See page 231 for suggested questions to begin discussion in your journal club.

Management of Temozolomide Toxicity by Nurse Practitioners in Neuro-Oncology

Hanneke Zwinkels, RN, MA, ANP, Krista Roon, MD, Frank J.F. Jeurissen, MD, Martin J.B. Taphoorn, MD, Wim C.J. Hop, PhD, and Charles J. Vecht, MD

Purpose/Objectives: To investigate the toxicity of temozolomide (TMZ) in patients with brain tumors and appropriate nursing interventions.

Design: Explorative analysis of prospective data.

Setting: A TMZ clinic led by a nurse practitioner (NP).

Sample: Group A (n = 71) received a standard dose of TMZ daily for five days 200 mg/m² every four weeks; group B (n = 19) received a dose-intense schedule of TMZ daily for 21 days 75 mg/m² every four weeks.

Methods: Toxicities were scored according to National Cancer Institute Common Terminology Criteria, and results in the two groups were compared.

Main Research Variables: Thrombopenia, neutropenia, and lymphopenia; nausea and vomiting; and NP interventions.

Findings: Of observed toxicities during six cycles, grade 3–4 thrombopenia was seen most frequently in group A. Neutropenia and subsequent interventions occurred more frequently in group A than in group B. Subsequent interventions consisted of dose delays and reductions. When patients were treated for a longer duration of time with TMZ, grade 3–4 lymphopenia occurred significantly more often in group B, necessitating *Pneumocystis carinii* pneumonia prophylaxis.

Conclusions: Degree of toxicity using a 5-day 200 mg/m² or 21-day 75 mg/m² schedule every four weeks was similar to that found in other studies.

Implications for Nursing: Through awareness of toxicity in relation to knowledge of brain tumors, NPs can become more effective in active management of TMZ toxicity.

Patients with gliomas are confronted with a disease with a poor prognosis and hardly any chance of cure. Median survival of such patients depends on a number of independent prognostic factors, including age, neurologic condition, cognitive function, tumor type, and tumor size. Clinically, patients may suffer from headache, seizures, poor cognition, and focal symptoms such as aphasia, hemiparesis, or hemianopia. Standard treatment of high-grade gliomas has consisted of resection or biopsy of the tumor, followed by radiotherapy (Kristiansen et al., 1981), even for older adult patients (Keime-Guibert et al., 2007). Treatment of glioblastoma multiforme (GBM), the most frequently occurring primary malignant brain tumor, with temozolomide (TMZ) with concomitant radiotherapy in the adjuvant setting has improved outcomes (Stupp et al., 2005). Efficacy of TMZ also has been demonstrated for recurrent low- and high-grade gliomas (Chang et al., 2004; van den Bent et al., 2003). For GBM, the two-year survival rate after surgery and radiotherapy plus TMZ is 26%, and 10% following radiotherapy without TMZ (Stupp et al.). Despite an initially good tumor response to TMZ, tumor progression may occur during treatment and often after a period of stable disease following therapy. TMZ is a novel oral alkylating agent with remarkable efficacy in patients with gliomas and a favorable toxicity profile (Taphoorn et al., 2005). Treatment with TMZ employing different types of administration is increasing steadily based on its generally good tolerability and few side effects (Wick et al., 2007).

With increasing use of more intensive therapies, oncology nurses can play a key role in management. This implies patient education, symptom management, and monitoring of the side effects of chemotherapy (Bedell, 2003; Crighton, 2004; Hartigan, 2003; Hollywood & Semple, 2001; Houston, 1997). In the authors' outpatient clinic for patients with brain tumors, this has led to an active role for the nurse practitioner (NP) in neuro-oncology to monitor TMZ toxicity and to initiate therapeutic interventions to help patients cope with TMZ toxicity.

Background

In the Netherlands, the NP is a relatively new role. Reallocation of tasks and responsibilities between nurses and physicians at university hospitals was the conceptual basis of the development of training and education

of experienced nurses at a master's level. The new role has contributed to careful, effective, patient-focused, and accessible care (Dutch Health Care Inspectorate, 2007), although it is still evolving.

