Cancer Chemotherapy Update

Bevacizumab and Temozolomide Plus Radiation Regimen for Glioblastoma Multiforme

Matthew R. Rutledge, BSc, BCOP*; J. Aubrey Waddell, PharmD, FAPhA, BCOP;
and Dominic A. Solimando, Jr, MA, FAPhA, FASHP, BCOP

The complexity of cancer chemotherapy requires pharmacists be familiar with the complicated regimens and highly toxic agents used. This column reviews various issues related to preparation, dispensing, and administration of antineoplastic therapy, and the agents, both commercially available and investigational, used to treat malignant diseases. Questions or suggestions for topics should be addressed to Dominic A. Solimando, Jr, President, Oncology Pharmacy Services, Inc., 4201 Wilson Blvd #110-545, Arlington, VA 22203, e-mail: OncRxSvc@comcast.net; or J. Aubrey Waddell, Professor, University of Tennessee College of Pharmacy; Oncology Pharmacist, Pharmacy Department, Blount Memorial Hospital, 907 E. Lamar Alexander Parkway, Maryville, TN 37804, e-mail: waddfour@charter.net.

Regimen name: Bevacizumab and temozolomide plus radiation

Origin of name: The regimen is named for the 3 components comprising the regimen; bevacizumab, temozolomide, and radiation.

COMMENTS

In this regimen, bevacizumab and temozolomide are administered concurrently with radiotherapy in the initial treatment phase (Table 1) followed by bevacizumab and temozolomide alone in the adjuvant or maintenance phase (Table 2) where the dose of temozolomide increases dramatically and changes from daily dosing to a 5-day pulse.

INDICATION(S)

Concomitant temozolomide and radiation followed by maintenance temozolomide is recommended for adjuvant treatment of newly diagnosed glioblastoma multiforme (GBM).¹ Bevacizumab is recommended in recurrent disease, as monotherapy or in combination with temozolomide.¹ The studies reviewed utilized

bevacizumab and temozolomide plus radiation as initial therapy in patients with newly diagnosed GBM.²⁻⁷

DRUG PREPARATION

Follow institutional policies for preparation of hazardous medications when preparing bevacizumab and dispensing temozolomide.

A. Bevacizumab

1. Use bevacizumab, 25 mg/mL injection.
2. Dilute dose in 100 mL 0.9% sodium chloride injection.

B. Temozolomide

1. Temozolomide is available as 5 mg, 20 mg, 100 mg, 140 mg, 180 mg, and 250 mg capsules.
2. Temozolomide capsules should be taken orally (PO).
3. The prescribed dose may necessitate a combination of capsule strengths. The temozolomide dose should be rounded to the nearest 5 mg.
4. The manufacturer recommends the capsules not be opened.⁸ An extemporaneous oral suspension, with limited stability, may be compounded for patients who are unable to swallow the capsules.⁹

*Chief, Hematology-Oncology Pharmacy Service, Department of Pharmacy, Madigan Army Medical Center, Tacoma, Washington. The opinions or assertions contained herein are the private views of the authors and are not to be construed as official or reflecting the views of the US Department of the Army or the Department of Defense.

Table 1. Bevacizumab, temozolomide, and radiation regimen^{2,3,7}

Concomitant phase				
Drug	Dose	Route of administration	Administered on day(s)	Total dose/cycle
Bevacizumab	10 mg/kg	IV	1, 15	20 mg/kg
Temozolomide	75 mg/m ²	PO	Daily	Maximum of 49 doses or 3,675 mg/m ²
Radiation	2 Gy/day		1, 2, 3, 4, 5 days a week for 6 weeks	60 Gy

Cycle repeats: Given as a single 6-week course of therapy.

Variations

1. Radiation therapy at 1.8 Gy per fraction to a total dose of 59.4 Gy.⁴
2. Temozolomide 75 mg/m² PO daily for 42 days.⁴
3. Radiation therapy: Total dose of 60 Gy in 6-Gy fractions. One fraction per day, 5 days a week.⁵
4. Radiation therapy: Six treatments at 6-Gy per treatment over 2 weeks and temozolomide 75 mg/m² PO daily for 2 weeks.⁶

Note: Gy = gray; IV = intravenous; PO = oral.

