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Authors

Robins, H Ian
Eickhoff, Jens
Gilbert, Mark R
et al.

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The association between BMI and BSA–temozolomide-induced myelosuppression toxicities: a correlative analysis of NRG oncology RTOG 0525

H. Ian Robins, Jens Eickhoff, Mark R. Gilbert, Terri S. Armstrong, Wenyin Shi, John F. De Groot, Christopher J. Schultz, Grant K. Hunter, Egils Valeinis, Mack Roach III, Emad F. Youssef, Luis Souhami, Steve P. Howard, Frank S. Lieberman, James G. Herman, Peixin Zhang, and Minesh P. Mehta

University of Wisconsin Hospital and Clinics, Madison (H.I.R., J.E., S.P.H.); National Institutes of Health Clinical Center Neuro-Oncology Branch, Bethesda, MD (M.R.G.); The University of Texas MD Anderson Cancer Center, Houston (T.S.A., J.F.D.G.); Thomas Jefferson University Hospital, Philadelphia, PA (W.S.); Froedtert and the Medical College of Wisconsin, Milwaukee (C.J.S.); Intermountain Medical Center, Salt Lake City, UT (G.K.H.); Pauls Stradiņš Clinical University Hospital, Riga, Latvia (E.V.); University of California San Francisco Medical Center-Mount Zion (M.R.); Saint Joseph's Hospital and Medical Center, Phoenix, AZ (E.F.Y.); McGill University Health Centre, Montreal, Québec, Canada (L.S.); University of Pittsburgh Cancer Institute, PA (F.S.L.); Michigan Cancer Research Consortium CCOP, Lansing (J.G.H.); NRG Oncology Statistics and Data Management Center, Philadelphia, PA (P.Z.); Baptist Hospital of Miami, FL (M.P.M.)

Corresponding Author: H. Ian Robins, MD, PhD, University of Wisconsin-Paul Carbone Comprehensive Cancer Center, 600 Highland Ave, Madison, WI 53792, USA (hirobins@wisc.edu).

Abstract

Background. Fearing increased myelotoxicity, many practitioners adjust the body surface area (BSA)-calculated doses in obese patients. Regarding temozolomide (TMZ), a prior study suggested men with a BSA >2 m^2 may experience increased toxicity; however, surprisingly, the inverse observation was noted in women, ie, BSA <2 m^2 was associated with higher toxicity. To further clarify this issue, data derived from a large clinical trial were analyzed.

Methods. The incidence of grade 3 and 4 myelotoxicity in a newly diagnosed glioblastoma phase 3 trial (RTOG 0525) was statistically correlated with BMI and separately with BSA. All patients received radiation and TMZ followed by adjuvant standard dose TMZ vs dose-dense TMZ; dosing regimen-associated myelotoxicity and BMI/BSA were analyzed separately. *Obesity* was defined as a BMI ≥30.

Results. There was no statistically significant correlation between gender and BSA and the occurrence of myotoxicities. For the standard arm, surprisingly the incidence of grade 3/4 myotoxicities in patients with a BMI <30 was significantly higher than in patients with a BMI ≥30 (12% vs 1%, odds ratio [OR] 12.5, $P < .001$). There was no significant difference between obese and nonobese patients (BMI "cut-point" of 30) in the dose-dense arm (OR = 0.9, 95% confidence interval: 0.4–1.6). The grade hematological 3/4 toxicity rate was significantly higher in women vs men (14% vs 8%) $P = .009$ in spite of the lack of association between gender and BSA or BMI.

Conclusion. TMZ dosing based on actual BSA is recommended with the caveat that woman are likely at higher toxicity risk.

