REVIEW OF MEDICAL TREATMENT WITH HEAVY CHARGED PARTICLE BEAMS

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Abstract

Particle beams including both neutrons and charged particles have been studied in a number of medical facilities in several countries during the past 2 decades. Only in recent years have beam delivery techniques, treatment planning and clinical utilization of these beams begun to be optimized. Neutrons do not have a dose localizatior advantage when compared to standard Xray therapy, but do offer some high LET biological advantages for certain types. Charged particles have distinct dose distribution advantages leading to a higher ratio of dose in the tumor compared to adjacent normal structures. This improvement of the therapeutic ratio has led to higher local control rates and prolongation of survival for a number of tumors adjacent to critical structures such as the brain and spinal cord. Heavy charged particles offer additional biological advantages to their physical dose localization parameters. Promise of improved control of unresectable, slowly proliferating tumors such as those arising in bone, soft tissue, prostate and salivary gland has been seen in preliminary studies. Further research in optimization of therapy techniques with heavy charged particles is warranted to maximize the potential benefit of the use of heavy charged particles in medical therapy.

Introduction

With the advent of improved diagnostic techniques for tumor localization, including computerized tomography (CT), magnetic resonance imaging (MRI), and positron emission tomography (PET), and reliable linear accelerators for hospital use, local and regional control of unresectable neoplasms has steadily increased. However, even with modern megavoltage radiotherapy, and multimodality treatment, including irradiation, chemotherapy and surgery, some human tumors remain resistant to therapy. Often their treatment by standard radiation techniques would require unacceptably high doses to nearby normal structures with loss of structural integrity or function. Heavy charged particle radiotherapy is almost unique in value where unresectable tumors lie in or near critical structures and may be the only treatment which can be successfully accomplished with preservation of quality of life.

Using heavy ion beams, significant advantages accrue in safely delivering high doses of radiation to tumors adjacent to the eye, brain, cranial nerves, spinal cord, heart, esophagus, kidney, intestine, bladder, and other vital structures.

This ability to deliver a lethal tumor dose while maintaining the dose to nearby critical structures at safe levels is a hallmark of heavy charged particle treatment, which we have termed dose-localization therapy. When this treatment is done with protons or helium ions, the physical dose-localization advantage is paramount [3,4,6]. With heavier ions such as carbon or neon, the biological advantages of high LET energy deposition are also present. Evidence has been gathered both from laboratory experiments and preliminary human trials that the high LET component of heavy ion treatment is effective in destroying some tumors which are radioresistant to standard low LET Xray treatment [2,5,10,11,16,18]. The rationale for the use of heavy charged particles in the treatment of human cancers is therefore based on:

1. The precise delivery of radiation dose to the tumor with a significantly lower dose to surrounding normal tissues.

2. The deposition of biologically more effective high LET radiation, affording a higher chance of tumor destruction.

Over the past several decades, research studies in the use of these heavy charged particles have been undertaken at the University of California Lawrence Berkeley Laboratory. In the early 1970s with the availability of the Bevatron for biology and medicine, a series of pretherapeutic studies were begun on the biophysical effects of heavy ion beams of interest in the treatment of human cancers [1,2,18,19]. The effects on cells, tissues and tumors relative to heavy ions were studied extensively in the laboratory as support for the human clinical research trial which began in 1975.

The goals of the clinical research trial are:

1. To develop the best methods for clinical use of heavy ions in the treatment of human cancers.

2. To demonstrate the clinical effectiveness of these beams for various human tumors.

About 1200 patients have been treated starting with helium ions in 1975 and progressing to heavier ions such as carbon, neon, silicon and argon. However, extensive availability of neon ions for Phase I-II studies did not occur until 1981.(Table 1).