Table 2. Maintenance regimen^{2,3,5,7}

Drug	Dose	Route of administration	Administered on day(s)	Total dose/cycle
Bevacizumab	10 mg/kg	IV	1, 15	20 mg/kg
Temozolomide	150 to 200 mg/m ²	PO	Days 1 thru 5	750 mg/m ² to 1,000 mg/m ²

Cycle repeats: Every 28 days for 6 cycles

Variations

1. Used 150 mg/m² daily x 5 days for cycle 1; then escalated to 200 mg/m² daily for subsequent cycles.^{2,3}
2. Option to extend treatment to total of 12 cycles.²
3. Temozolomide 150 mg/m² PO days 1 thru 7, every 28 days for 6 cycles. Bevacizumab administered on days 8 and 22 of each cycle.⁴
4. Option to extend treatment beyond original 6 cycles left to physician discretion.⁶
5. Started maintenance phase 2 weeks after completion of adjuvant/concomitant phase for maximum of 24 cycles.⁶

Note: IV = intravenous; PO = oral.

DRUG ADMINISTRATION**A. Bevacizumab**

1. Should not be administered within 28 days of major surgery, or until the surgical wound is fully healed.
2. Infuse the first dose over 90 minutes.
3. If the first dose is tolerated well, infuse the second dose over 60 minutes.
4. If the second dose is tolerated well, all subsequent doses may be infused over 30 minutes.

B. Temozolomide

1. Temozolomide is administered PO once a day.

2. Temozolomide should be taken on an empty stomach, with a glass of water to minimize the incidence of nausea. Food may increase the incidence of gastric irritation and can influence drug absorption unpredictably.⁸
3. The dose administered should be a multiple of 5 mg.
4. The administered dose usually consists of several capsules, often including multiple strengths (eg, 125 mg = one 100 mg capsule plus one 20 mg capsule plus one 5 mg capsule).
5. Care should be taken to ensure the patient understands that the daily dose potentially

consists of multiple capsule strengths. It may be more pragmatic to dispense each day's combination of capsules in separate containers to limit the potential for patients to erroneously combine capsules in the wrong dose.

SUPPORTIVE CARE

A. Acute and Delayed Emesis Prophylaxis: The risk of emesis for this regimen differs between the concomitant phase and the maintenance phase. The emetogenic risk for each phase will be discussed separately.

The risk of emesis in the concomitant phase is predicted to be less than 10%.¹⁰ For most patients, prophylactic antiemetic therapy is not required.¹¹⁻¹³ The studies reviewed reported grade 3 or greater nausea or vomiting in only 2% to 5% of patients.^{2,4,5} The risk of radiation-induced nausea and vomiting with this regimen is considered low and may warrant prophylaxis or rescue.^{11,12} If a patient develops nausea or vomiting requiring antiemetic therapy, prophylactic therapy is recommended for the balance of radiation treatments.¹¹ One of the following regimens is recommended:

1. Ondansetron 8 mg to 16 mg given PO 30 minutes before radiation.
2. Granisetron 1 mg to 2 mg given PO 30 minutes before radiation.
3. Dolasetron 100 mg given PO 30 minutes before radiation.

Patients who experience significant nausea or vomiting with one of these regimens should receive an agent from a different pharmacologic category.^{10,11,13} A few small studies suggest substituting granisetron for ondansetron in subsequent treatment cycles; however none of these reports found the improvement to be statistically significant.¹⁴⁻¹⁸ Dexamethasone, 4 mg to 24 mg per day, is commonly used for patients with disease-related cerebral edema.¹⁹⁻²¹ While these doses may also provide antiemetic benefit, additional dexamethasone is likely unnecessary.