Keywords

body mass index | surface area | temozolomide toxicity

In general, the relationship between chemotherapy dose intensity and clinical efficacy and toxicity has been well established in preclinical models, and more directly in retrospective and prospective clinical studies. Thus, as reviewed recently by Lyman and Sparreboom the overall trend in the oncology literature is to recommend dosing based on actual surface area.[1–3] Clearly, the concept of therapeutic index, balancing the morbidity of treatment with therapeutic outcome, is of paramount importance for practicing physicians. Owing to toxicity concerns, there is considerable evidence that in clinical practice practitioners often consider using ideal or adjusted surface area (using *adjusted body weight*), flat dosing, or capped dosing. This deviation from guidelines may result from the legitimate consideration that obesity can potentially affect the pharmacokinetics of any given drug. Hence, a case-by-case consideration of any drug regimen may be warranted. Indeed, a case can be made that the use of surface area for many chemotherapeutic agents may in fact be inappropriate, based on pharmacokinetics.[1–3]

The use of temozolomide (TMZ) is now standard of care in the treatment of newly diagnosed glioblastoma (GBM).[4] Although TMZ is generally well tolerated, its administration can result in grades 3, 4, and 5 myelotoxicity. Although TMZ undergoes rapid breakdown to its active moiety after administration and as such is predominantly isolated to a few physiologic and pathologic compartments, surface area dosing results in only a 35% relative reduction in variability for clearance.[5] The pharmacokinetics of TMZ follows a 1-compartment model with first-order absorption and elimination; it is hydrolyzed to the active intermediate stage at physiological pH and does not require hepatic metabolism or affect the cytochrome P450 (CYP) system to a major degree.[5] Relative to this, Armstrong et al previously reported in a multifactorial analysis that men with a BSA >2 m^2 (odds ratio [OR] = 2.712, $P = .04$) were at increased risk for myelotoxicity; alternatively in women, somewhat inexplicably, there was an increased risk for myelotoxicity with a BSA of <2 m^2 (OR = 4.178, $P = .04$).[6] These investigators also reported an increased female gender-related risk for myelotoxicity.[6]

We performed a secondary analysis to assess whether there is a relationship between TMZ-associated myelotoxicity (ie, grades 3 and 4) and BMI, as well as BSA, in Radiation Therapy Oncology Group (RTOG) 0525 (n = 833), a randomized trial testing 2 different TMZ regimens in patients with GBM.[7] This trial tested whether dose-intensified TMZ vs standard chemo-radiotherapy (chemo-RT) improves overall survival or progression-free survival in newly diagnosed GBM. The protocol-specified dosing of TMZ was 75 mg/m^2/day × 42 days, in both arms during the initial 6 weeks of RT. Four weeks after completion of RT, patients were randomized to Arm 1: standard TMZ (150–200 mg/m^2/day × 5 days, every 4 weeks) or Arm 2: TMZ (75–100 mg/m^2/day × 21 days) every 4 weeks for 6–12 cycles. All patients were treated on the basis of actual BSA, and not adjusted BSA. Dosing based on ideal BSA (or based on physician preference) would have constituted a protocol violation. Thus, the data set from this study provided the opportunity to test the hypothesis that obesity (ie, BMI ≥30) might negatively affect (increase) the incidence of grade 3/4 myelosuppression. Patients were grouped into 3 separate cohorts for this analysis: combined therapy (RT/TMZ; since the RT and TMZ doses were the same for both study arms); the 21-day adjuvant schedule; and the standard 5-day adjuvant schedule. The report to follow summarizes the results of this analysis.

Methods

Description of the Patient Population of RTOG 0525

In RTOG 0525, newly diagnosed GBM patients initiated concomitant TMZ with chemo-RT.[7] Patients were randomized at the end of chemo-RT to 2 treatment arms with different schedules of adjuvant TMZ. Not all patients eligible for randomization were randomized, as they had not completed chemo-RT as planned. For this analysis, patients with height and weight at the end of the chemo-RT phase (the earliest time point at which height and weight were collected in RTOG 0525) and with any grade 3, 4, or 5 myelosuppression were included.

