CORRESPONDENCE

Phase II Study of Temozolomide without Radiotherapy in Newly Diagnosed Glioblastoma Multiforme in an Elderly Populations

I read with interest the article by Chinot et al. who reported a Phase II study evaluating temozolomide in 29 patients age $>$ 70 years who were diagnosed with glioblastoma multiforme.[1] Although interesting overall survival durations of 13.3 months were obtained in the group of patients who achieved a partial response, this study raises certain issues that are frequently encountered in patients with this complex tumor. The first point is the inevitable selection of patients accrued in Phase II studies. Only half of the referred patients were enrolled in the study and the minimal admitted greatest tumor dimension was 2 cm. Exclusion criteria included psychologic, familial, sociologic, or geographic conditions, which frequently are encountered in the elderly but most likely are more easily managed in the setting of a university center. These criteria demonstrate that observation remains a major concern in patients receiving oral therapies. The evaluation of response remains particularly difficult in patients with brain tumors and ideally requires external and independent review. Interpretation of the results of the study was complicated by confusing factors. A notable fraction of the patients (22%) had undergone surgery and 12% had received second-line therapy with nitrosourea. The overall survival in those patients who underwent surgery was 8.8 months, compared with an overall survival of 6.3 months in the patients who underwent biopsy only. Only baseline tumor size was found to be a prognostic factor. The role of corticosteroids also is a major concern because these can decrease the overall tumor volume significantly. The decrease in steroid dosage reported in the study by Chinot et al. is difficult to interpret because it may depend on the initial dosage, especially unusually high dosages, but also on the rate and rhythm of the dosing decrease. For example, a decrease from 500 mg of methylprednisolone to 300 mg daily is of little significance. WHO Grade 3/4 nausea, which was reported to occur in 9% of the patients, is not negligible and might limit the administration of methylprednisolone to those patients with a certain tumor volume. Because of the poor prognosis of the tumor and also because chemotherapy does not appear to be of benefit to a majority of patients, Grade 3/4 toxicities should be avoided. Platelet transfusions and granulocyte–colony-stimulating factor each were necessary in 6% of the patients in the study. It must be taken into account that the follow-up of the patients in the study by Chinot et al. was optimal, although serious consequences might have occurred within another context.

The impact of temozolomide remains unclear and two fundamental questions need to be addressed. 1) Does temozolomide allow for chemotherapy to be administered in a larger proportion of pa-

tients; and 2) what are the respective impacts of chemotherapy and surgery on patient prognosis?

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DOI 10.1002/cncr.20707
Published online 3 November 2004 in Wiley InterScience (www.interscience.wiley.com).