Currently, about 800 NPs are working in the Netherlands in settings that include university and large teaching hospitals, nursing homes, home care, and general practitioners' offices, with differentiations among acute, chronic, preventive, and intensive care. In the authors' outpatient clinic, the role of the NP has expanded over the years—based on training, education, and the development of experience—to the point where NPs are responsible for protocol-based treatment with TMZ, which includes prescription of chemotherapy, antiemetics, and other necessary comedication, with the neuro-oncologist acting as supervisor. In evaluating the toxicity of TMZ, the NP decides on dose delay and dose adjustments by protocol, performs neurologic examinations to evaluate patients' conditions, and discusses the findings with the physician. Research of toxicities is performed to see how the NP can optimize guidance and treatment of patients receiving TMZ using Dutch oncology nursing guidelines in cases of nausea and vomiting, high risk for infection with neutropenia or lymphopenia, and hemorrhagic events from thrombopenia (Oncology Guidelines, 2008).

In the current observational study, the researchers compared the occurrence of toxicities of standard schedules of TMZ with a dose-intensive schedule to see whether the observation of toxicities would lead to changes in nursing strategies in the management of patients with brain tumors. Preliminary observations on side effects suggest that a shorter, five-day regimen would mainly cause thrombopenia and that dose-intense schedules would primarily result in lymphopenia (Su et al., 2004). The aim of this study was to report the toxicity of TMZ occurring in two different schedules of administration in the setting of a nurse-led clinic. Additionally, the researchers investigated the type of NP interventions (i.e., dose delay, dose reduction, and prescription of antiemetics, growth factors, and *Pneumocystis carinii* pneumonia [PCP] prophylaxis) required to cope with the toxicities.

Methods

From October 2001 to April 2006, in a nurse-led TMZ clinic, two groups of patients with low- or high-grade gliomas treated with TMZ according to different protocols were evaluated. TMZ could be prescribed for a first or second recurrence after treatment with external beam radiotherapy and primarily after diagnosis instead of radiotherapy in patients with either low- or high-grade gliomas (if the tumor volume was considered too large to be irradiated in the opinion of the neuro-oncology board).

Group A (n = 71) consisted of patients with newly diagnosed or recurrent low- or high-grade gliomas receiving TMZ daily for 5 days 200 mg/m² every four weeks; group B (n = 19) consisted of patients with newly diagnosed or recurrent low- or high-grade gliomas receiving TMZ daily for 21 of every 28 days 75 mg/m². The choice for each of the schedules was made by the responsible neurologist/oncologist. The NP explained the schedules to patients, evaluated the occurrence of toxicities, and recorded data. At a visit to the outpatient clinic, the NP, often in combination with the consultant neurologist/oncologist, took the clinical history and performed the physical and neurologic examinations. In group A as many as 18 cycles and in group B as many as 12 cycles could be administered. Tumor response was evaluated every three cycles; possible re-excision of the tumor before the start of chemotherapy was considered in some cases, and corticosteroids could have been prescribed depending on neurologic functioning. However, those aspects are not the focus of this study and will not be discussed.

Toxicity recordings included nausea and vomiting and blood counts according to the National Cancer Institute Common Terminology Criteria for Adverse Events (version 3.0) (see Table 1). At each cycle, patients' blood counts were taken on day 21 and day 27 or 28. Nausea and vomiting were reported as follows: 0 = no nausea or vomiting; 1 = loss of appetite, somewhat nauseous; 2 = nausea without vomiting, 3 = vomiting. The NP used a standardized protocol for prescribing TMZ and for interventions in the occurrence of toxicity. The protocol was developed together with responsible physicians and could be adjusted according to new findings of toxicity.

In cases of hematologic toxicity, the interventions by the NP consisted of TMZ dose reductions or delays, growth factors, prophylactic antibiotics, or thrombocyte transfusions. If necessary, the medical oncologist played a key role in deciding on the most appropriate type of intervention.

All patients received oral antiemetics on a prophylactic basis (i.e., group A received ondansetron 8 mg daily or twice a day and group B received ondansetron 4 mg daily or twice a day every cycle during the first three days).

Statistical analysis was performed with SPSS® (i.e., Mann-Whitney U test or chi-square test) to evaluate differences between the two groups during six cycles. Six patients in group A still were receiving TMZ (more than six cycles) at the time of data analysis. Repeated-measure analysis of variance was used to compare mean blood counts during the cycles between groups A and B. The limit of significance was 0.05 (two-sided) in all analyses.

