozolomide (TMZ) during radiation and maintenance therapy. This complexity is exacerbated by the availability of multiple TMZ capsule strengths. TMZ is an alkylating agent and the major toxicity of this class is dose-related myelosuppression. Inadvertent overdose can be fatal.

Methods—The websites of the Institute for Safe Medication Practices (ISMP), and the Food and Drug Administration (FDA) MedWatch database were reviewed. We searched the MedWatch database for adverse events associated with TMZ and obtained all reports including hematologic toxicity submitted from November 1st 1997 to May 30th 2012.

Results—The ISMP describes errors with TMZ resulting from the positioning of information on the label of the commercial product. The strength and quantity of capsules on the label were in close proximity to each other, and this has been changed by the manufacturer. MedWatch identified 45 medication errors. Patient errors were the most common, accounting for 21 or 47% of errors, followed by dispensing errors, which accounted for 13 or 29%. Seven reports or 16% were errors in the prescribing of TMZ. Reported outcomes ranged from reversible hematological adverse events (13%), to hospitalization for other adverse events (13%) or death (18%). Four error reports lacked detail and could not be categorized.

Conclusion—Although the FDA issued a warning in 2003 regarding fatal medication errors and the product label warns of overdosing, errors in TMZ dosing occur for various reasons and involve both healthcare professionals and patients. Overdosing errors can be fatal.

Keywords

Temozolomide; medication errors; adverse events

Corresponding Author: J. Lee Villano, M.D., Ph.D. Dept. of Medicine, University of Kentucky, Markey Cancer Center, 800 Rose Street, CC447, Lexington, KY 40536-0093, Tele: 859-323-0405, Fax: (859) 257-7715, jvillano@uky.edu.

This work was previously presented at the 2012 Society for Neuro-Oncology Annual Meeting.

All co-authors have contributed to the preparation of this manuscript and have approved the final version.

Financial disclosure: The authors have no financial disclosures.

Introduction

The United States Food and Drug Administration (FDA) granted accelerated approval of temozolomide, Temodar®, (TMZ) for treatment of refractory anaplastic astrocytoma in 1999.¹ Full approval was subsequently granted in 2005 based on the results of the phase III CE.3 study conducted by the EORTC (European Organization for Research and Treatment of Cancer) 22981/26981-NCIC (National Cancer Institute of Canada).² TMZ was found to improve survival in patients with glioblastoma (GBM) receiving radiotherapy. In this study, patients received oral TMZ at a daily dose of 75 mg/m² while receiving radiation therapy, followed by a 28-day break. This was followed by six cycles of adjuvant TMZ at a dose of 150 mg/m² for 5 days every 28 days for the first cycle and then 200 mg/m² for cycles 2 to 6.²

TMZ capsules are currently available in six different strengths: 5 mg, 20 mg, 100 mg, 140 mg, 180 mg, and 250 mg, and are also available as a generic version since 2013.³ Considering the multiple strengths of TMZ and different dosing regimens (during radiation therapy versus post-radiation adjuvant therapy), it is not surprising that medication errors have been seen. The FDA initially reported such errors in 2003.⁴ TMZ is among the most commonly prescribed oral anticancer agents and various errors related to TMZ use have been reported.^{5, 6} Our analysis focuses on medication errors with TMZ, based on reports in two large adverse event databases. This represents an extension of our previous study identifying severe hematologic adverse events with TMZ.⁷

The definition of a medication error is “any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the health care provider, patient or consumer”.⁸ These errors may be related to product labeling, prescribing, dispensing, compounding, administration and use of drugs, to name a few.⁹

Methods

The website of the Institute for Safe Medication Practices (ISMP) and the FDA MedWatch database were reviewed. The ISMP website was searched in early 2012 using the key words temozolomide and Temodar. All documents from the search containing these key words were reviewed and included in our analysis if relevant. We searched the MedWatch database for adverse events associated with TMZ and obtained, for the purpose of a previous study, reports submitted from November 1st 1997 to September 3rd 2008.⁷ We subsequently obtained an update from the MedWatch database from September 2008 to May 30th 2012. The key words medication error, overdose, and misuse were searched through the database. Paper copies of the reports containing these words were obtained from MedWatch and each report was sorted and analyzed. Multiple reports that described the same patient were grouped together and only counted once. Multiple reports describing the same patient were identified by comparing report numbers, age, gender, concomitant medications, primary tumor, TMZ dosing, and other medical history. Reports discussing medication errors not involving TMZ were excluded.

