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Management of malignant gliomas: present and future

Brain tumors: the time has come to amplify research

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Despite the considerable efforts and advances achieved in imaging techniques and treatment modalities, the survival of brain tumor patients has not been improved in the last decades.[5] The most promising way to improve survival in cancer patients is prevention, but no obvious frequent risk factor has been identified to date for glioma. This pessimistic yet realistic view should neither induce a nihilist attitude nor obscure the current progress that may ultimately lead to helping patients with brain tumors.

The first step in rendering appropriate treatment is the provision of a precise diagnosis, which is used to help define the prognosis of a given patient. Conventional pathological analysis remains the best method for diagnosis but has its limitations, particularly in predicting which Grade II astrocytomas will rapidly undergo anaplastic changes. The ongoing identification of the cascade of genetic events involved in malignant transformation provides new tools to improve the comprehensiveness of pathological classification. The integration of "molecular diagnosis" in prospective studies will undoubtedly be helpful in better appraising the prognosis for patients with glioma, lymphoma, leukemia, and sarcoma. Another innovative diagnostic tool is provided by magnetic resonance spectroscopy, a powerful technique that allows the identification of certain chemical compounds in brain tumors. Interesting observations of the use of this technique are reported by Tedeschi, et al.[18] They suggest that an increase in the choline signal may be a predictor of malignancy. If this theory can be confirmed in future prospective studies designed to correlate such data with pathological and molecular diagnosis and clinical outcome, this discovery will have a major clinical impact on the routine management of glioma patients who are suspected to be experiencing malignant progression or relapse. Another potential application of magnetic resonance spectroscopy might be the selection of the region in which a stereotactic biopsy specimen could be obtained, which might avoid the underestimation of malignancy due to sampling in nonrepresentative areas.

Better definition of diagnosis and prognostic factors is likely to benefit clinical research and obviously new active compounds are still being discovered. Temozolomide, an imidotetrazine analog of dacarbazine, is a very attractive candidate because of excellent oral bioavailability and biodistribution, as well as low and predictable toxicities. Preliminary results obtained in well-designed studies suggest an

unusual antitumor effect in anaplastic astrocytoma.[13] The paper by Allen, et al.,[1] represents another aspect of clinical research, in which information is obtained by coordinating efforts in a cooperative group. This is the first attempt, to our knowledge, to investigate the potential benefits of multimodality treatment in malignant spinal cord astrocytoma observed in children. The outcome in children with this extremely rare and devastating disease appears to be improved by a combination of surgery, irradiation, and "8-in-1" chemotherapy. The results could have been even more convincing had a better methodology been used,[14] including precalculation of sample size, definition of endpoints, evaluation of the confounding effect of corticosteroids, and use of classic response criteria (this could have been done in most cases if contrast imaging had been performed within 24-48 hours after surgery to better estimate resection extent than does the surgeon). On the other hand, this study emphasizes the absolute necessity for a centralized pathological review in multicenter studies, as five of 18 institutional diagnoses were not confirmed after revision.

New drug development is currently in competition with "biological" therapies. Indeed, our current understanding in tumor biology has opened new avenues to the treatment of malignant glioma patients by inhibiting cell proliferation, inducing cell death, and blocking neoangiogenesis or restoring an appropriate immune response. Several genes that contribute to the regulation of the delicate balance between cell proliferation and cell death have been characterized. Vogelbaum, et al.,[19] take advantage of the recent identification of genes directly implicated in the control of apoptosis to transduce C6 glioma cells with the **bax** gene, the product of which (BAX) plays a key role in promoting apoptosis. As expected, they observe a decrease in growth rate in vitro, probably due to an increase in spontaneous apoptosis. Furthermore, **bax**-transfected cells exhibit a high sensitivity to ara-C, whereas wild-type cells are resistant. As discussed by the authors, these data confirm previously reported results obtained in vitro and in vivo with other tumor lineages. More important, this paper further supports the rationale for a combination of gene therapy and conventional therapies, as already suggested by transfecting **p53** to sensitize tumor cells to chemotherapy.[9]

Even as advances achieved in molecular biology and vector technology offer attractive strategies to fight glioma, the development of gene therapies will face critical difficulties, such as the potential toxicities on normal cells, immune responses against the vectors that limit the efficacy of repetitive administrations, and a low rate of in vivo targeting of tumor cells with the current procedures. In addition to the low level of in vivo transfection, this last problem is partly due to the poor capabilities of molecular compounds to move through interstitial fluid without degrading. By using a high-flow microinfusion system that allows the induction of convection flux, Broaddus, et al.,[6] show that phosphorothioate antisense oligonucleotides can be widely distributed though the brain and are stable at least for 48 hours. Future studies in which this system is used should address critical questions: What is the duration of oligonucleotides stability in vivo (days, weeks, or months)? Does this stability increase the rate of in vivo transduction; in other words, are oligonucleotides located intracellularly? Obviously, this new technique has great potential, which will need to be intensively explored in the next several years.

The last paper published in the November issue of **Neurosurgical Focus** reminds us of the hopes and mysteries of immunotherapy. The role of the immune system in the control of cancer development, growth, and dissemination has been a subject of great controversy for the past few decades. It is now well recognized that immune cells can, in some circumstances, contribute to protect the host against cancer and that T lymphocytes play a critical role in the antitumor response. In the case of glioma, several aspects of the dialogue between tumor cells and T cells remain poorly characterized,[7] and several mechanisms occur to create a state of immunosuppression in the glioma microenvironment, including the

secretion of various cytokines such as transforming growth factor- β 2 or interleukin-10,[11,12] or cell-cell interactions such as expression of the Fas ligand by glioma cells.[16,20] Despite this, results obtained in animal models demonstrate that genetically modified glioma cells used as immunogens could tilt the balance in favor of an efficient antitumoral response.[2,8] Such immunogens induce a local immune response at the site of injection, and T cells primed by glioma cells in the periphery can recirculate and reach the brain to mediate their antitumor effects.[2,3,8] In addition, promising results have recently been reported in a model of melanoma (B16 murine melanoma) found in the central nervous system. Efficient antitumor response was attained using **GM-CSF** gene modified melanoma cells[17] or bone marrow-generated dendritic cells pulsed with tumor extracts or tumor RNA.[4]

The interesting results presented by Plautz, et al.,[15] suggest that such an immunization approach could be a realistic strategy in humans. Activated T cells isolated from draining lymph nodes a few days after intradermal immunization with irradiated autologous tumor cells and GM-CSF were expanded ex vivo in the presence of anti-CD3, staphylococcal enterotoxin A and a low dose of interleukin-2. When administered to 10 patients, these activated T cells induced three convincing clinical responses. Several aspects of treatment are insufficiently discussed or investigated. What is the rationale for a stimulation with superantigens? Because the expression of CD25 on cultured T cells was highly variable, is there a correlation between clinical response and activation phenotype of injected lymphocytes? These questions (and others) clearly deserve further research. The observation that human gliomas may be sensitive to lymphocytes alone when injected systematically demonstrates that gliomas are not an exception and are potential targets for immunotherapy. To some extent, these results can be compared with the graft versus leukemia effect induced by injection of donor lymphocytes in patients with chronic myeloid leukemia who relapse after bone marrow transplant. In the case of leukemia, such an adoptive immunotherapy was an experimental procedure a few years ago and is now routinely performed.[10] There are some reasons to hope!

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