Fast neutron therapy for malignant astrocytomas
A review

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Abstract

The treatment of supratentorial malignant gliomas has continued to be a major problem for neurosurgeons and oncologists. Post-operative conventional radiotherapy is known to prolong survival and to enhance the quality of life. Local persistence of tumor kills the majority of patients. Fast neutron irradiation is being utilized to treat malignant gliomas based on its reputed radiobiological advantages for treatment of large tumors and the encouraging preliminary reports showing tumor eradication in post-radiation biopsy and autopsy specimens. This paper reviews the results of fast neutron irradiation alone and in combination with photons and hypoxic cell sensitizers. Survival comparisons do not show any superiority for neutrons compared to conventional radiation. However, post-neutron radiation tissue samples have shown less aggressive and minimal residual tumor in many instances. At the same time radiation necrosis has emerged as a significant problem. In summary, even though neutron irradiation can eradicate malignant gliomas a therapeutic window has yet to be identified.

Introduction

Recent statistics (1) indicate that approximately 13,700 new cases of primary brain and central nervous system tumors occur each year in the United States. While there has been considerable improvement of survival in some other malignancies, treatment of primary brain tumors has continued to be a major problem for neurosurgeons and oncologists. Approximately 2.0% of all cancer-related deaths are from primary brain tumors (10,100 fatal cases every year). Anaplastic astrocytoma and glioblastoma multiforme are the most malignant of all intracranial neoplasms. They tend to be highly infiltrating in character and can rarely be completely removed surgically. Many authors believe that patients who have had some form of resection have a longer survival than patients who have biopsy only (2-4). However, surgical mortality rates are higher with more extensive resections. Some tumors are unresectable because of the close proximity to vital brain structures (5). The radiation oncologists sees many malignant astrocytomas after partial resection. Even in patients who have had an apparently total resection, recurrence occurs frequently and so radiation therapy has become an important part of overall management. Post-operative conventional radiation therapy with photons (X-rays or γ-rays) both prolongs survival and enhances quality of survival (2, 6-8). Survival can be measured in months and reported survival frequencies range from 55 to 67% at 6 months, 27 to 39% at 12 months and 8 to 20% at 24 months. Relentless local growth of tumor, rather than metastases, kills the patient. Age,
histology and Karnofsky performance status at the initial presentation were shown to be the most significant prognostic factors in all the glioma studies (6, 8, 9).

Investigators in recent years have shown considerable interest and effort in exploring new therapeutic options such as higher doses in conventional photon irradiation (2, 7, 10) and a combination of photon irradiation and chemotherapeutic agents that cross the blood brain barrier (6, 9, 11). Preliminary analysis suggests that no advantages have accrued so far from any of these maneuvers. Some improved results have been reported with radioactive implants or brachytherapy (suitable only for relatively well localized tumors) and with the use of heavily ionizing particles such as neutrons, heavy charged particles and pions.

Hypoxic cells are known to be present surrounding the necrotic foci in all solid tumors. Many malignant gliomas have multiple areas of necrosis (12). The necrosis may be a further indication of the hypoxic state. The hypoxic cell population is thought to be less responsive to the effects of conventional photon radiation since the presence of oxygen is important for the effects of low-LET (linear energy transfer) ionizing radiations. Attempts to improve the killing of hypoxic cells have involved the use of hyperbaric oxygen (13), hypoxic cell sensitizers (14–18) and high-LET radiation (19–22).

High-LET radiation such as neutrons or pi-mesons have been used alone and combined with conventional radiation. Hypoxic cell sensitizers have been used with both conventional X-rays and with neutrons. RTOG Phase I/II protocol 78–01, utilizing Misonidazole with conventional photon irradiation ± BCNU chemotherapy, evaluated 49 patients and found local tumor growth was still the primary cause of death (14). The lack of benefit from Misonidazole combined with photons and BCNU has also been reported in randomized RTOG study 79–18 where BCNU and radiotherapy was used as the standard treatment (23).

High-LET radiotherapy theoretically has three main advantages over conventional photon irradiation:

1. less dependency on oxygenation, that is, a lower oxygen enhancement ratio (OER) (24);
2. a predominantly single hit form of cell damage which is less susceptible to repair (24, 25);
3. absence of repair of potentially lethal damage which is believed to contribute to the radioreistance of many tumors (26).