Results

Group A consisted of 71 patients (median age of 49 years) with a first or second recurrence after initial diagnosis of the tumor and treatment with external beam

Table 1. National Cancer Institute Common Terminology Criteria: Adverse Events for Blood and Bone Marrow Toxicity Grades I–IV

Variable	Grade I	Grade II	Grade III	Grade IV
Leukocytes	< 3 x 10^9/L	< 3–2 x 10^9/L	< 2–1 x 10^9/L	< 1 x 10^9/L
Neutrophils	< 1.5 x 10^9/L	< 1.5–1.0 x 10^9/L	< 1–0.5 x 10^9/L	< 0.5 x 10^9/L
Lymphocytes	< 0.8 x 10^9/L	< 0.8–0.5 x 10^9/L	< 0.5–0.2 x 10^9/L	< 0.2 x 10^9/L
Thrombocytes	< 75 x 10^9/L	< 75–50 x 10^9/L	< 50–25 x 10^9/L	< 25 x 10^9/L

Note. Based on information from National Cancer Institute, 2003.

radiotherapy or primarily after surgery (12 patients). They received a total of 440 cycles with a median of 5 cycles. Group B consisted of 19 patients with a median age of 47 years, mainly after first recurrence and treatment with external beam radiotherapy, and they received a total number of 152 cycles, with a median of 10 cycles. At initial diagnosis in group A, 26 patients were biopsied and 44 patients underwent resection. In group B, 5 patients underwent biopsy and 13 patients had surgical resection. In both groups, one patient did not have a histologically proven diagnosis.

The main reason for discontinuation of TMZ was tumor progression as determined by neurologic evaluation and magnetic reasonance imaging. Ten patients in group A and three in group B had to discontinue TMZ because of neurologic deterioration (progressive disease without neuroimaging or the occurrence of severe comorbidities such as pneumonia or thromboembolic events). Immunosuppression secondary to the use of corticosteroids may have contributed to opportunistic infections in case of lymphopenia. Eight patients in group A and six in group B discontinued TMZ treatment after either 6 or 12 cycles, based on the presence of a responding tumor (i.e., stable disease or partially responding tumor). Two patients in group B had to stop TMZ because of toxicity and six patients were still continuing TMZ therapy (more than 6 cycles) at the time of analysis (see Table 2).

Tolerability and Interventions

Of all toxicities, thrombopenia was seen most frequently in both groups, with potential delay of the next cycle or a dose reduction of TMZ. Grade 3–4 thrombopenia (see Table 3) occurred more frequently in group A (16 of 71 patients, 23%) compared to group B, where grade 3–4 thrombopenia did not occur at all (p = 0.005). Further evaluation showed that in group A grade 3–4 thrombopenia occurred significantly more often in women as compared to men (10 of 32 women [31%] versus 6 of men 39 [15%]; p = 0.034). In group A, three patients required hospitalization for thrombocyte transfusion.

Data concerning lymphocytes and neutrophil counts were based on 66 of 90 patients with evaluable laboratory results (because of unawareness of the toxicity, the results were not always assessed in the first years of TMZ therapy). Figure 1 shows mean values of laboratory results for thrombocytes, neutrophils, and lymphocytes for groups A and B at day 21 (i.e., day of expected nadir) and day 0 (i.e., day of recovered blood counts at the day before the start of the next cycle). A decrease in mean values of thrombocytes, neutrophils, and lymphocytes during cycles can be extrapolated. Repeated-measure analysis of variance of the mean profiles of thrombocyte counts showed that the changes between cycles measured at day 0 did not significantly differ between groups A and B. However, this was not the case for cycle outcomes at day 21 (p = 0.002): Initially, group B had a higher mean value at cycle 1, whereas the difference disappeared after subsequent cycles. Evaluation of neutrophil counts showed no difference in the profiles between groups A and B. This applied to day 0 and day 21 outcomes. For lymphocyte counts, the difference between groups A and B strongly

