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## CORRESPONDENCE

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### Medical Research Council Adjuvant Trial in High-Grade Gliomas

*To the Editor:* The Medical Research Council (MRC) Brain Tumor Working Party has reported a phase III comparative trial of radiotherapy with adjuvant versus no adjuvant chemotherapy with procarbazine, lomustine, and vincristine (PCV) in patients with high-grade gliomas.<sup>1</sup> At the time of study design, PCV was considered to be potentially the best standard of care, although the superiority of this regimen over single-agent nitrosourea has recently been questioned.<sup>2</sup> The results of the MRC trial indicated no significant differences in survival between the two arms. The authors conclude that “. . . no-chemotherapy control arms remain ethical in randomized trials in high-grade astrocytoma and that it is reasonable and appropriate not to offer routine, adjuvant chemotherapy to individual patients outside trials.” We, however, suggest that caution be observed before one makes generalizations from these results to the treatment of individual patients, or even necessarily incorporate these data in the design of future trials of high-grade glioma. We therefore offer the following comments regarding the MRC trial.

First, conflicting results from earlier trials are not necessarily negated by observations on a newer trial. Of particular interest in the MRC trial is the observation that there was no statistical correlation of survival with the accepted prognostic variables of age, performance status, histologic grade, or extent of resection by proportional hazards regression analysis. In prior prospective trials, these specific prognostic factors have consistently been shown to represent independent variables in multivariate analyses that correlate significantly with survival.<sup>3-6</sup> The authors conclude that in their trial “. . . the results. . . do not directly contradict the results of any of the 14 adequately randomized trials evaluating nitrosourea-based chemotherapy that have been published to date.” However, the lack of correlation in the MRC trial of survival with these known prognostic variables is in contrast to the prior studies mentioned. At a minimum, this raises the possibility that the MRC patient population seemed to have varied from those in prior reported trials, based on unknown biologic factors or the unintentional introduction of additional bias.<sup>7</sup>

A second significant difference in this trial is the relatively poor outcome of the anaplastic astrocytoma subset, which in the MRC trial had a median survival of 13 months. This is unusually low in comparison with prior reported trials and actually is similar to that reported for glioblastoma. In contrast, a recent prospective randomized Radiation Therapy Oncology Group trial, with a larger cohort of anaplastic astrocytoma patients than in the MRC trial, involved a similar therapy (radiotherapy with PCV ± bromodeoxyuridine).<sup>8</sup> In this latter trial, treatment produced a median overall survival of 45 months. Because the anaplastic astrocytoma subset in the MRC study constituted nearly 20% of the study population, this finding also raises the question of whether the MRC population was in some way different from other populations reported previously.

Third, there are additional differences in the MRC trial as compared with prior reported trials, which may have had an effect on the outcome in the MRC trial. Eligibility parameters were vague and often defaulted to the standard of practice and, as such, contain a greater degree of subjectivity.<sup>9</sup> Comorbid medical conditions are not reported but, if present in a large number of patients, could have influenced survival.

The interval from surgery to initial treatment, a parameter that has been shown to be an important prognostic indicator, was not given. Surgery was comparatively nonaggressive, as reflected by the majority of patients undergoing biopsy or partial resections not otherwise radiographically quantified. It is mentioned that “radiotherapy was to commence within 6 weeks of surgery,” but it is not clear how many patients received radiotherapy within that time frame. Radiotherapy schedules were not standardized, and total prescribed dose varied between 45 and 60 Gy. Brain imaging was not routinely performed either to assess extent of surgical resection or response to therapy. Nineteen (6%) of the 335 patients randomized to the chemotherapy PCV arm did not receive any chemotherapy, which potentially could influence outcome on that arm, and the dose-intensity of PCV in the remaining PCV patients is not detailed. Most patients were not retreated at recurrence, which may be one explanation for why survival seemed shorter in this trial. Furthermore, twice as many patients randomized initially to the radiotherapy-only arm received subsequent chemotherapy at recurrence, which potentially may have influenced ultimate survival differences between the two groups. Finally, survival is defined in the MRC study as “to death date or date last known to be alive.” It is not stated how many patients fit into the latter category, which, if weighted heavily on one of the two arms, could influence survival.