All of these advantages might contribute to a clinical benefit in the treatment of malignant gliomas by neutrons.

Pilot studies

Pilot studies with fast neutrons

Some initial observations are available from pilot studies done with fast neutron radiotherapy to the whole brain. Preliminary results from Hamme-smith (19) and the University of Washington in Seattle (20, 21) indicate that fast neutron radiotherapy has the potential for eradicating high grade tumors in the brain. In a controlled pilot study Caterall et al. (19) have treated 30 patients with fast neutrons and 33 patients with conventional photon radiation therapy between 1973 and 1976. No difference in survival was demonstrated. A post treatment assessment was available for 16/30 patients treated with neutrons either at a second-look craniotomy or at autopsy. In 11/16 such patients, either no tumor was found or only microscopic foci of abnormal cells were observed. In 5/16, moderate to gross tumor recurrence was present. From the control group, seven patients went to autopsy; six had moderate to gross residual disease.

In the University of Washington, Seattle (20) 36 patients received either fast neutron therapy alone (26) or neutrons in combination with photons as a 'mixed beam' regimen (10). Apparent tumor eradication was recognized in 14/15 patients at autopsy. The interesting observations were coagulation necrosis in the region of tumor intermixed with reactive astrocytes. A diffuse gliosis and white matter demyelination were found in remote areas in the brain. This probably resulted in death since no survival advantage could be demonstrated compared to historical controls treated with conventional photon irradiation.

These investigators pointed out that several physical and biological factors have an important bearing on the interaction of neutrons with brain tissue since similar doses have been used without inflicting serious organ damage in large number of patients with tumors in other sites (27). Neutrons are selectively absorbed in hydrogen containing tissues...
such as fat. Therefore, the lipid content of the normal brain tissue produces a greater absorbed dose than would be the case in other tissues. The increased lipid content, oxygen metabolism, the relationship of blood vasculature with nervous tissue and the volume of brain irradiated were pointed out as some of the key factors. The inclusion of certain vital structures like the hypothalamus and brain stem in the high dose zone may have been even more critical.

**Fast neutrons in combination with photons**

In light of the Seattle experience, RTOG protocol (76–11) was designed to restrict the neutron irradiation to the primary volume as defined by CT scanning (28). Whole brain irradiation with photons consisted of 50 Gy (1 Gy = 100 rads) in 5 weeks, giving 1.80 and 2.00 Gy daily fractions, 5 fractions per week. Patients were then randomized to a boost with photons (15 Gy) or with neutrons (15 Gy equivalent). The equivalence of neutron and photon doses depends on physical (absorbed dose) and biological factors (relative biologic effectiveness or RBE). RBE ranges from 3.0 to 3.5 depending on beam energy.

The primary end point of the study was survival time, but radiation toxicity and time to symptomatic recurrence were also of interest. A total of 158 evaluable patients were analyzed. Approximately 10% of the patients in both arms had the more favorable histology of anaplastic astrocytoma. None of the patient characteristics were significantly out of balance between the treatment groups. Median survival was 9.7 months in the neutron boost group and 8.5 months in the photon boost group. There was no significant difference between treatment groups within any of the subgroups according to different prognostic variables, even with a stepwise Cox model analysis (28). The cause of death was attributed to tumor in most cases. An unpublished survival analysis through September 1, 1984 shows the same results. The 2, 3 and 4 year actuarial survival rates for the neutron boost are 12%, 5% and 3% as compared to 22%, 13% and 11% for the photon boost (Table 1). No treatment complications were reported.

Autopsies were reported in 42 subjects (about 25% of the deaths). In 12/15 patients who received the neutron boost and 24/27 patients who received photon boost, residual tumor was identified as post-mortem examination. The interesting finding was the difference in the histopathological picture in the two groups. In some of the patients who received the neutron boost, post-mortem examinations revealed significant necrosis of the primary tumor volume with scattered bizarre cells throughout. It was difficult to determine whether these were reactive astrocytes or viable tumor cells. It was felt that there was no expansively growing tumor. In contrast, there was a region of infiltrating proliferating tumor mass with actively proliferating vascular component surrounding a central necrotic region in the patients who had received photons as boost.