Table 2. Patient Characteristics

	Group A (N = 71)		Group B (N = 19)	
Characteristic	**$\bar{X}$**	**Range**	**$\bar{X}$**	**Range**
Age (years)	49	30–72	47	26–73
Characteristic	**n**	**%**	**n**	**%**
Gender				
Male	39	55	10	53
Female	32	45	9	47
Primary diagnosis				
Low-grade glioma	25	35	10	53
High-grade glioma	46	65	9	47
Mode of treatment				
First recurrence (after radiotherapy)	50	70	17	89
Primary after surgery	12	17	1	5
Second recurrence	9	13	1	5
End of temozolomide treatment				
Due to progression	47	66	8	42
With responding tumor	8	11	6	32
Because of toxicity	–	–	2	11
Because of neurologic deterioration or other comorbidities	10	14	3	16
Continuing patients	6	8	–	–
First six cycles with				
Dose delay	27	38	5	26
Dose reduction	21	30	1	5
Growth factor support	3	4	–	–

Note. Because of rounding, not all percentages total 100.

Table 3. Patients With Highest Grade of Thrombopenia During Six Cycles

	Group A (N = 71)		Group B (N = 19)	
Thrombopenia	n	%	n	%
No toxicity	27	38	13	68
Grade 1	20	28	5	26
Grade 2	8	11	1	5
Grade 3	10	14	–	–
Grade 4	6	9	–	–

Note. Thrombopenia in group A > group B, p = 0.005
Note. Because of rounding, not all percentages total 100.

increased with increasing cycle number (both $p < 0.001$ for day 0 and day 21). Grade 3–4 neutropenia (see Table 4) occurred in group A in 17% (9 of 66 patients) and in group B in 7% (1 of 14 patients), but the difference was not significant (p = 0.456). Three patients in group A needed growth factors following neutropenia.

Grade 3–4 lymphopenia (see Table 5) occurred significantly more often in group B (5 of 14 patients, 36%) compared to group A (2 of 52 patients, 4%) (p = 0.004). When patients were treated for a longer duration of time (more than six cycles) with TMZ, grade 4 lymphopenia occurred significantly more often in group B (3 of 14 patients, 21%) than in group A (no patients) (p = 0.001). In group B, two patients had to stop TMZ treatment after 10 cycles as a result of grade 4 lymphopenia. One patient in group B with grade 4 lymphopenia died of PCP. Dose delays because of thrombopenia and neutropenia during the first six cycles were seen more frequently in group A (27 of 71 patients; 38%) in 52 of 440 cycles. In contrast, 5 of 19 patients of group B (26%) had the same problem in 6 of 152 cycles (p = 0.03). As a result of thrombopenia, one patient in group A continued with a five-week cycle for all 18 cycles. Subsequent dose reductions following thrombopenia, mainly after the first cycle, or neutropenia at different moments during cycles occurred more frequently in group A as compared to B (21 of 71 [30%] compared with 1 of 19 [5%]; p = 0.03).

Nonhematologic Toxicities

No significant difference occurred in nausea and vomiting between groups A and B. The prescribed antiemetics were sufficient for most patients. Three of 71 patients in group A needed additional medication (dexamethasone 1–2 mg daily, lorazepam 2 mg twice a day, or both). One patient in group A had to be hospitalized during administration of TMZ because of anticipatory nausea and vomiting; a protocol (containing high-dose dexamethasone, lorazepam, and ondansetron) was developed. Because of the low-emetic profile of TMZ, the protocol for anticipatory nausea and vomiting had to be used only once.