Author Reply

We read with interest Dr. Alliot's letter, which raised the issues of a potential patient selection bias, the response evaluation, and toxicity in our study of treatment with temozolomide without radiotherapy in elderly patients with glioblastoma multiforme (GBM).[1] First, we agree that patient selection bias is always possible in such Phase II studies. However, it should be noted that, as previously described, although approximately half of the patients referred in our center (32 of 63 patients) were included in the study, the population of patients who were not included was rather heterogeneous and included not only 27% of patients with potentially poor prognostic characteristics (such as no prior biopsy or a Karnofsky performance status (KPS) $<$ 60) (17 of 63 patients), but also 22% of patients with a potentially good prognostic profile (such as anaplastic histology or status that permitted radiotherapy with or without nitrosourea) (14 of 63 patients). Because 63 of 65 patients with malignant glioma were referred directly to our center because of our regional neurooncology organization, it is unlikely that our status as a referral center had an impact on patient selection. The median tumor dimension of 15.75 cm^2 should be considered rather than a minimal tumor dimension, and it should be understood that patient inclusion was not restricted to those individuals with small tumors. Taken together, a median patient age of 75 years, a KPS of 60 (44% of patients), a median tumor size, and a percentage of macroscopic total resection of 3% do not reflect, in our opinion, a potentially favorable patient selection bias. Response evaluation is always critical in glioma patients because even well defined Macdonald response criteria have known potential limits. However, the reported response rate of 31% was confirmed by an external and independent expert (K.H.X.) as mentioned in our article. Response was evaluated in 29 patients, including 6 patients in whom an evaluable tumor remained after undergoing partial surgery whereas only 1 patient underwent macroscopic total resection with no evaluable residual tumor noted at the time of entry into the study. Moreover, the benefit of chemotherapy does not appear to be influenced by surgery as suggested by a meta-analysis performed by the Glioma Meta-analysis Trialists (GMT) Group,[2] whereas treatment at the time of recurrence appears to have no impact on response or progression-free survival. We agree that steroid decrease per se is not a significant criteria for therapeutic benefit, but we consider that improvements in the KPS and/or MMS, combined with a decrease in steroid use, may be valuable in a palliative setting such as glioblastoma multiforme occurring in the elderly. Toxicity is in fact critical in these palliative situations and approximately 9% rate of Grade 3/4 nausea and emesis should be decreased through an improvement in supportive medication, but overall toxicity data and temozolomide compliance need to be considered behind other forms of treatment such as radiotherapy or other chemotherapies. We agree that in specific centers such as our hospital, the management of toxicity may be optimal, which raises two comments. First, the adequate control of oral chemotherapy with toxicities, even if limited, should still be performed; and second, the adequate management of symptoms associated with brain tumors, such as seizures or brain edema, also is of critical importance for a patient's quality of life, which emphasizes the importance of coordinating all medical support for patients with brain tumors. Finally, the purpose of our study[1] was not to consider surgery and temozolomide as alternative treatments and we agree that the respective impact of surgery and temozolomide therapy cannot be addressed by this study. To our knowledge to date, surgical procedures mainly were discussed based on anatomic considerations and the patient's performance status, without any influence of the potential impact of other oncologic treatments noted. Independent of the surgical procedure performed, the first question raised with regard to elderly patients with glioblastoma multiforme concerns the role of oncologic complementary treatment. In that respect, the study conduct by the French group ANOCEF, which randomizes patients to receive ei-

ther radiotherapy or best supportive care, and in which we are actively involved, may help to provide an answer. Based on our results, which are in accordance with the study published by Glantz et al.,[2] the next step may be to compare the best treatment arm from the ANOCEF study with the use of temozolomide as exclusive treatment for elderly patients with glioblastoma multiforme.

The results of our study[1] may contribute further to the design of future appropriate comparative studies to determine the best standard of care for elderly patients with glioblastoma multiforme with respect to efficacy, treatment tolerance, convenience, and quality of life.

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DOI 10.1002/cncr.20708
Published online 3 November 2004 in Wiley InterScience (www.interscience.wiley.com).

Postsurgical Disparity in Survival between African Americans and Caucasians with Colonic Adenocarcinoma

We read with interest the article by Alexander et al. regarding race and mortality from colorectal carcinoma.[1] The authors considered racial disparities in cause-specific mortality in two hospital cohorts in which patients were reported to have been staged comparably and to have received similar treatment regimens. Nonetheless, the authors observed a persistent racial disparity with regard to colonic adenocarcinoma survival times, and concluded that this "may be due to differences in other biologic or genetic characteristics between African-American patients and caucasian patients."[1]

We would be interested to know whether the authors considered preexisting comorbidity and its potential impact on survival as a specific potential biologic explanation for this difference in survival. For example, diabetes mellitus is associated with an increased risk of colon carcinoma recurrence compared with patients without diabetes,[2] and is reported to have a substantially higher prevalence among African-Americans in Alabama and elsewhere compared with whites.[3] Recent work by Piccirillo et al. demonstrated that the comorbidity estimated from hospital tumor registry data is an important predictor of cancer survival outcomes, independently of patient age, race, gender, and tumor stage, and in a dose-response fashion.[4] Comorbidity has been shown to affect survival even for those malignancies with short average survival times, such as carcinoma of the lung.[5] We would welcome any data confirming or refuting the potential contribution of comorbidity, which appears to us to be a more likely and easily testable explanation than genetic predispositions toward poorer survival.

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DOI 10.1002/cncr.20702
Published online 19 October 2004 in Wiley InterScience (www.interscience.wiley.com).