There is no argument that adjuvant chemotherapy has had a very modest impact on survival of high-grade glioma patients, and such marginal benefit has to be considered in view of other chemotherapy-related factors such as toxicity, effects on quality of life, and cost.<sup>10</sup> However, it is also important to consider the results of earlier trials that show benefit of adjuvant chemotherapy, albeit modest and perhaps limited to selected subgroups (eg, younger patients with anaplastic astrocytoma). The differences observed in the MRC trial population compared with previously reported trials does not indicate that the MRC results are wrong, but instead may be reflective of differences in the treatment and design of the treated study population. This outcome may be influenced by multiple factors, some which may not be readily apparent. However, the results of the MRC trial, in our opinion, do not justify the conclusion that it is reasonable to not offer chemotherapy to these patients or to justify inclusion of a no-chemotherapy arm in clinical trials.

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*In Reply:* Drs Chamberlain and Jaeckle raise a number of points concerning the Medical Research Council BR5 trial to which we are happy to respond.

Their primary concern was that the BR5 trial population differed from previous trials with respect to the prognostic value of factors, such as age and performance status, and the median survival of the anaplastic astrocytoma subgroup. With respect to the first of these, the authors state "there was no statistical correlation of survival with the accepted prognostic variables of age, performance status, histologic grade, or extent of resection by proportional hazards regression analysis." In fact we did not present any such analyses and believe that this statement comes from a misunderstanding of the hazards ratio plots. These represented the results of the subgroup analyses, which we reported as showing "no evidence of a differential treatment effect across any of these factors." This does not mean that the factors themselves are not prognostic; certainly tumor grade, age, and performance status are prognostic factors in our trial population. It does mean they are not predictive of response to chemotherapy; ie, they do not define subgroups in which the effect of chemotherapy, as judged by the treatment hazards ratio, is greater or less than in other subgroups defined by the same factor. Thus, for example, younger glioma patients live longer than older patients regardless of whether or not they receive chemotherapy (ie, age is prognostic); however, we have found no evidence that any additional benefit that younger patients might gain through receiving chemotherapy is greater or less than any additional benefit that older patients might gain (ie, age is not predictive).

Concerning the outcome of the anaplastic astrocytoma (AA) patients, it is very difficult to compare outcomes across trials without data on the distribution of prognostic factors such as age and performance status within the AA populations. In addition, a more aggressive approach to surgery for both low- and high-grade tumors may well lead to apparently improved survival in each grade subgroup, without any overall change in survival, simply through stage/grade migration. For

example, centers with a policy of resection rather than biopsy for tumors that are considered low-grade radiologically are likely to identify a higher proportion of patients with anaplastic elements. These patients are then classified as having AA (and entered onto appropriate trials) but are likely to have a better prognosis than those with a high-grade appearance radiologically, who may comprise the bulk of AA patients in other trials. Such variation is inherent in any cross-trial comparison.

One further point we would make is that median survival is an isolated point on the survival curve, and just as one would not compare treatment results by focusing on a single time point but rather by comparing the whole survival curves, so one should apply the same principle here. Thus although our AA and glioblastoma multiforme populations differed by only a few months with respect to median survival, survival rates in the two groups beyond this point (ie, after 1 year) are systematically substantially different as illustrated in Fig 4 of the study report.

Regarding trial entry criteria, these were indeed quite broad to reflect practice outside of the trial setting and included all patients in whom there was the possibility that chemotherapy may be beneficial (thus those with comorbid conditions that would have made treating or assessing response to treatment impossible were excluded). Although potentially this may mean that a higher proportion of poorer (or indeed better) prognosis patients entered the trial than might otherwise have been the case, these patients would have been equally distributed across the trial arms by randomization. In addition, the subgroup analyses referred to above indicate that the overall negative result of the trial is not simply explained by poor chemotherapy response in the poorer prognosis patients; we were unable to identify any subgroups in which chemotherapy substantially improved survival.

Regarding time from surgery to start of radiotherapy, the median interval was 3 weeks; 90% started within 6 weeks and 95% within 7 weeks; the remaining patients incurred additional short delays for a variety of practical and personal reasons. We found no evidence that chemotherapy was more beneficial in patients with a short interval between surgery and the start of radiotherapy.

As reported in the article, the median number of cycles received appears comparable with previous trials, but most trials report insufficient data to compare dose-intensity.