Results

The ISMP website described a dispensing error in 2004 that was thought to result from confusion between the quantity printed on the label, and the capsule strength. It is not known if the error was a potential or actual error (i.e., if it reached the patient). Nor are the consequences, if any, of the error provided. Forty-five cases of medication errors involving TMZ were reported through MedWatch from 1997 to 2012. Patient characteristics are shown in Table 1. Of those reports that included the indication for TMZ, the most common indication was primary brain tumor. The median age was 54 years. Errors were classified into one of three categories: errors involving the prescribing of TMZ, errors involving the dispensing of the drug, and errors made by the patient or caregiver in administering TMZ (Table 2). Because of incomplete information provided on the MedWatch reports, not all errors could be categorized. Information about patient characteristics and outcomes was also largely unavailable.

Patient or caregiver errors were the most common, accounting for 47% of errors. There were two reports describing patients who took an intentional overdose or misused the drug. Three patients also took the wrong capsule strength by accident (e.g. four capsules of 100 mg instead of four capsules of 5 mg). A seventy-seven-year old female patient and a ninety-one year old female patient mistakenly took all of their doses in one day. Five patients continued TMZ for longer than the intended cycle length (e.g. 13 or 16 days in a row instead of 5 days). These reports did not specify how the patient obtained more drug than was intended (i.e. the number of capsules dispensed was not provided in the report).

Dispensing errors were the second most common (29%). The majority of dispensing errors involved the incorrect capsule strength (e.g. 100 mg or 250 mg instead of 20 mg capsules). Only one case described an “underdosing” dispensing error. In this case, the patient received a daily dose of 20 mg instead of 100 mg. The error was discovered at the subsequent cycle. Two cases of dispensing the wrong drug in a bottle labeled as TMZ were reported and included flecainide (Tambocor®) being dispensed instead of TMZ. One of these patients was hospitalized for heart block.

Seven reports (15%) involved errors in prescribing TMZ. Three patients were prescribed a dose that was too high (e.g. 200 mg/m² instead of 150 mg/m²). Three patients were prescribed TMZ for too long a duration (e.g. 14 and 23 days instead of 5 days). The reports did not mention if the prescriptions were written on standard order forms.

Our analysis also revealed minor errors and near misses. Four patients chewed the capsule or dissolved it in water or glycerin rather than swallowing the capsule whole. Two of the dispensing errors reported were caught before the patients actually received the drug.

Reported outcomes ranged from reversible hematologic adverse events such as pancytopenia or bone marrow failure (13%), to hospitalization for other adverse events (13%) and death, mostly due to infection secondary to hematologic toxicity (18%).

Discussion

Our study is a retrospective analysis of the ISMP and MedWatch databases, and it is limited by important missing information. In particular, information about the source of the error, patient characteristics and patient outcome was unavailable, preventing correlation analyses. Medication errors tend to be underreported in voluntary databases, thus there were likely many errors not captured in our analysis. Indeed, the genesis of our study was a personal communication describing a fatal dosing error that was never reported to either MedWatch or ISMP. In addition, we were unable to obtain error reports or estimates of error frequency from the brand manufacturer of TMZ. This is in keeping with a concerning trend to underreport errors to the FDA and for lack of standardization in reports for pharmaceutical companies.^{10, 11}