Discussion

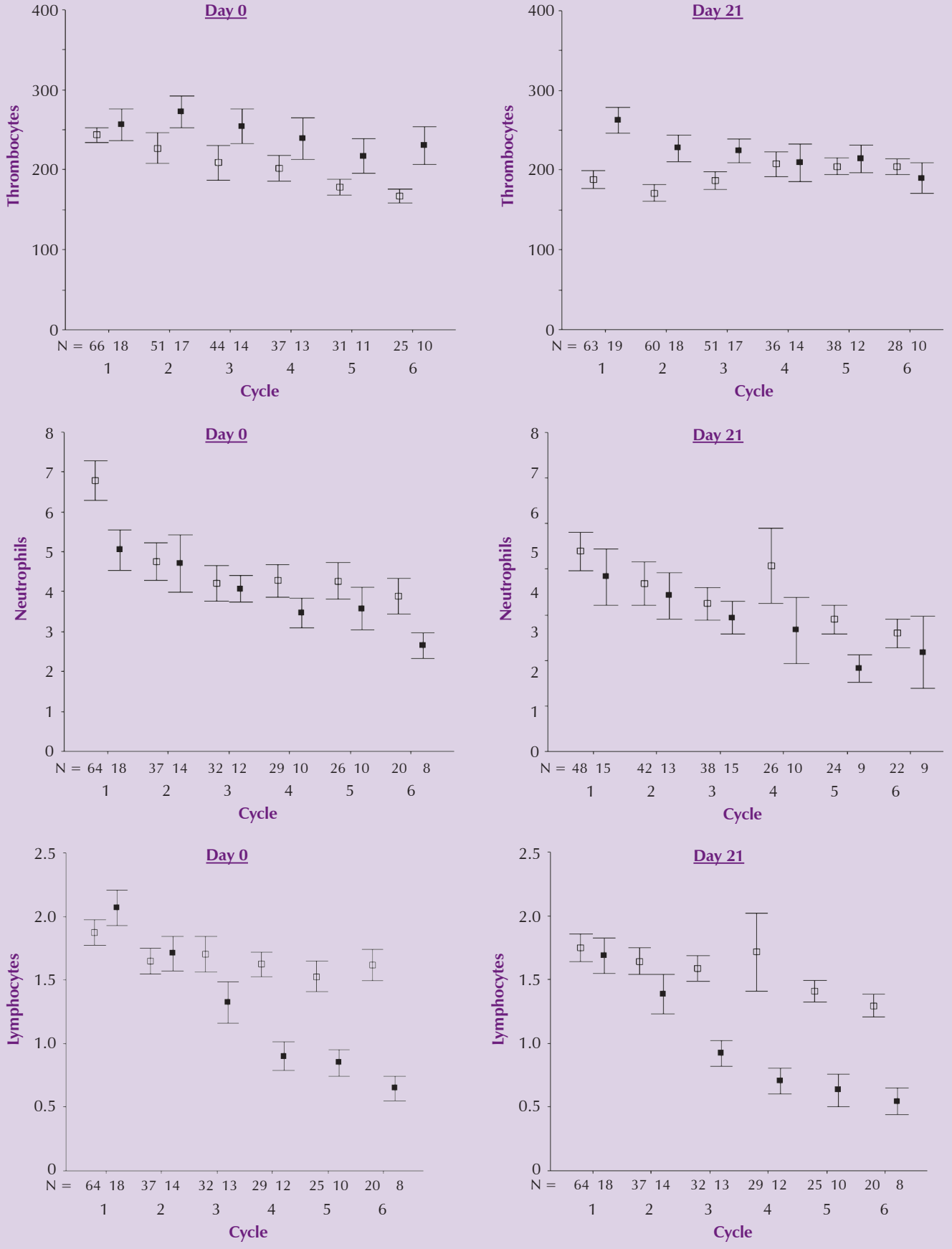
With the ever-increasing use of more intensive therapies, oncology nurses can play a key role in management. In the authors' outpatient clinic for patients with brain tumors, this led to an active role for the NP in neuro-oncology with responsibilities for carrying out therapeutic interventions related to TMZ toxicity. The aim of this study was to report the toxicities of TMZ, exploring two different schedules of administration in a nurse-led clinic. The NPs are responsible for explaining schedules to patients, recording toxicity data, evaluating toxicity, and acting according to findings. The researchers investigated the type of NP interventions required to cope with the toxicities.

The researchers compared two TMZ schedules with respect to toxicity and interventions. The grade 3–4 toxicities are comparable with other studies (Gerber, Grossman, Zeltzman, Parisi, & Kleinberg, 2007). Gerber et al. also found thrombopenia to be more pronounced in women; grade 3–4 thrombocytopenia occurred in 25% of women and 14% of men. TMZ clearance increases with body surface area (BSA) for both genders, but mean clearance is higher in male patients with BSA equal to 2 m^2 than for female patients with BSA equal to 1.7 m^2 (Jen et al., 2000). Those differences might explain the influence of gender in the frequency of thrombopenia.

