deliberation in the respondent. Third, nothing in the physician questionnaire required the respondent to state the amount of experience he or she had with chemonucleolysis, so that it is inappropriate to count these judgments without regard to the experiential base underlying the judgment. This is all the more true for those neurosurgeon-respondents who never performed chemonucleolysis, who were encouraged by the questionnaire to reply — a category that includes Dr. Fager himself.

I agree with Dr. Fager that there should be a prospective randomized study comparing the efficacy of chymopapain and laminectomy in appropriately selected patients. However, unlike Dr. Fager, I am not jumping to unwarranted conclusions about the outcome of such a study. It is imperative that a study of that nature be performed by surgeons who are experienced in the performance of both laminectomy and chemonucleolysis, and that this study should be conducted on a worldwide basis.

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References

Rationale for Preirradiation Chemotherapy in Treatment of Malignant Gliomas

TO THE EDITOR: Despite advances in neurosurgical technique, radiotherapy, and the administration of chemotherapeutic agents, the survival period of patients with malignant gliomas has not changed in the past 16 years. The increase in life expectancy which followed the addition of irradiation after surgical resection resulted in a median survival time of 37.5 weeks as compared to 17 weeks following surgical resection alone. The further addition of nitrosourea chemotherapy added little, lengthening survival to 51 weeks. These disappointing clinical results are in contrast to findings from pre-clinical studies which indicated that these agents are ideal choices for brain-tumor therapy by virtue of steep dose-response effects, when evaluated against brain-tumor targets in tissue culture and animal model systems.

By providing chemotherapy prior to irradiation, these drugs may be more effectively used. To understand why chemotherapy has traditionally followed irradiation, we evaluated the assumptions that underlie this approach. These include: 1) new radiotherapy approaches continue to further improve the duration and quality of patient survival; 2) chemotherapy does not work because the drugs are ineffective; 3) laboratory and clinical studies support the scheduling of irradiation before chemotherapy; 4) the neurotoxicity following irradiation and chemotherapy is independent of the sequence of their administration; and 5) postoperative irradiation is most convenient from a patient's perspective.

We will discuss each of these assumptions individually.

Assumption 1: New radiotherapy approaches continue to further improve the duration and quality of patient survival

The benefits of conventional radiotherapy reached a plateau in the early 1960's. The use of radiosensitizers, exotic particles, and alternative fractionation schedules have not improved the quality or length of survival associated with "standard" irradiation approaches. Thus, irradiation currently has palliative rather than curative intent. Brachytherapy has shown great utility when applied to a small selected group of patients, and then with risk of localized neurotoxicity. Tumor control can be achieved when high-dose external irradiation is used. Doses above 7000 rads are associated with the subacute appearance of brain necrosis or the late appearance of dementia, hypothalamic failure, or growth retardation. Pending the arrival of newer radiosensitizers or the emergence of monoclonal antibodies as carriers of radioactive materials, we are in need of alternative approaches in the treatment of malignant gliomas.

Assumption 2: Chemotherapy does not work because the drugs are ineffective

The nitrosoureas, in particular BCNU (1,3-bis(2-chloroethyl)-1-nitrosourea), have been found to be most active against glioma cells. Steep dose:response curves have been demonstrated by this class of drugs when
tested against glial cell lines in tissue culture or animal-model systems. These studies indicated that effective therapy required a high total dose of drug. Early clinical trials demonstrated a limited benefit at doses to 400 mg BCNU/sq m when the drug was administered after irradiation. However, in 1976, the EORTC Brain Tumor Group suggested that these unsatisfying results might be a product of the schedule of radiation prior to drug administration. Patients receiving CCNU (1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea) immediately after irradiation survived 50 weeks whereas those receiving CCNU at the time of tumor recurrence survived 77 weeks.