Author Reply

We appreciate the constructive criticism offered by Drs. Hall and Kaufman. It is well documented that in patients with colorectal carcinoma, several comorbid health conditions such as hypertension and diabetes mellitus have been reported to impact patient survival. We too were concerned about the potential confounding impact of comorbidity on the survival discrepancies between the ethnic groups discussed in our article.[1] In our analyses, we considered colorectal carcinoma-specific mortality to be the primary outcome of interest in our proportional hazards models, and patients who died of other causes were right censored at their time of death. As illustrated by Table 1 in our article,[1] the proportion of patients who died of causes other than colorectal carcinoma was similar in both ethnic groups. This may be a reflection of comorbid similarities between African Americans and Caucasians in our study population.

Two of us (C.C. and U.M.) collected information regarding comorbidity by extracting data from medical records for each patient in the study. As a guideline for comorbid conditions, we used the diseases described in Table 1 of the National Institute on Aging (NIA)/National Cancer Institute (NCI) Collaborative study that was published previously in *Cancer*.[2] In 13% of the African-American patients (25 of 199 patients) and 11% of the Caucasian patients (33 of 292 patients), data concerning comorbidity was either missing from the medical records or the information was insufficient to assign comorbid conditions. Approximately 70% of the African-American patients (140 of 199 patients) and 68% of the Caucasian patients (199 of 292 patients) had at least 1 of the comorbid conditions listed in the NIA/NCI Collaborative study.[2] Among African-American patients, the majority of comorbid conditions included hypertension (56%), diabetes mellitus (33%), anemia (29%), smoking (23%), and cardiovascular disease (19%). The primary comorbid conditions in Caucasian patients were hypertension (41%), smoking (33%), gallbladder disease (23%), cardiovascular disease (23%), and diabetes mellitus (17%). As shown in a previous study,[3] there were more African-American patients with diabetes mellitus compared with Caucasians in our study. However, when we included comorbid characteristics in our multivariate proportional hazards model, the racial difference with regard to survival remained unchanged. Therefore, we did not include comorbidity in our final models. Because we used a retrospective follow-up study design with patient accrual beginning in 1981, the complete presurgical comorbidity information may be lacking for a subset of our patient population. Currently, we are ascertaining comorbidity information from a larger patient population, which may allow us to evaluate the impact of comorbidity in a Cox regression model, based on tumor stage and race.

Again, we thank Drs. Hall and Kaufman for their comments and hope that our response appropriately addresses their concerns.

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DOI 10.1002/cncr.20703
Published online 19 October 2004 in Wiley InterScience (www.interscience.wiley.com).

Immunochemotherapy with Rituximab and Temozolomide for Central Nervous System Lymphomas

We read with great interest the article by Wong et al.,[1] who report the results of an immunochemotherapy regimen involving rituximab and temozolomide in seven patients with central nervous system lymphoma (CNSL). Five patients achieved a complete radiographic response and two patients experienced a partial response after induction treat-

ment. At the conclusion of their well documented report, Wong et al. offered the undocumented claim that rituximab may sensitize B-lymphoma cells to the cytotoxic effects of temozolomide. Generally speaking, tumor regression induced by rituximab treatment in vivo is believed to involve complement-dependent cytotoxicity, antibody-dependent cell-mediated cytotoxicity, and inhibition of cell proliferation. All of these mechanisms are linked closely to the concentration of the antibody as demonstrated in vivo and in vitro.[2] The mechanisms involved in the reversal of drug resistance and sensitivity to chemotherapeutics by rituximab are quite different and are related closely to the activity of rituximab in the selective disruption of interleukin-10 autocrine/paracrine loops with subsequent down-regulation of the expression of the antiapoptotic Bcl-2 gene product. However, the decrease in Bcl-2 protein expression is correlated with rituximab concentration.[3] In patients with CNSL who were treated intravenously with rituximab, the concentration of the drug in the cerebrospinal fluid (CSF) was very low and decreased at an early stage,[4] just as we had noted in a series of five patients. In this setting, from a pharmacologic point of view, intraventricular rituximab treatment warrants attention, even if only for the finding that leptomeningeal lymphoma nodules have been eradicated as a result.[5] Therefore, one would assume that the higher the concentration of rituximab in the CSF, the better the response to rituximab would be, as has been observed in all clinical studies.