The current results also show that dose-intense TMZ has a limited effect on bone marrow, but the incidence of grade 3–4 lymphopenia increases when patients are treated for a longer period with TMZ (i.e., more than six cycles). This has led to revision of the protocol to include interventions with prophylaxis after checking CD4 counts in case of grade 3 lymphopenia. If CD4 counts are below 200/mm^3, antibiotics are given; 4 of 19 patients in group B were given PCP prophylaxis (cotrimaxozol 480 mg daily until CD4 counts increased).

Su et al. (2004) used an extended TMZ dosing regimen of 75 mg/m^2 daily for six weeks of every eight weeks in patients with melanoma (N = 97) and found no significant neutropenia or thrombocytopenia but a high incidence of lymphopenia (58 of 97 patients had higher than grade II toxicity) and 2 patients with opportunistic infections. Brandes et al. (2006) used a similar schedule as group B for recurrent GBM (N = 33), in 153 treatment cycles delivered, and described the most common toxicity to be lymphopenia grade 3–4 (55% of 33 patients treated with more than three cycles; median number of cycles per patient = 3, range = 1–15).

The current authors conclude that the standard regimen mainly leads to grade 3–4 thrombopenia after the first cycle, which requires dose reduction. Dose-intense schedules mainly lead to lymphopenia as the number of cycles increases and more so during prolonged schedules.



Note. Group A is represented by open symbols. Group B is represented by closed symbols. Data shown are means; error bars represent standard error of the mean.

Figure 1. Thrombocyte, Neutrophil, and Lymphocyte Counts by Treatment Group

Table 4. Patients With Evaluable Highest Grade of Neutropenia During Six Cycles

	Group A (N = 52)		Group B (N = 14)	
Neutropenia	n	%	n	%
No toxicity	37	71	11	79
Grade 1	2	4	1	7
Grade 2	4	8	1	7
Grade 3	2	4	1	7
Grade 4	7	13	–	–

Note. Neutropenia in group A > group B, p = 0.456

Note. Based on 66 of 90 patients with evaluable laboratory results concerning lymphocyte and neutrophil counts; the results were not always standardly assessed in the first years of temozolomide therapy.

In the current study, the researchers compared two groups of patients; however, group A was larger than group B. However, the results of the study in which the NP monitored the toxicity of chemotherapy are similar to results of others where toxicity was monitored by oncologists or neurologist/oncologists.

Other studies have not specified interventions such as dose delay or reduction, administration of growth factors and PCP prophylaxis, or numbers of patients who received platelet transfusions or discontinued TMZ because of toxicity. Intensive follow-up by the NP for the group of patients using TMZ, concentrating on toxicity, probably explains the specific attention on and the reporting of the interventions associated with the use of TMZ.

Nursing Implications

In a nurse-led TMZ clinic, the NP instructs and evaluates patients with brain tumors during neoadjuvant, adjuvant, or recurrent treatment with TMZ. The NP can rely on two neurologist/oncologists and a medical oncologist for back-up. The NP plays a crucial role in administering chemotherapy cycles, controlling laboratory results, and deciding and carrying out interventions. When hematologic toxicity occurs and is not resolved by dose delay or reduction, the NP participates in decision-making regarding discontinuing TMZ treatment if necessary and carrying out necessary interventions such as administration of growth factors, prophylactic antibiotics, or thrombocyte transfusions. Nausea, vomiting, and loss of appetite are the most well-known side effects of chemotherapy, which often affect quality of life of patients with cancer. When nausea or vomiting occurs, antiemetics are adjusted or medications are added. For anticipatory nausea and vomiting, a protocol (hospitalization and IV antiemetics) was developed by the NP together with the responsible physicians.

Chemotherapy-induced neutropenia is the most frequent side effect of chemotherapy (Crighton, 2004). With regards to neutropenia or other side effects secondary to hematologic toxicity, the NP questions the patient or a family member about potential side effects before the start of each cycle and evaluates laboratory results of blood counts. Before administering the next cycle, the NP advises and intervenes according to guidelines and protocols. Lymphopenia is reversible, but the condition can take many weeks or months to resolve, during which time the patient remains at high risk of developing opportunistic infections, such as PCP and endocarditis, and will remain at risk after ending chemotherapy until CD4 counts normalize. After discontinuation of TMZ treatment, CD4 counts must be checked by the NP until they recover, and prescriptions for PCP prophylaxis should be provided.

