Summary of Seventh International Conference of Brain Tumor Research and Therapy

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Summary

The Seventh International Conference of Brain Tumor Research and Therapy was held from 18–21 October 1987 in Moto-Hakone, Japan. This summary of the major topics of the conference includes discussion of presentations on oncogenes and growth factors, molecular genetics, cytokines and immunotherapy in clinical treatment, novel radiotherapeutic approaches, and drug resistance and cytotoxic chemotherapy.

This international conference, co-chaired by Masakatsu Nagai and Victor Levin, followed two years after a similar conference in Asheville, North Carolina. The major topics discussed were oncogenes and growth factors, molecular genetics, cytokines and immunotherapy in clinical treatment, novel radiotherapeutic approaches and, finally, drug resistance and cytotoxic chemotherapy.

The current information on oncogenes and growth factors was reviewed by Bengt Westermark, whose breadth and depth of knowledge in this area became evident as he described interactions between oncogenes, growth factors, clonal individuality, and heterogeneity within gliomas. He suggested that one way to view the process of oncogene activation is, by analogy, to relate the activation of proto-oncogenes to pushing an accelerator, and the deletion of anti-oncogenes to releasing the brake. Westermark described A-chain and B-chain platelet-derived growth-factor dimers expressed in gliomas. Glioma cells have many receptors and growth factors to which endothelial cells and glioma cells respond. In addition, endothelial cells may be driven by separate autocrine mechanisms. Epidermal growth factor (EGF) receptors are present in at least 50% of glioblastomas; and, although these amplified receptors may play a role in cellular proliferation, there is substantial inhomogeneity in this expression of EGF receptors.

There is great interest in glioma-derived growth factors, both small and large. The small glioma-derived growth factor could be a c-sis product or a PDGF-like molecule. Research into these growth factors, which are possibly unique to gliomas, should be pursued. A question was posed early in the conference: what should be the focus of therapy? Clearly this will require specific approaches related to specific tumors — not as traditionally defined, but according to their patterns of activated oncogenes.

A high point in the conference was a lecture by Mark Israel, who began by indicating that variations in the pattern of proto-oncogene expression within a specific tumor type may denote an underlying difference in the biology among those tumors. He showed that certain patterns of gene expression might differentiate gliomas according to individually type-specific characteristics. He unfolded the fascinating story of neuroepitheliomas and their
differentiation from the larger group of neuroblastomas. Based on the presence of identical expressed oncogenes in Ewing's sarcoma and neuroepithelioma, patients with neuroepitheliomas were treated and cured by therapy that had been applied successfully to Ewing's sarcoma. In a genetically defined tumor, the expressed oncogenes are predictable. If, for example, glioblastomas could be separated into classes of genetically defined tumor types according to expressed genes, entirely new therapeutic correlations might be possible. If a marker of biologic homogeneity were defined within even a single subgroup of glioblastomas, the impact in promoting the design of new therapeutic approaches to these lesions would be profound.

Because Ewing's sarcoma and neuroepithelioma are histologically identical, Israel suggested studies of extracranial tumors that have a close resemblance to glioblastomas. Such candidates might be hypernephroma, amelanotic melanoma, and osteogenic sarcoma. The distinction of neuroepitheliomas from the neuroblastomas was facilitated by the detailed knowledge of neuroblastic differentiation; a parallel knowledge of astrocytic differentiation is lacking.

In one presentation dealing with molecular genetics and lineage-specific expression, Paul Kleihues made a novel observation on the differential effect of pregrafting and postgrafting exposure to \( \text{N-nitrosoethylurea} \). This work has implications for the influence of environmental extracellular factors in the evolutionary progression of neoplasia. In a somewhat simpler observation, James Rutka described extracellular matrix and its ability to inhibit proliferation and induction of differentiation in a glioma cell line.

The mapping of chromosomes using modern techniques has become more important in a continuing search for patterns by which to group and correlate other observations. This contribution of chromosome analysis was emphasized by other speakers, particularly Joan Shapiro and Mark Israel.

In the series of papers dealing with cytokines and immunotherapy in clinical treatment, one of the moderators, Nicholas de Tribolet, opened the session by pointing out a major limitation of immunotherapy: tumor-associated antigens of a given type are expressed in more than one tumor type, and not all tumors of a given type express them. Even within a tumor that expresses a specific tumor-associated antigen, not all cells have the same tumor-associated antigen.

De Tribolet reported a low specific index of localization for a radiolabeled monoclonal antibody in human gliomas. Although there was definite uptake of the specific antibody within the tumor, the relatively low specificity index indicated that the accumulation of antibody was due, to a significant extent, to alterations in the blood-brain barrier.

Yoshiyuki Hashimoto presented data on chemoimmunoliposomes and clearly defined the therapeutic potential of monoclonal antibodies combined with liposomes. However, there are major problems in their use as therapeutic agents, most notably the obstacles the blood-brain barrier poses to such large, complex aggregates.

De Tribolet has shown that the lymphocytes infiltrating gliomas can be cloned and that these cells are specifically sensitized to the autogenous tumor. The notion of expanding these infiltrating and specifically sensitized lymphocytes with interleukin-2 (IL-2) is an intriguing possibility.

Interferon trials continue, the most effective type of interferon and its route of administration being matters of controversy. Interferons remain of interest because they are unique and in general very well-tolerated by patients.

As the work presented from several groups indicated, \textit{in vivo} studies on lymphokine-activated killer (LAK) cells are promising because the activated cells have been well-tolerated in clinical applications. However, they have had no impact on glioma cells, despite the unquestioned scientific logic of their use. Harold Young suggested that LAK cells would be most effective when applied locally following gross complete resection of a glioma. Clearly needed is a phase III study in which patients considered candidates for treatment with LAK cells would be randomized to treated and control groups. Such patient randomization would be essential because not all tumors are suitable for this local treatment, which is usually performed by injecting cells directly into the cavity produced after resecting a glioma.

Tumor necrosis factor has been shown to have an immunomodulatory effect on glioma cells through