The maintenance phase of this regimen utilizes a higher dose of temozolomide and is predicted to cause nausea in 30% to 90% of patients.^{10,12}

In one of the studies reviewed, where use of a 5-hydroxytryptamine receptor antagonist was strongly recommended, grade 3 nausea or vomiting was reported in the maintenance

phase in 5% of patients.² Other studies reviewed failed either to report any nausea or vomiting or to distinguish between the concomitant and maintenance phases.³⁻⁷ Prophylactic antiemetic therapy with a serotonin antagonist is recommended prior to each temozolomide dose during the maintenance phase.^{10,12,13} One of the following regimens may be given 30 minutes prior to therapy:

1. Ondansetron 16 mg to 24 mg PO given once daily before temozolomide.
2. Granisetron 1 mg to 2 mg PO given once daily before temozolomide.
3. Dolasetron 100 mg PO given once daily before temozolomide.

B. Breakthrough Nausea and Vomiting^{10,11,13}: Patients should receive a prescription for an antiemetic to treat breakthrough nausea. One of the following regimens is suggested:

1. Metoclopramide 10 mg to 40 mg PO every 4 to 6 hours if needed, ± diphenhydramine 25 to 50 mg PO every 6 hours if needed.
2. Prochlorperazine 10 mg PO every 4 to 6 hours if needed, ± diphenhydramine 25 to 50 mg PO every 6 hours if needed.
3. Prochlorperazine 25 mg rectally every 12 hours if needed, ± diphenhydramine 25 to 50 mg PO every 4 to 6 hours if needed.
4. Promethazine 25 to 50 mg PO every 4 to 6 hours if needed, ± diphenhydramine 25 to 50 mg PO every 4 to 6 hours if needed.

A few small studies suggest that higher doses of granisetron (3 mg IV or 40 mcg/kg to 240 mcg/kg)¹⁴⁻¹⁸ may be effective in treating breakthrough nausea; however none of these reports found the improvement to be statistically significant.

C. Hematopoietic Growth Factors: Accepted practice guidelines and pharmacoeconomic analysis suggest that an antineoplastic regimen have a greater than 20% incidence of febrile neutropenia before prophylactic use of colony stimulating factors (CSFs) is warranted. For regimens with an incidence of febrile neutropenia between 10% and 20%, use of CSFs should be considered. For regimens with an incidence of febrile neutropenia less than 10%, routine prophylactic use of CSFs is not recommended.^{22,23} None of the trials reviewed reported febrile neutropenia.^{2-5,7} Severe (grade 3 or 4) neutropenia was reported in 7% to 33% of patients in the bevacizumab

and temozolomide trials reviewed.^{2,5} While likely in the maintenance period, no distinction was made as to what phase of treatment the patient experienced the neutropenia. Prophylactic use of CSFs is not recommended.^{2-5,7} CSFs may be considered if a patient experiences febrile or grade 4 neutropenia in a prior cycle of bevacizumab and temozolomide.

- D. Pulmonary:** Prophylaxis against *Pneumocystis jirovecii* or *Pneumocystis carinii* (PCP) is advised for all patients receiving concomitant temozolomide and radiotherapy and should be continued until recovery from lymphocytopenia.²⁴ In the studies reviewed, Gilbert et al² utilized pneumocystis prophylaxis in patients with CD4 counts less than 200 per cubic millimeter; Ney et al⁵ did not require prophylaxis, but instead left it to the discretion of the treating physician; and Omuro et al⁶ recommended prophylaxis for all patients.

MAJOR TOXICITIES

Most of the toxicities listed below are presented according to their degree of severity. Higher grades represent more severe toxicities. Although there are several grading systems for cancer chemotherapy toxicities, all are similar. One of the frequently used systems is the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf). Oncologists generally do not adjust doses or change therapy for grade 1 or 2 toxicities, but make, or consider making, dosage reductions or therapy changes for grade 3 or 4 toxicities. Incidence values are rounded to the nearest whole percent unless incidence was less than or equal to 0.5%.