Outcome Measures

The following myelosuppression toxicities were evaluated: leukopenia, neutropenia, CD4 lymphocytopenia, and thrombocytopenia. Common Terminology Criteria for Adverse Events version 3.0 was used to define grades of hematologic toxicities. BSA was calculated using Mosteller's formula (BSA [m^2] = [height (cm) × weight (kg)/3600]^{½}), and BMI was calculated using the following formula: BMI = weight (in kg)/[height (in m)]^2. Obesity was defined as a BMI ≥30.

Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

Statistical Analysis

The frequencies and percentages of myelosuppression toxicities were summarized by type, study arm, BMI categories (≥30 [defined as obese] vs < 30 [defined as nonobese]), and BSA categories (≥2.0 m^2 vs <2.0 m^2). The incidence of myelosuppression toxicities between BMI and BSA categories were compared using the Fisher exact test. Exact logistic regression analyses were conducted to evaluate the interaction effect between BMI categories and dosing schedule as well as the interaction effect between BSA categories and gender. All reported P values are 2 sided and $P < .05$ was used to define statistical significance. These analyses were post hoc and were not adjusted for multiple comparisons to minimize the type II errors. All analyses were conducted using SAS software (SAS Institute Inc, Cary, NC) version 9.4.

Table 1 Frequencies (%) and Comparisons of Grade 3/4 Toxicity Rates Between Patients With BMI <30 vs BMI ≥30

	Arm	BMI <30	BMI ≥30	OR	*P*-Value
	Standard Dose (N = 392)	N = 295	N = 97		
Leukopenia		15 (5%)	1 (1%)	5.1	.134
CD4 Lymphocytes		5 (2%)	0 (0%)	NA	.339
Neutrophil counts		17 (6%)	1 (1%)	5.9	.054
Platelet counts		20 (7%)	1 (1%)	7.0	.034
Any grade 3/4		34 (12%)	1 (1%)	12.5	<.001
	Dose Dense (N = 401)	N = 290	N = 111		
Leukopenia		19 (7%)	4 (4%)	1.9	.340
CD4 Lymphocytes		14 (5%)	9 (8%)	0.6	.231
Neutrophil counts		14 (5%)	4 (4%)	1.4	.789
Platelet counts		5 (2%)	2 (2%)	1.0	.999
Any grade 3/4		34 (12%)	15 (14%)	0.9	.613
	Combined (N = 793)	N = 585	N = 208		
Leukopenia		34 (6%)	5 (2%)	2.5	.061
CD4 Lymphocytes		19 (3%)	9 (4%)	0.7	.512
Neutrophil counts		31 (5%)	5 (2%)	2.3	.119
Platelet counts		25 (4%)	3 (1%)	3.1	.078
Any grade 3/4		68 (12%)	16 (8%)	1.6	.148

Abbreviations: NA, not available; OR, odds ratio.

Results

Of the 833 patients randomized in the trial, 793 with nonmissing height and weight measurements were evaluable for toxicities and are included in this analysis. The median age was 57 years with a range of 21-84. Fifty-seven percent were male, and 208 (26%) had a BMI ≥30. The comparison of grade 3/4 myelotoxicities between obese and nonobese patients is shown in Table 1. There was a strong interaction between dose arm and BMI ($P = .012$) on the incidence of grade 3/4 myelotoxicities. For the standard dose arm, the incidence rate of grade 3/4 myelotoxicities in patients with a BMI <30 was significantly higher than in patients with a BMI ≥30 (12% vs 1%, OR 12.5, $P < .001$). There was no significant difference in rates of myelotoxicities by BMI dichotomization (≥30 vs <30) in the dose-dense arm (OR = 0.9, 95% confidence interval [CI]: 0.4-1.6). Table 2 shows the comparisons of grade 3/4 myelotoxicities between patients with a BSA ≥2.0 m^2 and patients with a BSA <2.0 m^2. There were no significant differences detected between the 2 groups, regardless of dosing schedule. We further evaluated the impact of gender on the incidence of grade 3/4 myelotoxicities by dichotomizing the patients into 2 further groups, BSA ≥2.0 m^2 or <2.0 m^2 (Table 3) and BMI ≥30 vs BMI <30 (Table 4). The interaction effect between BSA groups and gender on the incidence of grade 3/4 myelotoxicities was not statistically significant ($P = .1495$). Furthermore, no significant interaction effect between BMI groups (BMI ≥30 vs BMI <30) and gender on the incidence of grade 3/4 myelotoxicities was observed ($P = .1448$). However, a significant difference in grade 3/4 hematological toxicity incidence rates was observed by gender, ie, women vs men (14% vs 8%, $P = .009$).