**Fast neutrons in combination with Misonidazole**

Of the hypoxic cell sensitizers, the Misonidazoles (14–18) have been used most in clinical studies. Animal experiments have suggested reduction of OER (oxygen enhancement ratio) from 1.6 to nearly 1.0 with the use of neutrons and hypoxic cell sensitizers in combination (24). A phase I-II study was done at the Fermilab Neutron Therapy Facility to evaluate the feasibility and toxicity of combining neutron radiation with Misonidazole in the treatment of malignant astrocytomas (29). The incremental neutral dose was 3 Gy per fraction. A total absorbed dose of 18 Gy was delivered to tumor bed, of which 12 Gy were given to the whole brain (30). Assuming an RBE of 3, 18 Gy of neutrons is biologically equivalent to 54 Gy of conventionally fractionated photon therapy. Figure 1 represents the isodose distribution in a patient with glioblastoma multiforme in the occipital lobe. Each treat-

| Table 1. Updated survival rates for 76-11 whole brain photon plus boost. |

<table>
<thead>
<tr>
<th>1 Year (%)</th>
<th>2 Years (%)</th>
<th>3 Years (%)</th>
<th>4 Years (%)</th>
<th>Median (months)</th>
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<tr>
<td>Photon boost</td>
<td>40</td>
<td>22</td>
<td>13</td>
<td>11</td>
</tr>
<tr>
<td>Neutron boost</td>
<td>38</td>
<td>12</td>
<td>5</td>
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ISODOSES FOR GLIOBLASTOMA MULTIFORME OCCIPITAL LOBE

Fig. 1. Typical neutron isodose distribution for a patient treated for malignant astrocytoma arising from the occipital lobe.

Tissue was available for post-treatment histopathological examination in 13 patients, either from second craniotomy and debulking surgery or autopsy examination. One of these patients had random biopsies in which only atypical astrocytes were present. Residual tumor was identified in the remaining 12 patients, 6 of them with similar histopathological characteristics but with reduced tumor cell density overall. In 6 of these 12 patients astrocytic tumor without the diagnostic features of glioblastoma was identified in the post irradiation specimens while the original surgical specimen had been diagnosed as unequivocal glioblastoma multiforme. Parenchymal necrosis, chiefly of white matter, and vascular changes typical of radiation effect in and around the necrotic areas were identified in each of the 12 patients.

A comparable group of 25 patients was subsequently treated with similar dose, time and fractionation, but without the Misonidazole. The median survival for the whole group was 12.5 months. There was no difference in survival between the patients treated with Misonidazole plus neutrons versus patients treated with neutrons only (Fig. 2). In the few patients where post-radiation tissue was available for histopathological analysis, both residual tumor and necrosis associated with vascular changes were identified.

Figure 3 depicts the survival comparison of glioblastoma multiforme patients of age 70 years or less with initial Karnofsky performance score of 80 or more. There were no differences in survival (p=0.36) between patients treated with photons with or without a neutron boost and patients treated with neutrons with or without Misonidazole. Median survivals are similar and the one-year survival rates are 36%, 49% and 45% for patients treated with photons only (60 Gy), photons (60 Gy) plus a neutron boost (10 Gy) and neutrons with or without Misonidazole, respectively. Forty-
Current studies

Current protocols are designed to further utilize the potential ability of fast neutrons to eradicate these tumors while preserving normal tissue as much as possible. These studies include a mixed modality protocol (RTOG 80-07) and a trial of accelerated fractionation (Fermilab) delivered over a shorter overall period (3 weeks compared to 6 weeks in the previous studies). In the latter study, 10 Gy (neutrons) is delivered to the whole brain in 2 weeks time with two treatments each week (four fractions) followed by a boost to the tumor bed of 6 Gy in two fractions. The total tumor dose is, therefore, 16 Gy in six fractions over 3 weeks. This new study was prompted by the finding of both residual tumor and radiation necrosis in the majority of patients treated with slightly higher doses over a longer period. It is believed that with fast neutron irradiation, the overall time period in which the course of therapy is delivered is highly significant for the final outcome (31), particularly when the tumor cells proliferate faster than those of the associated normal tissue.