- A. Cardiovascular:** Hemorrhage (grade 3) 1%²; cerebral hemorrhage (grade 3) 1%,⁷ (grade 4) 1%⁷; mucocutaneous bleeding (grade 3 or 4) 1%³; congestive heart failure (grade 3 or 4) 0.44%³; stroke (grade 3 or 4) 3%⁵; cerebrovascular ischemia (grade 4) 9%⁷; epistaxis (grade 3) 1%⁷; hypertension (grade 3) 6% to 11%,^{2,7} (grade 3 or 4) 11%³; thromboembolic events (grade 3) 4% to 10%,^{2,4,7} (grade 4) 2% to 9%,^{2,4,7} (grade 3 or 4) 3% to 8%.^{3,5}
- B. Gastrointestinal:** Nausea and vomiting (grade 3) 2% to 5%,^{2,4} (grade 3 or 4) 3%⁵; diarrhea (grade 3) 1%⁷; perforation (grade 3) 1%,^{2,7} (grade 4)

0.4% to 1%^{2,7}; abscess and fistula 0.44%³; gastrointestinal bleed (grade 3) 3%.⁷

- C. Hematologic:** Anemia (grade 3) 2%,² (grade 4) 1%²; leukopenia (grade 3) 11%,² (grade 4) 3%²; lymphopenia (grade 3) 18%,² (grade 4) 5%²; neutropenia (grade 3) 10% to 33%,^{2,5} (grade 4) 7% to 10%^{2,5}; thrombocytopenia (grade 3) 6% to 10%,^{2,4} (grade 4) 4% to 17%,^{2,4,5} (grade 3 or 4) 15%.³
- D. Hepatic:** Alanine aminotransferase (ALT) elevations (grade 3) 3%,⁷ (grade 4) 1%⁷; aspartate aminotransferase (AST) elevations (grade 3) 3%.⁷
- E. Neurologic:** Fatigue/asthenia (grade 3) 2% to 20%,^{2,4,7} (grade 4) 1%,² (grade 3 or 4) 7% to 13%^{3,5}; dizziness, light-headedness, syncope (grade 3) 7%⁷; seizure (grade 3) 9%.⁷
- F. Renal:** Elevated serum creatinine (grade 3) 1%⁷; proteinuria (grade 3) 9%,⁷ (grade 3 or 4) 5%,³ (grade 4) 3%⁷; hyponatremia (grade 3) 10%,⁷ (grade 4) 1%.⁷
- G. Other:** Wound dehiscence or wound healing complications (grade 3) 2%,² (grade 4) 0.4%,² (grade 3 or 4) 3% to 7%^{3,5}; infection (grade 3) 13%⁷; hyperglycemia (grade 3) 10%⁷; hypoglycemia (grade 3) 1%,⁷ (grade 4) 1%⁷; unspecified ocular problem (grade 3) 1%,⁷ (grade 4) 1%.⁷
- H. Treatment-Related Deaths:** Thromboembolic disease 0.4%,^{2,3} hemorrhage 0.2% to 0.4%,^{2,3} cranial wound dehiscence/infection 2% to 7%,^{3,5} sepsis 3%,⁵ sudden death from presumed seizure 3%,⁵ respiratory or lung disorders 0.2%,³ cardiac disorders 1%,³ general health deterioration 0.4%,³ gastrointestinal perforation 0.2%,³ brain edema 0.2%,³ hepatotoxicity 0.2%,³ unspecified 3%.⁶

PRETREATMENT LABORATORY AND PHYSICAL ASSESSMENTS NEEDED

- A. Baseline**
1. AST/ALT
 2. Total bilirubin
 3. Serum creatinine
 4. Complete blood count (CBC) with differential
 5. Blood pressure
 6. Urine dipstick analysis
- B. Prior to each treatment**
1. CBC with differential
 2. Blood pressure
 3. Urine dipstick analysis

C. Recommended Pretreatment Values: In the trials reviewed, the following minimally acceptable pretreatment lab values were required to begin treatment or a new cycle with full-dose therapy.

1. Absolute neutrophil count, greater than or equal to 1,500 cells/mcL.⁵
2. Platelet count, greater than or equal to 100,000 cells/mcL.⁵
3. Hemoglobin, greater than or equal to 9 g/dL.⁵
4. Serum creatinine, less than or equal to 1.5 mg/dL.⁵
5. AST, less than or equal to 1.5 times the upper limit of normal (ULN).⁵
6. Serum bilirubin, less than or equal to 1.5 times ULN.⁵
7. Proteinuria, defined as urine protein creatinine ratio less than or equal to 1.⁵

In clinical practice, a pretreatment absolute neutrophil count (ANC) of 1,000 cells/mcL and platelets of 75,000 cells/mcL are usually considered acceptable.