Discussion

The focus of this retrospective analysis was to address the potential issues of obesity (and/or underweight)-associated increased myelotoxicity, especially regarding TMZ dosing in the treatment of GBM. The literature regarding other chemotherapeutic agents and obesity based on BSA at times is cautionary[1] as well as contradictory. For example, observations such as a decrease in doxorubicin clearance between a normal and an obese group sensitizes practitioners to pharmacokinetic differences that can potentially result in increased morbidity for this patient population.[8] Further, as reviewed by Mathijssen and colleagues, pharmacokinetic studies relating to obesity at times can be inconsistent, possibly as a result of small patient numbers.[2] Interestingly, Jenkins et al (in analyzing their own data collectively) concluded that "Obesity is not associated with increased myelosuppression in patients receiving chemotherapy for breast cancer," but also reported that neutropenic fever was "more common in overweight patients (31/282 (11%) vs 14/254 (6%), $P = .02$)."[9] Understandably, such concerns and considerations often results in "dose capping," conceivably affecting efficacy.[1] It was with the aforementioned considerations that we elected to address the potential issue

Table 2 Frequencies (%) and Comparisons of Grade 3/4 Toxicity Rates Between Patients With BSA<2.0 m^2 vs Patients With BSA ≥2.0 m^2

	Arm	BSA<2.0 m2	BSA ≥2.0 m2	OR	*P*-Value
	Standard Dose (N = 392)	N = 220	N = 172		
Leukopenia		10 (5%)	6 (3%)	1.3	.798
CD4 Lymphocytes		5 (2%)	0 (0%)	NA	.070
Neutrophil counts		11 (5%)	7 (4%)	1.2	.809
Platelet counts		13 (6%)	8 (5%)	1.3	.656
Any grade 3/4		23 (10%)	12 (7%)	1.6	.285
	Dose Dense (N = 401)	N2 = 214	N = 187		
Leukopenia		16 (7%)	7 (4%)	2.1	.133
CD4 Lymphocytes		9 (4%)	14 (7%)	0.5	.108
Neutrophil counts		12 (6%)	6 (3%)	1.8	.335
Platelet counts		5 (2%)	2 (1%)	2.2	.457
Any grade 3/4		25 (12%)	24 (13%)	0.9	.761
	Combined (N = 793)	N = 434	N = 359		
Leukopenia		26 (6%)	13 (4%)	1.7	.139
CD4 Lymphocytes		14 (3%)	14 (4%)	0.8	.799
Neutrophil counts		23 (5%)	13 (4%)	1.5	.305
Platelet counts		18 (4%)	10 (3%)	1.5	.339
Any grade 3/4		48 (11%)	36 (10%)	1.1	.728

Abbreviations: NA, not available; OR, odds ratio.

Table 3 Frequencies (%) and Comparisons of Grade 3/4 Toxicity Rates Between Patients With BSA<2.0 m^2 vs Patients With BSA ≥2.0 m^2 for Both Arms Combined, Data Shown by Gender

	Gender	BSA<2.0 m2	BSA ≥2.0 m2	OR	*P*-Value
		N = 434	N = 359		
	Male (N = 451)	N = 166	N = 285		
Leukopenia		1 (1%)	10 (4%)	0.2	.062
CD4 Lymphocytes		6 (4%)	10 (4%)	1.0	.999
Neutrophil counts		1 (1%)	11 (4%)	0.2	.064
Platelet counts		2 (1%)	9 (3%)	0.4	.342
Any grade 3/4		9 (5%)	27 (9%)	0.5	.151
	Female (N = 342)	N = 268	N = 74		
Leukopenia		25 (9%)	3 (4%)	2.4	.228
CD4 Lymphocytes		8 (3%)	4 (5%)	0.5	.299
Neutrophil counts		22 (8%)	2 (3%)	3.2	.125
Platelet counts		16 (6%)	1 (1%)	4.6	.135
Any grade 3/4		39 (15%)	9 (12%)	1.2	.707

Abbreviation: OR, odds ratio.

of obesity (and/or underweight)-associated increased TMZ myelotoxicity.