In the current study, the NP investigated data gathered from patients receiving TMZ. With the help of a medical protocol developed by the NP together with the responsible physicians, good guidance for the interventions has been made available. Patients with brain tumors who are facing a disease with a poor prognosis should be guided through their chemotherapy with attention to side effects and quality of life using evidence-based guidelines and supportive care. Knowledge of brain tumors and experience with this specific patient group are the basis of good care.

The authors' experience has taught them that patients value the NP because he or she can be reached easily, usually has more time, informs them properly, and has direct access to other disciplines with their questions. Future nursing research should focus on the effect of protocolized NP interventions for toxicities, such as dose delays and reductions, on the quality of life of patients and on adaptation of guidelines for oral TMZ in patients with brain tumors. Oncology nurses can play a key role in such matters.

Table 5. Patients With Evaluable Highest Grade of Lymphopenia During Six Cycles

	Group A (N = 52)		Group B (N = 14)	
Lymphopenia	n	%	n	%
No toxicity	34	65	5	36
Grade 1	6	12	–	–
Grade 2	10	19	4	29
Grade 3	2	4	3	21
Grade 4	–	–	2	14

Note. Lymphopenia in group B > group A, p = 0.004

Note. Based on 66 of 90 patients with evaluable laboratory results concerning lymphocyte and neutrophil counts, the results were not always standardly assessed in the first years of temozolomide therapy.

Conclusion

This study illustrates the role and responsibilities of an NP in neuro-oncology concerning evaluation of laboratory results and potential side effects in patients treated with TMZ, and consideration of interventions in relation to observed toxicities. The occurrence of toxicities may lead to decision-making by the NP on necessary interventions, improving quality and continuity of multidisciplinary care, and emphasizing the role of NPs in care and cure.

Hanneke Zwinkels, RN, MA, ANP, is a nurse practitioner and Krista Roon, MD, is a physician, both in the Department of Neurology, Frank J.F. Jeurissen, MD, is a physician in the Department of Internal Medicine, and Martin J.B. Taphoorn, MD, is a professor in the Department of Neurology, all at the Medical Centre Haaglanden in the Hague in the Netherlands; Wim C.J. Hop, PhD, is a statistician in the Department of Biostatistics at Erasmus MC Rotterdam in the Netherlands; and Charles J. Vecht, MD, is a physician in the Department of Neurology at the Medical Centre Haaglanden. Mention of specific products and opinions related to those products do not indicate or imply endorsement by the Oncology Nursing Forum or the Oncology Nursing Society. Zwinkels can be reached at h.zwinkels@mchaaglanden.nl, with copy to editor at ONFEditor@ons.org.
(Submitted March 2008. Accepted for publication May 24, 2008.)

Digital Object Identifier: 10.1188/09.ONF.225-231

References

Bedell, C.H. (2003). A changing paradigm for cancer treatment: The advent of new oral chemotherapy agents. *Clinical Journal of Oncology Nursing, 7*(6, Suppl.), 5–9.

Brandes, A.A., Tosoni, A., Cavallo, G., Bertorelle, R., Gioia, V., Franceschi, E., et al. (2006). Temozolomide 3 weeks on and 1 week off as first-line therapy for recurrent glioblastoma: Phase II study from Gruppo Italiano Cooperativo di Neuro-Oncologia (GICNO). *British Journal of Cancer, 95*(9), 1155–1160.

Chang, S.M., Theodosopoulos, P., Lamborn, K., Malec, M., Rabbitt, J., Page, M., et al. (2004). Temozolomide in the treatment of recurrent malignant glioma. *Cancer*, *100*(3), 605–611.

Crighton, M.H. (2004). Dimensions of neutropenia in adult cancer patients: Expanding conceptualizations beyond the numerical value of the absolute neutrophil count. *Cancer Nursing*, *27*(4), 275–284.

Dutch Health Care Inspectorate. (2007). *State of health report 2007.* Retrieved January 7, 2008, from http://www.igz.nl/34044/Staat_van_de_Gezondheidszor1.pdf

Gerber, D.E., Grossman, S.A., Zeltzman, M., Parisi, M.A., & Kleinberg, L. (2007). The impact of thrombocytopenia from temozolomide and radiation in newly diagnosed adults with high-grade gliomas. *Neuro-Oncology, 9*(1), 47–52.