The true incidence of medication errors with TMZ cannot be determined. We found a small number of reported errors; however, it is estimated that more than 8000 cases of glioblastoma occur in the US each year and that most may be candidates for radiation and TMZ treatment.^{12, 13} Use of TMZ for off-label indication is also increasing,¹⁴ and it is recognized as the most frequently prescribed oral anticancer agent. In an evaluation of an enhanced electronic prescribing module for oral chemotherapy, Weingart *et al.* reviewed 6,673 prescriptions ordered for 2,043 patients during a 17-month period and TMZ was the most frequently ordered oral agent, accounting for 1,585 prescriptions.¹⁵ Oral chemotherapy in general carries the potential for patient errors in addition to prescribing and dispensing errors.^{15, 16} The use of multiple concomitant medications (e.g. steroids, anticonvulsants, antibiotics), and cognitive deficits due to the underlying disease, can increase the risk of patient errors.^{6, 15, 17} In our analysis, errors in dose were the most common type of error noted and were seen in all categories: accidental overdoses on the part of the patient, incorrect capsule strength dispensed, and incorrect dose prescribed.

When TMZ was initially marketed the commercial label displayed the same font size for the quantity of capsules in each bottle and for the strength of the capsules in the bottle.⁴ This led to many errors, such as the one described on the ISMP website and by the FDA in a safety report. The manufacturer made changes to the label in 2003, but errors continued to occur. In our review, the majority of errors reported occurred after the label change. Generic versions of TMZ are now available in the US. Importantly, versions of the generic and Temodar® drug differ in color, which enhances the risk of medication error.

TMZ is most often given on an intermittent schedule (*i.e.*, daily for five days, every 28 days). The drug is available in multiple strengths, in amber glass bottles containing 5 or 14 capsules.⁴ It is possible that when the original bottle is dispensed, medication remains at the end of a treatment cycle. This could be confusing, and patients might continue on the medication until the bottle is finished. Indeed, the most common type of patient error in our analysis was accidental overdose. The prescribed dose of TMZ often requires a combination of different strength capsules, further increasing the likelihood of error. Taylor *et al.* described medication errors in 18.8% of 69 pediatric patients receiving outpatient oral chemotherapy for acute lymphoblastic leukemia.¹⁸ In this study, errors were identified by asking caregivers to demonstrate (by recall) how each oral medication had been

administered. Most of the errors in administration were seen with corticosteroids (dexamethasone and prednisone). Similar to TMZ, corticosteroids required a combination of different strength tablets to equal the prescribed dose.

Our analysis only identified a single underdosing error, but this type of error is less likely to be reported as there is no obvious resulting complication. Underdosing may in fact be “planned” in clinical practice (e.g. skipping TMZ on weekends during radiation therapy or remaining on 150 mg/m² versus increasing to 200 mg/m² during the maintenance portion of therapy for patients experiencing adverse events). The impact of underdosing is not known. Medication errors in general are underreported and those involving underdosing may be even less likely to be reported since consequences may be perceived to be less severe.¹⁹

Consideration should be given to remedy the likely source of these errors. Pharmacies in the United States generally dispense TMZ in the original bottles by affixing the prescription label to the bottle or to the outer packaging (box). One way to prevent these dispensing errors would be to provide the exact quantity of drug needed for the treatment cycle instead of dispensing the whole bottle. A packaging method such as Dispill™, which is used widely in Canada, could reduce these errors. To avoid errors related to names that sound similar, such as the Tambocor® error, prescriptions should be ordered using the generic name. Such errors might also be minimized if pharmacists had access to the indication/diagnosis. In addition, currently TMZ can be dispensed by any retail pharmacy pursuant to a valid prescription. Some organizations suggest that pharmacies should be credentialed or trained to dispense anti-neoplastic agents.⁹

Awareness of errors associated with chemotherapy and targeted agents have increased in recent years. Many organizations have published guidelines and recommendations to optimize the use and administration of these agents. It is too early to measure the outcomes of these guidelines.^{8, 9, 20, 21} Education is a key component of reducing medication errors. Organizations such as the Multinational Association of Supportive Care in Cancer (MASCC) have developed tools to educate patients about oral anticancer agents.²² The MASCC Teaching Tool for Patients Receiving Oral Agents for Cancer (MOATT)® was developed by MASCC members and is translated to many languages. Multidisciplinary teams comprised of oncologists, oncology nurses, hospital and community pharmacists should work together to implement programs to improve medication error rates.²⁰