The results of our retrospective analysis demonstrated no relationship between BSA and myelotoxicity. Regarding BMI, however, there was an unexpected finding: The incidence rate of grade 3/4 myelotoxicities in patients with a BMI <30 was significantly higher than in patients with a BMI ≥30 (12% vs 1%, OR 12.5, $P < .001$). These results may reflect a low incidence of toxicity with a BMI >30. This difference is not present when a BSA of >2 m^2 is used, in which

Table 4 Frequencies (%) and Comparisons of Grade 3/4 Toxicity Rates Between Patients With BMI <30 vs BMI ≥30 for Both Arms Combined, Data Shown by Gender

	Gender	BMI <30	BMI ≥30	OR	*P*-Value
		N = 585	N = 208		
	Male (N = 451)	N = 336	N = 115		
Leukopenia		8 (2%)	3 (3%)	0.9	.999
CD4 Lymphocytes		12 (4%)	4 (3%)	1.0	.999
Neutrophil counts		8 (2%)	4 (3%)	0.7	.512
Platelet counts		8 (2%)	3 (3%)	0.9	.999
Any grade 3/4		27 (8%)	9 (8%)	1.1	.999
	Female (N = 342)	N = 249	N = 93		
Leukopenia		26 (10%)	2 (2%)	5.0	.013
CD4 Lymphocytes		7 (3%)	5 (5%)	0.5	.320
Neutrophil counts		23 (9%)	1 (1%)	10.0	.007
Platelet counts		17 (7%)	0 (0%)	NA	.009
Any grade 3/4		41 (16%)	7 (8%)	2.4	.036

Abbreviations: NA, not available; OR, odds ratio.

case the grade 3/4 toxicities are fairly well balanced between <2 and >2 m^2 (Table 2) in the standard dose arm (10% vs 7%), as well as in the dose-dense arm (12% vs 13%).

These results may in part reflect our use of a "cut off" of 2 for BSA, the relatively small number of grade 3/4 cases in the series, and/or the potential presence of confounding factors. Alternatively, one could speculate that the volume of distribution may have increased because of body fat (ie, BMI >30) resulting in a decrease both in initial drug concentration and maximum peak concentration. This result perhaps adds further comfort to the concept of dosing on the basis of actual BSA for physicians who are wary of dosing obese patients.

Armstrong and colleagues in a retrospective study (total n = 680) reported a marked gender-specific grade 3/4 myelotoxicity: Women were more likely to experience grade 3 or 4 myelotoxicity than were men (women, 43 of 265, 16%; men, 30 of 415, 7%; $P = .015$).[6] We confirmed their observation (14% woman vs 8% men, $P = .009$). Such data are consistent with the preexisting literature regarding gender-specific pharmacologically increased toxicity as reviewed by Anderson.[10] These authors also noted in men increased toxicity in association with a BSA >2 and in women <2: In our study (n = 793), although our data demonstrated a similar trend, it did not reach statistical significance.

As highlighted by Armstrong and colleagues,[6] variables such as age, gender, treatment, and clinical score are always potential factors in any assessment of predisposition to myelotoxicity. We agree with their assertion for the need to develop clinical models to predict risk, as well as the identification and evaluation of genetic polymorphisms related to myelotoxicity. Such efforts may allow for individualized dosing, optimizing patient management.

In summary, our results taken collectively recommend patient dosing on the basis of actual BSA with the caveat that women are likely at higher risk for hematological toxicity.

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