To our knowledge, no study to date has incorporated investigation of the biology of CNSL into the treatment protocol. Nevertheless, efforts in this area may ultimately affect treatment choices for individual patients.

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DOI 10.1002/cncr.20704
Published online 4 November 2004 in Wiley InterScience (www.interscience.wiley.com).

Author Reply

Dr. Pitini and colleagues correctly point out that the concentration of rituximab in the cerebrospinal fluid (CSF) is low after intravenous infusion. By administering rituximab intrathecally, they argue that one could produce a more favorable response. However, we believe that treatment for central nervous system lymphoma (CNSL) involves more than merely circumventing pharmacokinetic obstacles posed by the blood-brain barrier. First, the rituximab level in the CSF may not reflect the true antibody concentration in brain parenchyma, as systemic circulation, via a leaky tumor vasculature, could deliver a higher concentration of rituximab compared with intrathecal administration. In support of this concept, Pels et al.[1] found no treatment benefit from intrathecal rituximab alone for parenchymal primary CNSL. Therefore, the brain parenchyma and CSF/subarachnoid space should be treated as separate compartments. Because only one patient (who had received intrathecal chemotherapy) in our study had cytologic findings that were positive for lymphoma,[2] our data cannot be used to comment on the efficacy of intravenous rituximab for lymphomatous meningitis.

Second, the duration of response is a key treatment issue. Although recurrent CNSLs are believed to arise from sanctuary sites, such as the vitreous humor or loculated subarachnoid space, we would argue that these lymphomas also could originate from cells in the systemic circulation that have escaped immune surveillance. Support for this idea is provided by various observations. For example, although primary CNSL cells are found in the brain parenchyma surrounding blood vessels, lymphoma cells in intravascular lymphomatosis appear to be

stuck in blood vessel lumina on their way into the brain. A migrational defect arising from selectin or adhesion molecule expression could explain this phenomenon, but definitive data are unavailable. In patients with testicular non-Hodgkin lymphoma with brain metastases, the same migrational mechanism could guide lymphoma cells to cross blood-testis and blood-brain barriers. Another notable mechanism was observed in patients with acquired immunodeficiency syndrome who were predisposed to systemic and primary CNSLs; in these patients, reversal of immunodeficiency was found to improve CNSL responses. Finally, Pels et al.[3] reported on a patient with primary CNSL who had the same immunoglobulin H gene rearrangements but different somatic mutations in surgical specimens obtained after initial diagnosis and at disease recurrence, respectively, suggesting a common clonal precursor. If there is persistent trafficking of lymphoma cells from systemic circulation into the CNS, then sustained systemic therapy will prevent CNS recurrence. The maintenance of temozolomide in our immunochemotherapy regimen is designed specifically for this purpose.

We do agree that more translational correlative studies should be incorporated into future clinical trials involving CNSL to help us understand the underlying biology of lymphoma cells.

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DOI 10.1002/cncr.20705
Published online 4 November 2004 in Wiley InterScience (www.interscience.wiley.com).

Lobular Neoplasia on Core-Needle Biopsy—Clinical Significance

Arpino et al.[1] raise the concern that finding lobular neoplasia on core needle biopsy sampling carries with it a risk for coexistent ductal carcinoma in situ (DCIS) or invasive carcinoma that, coupled with other reports, supports the use of excisional biopsy in patients who are diagnosed with lobular neoplasia (LN) using core needle biopsy. Unfortunately, their review, as well as others,[2] does not answer the question of how often is DCIS or an invasive carcinoma present when the targeted abnormality is sampled accurately by core needle biopsy and lobular carcinoma in situ (LCIS) or atypical lobular hyperplasia are found alongside the tumor?