Currrent prospective trials underway at LBL include:

1. Randomized Phase III trial of helium ions versus I^{125} plaque therapy for uveal melanoma.

2. Randomized Phase II dose searching study for head and neck chordoma/chondrosarcoma.

3. Randomized Phase III trial for carcinoma of the prostate (neon vs megavoltage Xray).

4. Randomized Phase II trial of helium versus neon for sarcoma, base of skull tumors, unusual histology.

5. Randomized Phase II dose searching study for glioblastoma of the brain.

Helium Ions

The hallmark of dose localization therapy with protons and helium ions is the superb dose distribution available secondary to the physical parameters of these beams. A high level of control can be achieved for unresectable tumors in critical locations because the tumor dose can be increased by 20-40% over that

Table 1

Patients treated at LBL

1975 - 1989

Helium Only	616
Helium + Xray	157
Neon Only	88
Neon + Other	282
Other Heavy Ions	29
TOTALS	1172

possible with low LET Xray therapy.

Clinical trials with protons or helium ions have shown excellent tumor control results in a number of tumor sites [3,4,7,15,20] in the skull, orbit, nasopharynx, paranasal sinuses, and for soft tissue and bony tumors in other parts of the body. We have now treated about 40 patients with the helium ion beam for tumors of the paranasal sinuses and nasopharynx invading the base of skull, paraaortic lymphatic metastases, or unresectable soft tissue tumors in the retroperitoneum or pelvis. In these selected patients, long term local control rates of approximately 60% have been achieved.

We have also treated 123 patients with helium charged particle irradiation for chordoma, chondrosarcoma, or meningioma of the skull base or juxtaspinal area after partial surgical excision. Overall control of tumor in the irradiated volume was obtained in 78 of 123 patients (63%), with tumor control rates greater than 80% in patients with small tumors (less than 20 cc). The median followup in 86 living patients is 34 months and in all 123 patients is 31 months, range 4-153 months. Crude local control rates are highest in meningioma (84%) followed by chondrosarcoma (65%) and chordoma (60%). The actuarial survival calculated by the Kaplan-Meier method is 68% at 5 years and 50% at 9 years post treatment.

The results of treatment in 328 patients with localized melanoma arising in the choroid lining of the eye were also excellent [8,12,13,14]. A local tumor control rate of 97% with followup from 3 to 139 months (median: 48 months) was achieved. Nine of 328 patients with local failure of initial helium ion treatment received further treatment with enucleation (5 pts), reirradiation (3 pts) or laser therapy (1 pt). Tumor control was excellent at all studied dose levels of 5000-8000 centiGray equivalent.

Overall, 85% of patients have avoided the need for enucleation of their eyes and a significant number have kept useful vision. Of 291 patients who had pretreatment visual acuity of 20/400 or better, 145 (50%) retained useful post treatment vision of 20/400 or better (Table 2). The actuarial survival is 80% at 5 years, because about 20% of patients have developed distant metastases, a rate which is the same when using surgical removal of the eye as local treatment for the tumor in the eye. Risk factors for the development of metastatic disease outside the eye have been studied and we hope to develop adjuvant treatment for patients at high risk for metastases.

We are currently carrying out a randomized trial to better define the role of helium ions versus 125 Iodine plaque therapy in the treatment of melanoma of the eyes. One hundred sixty patients have been entered in this Phase III study which will help to define which lesions are best treated with charged particles and which might be well treated by plaque therapy. We also envision the future use of proton or helium beams to treat other tumors of the eyes such as retinoblastoma in infants in order to prevent the need for enucleation.

For more than 100 patients with esophageal, pancreatic, gastric and biliary tract tumors, helium ion therapy was well tolerated but produced only a modest improvement in local control and little impact on survival [9]; these results might be improved in the future with dynamic conformal charged particle therapy where higher tumor doses might be possible.

Limitations on beam availability at UCLBL have not permitted that all possible tumor sites for proton or helium ion therapy be tried as yet. Collaborative studies with the Massachusetts General Hospital-Harvard Cyclotron Department of Radiation Medicine, the Proton Treatment Facility at Loma Linda Medical School, the National Institute of Radiological Sciences of Japan, and the University of Heidelberg-GSI, Darmstadt, West Germany are planned or underway to increase the numbers of patients entered in clinical research trials [17].

