

Chemotherapy for Brain Tumors: Current Status and Controversy

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The current status of chemotherapy for primary malignant tumors of the central nervous system (CNS) is controversial and complex. Despite the fact that it is well known in the oncology community that cancer is virtually never cured with single agent chemotherapy (monotherapy), the current “standard” treatment for glioblastoma, the most lethal of all CNS tumors, is single agent temozolomide (TMZ). This relatively new drug has the advantage of being an oral agent, relatively low toxicity profile and crossing the blood brain barrier. Furthermore, it is easy for oncologists to give. A recent study has clearly demonstrated that survival is improved (3 months) if this drug is given both during and after radiation therapy.¹ However, the disease remains essentially incurable with this approach. The principle argument against using TMZ in combination with other drugs is that, thus far, studies have not established the safety and efficacy of such combinations.

It is unlikely that studies conducted in the classical clinical trial model will lead to the acceptance of combination chemotherapy as best treatment for high-grade CNS tumors. Classical therapeutic clinical trials must show a statistically significant advantage of a combination over a single agent sufficient to justify the cost and added risk that is inherent when additional agents are given. This experimental model assumes that the treatment is being given to a

relatively homogeneous group. Therefore, if only a small percentage of patients benefit and the rest do not, the treatment is deemed ineffective. Suppose, however, that the disease is not homogeneous, but heterogeneous, which is almost certainly the case. For example, the prognosis for patients with tumors that can only be biopsied, no matter how effective the postsurgical treatment, is substantially worse than those with gross total resections. Furthermore, genetic and metabolic studies indicate that these tumors are extremely complex and diverse. It is, therefore, naive to think that the majority of patients are likely to benefit from any single treatment or any combination of drugs. However, a certain subgroup might benefit substantially from such treatments.

In this context, it would be reasonable to consider not one, but perhaps several treatment options for each patient until either an effective combination is found, or all options have been exhausted. There are at least 10 drugs that have been shown to be efficacious in treatment of high-grade gliomas (carmustine, lomustine, vincristine, procarbazine hydrochloride, irinotecan, carboplatinum, etoposide, paclitaxel, vinorelbine tartrate, temozolomide, nitrogen mustard). Further, the response rate to these drugs is not dramatically different one from another. The possible combinations of these drugs are mathematically enormous given the



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1. Stapp R, et al. Concomitant and temozolomide (TMZ) and radiotherapy (RT) for newly diagnosed glioblastoma multiforme (GBM). Conclusion results of a randomized, phase III trial by the EORTC Brain and RT groups and NCIC clinical trials group. *JCO Supplement*. 2, July 15, 2004.

variety available. Nevertheless, most patients receive only one of these drugs before they fail and progress to a fatal outcome. In our Program, much to the dismay of some of the payers, we approach each patient as a unique individual. If our current first line treatment is not successful, we change to another approach provided the patient wishes to continue and has the quality of life sufficient to justify such an approach. In this manner, we have improved overall survival for the entire group and have achieved long-term survival or, perhaps cure, for some patients where such an outcome would appear to be unthinkable.

Certainly our approach is controversial. It must be continued in a manner which will allow its critical scrutiny by others and have the potential to be made available to patients outside our Program. This will require much ingenuity and creativity, but it will be done.

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