Conclusion

Although the FDA issued a warning regarding fatal medication errors associated with TMZ in 2003 and the product label warns of the potential risk of overdose, errors in TMZ dosing are prevalent and involve both healthcare professionals and patients. Overdosing errors can be fatal. Underdosing, however, might compromise desired outcomes. The recent launch of generic TMZ is welcomed (Genetic Engineering and Biotechnology News Aug 12, 2013), but the availability of additional capsules, with different colors could lead to even further confusion. Healthcare professionals should review dosing regimens and capsule strengths when prescribing and dispensing TMZ, and they should provide clear instructions including followup for patients receiving TMZ. Guidelines for administration of chemotherapy should

be implemented and followed.²³ The use of oral chemotherapy also provides an opportunity to engage patients in error prevention.²⁴ Guidelines developed for physician practices or cancer center ambulatory facilities may not reach community pharmacies that are not affiliated with these practice sites, thus prescriptions must be double checked before they are dispensed to patients.²⁵ In addition, communication with community pharmacies that dispense TMZ should be enhanced. We encourage clinicians to report all errors that occur to accurately identify the true incidence.

Acknowledgments

Funding: None of the authors received financial support based on the generation of this submission.

References

1. Yung WK, Prados MD, Yaya-Tur R, et al. Multicenter phase II trial of temozolomide in patients with anaplastic astrocytoma or anaplastic oligoastrocytoma at first relapse. Temodal Brain Tumor Group. *J Clin Oncol.* 1999; 17:2762–2771. [PubMed: 10561351]
2. Stupp R, Hegi ME, Mason WP, et al. Effects of radiotherapy with concomitant and adjuvant temozolomide versus radiotherapy alone on survival in glioblastoma in a randomised phase III study: 5-year analysis of the EORTC-NCIC trial. *Lancet Oncol.* 2009; 10:459–466. [PubMed: 19269895]
3. MERCK & CO. INC. http://www.merck.com/product/usa/pi_circulars/t/temodar_capsules/temodar_pi.pdf. [accessed April 20 2014].
4. Phillips J. FDA Safety Page: Fatal medication errors associated with Temodar. *Drug Topics.* 2003; 7:42.
5. Weingart SN, Toro J, Spencer J, et al. Medication errors involving oral chemotherapy. *Cancer.* 2010; 116:2455–2464. [PubMed: 20225328]
6. Weingart SN, Spencer J, Buia S, et al. Medication safety of five oral chemotherapies: a proactive risk assessment. *J Oncol Pract.* 2011; 7:2–6. [PubMed: 21532801]
7. Villano JL, Letarte N, Yu JM, Abdur S, Bressler LR. Hematologic adverse events associated with temozolomide. *Cancer Chemother Pharmacol.* 2012; 69:107–113. [PubMed: 21614470]
8. National Coordinating Council on medication Error Reporting and Prevention. About medications errors.
9. Medication Misadventures, Guidelines. ASHP; ASHP Guidelines on Preventing Medication Errors with Antineoplastic Agents. [accessed April 16 2014]
10. Bennett CL, Nebeker JR, Lyons EA, et al. The Research on Adverse Drug Events and Reports (RADAR) project. *JAMA.* 2005; 293:2131–2140. [PubMed: 15870417]
11. Cooper MA, Ibrahim A, Lyu H, Makary MA. Underreporting of Robotic Surgery Complications. *J Healthc Qual.* 2013
12. Koshy M, Villano JL, Dolecek TA, et al. Improved survival time trends for glioblastoma using the SEER 17 population-based registries. *J Neurooncol.* 2012; 107:207–212. [PubMed: 21984115]
13. Ostrom QT, Gittleman H, Farah P, et al. CBTRUS statistical report: Primary brain and central nervous system tumors diagnosed in the United States in 2006–2010. *Neuro Oncol.* 2013; 15(Suppl 2):ii1–56. [PubMed: 24137015]
14. Tatar Z, Thivat E, Planchat E, et al. Temozolomide and unusual indications: review of literature. *Cancer Treat Rev.* 2013; 39:125–135. [PubMed: 22818211]
15. Weingart SN, Mattsson T, Zhu J, Shulman LN, Hassett M. Improving electronic oral chemotherapy prescription: can we build a safer system? *J Oncol Pract.* 2012; 8:e168–173. [PubMed: 23598852]
16. Schwappach DL, Wernli M. Medication errors in chemotherapy: incidence, types and involvement of patients in prevention. A review of the literature. *Eur J Cancer Care (Engl).* 2010; 19:285–292. [PubMed: 19708929]