The studies reviewed also required a minimum of 4 weeks after surgical debulking before starting bevacizumab.²⁻⁶

None of the studies reviewed provided specific parameters for pretreatment blood pressure, however the manufacturer of bevacizumab recommends blood pressure be monitored every 2 to 3 weeks during treatment.²⁵

DOSAGE MODIFICATIONS

No dose modifications for temozolomide or bevacizumab were made in the trials reviewed for renal or hepatic dysfunction.²⁻⁷ While not affecting GFR, bevacizumab may induce nephrotic proteinuria and severe hypertension.²⁶ According to the manufacturer, if the patient develops hypertension, it should be treated with appropriate antihypertensive therapy; further administration of bevacizumab should be temporarily suspended if hypertension cannot be medically controlled; bevacizumab should be discontinued in those patients with hypertensive crisis or hypertensive encephalopathy; and blood pressure should be monitored at regular intervals in patients with bevacizumab-induced or -exacerbated hypertension after discontinuation of bevacizumab.²⁵ In patients with greater than grade 2 proteinuria without nephrotic syndrome, additional bevacizumab doses should be held until resolution.²⁶ The manufacturer recommends urine dipstick analysis to identify proteinuria.²⁵ Patients demonstrating a 2-plus or greater

dipstick reading should undergo further assessment with a 24-hour urine collection. Bevacizumab should be held in patients demonstrating 2 g or greater proteinuria in a 24-hour period until proteinuria is less than 2 g in a 24-hour collection.²⁵

Ney et al⁵ utilized a 25% temozolomide dose reduction for unspecified grade 3 or 4 hematological toxicities, whereas Lai et al⁷ modified the temozolomide dose per the manufacturer's package insert for unspecified hematological toxicities. Narayana considered grade 4 toxicities or any evidence of a temozolomide rash a contraindication to further therapy.⁴

REFERENCES

1. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines – Central Nervous System Cancers. V.1.2015. National Comprehensive Cancer Network Web site. http://www.nccn.org/professionals/physician_gls/pdf/cns.pdf. Accessed May 29, 2015.
2. Gilbert MR, Dignam JJ, Armstrong TS, et al. A randomized trial of bevacizumab for newly diagnosed glioblastoma. *New Engl J Med*. 2014;370(8):699-708.
3. Chinot OL, Wick W, Mason W, et al. Bevacizumab plus radiotherapy-temozolomide for newly diagnosed glioblastoma. *New Engl J Med*. 2014;370(8):709-722.
4. Narayana A, Gruber D, Kunnakkat S, et al. A clinical trial of bevacizumab, temozolomide, and radiation for newly diagnosed glioblastoma. *J Neurosurg*. 2012;116(2):341-345.
5. Ney DE, Carlson JA, Damek DM, et al. Phase II trial of hypofractionated intensity-modulated radiation therapy combined with temozolomide and bevacizumab for patients with newly diagnosed glioblastoma. *J Neurooncol*. 2015;122(1):133-143.
6. Omuro A, Beal K, Gutin P, et al. Phase II study of bevacizumab, temozolomide, and hypofractionated stereotactic radiotherapy for newly diagnosed glioblastoma. *Clin Cancer Res*. 2014; 20(19):5023-5031.
7. Lai A, Tran A, Nghiemphu PL, et al. Phase II study of bevacizumab plus temozolomide during and after radiation therapy for patients with newly diagnosed glioblastoma multiforme. *J Clin Oncol*. 2011;29(2):142-148.
8. *Temodar* [product information]. Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc. Whitehouse Station, NJ 08889. http://www.merck.com/product/usa/pi_circulars/t/temodar_capsules/temodar_pi.pdf. Accessed April 22, 2015.
9. Trissel L, Zhang Y, Koontz S. Temozolomide stability in extemporaneously compounded oral suspensions. *Int J Pharm Compd*. 2006;10(5):396-399.
10. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines - Antiemesis. V.1.2015. National Comprehensive Cancer Network Web site. http://www.nccn.org/professionals/physician_gls/pdf/antiemesis.pdf. Accessed April 6, 2015.

