Non-Hodgkin’s Lymphoma in Patients With Glioma Treated With Temozolomide

To the Editor: Temozolomide (Temodal; Schering-Plough Labo NV, Heist-op-den-Berg, Belgium) is a DNA-alkylating drug that is registered for the treatment of patients with newly diagnosed glioblastoma and recurrent gliomas.1 Sensitivity to temozolomide is correlated with the hypermethylation of the O6-alkylguanine-DNA-alkyltransferase promoter in glioma cells (which leads to an absence of the AGAT DNA repair protein that repairs the O6-methylguanine adduct created by temozolomide).2 Temozolomide is most often prescribed as a 5 of 28 days regimen at a dose of 150 to 200 mg/m² every 28 days. Alternatively, temozolomide can be administered by extended daily dosing, resulting in an up to 210% higher dose density over a period of 28 days (eg, 7 of 14 days at a dose of 150 mg/m², 21 of 28 days at a dose of 100 mg/m², or 6 of 8 weeks at a dose of 75 mg/m²).3,4 Such regimens more profoundly deplete AGAT activity in peripheral blood mononuclear cells and may improve the antitumor activity.5 Daily dosing for 6 weeks during radiation therapy has become part of standard care for newly diagnosed glioblastoma, and the 21 of 28 days regimen is under study in two large randomized phase III trials for newly diagnosed low-grade glioma (European Organisation for Research and Treatment of Cancer/National Cancer Institute of Canada protocol 22033-26033) and glioblastoma (Radiation Therapy Oncology Group/European Organisation for Research and Treatment of Cancer protocol 26052-22053).

The 5 of 28 days temozolomide regimen has remarkable low acute toxicity (< 10% thrombocytopenia and neutropenia), no cumulative toxicity, and has not been associated with an increased incidence of secondary malignancies, such as treatment-related myelodysplastic syndrome or acute leukemia2,4 or cases of aplastic anemia.5,10 The short life expectancy of patients with glioblastoma and recurrent gliomas might, however, have obscured observations of such delayed adverse effects that have a peak incidence between 5 and 10 years after exposure to the mutagenic alkylating chemotherapy. In contrast to the 5 of 28 days regimen, extended dose-dense regimens have been associated with a high incidence (50% to 100%) of treatment-related lymphopenia in a number of phase II trials, resulting in a state of immunosuppression with an increased incidence of opportunistic infections and possibly also immunosuppression-related neoplasms, such as Kaposi’s sarcoma.11,12 During the past year we have become aware of three patients with glioma treated with temozolomide who subsequently developed a malignant lymphoma.

The first case concerns a 53-year-old Italian woman with a 10-year history of low-grade oligodendroglioma diagnosed in 1998. After the initial diagnosis, she was treated with three cycles of procarbazine, lomustine, and vincristine. After the patient experienced disease progression in January 2006, a second surgery was performed, and the diagnosis of transformation to an anaplastic oligodendroglioma was established. She was treated with one cycle of neoadjuvant temozolomide (5 of 28 days at a dose of 150 mg/m²) followed by radiotherapy (54 Gy) with concomitant temozolomide (75 mg/m²/d × 42 days) and five cycles of adjuvant temozolomide (5 of 28 days at a dose of 150 mg/m²). Seven months after the end of temozolomide therapy, she was diagnosed with a diffuse large B-cell lymphoma of the neck. The patient was treated with cyclophosphamide, doxorubicin, vincristine, and prednisone. Both her diffuse large B-cell lymphoma and glioma were in remission in January 2008.

The second case concerns a Belgian male patient who, in 1998 at the age of 48 years, was diagnosed with a low-grade oligoastrocytoma that could be partially resected. In September 2003, transformation to an anaplastic oligoastrocytoma was diagnosed, for which he underwent radiation therapy (60 Gy). In April 2005, a first recurrence was treated with 5 of 28 days temozolomide. Because of progressive disease, treatment was stopped after two cycles, and the patient received cetuximab in a phase II trial. Because of further disease progression, temozolomide was reintroduced in August 2005 and administered on a 21 of 28 days regimen (at a daily dose of 100 mg/m²). The patient had a regression of his glioma and improvement in his neurologic condition and continued temozolomide for 25 uninterrupted treatment cycles. In August 2008, a plasmablastic diffuse large B-cell lymphoma of the stomach was diagnosed. Temozolomide was stopped and the patient received treatment with rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone, to which he responded favorably. In November 2008, progression of his glioma was diagnosed, for which he underwent re-irradiation.

