

# PRIMARY BRAIN TUMORS - RADIATION PLUS CHEMOTHERAPY

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There are many approaches for high-grade primary brain tumors. Brain cancers are those defined as starting within the brain. Another major category of patients are those with brain metastases, which are cancers that start from other organs in the body and spread to the brain. These are not considered primary brain cancers but metastases and will be spoken of in a subsequent column.

While brain tumors occupy only about 2% of malignancies, they are notable for their high visibility and high lethality. There are about five cases per hundred thousand Americans. Thus about seventeen thousand Americans are diagnosed annually with thirteen thousand deaths. Some of the most common malignancies include anaplastic astrocytomas, which are considered grade III primary brain tumors and glioblastoma multiformes, which are grade IV.

The usual therapy includes surgery, radiation and/or chemotherapy. The overall prognosis is bleak with standard therapy. The median survival for glioblastoma patients is about nine to twelve months and two-year survival is only about 10%. Anaplastic astrocytomas, which would be considered grade III, have a better survival rate. Over many decades a type of chemotherapy called Nitrosoureas has been the standard of care in the chemotherapy department because it penetrates the blood/brain barrier although the improvement in survival is only modest and some chemotherapists have steered clear of this approach.

Supp et al, in a study published in the Journal of Clinical Oncology, discusses the Phase II study of the use of Temozolomide.

A relatively new drug - Temozolomide or Temodal or Temodar is an alkylating agent that has shown activity for recurrent gliomas. The medicine is given orally and is well absorbed. It does cross through the blood/brain barrier, which limits other chemotherapies being effective for brain tumors. For those with recurrent glioblastomas there was a response rate of 8%, but about 45% more had stabilization of the cancer with a six-month progression free rate for those treated and Temozolomide might have eighteen percent and six months survival rate of 46%.

In these trials Temozolomide was given at a dose of 150 to 200mg/m<sup>2</sup> per day for five days every twenty-eight days. Less than 10% of the patients had severe blood reactions.

There is data suggesting synergistic activity between Temozolomide and radiation, with radiation given concurrently. For this reason a study was instituted using radiation plus Temozolomide followed by adjuvant or additional Temozolomide for patients with newly diagnosed glioblastomas.

Patients were diagnosed to have glioblastomas for this study. Blood tests had to be adequate and enrollment had to be within twenty-eight days from biopsy or resection. Patients had to have no other underlying diseases such as AIDS, HIV or hepatitis.

Patient received Temozolomide - 75mg./m<sup>2</sup> times seven days a week for six to seven weeks, one hour before radiation. Radiation was given at 200 rad a day, five days a week for a total dose of 6000 rad. Treatment and volume included the enhancing lesion plus a 2cm to 3cm margin. Three-dimensional reconstruction was used. Four weeks after radiation the patient received adjuvant Temozolomide 200mg/m<sup>2</sup> daily for five days every twenty-eight days for six cycles.

In the study by Stupp, et al sixty-four patients were enrolled with six patients ineligible. Two-thirds of patients were fifty years or older with 20% between the ages of forty and fifty. Seventy-seven percent had undergone debulking surgery, with 42% being considered macroscopically complete resections. However, it should be noted that post-operative imaging was not performed in all patients. Twenty-three percent had stereotactic biopsy only. On average, the start of treatment

took place twenty-five days after surgery.

Sixty-two patients had radiation plus Temozolomide. Temozolomide was discontinued in four patients because of toxicity - two with infection and two with lowering of the platelet count. Adjuvant Temozolomide was given to forty-nine patients. The dose limiting toxicity of Temozolomide was suppression of the blood counts. Thirty-eight patients died at time of analysis with the median follow-up duration at twenty-three months and minimum follow-up of surviving patients at ten months.

The median survival was sixteen months with 58% of the patients alive at one year and 31% alive at two years. With patients less than fifty years of age the eighteen month survival rate was 56%. In patients more than fifty years old the median survival rate was eleven months. People who had debulking surgery had a median survival of seventeen months. For those who did not have debulking surgery, the survival rate was five months.

In general it is well known that older patients do less well with glioblastomas than younger patients. Also patients who have debulking surgery where the cancer is said to be totally removed tend to have smaller tumors in locations of the brain that are more amenable to surgery or more superficial.

While this data certainly is impressive the fact is that patients who do not undergo debulking surgery certainly have a poorer survival. It was also true that patients who were fifty years or older also did modestly.

The authors concluded, "Non-randomized comparisons between trials have to be approached with caution. Differences in study of protocols and changes in response evaluations, pathologic classifications, imaging techniques, standard and support of care make comparing trials difficult. This prognostic classes model may overcome some of the shortcomings associated with comparing trials." Furthermore, "In summary the results of this trial demonstrate that concomitant 5FU plus continuous daily Temozolomide therapy followed by additional cycles of the standard regimen of adjuvant Temozolomide is well tolerated and may prolong survival in patients with malignant glioma. However it remains unclear whether the improved survival resulted from continuous administration schedule of Temozolomide and additive cytotoxic effect of combined radiation and Temozolomide, or simply because of adjuvant treatment with an active agent. The survival benefits may be attributed to the ability of Temozolomide to penetrate the CNS to a greater extent than to many other chemotherapy agents. Temozolomide and concurrent radiation, followed by adjuvant Temozolomide/chemotherapy is a promising regimen for patients with malignant glioma. This regimen is currently being compared with standard radiation alone in a national randomized trial coordinated by the European Organization for Research and Treatment of Cancer and the National Cancer Institute of Canada."

While our group has many patients undergoing sophisticated radiation such as stereotactic brain radiosurgery both in daily and high dose hyperfractionated techniques some patients are currently receiving daily Temozolomide in an attempt to enhance the radiation effects.

Our best results for recurrent glioblastoma include a combined modality approach using the best of surgery, fractionated radiosurgery, concurrent chemotherapy followed by immunotherapy injected directly into the tumor area.

Survival data for recurrent glioblastomas from the time of this innovative treatment is double the average survival for newly diagnosed glioblastomas in America. This is remarkable. Our data has been sent to national and international medical meetings for presentation. In the meanwhile, our patients have access to this technology.

Other patients with recurrent brain cancers are undergoing Temozolomide or other sophisticated therapies such as hyperfractionated stereotactic radiosurgery with concurrent chemotherapy,

immunotherapy directly infused into the tumor crater or combined approaches.

Our ongoing analysis is being reported. Just recently an abstract was prepared using immunotherapy and sequential stereotactic brain radiosurgery for high-grade primary brain tumors showing very promising results. It is anticipated that our data will be presented at major medical meetings worldwide.