11. Basch E, Prestrud AA, Hesketh P, et al. Antiemetics: American Society of Clinical Oncology clinical practice guideline update. *J Clin Oncol*. 2011;29(31):4189-4198.
12. Roila F, Herrstedt J, Aapro M, et al. Guideline update for MASCC and ESMO in the prevention of chemotherapy- and radiotherapy-induced nausea and vomiting: Results of the Perugia consensus conference. *Ann Oncol*. 2010;21(suppl 5):v232-v243.
13. Multinational Association for Supportive Care in Cancer. Antiemetic Guidelines. 2013. http://www.mascc.org/assets/Guidelines-Tools/mascc_antiemetic_english_2014.pdf. Accessed April 7, 2015.
14. Terrey JP, Aapro MS. The activity of granisetron in patients who had previously failed ondansetron antiemetic therapy. *Eur J Clin Res*. 1996;8:281-288.
15. Carmichael J, Keizer HJ, Cupissol D, Milliez J, Scheidel P, Schindler AE. Use of granisetron in patients refractory to previous treatment with antiemetics. *Anticancer Drugs*. 1998;9(5):381-385.
16. de Wit R, de Boer AC, vd Linden GH, Stoter G, Sparreboom A, Verweij J. Effective cross-over to granisetron after failure to ondansetron, a randomized double blind study in patients failing ondansetron plus dexamethasone during the first 24 hours following highly emetogenic chemotherapy. *Br J Cancer*. 2001;19;85(8):1099-1101.
17. Smith IE. A dose-finding study of granisetron, a novel antiemetic, in patients receiving cytostatic chemotherapy. The Granisetron Study Group. *J Cancer Res Clin Oncol*. 1993;119(6):350-354.
18. Soukop M. A dose-finding study of granisetron, a novel antiemetic, in patients receiving high-dose cisplatin. Granisetron Study Group. *Support Care Cancer*. 1994;2(3):177-183.
19. Dietrich J, Rao K, Pastorino S, et al. Corticosteroids in brain cancer patients: Benefits and pitfalls. *Expert Rev Clin Pharmacol*. 2011;4(2):233-242.
20. Kostaras X, Cusano F, Kline G, et al. Use of dexamethasone in patients with high-grade glioma: A clinical practice guideline. *Curr Oncol* 2014;21(3):e493-503.
21. Roth P, Wick W, Weller M. Steroids in neurooncology: Actions, indications, side effects. *Curr Opin Neurol*. 2010;23(6):597-602.
22. Smith TJ, Khatcheressian J, Lyman GH, et al. 2006 Update of recommendations for the use of white blood cell growth factors: An evidence-based clinical practice guideline. *J Clin Oncol*. 2006;24(19):3187-3205.
23. NCCN Clinical Practice Guidelines in Oncology - Myeloid Growth Factors. V.2.2014. National Comprehensive Cancer Network Web site. http://www.nccn.org/professionals/physician_gls/pdf/myeloid_growth.pdf. Accessed April 16, 2015.
24. NCCN Clinical Practice Guidelines in Oncology – Prevention and Treatment of Cancer-Related Infections. V2.2015. National Comprehensive Cancer Network Web site. http://www.nccn.org/professionals/physician_gls/pdf/infections.pdf. Accessed June 10, 2015.
25. *Avastin* [product information]. Genentech, Inc., San Francisco, CA. http://www.gene.com/download/pdf/avastin_prescribing.pdf. Accessed April 21, 2015.
26. Shahab I, Patterson WP. Renal and electrolyte abnormalities due to chemotherapy. In: Perry, MC, ed. *The Chemotherapy Sourcebook* (4th ed). Philadelphia, PA: Lippincott Williams and Wilkins; 2008:223-233. ■