Hartigan, K. (2003). Patient education: The cornerstone of successful oral chemotherapy treatment. *Clinical Journal of Oncology Nursing, 7*(6, Suppl.), 21–24.

Hollywood, E., & Semple, D. (2001). Nursing strategies for patients on oral chemotherapy. *Oncology, 15*(1, Suppl. 2), 37–39.

Houston, D. (1997). Supportive therapies for cancer chemotherapy patients and the role of the oncology nurse. *Cancer Nursing*, *20*(6), 409–413.

Jen, J.F., Cutler, D.L., Pai, S.M., Batra, V.K., Affrime, M.B., Zambas, D.N., et al. (2000). Population pharmacokinetics of temozolomide in cancer patients. *Pharmaceutical Research, 17*(10), 1284–1289.

Keime-Guibert, F., Chinot, O., Taillandier, L., Cartalat-Carel, S., Frenay, M., Kantor, G., et al. (2007). Radiotherapy for glioblastoma in the elderly. *New England Journal of Medicine, 356*(15), 1527–1535.

Kristiansen, K., Hagen, S., Kollevold, T., Torvik, A., Holme, I., Nesbakken, R., **et al. (1981). Combined modality therapy of operated** astrocytomas grade III and IV. Confirmation of the value of postoperative irradiation and lack of potention of bleomycin on survival time: A prospective multicenter trial of the Scandinavian Glioblastoma Study Group. *Cancer, 47*(4), 649–652.

National Cancer Institute. (2003). *Common Terminology Criteria for Adverse Events: Blood and bone marrow toxicity* [version 3.0]. Bethesda, MD: Author.

Oncology Guidelines. (2008). Retrieved February 17, 2009, from http://www.oncoline/richtlijn/item/index.php?pagina=/richtlijn/item/pagina.php&richtlijn_id=567

Stupp, R., Mason, W.P., van den Bent, M.J., Weller, M., Fisher, B., Taphoorn, M.J., et al. (2005). Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. *New England Journal of Medicine, 352*(10), 987–996.

Su, Y.B., Sohn, S., Krown, S.E., Livingston, P.O., Wolchok, J.D., Quinn, C., et al. (2004). Selective CD4+ lymphopenia in melanoma patients treated with temozolomide: A toxicity with therapeutic implications. *Journal of Clinical Oncology, 22*(4), 610–616.

Taphoorn, M.J., Stupp, R., Coens, C., Osoba, D., Kortmann, R., van den Bent, M.J., et al. (2005). Health-related quality of life in patients with glioblastoma: A randomised controlled trial. *Lancet Oncology, 6*(12), 937–944.

van den Bent, M.J., Taphoorn, M.J., Brandes, A.A., Menten, J., Stupp, R., Frenay, M., et al. (2003). Phase II study of first-line chemotherapy with temozolomide in recurrent oligodendroglial tumors: The European Organisation for Research and Treatment of Cancer Brain Tumor Group Study 26971. *Journal of Clinical Oncology, 21*(13), 2525–2528.

Wick, A., Felsberg, J., Steinbach, J.P., Herrlinger, U., Platten, M., Blaschke, B., et al. (2007). Efficacy and tolerability of temozolomide in an alternating weekly regimen in patients with recurrent glioma. *Journal of Clinical Oncology, 25*(22), 3357–3361.

Journal Club Questions

This article has been chosen as particularly suitable for reading and discussion in a Journal Club format. The following questions are posed to stimulate thoughtful critique and exchange of opinions, possibly leading to changes on your unit. Formulate your answers as you read the article. Photocopying of this article for group discussion purposes is permitted.

1. What is our experience with patients with brain tumors treated with temozolomide?
2. What barriers exist to the use of nurse practitioners in our patient-management areas?
3. Do we have protocols established to support the use of nurse practitioners to care for these patients?
4. What other challenges exist for the delivery of accurate temozolomide therapy to patients?
5. What strategies do we have in place to overcome these challenges?

At the end of the session, recap the discussion and make plans to follow through with suggested strategies.