17. Schwappach DL, Wernli M. Barriers and facilitators to chemotherapy patients' engagement in medical error prevention. *Ann Oncol.* 2011; 22:424–430. [PubMed: 20616197]
18. Taylor JA, Winter L, Geyer LJ, Hawkins DS. Oral outpatient chemotherapy medication errors in children with acute lymphoblastic leukemia. *Cancer.* 2006; 107:1400–1406. [PubMed: 16909415]
19. [accessed April 28 2014] A Call to Action: Protecting U.S. citizens from inappropriate medication use. <http://www.ismp.org/pressroom/viewpoints/CommunityPharmacy.pdf> [serial online]
20. Birner AM, Bedell MK, Avery JT, Ernstoff MS. Program to support safe administration of oral chemotherapy. *J Oncol Pract.* 2006; 2:5–6. [PubMed: 20871728]
21. Spoelstra SL, Given BA, Given CW, et al. An intervention to improve adherence and management of symptoms for patients prescribed oral chemotherapy agents: an exploratory study. *Cancer Nurs.* 2013; 36:18–28. [PubMed: 23235499]
22. [accessed April 28 2014] MASCC teaching tool for patients receiving oral agents for cancer. http://www.mascc.org/assets/documents/MOATT_English_2010.pdf [serial online]
23. Neuss MN, Polovich M, McNiff K, et al. 2013 updated american society of clinical oncology/ oncology nursing society chemotherapy administration safety standards including standards for the safe administration and management of oral chemotherapy. *J Oncol Pract.* 2013; 9:5s–13s. [PubMed: 23914148]
24. Schwappach DL. Risk factors for patient-reported medical errors in eleven countries. *Health Expect.* 2014
25. Jatoi A, Smith EL, Gunderson HD, et al. Capecitabine and temozolomide: design, implementation, and preliminary outcomes from a pilot project to ensure safe prescribing of oral chemotherapy. *J Oncol Pract.* 2010; 6:210–212. [PubMed: 21037876]

Table 1**Patient characteristics**

Patients	N =45
Gender	
- Male	17 (38%)
- Female	19 (42%)
Age (mean [SD])	54 (2) y
Age (median [SD])	54(2) y
Indication for temozolomide use	
- Glioblastoma	14
- Other CNS tumor (NOS)	6
- Melanoma	4
- CNS metastasis	1
- Not reported	20

NOS: not otherwise specified, CNS: Central nervous system

Medication error reported

Table 2

Types of errors reported	N (%) 45(100%)	Deaths (n)
Patient error	21 (47%)	5
- Accidental overdose	10	3
- Intentional overdose	2	
- Wrong duration of treatment	5	2
- Wrong method of administration	4	
Dispensing error	13 (29%)	1
- Quantity dispensed (duration of treatment)	2	
- Dose dispensed (capsule strength to high)	7	1
- Dose dispensed (capsule strength to low)	1	
- Wrong dilution (IV formulation)	1	
- Wrong medication dispensed (flecainide instead of temozolomide)	2	
Prescribing error	7 (15%)	1
- Dose	4	
- Duration of treatment	3	1
Type of error not reported – no details available	4 (9%)	1