The third case concerns a 48-year-old man who was diagnosed with a low-grade oligodendroglioma (1p/19q deleted) in January 2005. The tumor demonstrated modest shrinkage in response to 12 cycles of protracted low-dose temozolomide (75 mg/m²/d, 21 of 28 days).13 However, the patient developed odynophagia and cervical lymphadenopathy; tonsillectomy revealed a malignant tissue consistent with mucosa-associated lymphoid tissue lymphoma. The patient was treated with two cycles of rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone because of concern for aggressive disease. In March 2006, he was diagnosed with disseminated, progressive disease, involving the lung, liver, pelvis, and CNS. On progression, he was treated with and responded well to rituximab and methotrexate for CNS symptoms (eg, diplopia). Having responded well to CNS therapy, he was then treated with rituximab, ifosfamide, carboplatin, and etoposide (R-ICE) for systemic disease. Unfortunately, despite two cycles of R-ICE, imaging revealed progressive disease. In light of progressive disease, altered mental status, and multiple complications owing to chemotherapy, including pancytopenias, recurrent GI bleeding, and chronic diarrhea, active treatment was stopped. The patient died in August 2006.
Excess risk of non-Hodgkin’s lymphoma has been observed after treatment for Hodgkin’s disease (the cause for this is not well understood) and also in immunosuppressed organ transplant recipients and patients with HIV. Temozolomide has a strong mutagenic potential on mouse bone marrow cells in vivo, and patients who are treated with dose-dense extended dosing regimens of temozolomide for an extended period of time might present with particular risk for secondary malignancy because of treatment-associated immunosuppression and a high cumulative dose of a potentially carcinogenic alkylating drug.

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From Bench to Bedside: A Case of Rapid Reversal of Bortezomib-Induced Neuropathic Pain by the TRPM8 Activator, Menthol

TO THE EDITOR: Chemotherapy-induced neuropathic pain can be a major treatment-limiting factor, causing a significant reduction in quality of life. Improved management of chemotherapy-induced peripheral neuropathy is high on the supportive and palliative care research agenda.

Bortezomib, a proteasome inhibitor, is an important new treatment for multiple myeloma, with potential application in the treatment of other malignancies. Unfortunately a treatment-emergent neuropathy has been reported in 35% of patients, with up to 15% suffering from severe neuropathic pain, often requiring the cessation of treatment.

We report a case of severe bortezomib-induced neuropathy in a 69-year-old man with a 39-month history of multiple myeloma. Previous treatment included melphalan, cyclophosphamide, dexamethasone, and thalidomide (which was discontinued because of attainment of stable partial response, with no neuropathic symptoms). After a symptomatic increase in paraprotein levels, bortezomib was commenced as third-line antimyeloma treatment. Unfortunately, after two cycles of bortezomib, the patient complained of paraesthesia, numbness, and “lightning-like” pains in both hands, which did not resolve despite a 50% dose reduction for the third cycle.

A month later, he developed an extremely painful peripheral neuropathy (grade 4) in his lower limbs, in a stocking distribution, while his hand symptoms remained mild and unchanged. The pain was characteristic of that found in bortezomib-induced neuropathy. The predominant feature was severe burning, with significant sleep disturbance, high levels of distress, and reduced general function, such that he was virtually bed-bound. Bortezomib was therefore discontinued, despite a more than 90% reduction in the paraprotein level (36 g/L to 3 g/L).

Treatment for neuropathic pain was limited by significant adverse effects with systemic agents including opioids, gabapentin,

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The October 1, 2008, article by Schneider et al, entitled, “Association of Vascular Endothelial Growth Factor and Vascular Endothelial Growth Factor Receptor-2 Genetic Polymorphisms With Outcome in a Trial of Paclitaxel Compared With Paclitaxel Plus Bevacizumab in Advanced Breast Cancer: ECOG 2100” (J Clin Oncol 26:4672-4678, 2008) contained an error. In Table 2, under VEGF-1154, the frequency for GA was given as 38.8% and should have been 33.8%.

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The December 10, 2008, editorial by Wong and Cunningham entitled, “Using Predictive Biomarkers to Select Patients With Advanced Colorectal Cancer for Treatment With Epidermal Growth Factor Receptor Antibodies” (J Clin Oncol 26:5668-5670, 2008) contained errors. In Figure 1, P13K was used in the label for the blue section of the pie chart, whereas it should have been PI3K as follows: “Nonresponder: Loss of PTEN or PI3K mutation % unknown.” Also in Figure 1, the following footnote was inadvertently omitted: (*) Possibly overcomes upregulated EGFR or circulating soluble EGFR. The following Acknowledgment was inadvertently omitted: “The authors acknowledge NHS funding to the NIHR Biomedical Research Centre.” The online version has been corrected in departure from the print.

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The February 10, 2009, ASCO special article by Winer et al, entitled, “Clinical Cancer Advances 2008: Major Research Advances in Cancer Treatment, Prevention, and Screening—A Report From the American Society of Clinical Oncology” (J Clin Oncol 27:812-826, 2009), contained errors. In the Breast Cancer section, under Notable Advances, reference 10a should have been cited in the last sentence of the third paragraph.

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In the References section, the following references were inadvertently omitted:

9. Miles D, Chan A, Romieu G, et al: Randomized, double-blind, placebo-controlled, phase III study of bevacizumab with docetaxel or docetaxel with placebo as first-line therapy for patients with locally recurrent or metastatic breast cancer (mBC): AVADO. J Clin Oncol 26:43s, 2008 (suppl; abstr LBA1011)
10a. Goodwin PJ, Ennis M, Pritchard KI, et al: Vitamin D (Vit D) deficiency is common at breast cancer (BC) diagnosis and is associated with a significantly higher risk of distant recurrence and death in a prospective cohort study of T1-3, N0-1, M0 BC. J Clin Oncol 26:9s, 2008 (suppl; abstr 511)

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In Figure 1, the lower right-hand box indicated that 31 patients had EGFR mutations, whereas it should have shown that 31 patients had no EGFR mutations.

The online version has been corrected in departure from the print.

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