With regard to treatment at recurrence, the re-treatment rate was low, although the extent to which overall survival may have been extended had the rate been higher is perhaps debatable. Certainly the consistency of the trial results with respect to progression-free and overall survival suggest that cross-over in the radiotherapy arm did not have a major influence on the overall survival results.

Finally, with regard to the number of patients followed-up not to death but to date last known to be alive, these comprised less than 10% of the total randomized population, and the numbers according to treatment arm are given in Fig 1 of the trial report; 29 of the radiotherapy patients and 28 of the patients who received radiotherapy plus procarbazine, lomustine, and vincristine were still alive at the time of the final analysis, with a median follow-up for survivors of approximately 4 years in each group.

It is clear that any benefit to chemotherapy is indeed marginal, a statement supported not just by BR5 but by the most recent quantitative summary of the worldwide evidence.<sup>1</sup> Equally, it is clearly wholly appropriate that patients and their physicians should make decisions regarding the need for chemotherapy on an individual patient basis and that some will choose to have chemotherapy even in the absence of unequivocal evidence of survival gain. This is entirely compatible with our conclusion that it is currently reasonable and appropriate not to

offer routine adjuvant chemotherapy to individual patients outside of clinical trials.

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### A “Good Death” Revisited in the Context of Doctor-Patient Relationships

*To the Editor:* The article on the care of dying patients by Gazelle skillfully describes some of the ways in which the death can be made more peaceful.<sup>1</sup> She notes the medical management of symptoms and the integration of the medical support services to improve the quality of life of patients. She also notes the need to help people live as well as possible until they die and alludes to doctors bearing witness to physical, emotional, and spiritual suffering.

This may be interpreted, perhaps inadvertently, as reflecting a paradigm in which health care personnel undertake active management and the patient is a passive recipient of their care. The nature and importance of the doctor-patient relationship merits further elaboration in the care of dying patients. The ethical background, as well as the emotional and spiritual consequences of this relationship, is discussed below.

As professionals, physicians have enjoyed considerable authority in the care of ill and dying patients because of their medical knowledge. This is recognized as a paternalistic model when the consequent doctor-patient relationship is based largely on patients' trust and physicians' conscience. More recently, society has increasingly wished to set limits on doctors' authority in order that medical decisions might be more informed and determined by patients' values and goals. For example, in patients with progressive cancer, it is the patient's values that will direct a decision on continuing anticancer therapy when there is limited possible gain.

There is, therefore, a shift toward shared decision making in health care. This may occur on the understandings of, for example, a “contract model.” Key components of this model are patient autonomy coupled with professional duties and competence. This model, however, has been criticised as representing the interactions of strangers. A richer model is one based on a care ethic, which emphasizes the development of authentic human relationships between health care professionals and patients.<sup>2</sup> It includes elements of the contract model but elaborates on the conditions for significant relationships. These conditions include openness, responsiveness, and fidelity. They also include a sense of mutual interest, although the goal is always the patient's well being.

Openness and responsiveness within a relationship involves appreciation of and response to patients' individuality in terms of their perspectives, their values, and the contributions they have to make toward their health care. Fidelity touches on the justified expectations that are part of a relationship. It includes the anticipation that doctors will stand by them in difficult times.

There is greater scope for the expression of, and a sympathetic response to, emotions within a relationship. Appropriate emotions are not a disruption of reason and are part of the integrated response to the outside world. They are particularly relevant in patients with life-threatening illnesses. Doctors can recognize and often reciprocate feelings of sadness or indeed cheerfulness. Patients are best helped to deal with anger through sympathetic understanding. Responding to emotions allows doctors to draw closer to their patients.

Serious and progressive illness is a time when patients may confront and think deeply about illness and death and put them into a larger framework of spiritual issues. Spirituality is about moving beyond immediate physical realities and the biomedical engineering model of health care, where the focus is on the patient's cells, organs, and reflexive emotional responses. Spirituality concerns deeper values and issues, such as meaning and purpose—be they from a religious or nonreligious viewpoint. It embraces a unitary perspective of life, which includes health and illness. It directs decisions where science alone is not sufficient, and assists when science has reached its limit in disease and symptom management.