Histopathological review

Tissue from 25 patients has been available for post-treatment histopathological examination as a result of second craniotomy and debulking surgery or autopsy. Each patient had received a total of 18 Gy. Residual tumor was identified in 24 patients; one patient had random biopsies in which only atypical astrocytes were present. The pre- and post-treatment diagnosis coincided in 16 patients with identifiable residual tumor. In seven patients the pre-treatment diagnosis was glioblastoma multiforme while the post-treatment tumor was less cellular, more uniform, and was diagnosed as astrocytoma with atypical or anaplastic features. In one patient the tumor had evolved over a 24-month period from astrocytoma with atypical or anaplastic features (pre-treatment) to frank glioblastoma multiforme (autopsy).

Necrosis and vascular changes characteristic of radiation effect were present in all of the cases examined including the patient with post-treatment atypical astrocytosis. The anatomic extent of these changes is indicated best by the results of neuro-pathologic examination by one of us (JSN) on the whole brain from ten cases. In nine of these, radiation lesions involved tumor and parenchyma in the cerebral hemispheres bilaterally. The changes were usually most extensive in the hemisphere in which the tumor had originated. With one exception the contralateral hemisphere was less severely affected. In the only case without bilateral lesions, the patient had died 4 months following completion of radiation therapy. In addition to the cerebral hemispheres, lesions were noted in the corpus callosum, midbrain, striate pons and cerebellar white manner.

We have shown that the presence of coagulation necrosis is a major prognostic criterion with regard to malignant supratentorial astrocytomas (12). The application of this criterion is limited following radiation treatment because the therapy induces tumor necrosis which is indistinguishable from spontaneously occurring necrosis characteristic of
glioblastoma multiforme. In our examination of post-treatment specimens, the diagnosis of glioblastoma was based upon the following histologic features: marked cell density and pleomorphism; pseudopalisades with central necrosis; and vascular hyperplasia with formation of glomeruloid structures. In 7 of 24 patients with residual tumor, the histologic characteristics of the post-treatment tumor had changed and were no longer typical of glioblastoma. Little information is available, however, regarding the correlation between the histologic appearance of malignant astrocytomas following neutron treatment and their subsequent biological behavior. It is not clear whether the residual astrocytic tumor seen following treatment in the seven cases with the pre-treatment diagnosis of glioblastoma multiforme would eventually develop, once again, into frank glioblastoma or grow in a less aggressive manner. This area requires further investigation.

Summary

Interesting and encouraging results have been reported by Dr. Catterall (27) in treating locally advanced and radioresistant malignancies with fast neutrons. Since malignant gliomas present a significant problem in oncologic management, many investigators have utilized new and experimental approaches. Preliminary studies (19–21) with fast neutrons in the treatment of malignant gliomas revealed the efficacy of neutrons in eradicating these tumors. However, survival was unchanged since patients were dying of, possibly, treatment-related problems. Subsequently in the U.S., studies were designed to combine neutrons and conventional radiation in the treatment of malignant gliomas. The idea was to make use of the potential of neutrons to eradiate tumor at the same time minimizing the risk of radiation necrosis. The results from this study (28) confirmed the efficacy of neutrons in eradicating tumor as seen by autopsy information. However, survival was still unchanged compared to conventional radiation.

Hypoxic cell sensitizers were combined with fast neutrons in a later study (29) in an effort to radically attack the hypoxic problems. Survival was identical in a similar group of patients treated with conventional radiation. Post-radiation histopathological analysis was interesting in this group of patients. Although residual tumor was identified in almost all patients, the cell density was diminished compared to the original surgical or biopsy material and in a few cases only minimal residual tumor was found. In spite of this, no real therapeutic gain could be demonstrated, since radiation necrosis was identified in almost all instances.

Current studies have been modified in dose, time, fractionation and also in the way neutrons are combined with photons in mixed beam therapy. The aim is to identify a therapeutic window where aggressive treatment might result in complete eradication of the tumor at the same time minimizing injury to the normal brain. So far, survival comparisons with conventional radiation have shown no superiority for neutrons either alone or in combination with photons or hypoxic cell sensitizers.

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