



The
CHRISTOPHER S. ELLIOTT
MEMORIAL
Glioblastoma Brain Tumor Research Fund

Update 2006

Brain Tumor Research at Dana-Farber/Brigham/Christopher S. Elliott Neuro-Oncology Lab for Glioblastoma Brain Cancer Research and Women's Cancer Center

Background

Each year in the United States, approximately 40,000 people will be diagnosed with primary brain tumors, of which nearly 20,000 are malignant. The most common and most serious form of malignant brain tumor is glioblastoma multiforme. In addition over 170,000 people each year will be diagnosed with metastatic brain tumors (tumors that have spread to the brain from a cancer elsewhere in the body). Despite advances in treatment, the outcome is still poor and we desperately need better therapies.

In recent years, the advances in our understanding of the molecular basis of cancer have led to the potential for rational drug development based on the molecular changes of specific tumors. The prime example of this kind of dramatic breakthrough in the treatment of cancer is the success of the drug Gleevec in the treatment of chronic myelogenous leukemia (CML) and gastrointestinal stromal tumors (GIST). Promising preliminary results have also been produced by a number of other targeted molecular therapies. However, unlike CML and GIST, which have only one molecular abnormality that is blocked by Gleevec, malignant brain tumors have multiple genetic abnormalities. Therefore, it is likely that combinations of targeted molecular drugs will be more effective than single drugs in these tumors.

Research

1. Targeted Molecular Therapy

The Center For Neuro-Oncology at Dana-Farber/Brigham and Women's Cancer Center has been one of the leaders in the country in developing targeted molecular therapies for brain tumors. There are a large number of ongoing clinical trials evaluating targeted agents for brain tumors. Preliminary results from these studies suggest that most of these drugs have some anti-tumor activity. However, ultimately these drugs have the best chance of working

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when combined with one another or with radiation therapy or chemotherapy. Currently we have a very active laboratory research program seeking to identify the most promising new drugs and studying the best combinations of these drugs for patients with brain tumors. This work has led to a second generation of clinical trials using combinations of targeted molecular drugs. One particularly promising clinical trial using the combination of Tarceva and CCI-779 is currently in progress. These two drugs block the two main molecular abnormalities in glioblastoma, significantly increasing the likelihood of success in killing the tumor cells. Several other trials using different combinations of molecular drugs are scheduled to begin in the near future.

There is also a large laboratory effort studying drugs that block novel targets in brain tumor cells including HSP 90, Notch, Akt, PI3 kinase, CXCR4, insulin-like growth factor receptor, and histone deacetylase. Many of these drugs are showing promise in the laboratory and will be brought to clinical trials in the near future,

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2. Molecular Profiling of Tumors

An important focus of research is to characterize the molecular changes in brain tumors and understand the genes that cause these tumors and enable them to become resistant to treatment with radiation therapy and chemotherapy. The ultimate goal is to determine the molecular characteristics of each person's tumor and select the most appropriate targeted molecular treatment based on these molecular abnormalities. This tailoring of treatment to each person gives us the greatest chance of achieving a cure. The technology that allows us to characterize the molecular changes in each person's tumor is developing rapidly and this will be a reality in the very near future.

3. Inhibition of Angiogenesis

Another area of research is the development of drugs that block a tumor's ability to make new blood vessels, a process termed angiogenesis. There is large laboratory effort studying new drugs that block angiogenesis and combining these drugs with radiation therapy and chemotherapy to increase their effectiveness. We have started trials of several drugs (AZD2171, sorafenib, enzastaurin, avastin and VEGF-Trap) that block VEGF, the main cause of angiogenesis in brain tumors. Preliminary results have been very exciting with 50% of patients showing responses

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4. Stem Cells

There is increasing evidence that brain tumors may arise from abnormal stem cells in the brain. Dr Santosh Kesari in the Center For Neuro-Oncology has been working with a large number of colleagues to understand the role of stem cells in the development of brain tumors. Understanding the function of stem cells will allow us to specifically target these cells to treat brain tumors. The Neuro-Oncology Laboratories at Dana Farber have discovered that *Olig* genes play a crucial role in allowing stem cells to become gliomas. Therapies directed against these genes may represent a novel way to treat malignant gliomas.

Information

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