For many people, spirituality is closely linked with their sense of community, which includes the medical personnel with whom they have a relationship at this crucial time of their lives. Within a relationship, there are mutual opportunities to develop and grow. Both patients and doctors can learn about appreciating life, about equanimity, and about caring for others. In addition, some patients are able to show leadership by example. They create new possibilities and inspire those around them.

It is a great privilege to care for patients with serious illnesses, whatever the outcome. The nature of the doctor-patient relationship is a central value in dying patients for both doctors and patients.

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### Aromatase Inhibitors: Treatment of Advanced Breast Cancer

*To the Editor:* The report of the superior efficacy of letrozole versus tamoxifen in the first-line treatment of advanced breast cancer in postmenopausal women is an excellent and carefully analyzed randomized trial. It is apparent that letrozole is significantly superior to tamoxifen in terms of time to progression, time to treatment failure, and overall response. It is too early to say whether this treatment will have

an effect on survival. As can be noted in Fig 2 of the original report, approximately 20% of the patients are still responding to treated at 2 years.<sup>1</sup>

The selective aromatase inhibitors are nontoxic compounds used in the short-term treatment of patients with metastatic breast cancer. However, as one of the participants in the initial trial of letrozole versus megestrol acetate for second-line treatment of breast cancer,<sup>2</sup> I had a patient who experienced a complete remission on letrozole that lasted approximately 4 years. When that patient experienced relapse, she developed severe back pain. Although there was evidence of metastatic disease in the bones, there was also evidence of osteoporosis. The aromatase inhibitors decrease serum estrogen levels and, theoretically, could accelerate osteoporosis. Have any of the patients on the current study who are still being treated beyond 2 years undergone bone density analysis to determine whether there seems to be an increased incidence of osteoporosis with letrozole versus tamoxifen? If the aromatase inhibitors cause osteoporosis and if there is not difference in survival in your current study, then perhaps it would be more prudent to continue using tamoxifen as first-line hormonal therapy.

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*In Reply:* Osteoporosis is not a rare phenomenon in elderly women and may even be more frequent in patients with metastatic breast cancer because of decreased mobility. Although there are concerns as to the potential association between prolonged estrogenic suppression and bone morbidity in terms of osteoporosis/fractures, it should be noted that in postmenopausal women, the magnitude of suppression of estrogens effected by aromatase inhibitors is far smaller than the suppression that occurs when premenopausal women turn postmenopausal. This latter suppression often leads to bone loss and accelerated osteoporosis and possibly fractures.

The current study was not designed specifically to address these concerns. However, osteoporosis was reported as an adverse event in one patient who was treated with tamoxifen. This 64-year-old patient entered the study with three assessable bone lesions and no other disease sites. At 6 months, she complained of lumbar and thoracic bone pain, and osteoporosis was also reported. Treatment with tamoxifen was continued until progression of disease 15 months later. At that time, her treatment was switched to letrozole, with which she is currently being treated.

Another patient, 56 years old when she entered the study, had three soft tissue lesions at baseline and no other site of disease. After 3 years of tamoxifen, symptoms of osteoporosis were reported. Tamoxifen was continued for a further 3 months, at which time progression of disease in soft tissue was diagnosed.

At study entry, 12 patients in the letrozole arm and 18 in the tamoxifen arm had osteoporosis. There was no suggestion that there was a deterioration in the osteoporosis. Our article referred to a median follow-up of approximately 18 months. Further data for approximately another 18 months will be available later this year.

The important question about the impact of prolonged estrogen suppression is being addressed in ongoing adjuvant studies, but so far no valid conclusions can be drawn.

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## Prior Invasive Fungal Infection Is Not a Contraindication for Subsequent Allogeneic Bone Marrow Transplantation in Adult Patients With Hematologic Malignancies

*To the Editor:* Invasive fungal infection, with an incidence ranging from 4.5% to 11%, is a major infectious complication associated with a high morbidity and mortality rate in patients with acute leukemia undergoing cytotoxic chemotherapy with or without subsequent bone marrow transplantation (BMT).<sup>1-3</sup> Even after an apparently curative antifungal treatment, nearly 50% of the cases of invasive fungal infections relapse when patients undergo subsequent courses of cytotoxic chemotherapy and BMT,<sup>1</sup> and the mortality rate may be as high as 80%.<sup>2</sup> Therefore, prior invasive fungal infections, especially those caused by molds, has been considered a relative contraindication for subsequent BMT. With the improvement of antifungal therapy, successful transplantation without recurrence of prior invasive fungal infections has been increasingly reported in adult patients undergoing BMT since 1988.<sup>4-9</sup> As of December 31, 2000, a total of 12 such patients have been reported in the literature, and most of them underwent autologous BMT. Successful allogeneic BMT in the adult patients with prior invasive mold infections has been rarely described, however.