As acknowledged, this review was retrospective. It relied on the fact that some patients, who happened to be found to have LN on core needle biopsy, had gone on to undergo an excisional biopsy. The carcinoma cases were found among these patients. The authors could not deduce why some patients went on to undergo an excisional biopsy and others did not. Regardless, this introduces a major selection bias. It is nearly certain that the physicians who performed these biopsies, on finding that the most significant lesion was LN, were not satisfied that this explained the imaging findings. The diagnosis was incomplete and, consequently, they recommended that the lesion be removed. In the patients who did not undergo excisional biopsies, the benign pathologic findings provided a satisfactory explanation for the imaging findings and no further surgery was undertaken. The patients who were rebiopsied would, a priori, be more likely to have carcinoma. For example, if the targeted lesion was a spiculated mass (which virtually is always carcinoma) and the most significant pathologic finding in the core needle biopsy samples was LCIS, it is clear that the lesion was not sampled accurately and the patient would undergo a surgical excision that would reveal carcinoma. It is the standard of care to repeat the biopsy for a lesion when the core needle pathology result is not concordant with the imaging findings. This would bias the results in these retrospective reviews.

Coincidental LCIS has reportedly been found for decades at the time of surgical excision with no increased risk of simultaneous, coexistent carcinoma. It is unlikely that a technique that provides a smaller sample would detect lesions with an increased risk of synchronous carcinoma. Until there is more accurate evidence of a true risk, patients who are found to have coincidental LN on core needle biopsy should not,

routinely, undergo an excisional biopsy outside of a clinical trial unless the core needle biopsy results are discordant with the imaging findings.

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DOI 10.1002/cncr.20682
Published online 12 October 2004 in Wiley InterScience (www.interscience.wiley.com).

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In the past, lobular neoplasia was thought of as only a marker for increased risk rather than a direct precursor of invasive lesions. However, the paradigm is shifting. Support for the hypothesis that lobular neoplasia is also a direct precursor of invasive breast carcinoma comes from several converging lines of evidence; 1) pathologic studies have demonstrated a high incidence of lobular neoplasia in patients with an invasive tumor, which is nearly always an invasive lobular carcinoma (i.e., histologic continuum); 2) the risk of developing invasive carcinoma after a diagnosis of lobular neoplasia is three times more likely to occur in the ipsilateral rather than in the opposite breast; and 3) molecular analysis demonstrating shared genetic alterations between lobular neoplasia and adjacent invasive breast carcinoma clearly demonstrates that, similar to atypical ductal hyperplasia (ADH) and ductal carcinoma in situ (DCIS), lobular neoplasia can lead directly to invasive carcinoma. It often is stated that lobular neoplasia is a radiographically silent disease, yet our study[1] and others[2,3] have found microcalcifications in lobular neoplasia in approximately one-third of cases. Therefore, past theories should be revisited as our current knowledge base evolves.

We agree that retrospective studies may be biased and therefore should be interpreted in that light. However, we were unable to identify any clinical or radiologic differences when comparing those patients who underwent an excision with those patients who did not. Some of the follow-up surgical procedures may be explained as a joint decision made by the physician and the patient after a discussion regarding the risk and benefits of available options. At other times, it could have be due to a physician preference. As a routine procedure, if there is discordance between the results of core needle biopsy and mammographic findings, the patients undergo either a second core needle biopsy or surgical excision. However, the rate of discordance in patients with lobular neoplasia was not found to be higher than in patients with ADH.

Of course, undetected bias cannot be excluded; nevertheless, if one considers all cases of lobular neoplasia and assumes that patients who do not undergo surgical excision have a 0% incidence of carcinoma, the risk of adjacent malignancy remains at 6.7%.

Given the results of a literature review,[1] it is difficult to explain how lobular neoplasia comes to be considered just a risk factor when the rate of DCIS and invasive carcinoma across retrospective studies is reported to be 17%. A policy of not performing surgical excision when lobular neoplasia is found on core needle biopsy perpetuates lingering uncertainty and a lack of consensus. It also has been noted that a policy of not routinely excising areas of lobular neoplasia is not supported by any prospective clinical study data. Prospective studies in which all patients underwent surgical excision would provide a higher level of evidence and better insight with regard to how to select the best candidates for follow-up surgery, but to our knowledge no such study has been performed to date. We would support the performance of such a study.

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DOI 10.1002/cncr.20684
Published online 12 October 2004 in Wiley InterScience (www.interscience.wiley.com).