We have noted similar benefits when high doses of BCNU were provided to patients with postirradiation recurrent glioblastoma. These patients received 600 to 2000 mg BCNU/sq m along with autologous bone marrow infusion to prevent myelosuppression. Their survival for more than 1 year (11 of 12 patients) for the group and for more than 4 years for three patients is noteworthy. In our article in this issue of the Journal of Neurosurgery (Hochberg FH, Pruitt AA, Beck DO, et al: The rationale and methodology for intra-arterial chemotherapy with BCNU as treatment for glioblastoma. J Neurosurg 63:876–880, December, 1985), we report a median survival time of 92 weeks for patients with recurrent postirradiation glioblastoma treated with intra-arterial BCNU chemotherapy. When this same arterial infusion approach is applied to recently irradiated patients, white matter toxicity is produced and the survival time is limited to 64 weeks. This toxicity can be prevented by infusion of chemotherapeutic agents prior to irradiation — an approach that should combine the benefits of high-dose chemotherapy with a reduction of radiation- and chemotherapy-induced white matter toxicity. West, et al., have reported a median survival time of 12.7 months for 14 patients (of whom 78% were responders) who received chemotherapy (intra-arterial BCNU and systemic drugs) without irradiation.

**Assumption 3: Laboratory and clinical studies support the scheduling of irradiation before chemotherapy**

The provision of irradiation prior to chemotherapy was selected during the early stages of chemotherapy development when drug doses, schedules, and efficacy were still under evaluation. This sequence became engrained and was never subjected to the scrutiny applied to the evaluation of drug schedules for the treatment of systemic cancer. Indeed, experiments with the rat 9L tumor line in culture or injected into animal brain revealed that BCNU given before irradiation extended target cell life longer than either BCNU or irradiation alone or BCNU after irradiation. Preirradiation chemotherapy is used to treat systemic small-cell carcinoma of the lung, head, and neck; advanced Hodgkin’s lymphoma; embryonal cell carcinoma; and breast carcinoma. Schedules include radiation sensitization with drugs, and “sandwiches” in which drugs are given prior to and following irradiation. The malignant gliomas should not be excluded from trials that include alternative sequences.

**Assumption 4: The neurotoxicity of irradiation and chemotherapy is independent of the sequence of their administration**

The interaction between irradiation and chemotherapy may produce profound central nervous system damage. Proliferative changes of blood vessels occur following irradiation. Microscopically, these changes include fibrinoid necrosis with thickening of the vascular wall, fibrinoid deposits within the lumen, and vascular occlusion with fibroelastic and endothelial proliferation. Capillary permeability and drug uptake may be altered by such changes. Alterations in the capillary basement membrane with the development of fenestrations allow leakage of filtrates of serum and drugs. There may emerge a relationship between drug-radiation toxicity and these changes. Thus, patients receiving craniospinal irradiation followed by methotrexate (either in high systemic or subarachnoid doses) for the treatment of acute leukemia and carcinomatous meningitis develop white matter lesions that are both irreversible and often life-threatening. A similar syndrome follows intraarterial BCNU provided after irradiation: in these patients, seizures and intellectual impairment can occur, and computerized tomography reveals diffuse low absorption areas in the white matter.

**Assumption 5: Postoperative irradiation is most convenient from a patient’s perspective**

Conventional radiotherapy fractionation requires an average of 42 daily treatments. During the postoperative period the patient is obliged to undergo daily irradiation at a time when he can still experience maximum quality of life. This commitment interferes with the personal and social needs of patients. The limited value of radiotherapy may not merit this commitment by the patient during this phase of the illness. Postoperative monthly chemotherapy as an outpatient minimizes the patient’s hospital time.

In conclusion, the current schedule for combined-modality therapy of malignant gliomas is predicated upon several assumptions. Reassessment of these assumptions suggests that the provision of radiation therapy prior to chemotherapy is not optimal. The alternatives include: 1) preoperative or postoperative preirradiation chemotherapy; 2) simultaneous chemotherapy and irradiation; or 3) use of alternative drugs (5-fluorouracil, vincristine, procarbazine) provided in sequence.

Based on this evaluation, we recommend postponing chemotherapy for patients presenting immediately.