From October 1998 to May 2000, seven adult patients with a median age of 27 years (range, 20 to 50 years) who had had prior invasive mold infections underwent subsequent BMT or peripheral-blood stem-cell transplantation (PBSCT) in our hospital: five with acute myelogenous leukemia, one with severe aplastic anemia, and one with non-Hodgkin's lymphoma (stage IVB). Four achieved first complete remission and two achieved second remission before undergoing BMT. The diagnosis of invasive fungal infections was definitely made by positive cultures of the sterile sites or histopathologic examination of biopsy specimens in four patients and was presumptively made in another three based on the presence of positive cultures for molds from nonsterile sites and suggestive radiographic findings, plus prolonged neutropenic fever without responses to broad-spectrum antibiotics. Four of the patients underwent surgical resection of the invasive mold infections of the lung. The median duration between diagnosis and BMT was 82 days (range, 24 to 251 days), during which time four patients continued to receive courses of chemotherapy. The median total dose of amphotericin B was 1,150 mg (range, 450 to 2,000 mg) before resolution of clinical and radiographic findings suggestive of invasive mold infections was observed before BMT. Amphotericin B

was subsequently replaced with itraconazole at a daily dose of 400 mg for a median duration of 60 days (range, 12 to 240 days).

All of the seven patients continued to receive amphotericin B from the beginning of conditioning for BMT to the recovery of granulocyte count to greater than  $500 \times 10^6/L$ . The median duration between transfusion of bone marrow or peripheral-blood stem cells to recovery of granulocyte count was 18 days (range, 13 to 41 days). As of December 31, 2000, four of the seven patients were still alive, and no relapses of prior invasive mold infections and underlying diseases were observed after a median duration of 327 days after transplantation (range, 105 to 796 days). Three other patients died: two as a result of disseminated tuberculosis on day 105 and 110 post-BMT and one as a result of septic shock owing to *Stenotrophomonas maltophilia* after relapse of underlying disease on day 183 post-BMT. No evidence of relapse of prior fungal infections was found in the three fatal cases.

During the same study period, another 21 adult patients who had no prior invasive fungal infections underwent BMT or PBSCT in our hospital. Seven patients with identical underlying hematologic diseases were selected as control on the basis of the identical risk stratifications for BMT or PBSCT. In the control group, the median duration between transfusion of bone marrow or peripheral-blood stem cells to recovery of granulocyte count was 16 days (range, 10 to 20 days), which was not statistically different from that of the case patients ( $P = .305$ , by Mann-Whitney rank sum test). The mortality rate of the 32 patients and the seven patients in the control group was 40.6% and 57%, respectively, which was similar to that of the case patients ( $P = .99$ , by Fisher's exact test).

As of December 31, 2000, five patients had been described in the literature who had had prior invasive fungal infections caused by molds and subsequently underwent allogeneic BMT. Two of the patients died. Patients undergoing allogeneic BMT would be more intensively immunosuppressed during the post-BMT period than those undergoing autologous BMT. Therefore, the patients with prior invasive fungal infections who are going to undergo allogeneic BMT might have a higher risk of developing relapse of prior invasive fungal infections. In our limited experience of seven patients, none had relapse of prior invasive fungal infections after BMT or PBSCT after surgical resection of the involved lungs and prolonged treatment with antifungal agents.

Our findings suggest that with the concurrent use of antifungal agents during and after the neutropenic period following BMT, prior invasive mold infections in selected adult patients with hematologic diseases might not be a contraindication for their subsequent allogeneic BMT. Our study was limited by the retrospective study design and small number of cases, however. Prospective, randomized studies of a

larger case number and longer follow-up duration are desperately needed to assess whether patients with prior invasive fungal infections may fare better post-BMT if they are treated aggressively with surgical resection and prolonged antifungal therapy.

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