Boron neutron capture enhanced fast neutron radiotherapy for malignant gliomas and other tumors*

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Summary

Both fast neutron radiotherapy and boron neutron capture therapy have been investigated as new radiation treatment techniques for patients with malignant gliomas. While each of these techniques individually has shown the potential for pathological eradication of malignant glioma, to date neither has evolved into an accepted, improved method of treatment. We have recently begun a research program investigating the feasibility of combining the benefits of both types of therapy. As a fast neutron beam penetrates tissue some of the particles are degraded to thermal energies. These can be captured by $^{10}$B or other suitable isotopes resulting in a highly-localized release of additional energy during a course of fast neutron radiotherapy. In this article we will review the rationale for such an approach, and review the underlying physics as well as in vitro, in vivo, and early human studies testing its feasibility. If appropriate carrier agents can be found that preferentially-localize in tumor cells, this approach can be applied to many different tumor systems.

Introduction

Conventional treatments for malignant glioma, particularly glioblastoma multiforme, have yet to provide patients with long-term disease free survival [1]. Improvements in surgery, chemotherapy, and radiation have been unable to eradicate malignant glioma, and survival for patients with these malignancies remains limited. As the majority of patients with malignant glioma ultimately succumb to locally recurrent disease, the challenge for improved local therapy remains. Surgery is inherently limited by the microscopic interdigitation of the disease with the normal brain which may extend a considerable distance from the primary tumor mass. Because of its intrinsic radioresistance, conventional photon radiation is not effective in sterilizing residual disease left behind after surgery since the required doses exceed the tolerance of normal brain tissue. New strategies of radiation treatment need to be developed if the local failure problem is to be overcome for malignant glioma. One potential new strategy is neutron radiation. Neutron radiation treatments of malignant glioma have been investigated both as fast neutron radiation and as boron neutron capture therapy (BNCT). While aspects of each of these two types of neutron treatments have shown promise, independently, neither has developed into a clearly improved method of radiation treatment.

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Fast neutron radiotherapy and boron neutron capture therapy have existed as separate forms of therapy since their conception shortly after the discovery of the neutron by Chadwick in 1932. The reason for these independent development paths is likely due to the difference in the energy of the neutrons required for each of the two treatments. BNCT utilizes thermal or epithermal neutrons which are currently generated using neutron reactors. Thermal neutrons cause few ionizations within tissues and thereby produce little DNA damage and biological effects independently. Because of their low energies, however, thermal neutrons have a larger capture cross section by selected neutron isotopes. The probability of such a capture reaction occurring is related to the energy of the neutron and decreases approximately as $E^{-1/2}$ where $E$ is the neutron energy. BNCT achieves therapeutic effects through the capture of a thermal neutron by $^{10}$B which then goes into an excited state of $^{11}$B. $^{11}$B instantly decays according to the following equation:

$$^{11}\text{B} \rightarrow ^{7}\text{Li} + ^{4}\text{He} + \gamma (2.32 \text{ MeV}) \quad 93.7\%$$

$$^{10}\text{B} + ^{1}\text{n} \rightarrow ^{11}\text{B} \rightarrow ^{7}\text{Li} + ^{4}\text{He} + \gamma (2.79 \text{ MeV}) \quad 6.3\%$$

The $^7\text{Li}$ and $^4\text{He}$ fission fragment release large amounts of energy, causing a dense ionization pattern within a precisely localized area (track lengths of $^7\text{Li}$ and $^4\text{He}$ are 6 and 9 microns, respectively). The tagging of tumor cells with $^{10}$B and treatment with BNCT was first proposed in the 1930's [2]. Subsequently, ample laboratory work provided proof of this concept but unfortunately, early human trials of BNCT in patients with malignant brain tumors showed no therapeutic benefit and high rates of normal tissue complications [3]. These early human trials were suboptimal in terms of both the boron carrier agent and the neutron beam. A present further BNCT studies using both improved compounds and beams are taking place in both Japan and the United States and shortly will begin in Europe as well.

Unlike BNCT, fast neutron radiotherapy achieves therapeutic effects directly through the disposition of energy from high energy neutrons in the range of several tens of MeV. These high energy neutrons are generated using cyclotrons or high-energy particle accelerators. Compared to conventional photon radiation, fast neutron radiation creates more dense ionization tracts within tissue. This difference allows fast neutrons to cause a greater degree of double-strand DNA injury within tumor cells and thereby achieve a higher relative biological effectiveness (RBE) than conventional photon therapy. This increased percentage of double-strand DNA injury within tumor cells reduces tumor sublethal damage repair, and tumor radiosensitivity secondary to cell cycle effects [4]. Additionally, fast neutrons rely less on oxygen to achieve DNA damage, and as such, radiosensitivity secondary to tumor hypoxia is reduced [4]. The earliest trials were carried out in the 1930's and showed considerable toxicity and little efficacy [5]. However, the potential biological advantages over conventional photon radiation have led to the continued, extensive testing of fast neutron radiotherapy in phase III human trials. While an improved therapeutic outcome has been observed for certain tumor sites such as salivary gland tumors [6], locally-advanced prostate cancer [7], and sarcomas of bone and soft tissue [8]; in many other tumors no therapeutic advantage has been found. In particular for malignant gliomas, fast neutron treatment did not achieve an advantage over conventional photon radiation [9–12]. A autopsy information from these trials showed a high degree of tumor sterilization but damage to surrounding normal brain issue caused the patients' demise. In contrast, patients treated on the photon control arms of these studied uniformly died of expansively growing tumor.

There may exist an opportunity for combining the effectiveness of fast neutron radiotherapy and BNCT. During fast neutron radiotherapy, a small fraction of the neutron beam is degraded to thermal energies at tumor depths. Thus far, this 'slow' component of the neutron beam has never been utilized therapeutically. Boron neutron capture (BNC) may provide a selective mechanism in which to augment the therapeutic ratio achievable with fast neutron radiotherapy. Due to the steep dose-response tumor control curve, a small enhancement may achieve a clinically-relevant change in the therapeutic ratio [13]. We have recently begun prelimi-