Heavier Ions

For high LET ions such as carbon, neon or silicon, significant biologic potential is added to the physical dose attributes of charged particles. These ions are more effective in destroying hypoxic tumors and can overcome some of the normal repair mechanisms of radiation damage. With the use of their advantageous dose distributions, the major radiation damage is largely confined to the tumor volume rather than nearby normal tissues. Preliminary studies have been done with neon ions at LBL with promising results in several sites especially in tumors of bone and soft tissue with slow growth rates. Other potentially valuable ions such as carbon or silicon have been tested only sparingly because of limited beam availability. Although patient numbers are relatively small because of the need for proceeding slowly to assure patient safety, and the advanced nature of the neoplasms, we have accrued 239 patients in the preliminary neon ion research trial [10].

For locally advanced tumors of the salivary gland, prostate gland, bone and soft tissue, biliary tract, nasal cavity, nasopharynx and paranasal sinus, there are local control rates which range from 40-90% (Table 3). These tumors are often not completely resectable and tend to be resistant to standard radiotherapy, probably because of their ability to repair low LET radiation damage. We believe these results are promising in comparison to results with standard Xray therapy and are currently carrying out additional prospective trials to further define the role of high LET charged particle radiotherapy in the treatment of cancer.

Other advanced tumors such as those arising in the pancreas, stomach or esophagus did not fare so well although the results were at least equal to standard radiation modalities. This is felt to be due to the proximity of intestine which limited the dose, even using heavy ions, and the radioresistance of these tumors. It is planned to restudy these tumors in the future with the scanned beam delivery techniques and with radiosensitizing drugs to try to augment the

Table 2

Results in Helium Ion Radiotherapy
Lawrence Berkeley Laboratory
1975 - 1988

Tumor Treated	Pts	Local Control	Median Followup
Chordoma Chondrosarcoma Meningioma	123	78/123 (63%)	31 mos (4-153 mos)
Other Tumors (Skull, sinuses, soft tissue)	38	25/38 (66%)	25 mos (2-133 mos)
Uveal Melanoma	328	319/328 (97%)	46 mos (3-146 mos)

effect of heavy ion irradiation on these tumors.

We also continue to search for reasons to explain why some tumors are susceptible to high LET charged particle therapy. We believe the ability to deliver higher local doses with charged particles is part of the explanation, but there are important biological reasons which require further elucidation. Since some tumors are resistant to standard radiotherapy, effective predictive assays are needed which would determine in advance if an individual's tumor was more susceptible to high LET charged particle radiotherapy than other modalities of treatment. Such techniques as pretherapy sampling of an individual tumor to determine its growth characteristics or radiation sensitivity would enable improved selection of patients for high LET therapy and could lead to treatment tailored to an individual patient.

Optimization of beam delivery and treatment techniques including three-dimensional dynamic conformal particle therapy will permit improved irradiation of irregular tumors. Such a scanning beam technique is now being developed at UCLBL and should lead to further advances in tumor control. Coupled with improved treatment delivery, improvements in therapy planning will include better techniques to localize the tumor, optimization of 3-dimensional radiation treatment planning, refining techniques for transfer of data from one imaging modality to another such as from MRI scans or PET scans, integration of PET scanning into radiation treatment planning and improved systems for monitoring patient positional stability during the treatment.

One of the unique attributes of heavy charged particles is the possibility to utilize a small beam of radioactive particles such as 19 Neon to be injected into the tumor just prior to treatment. This radioactive beam emits positrons which can be measured outside the body by their Xray emission. Thus the stopping area of the charged particles can be accurately imaged and matched to the previously determined tumor volume. This technique was developed at UCLBL and has been successfully demonstrated in both animal and human studies. It has great potential as a clinical tool to independently verify the accuracy of treatment planning and delivery.

It has been estimated that 5-10% of patients treated with curative radiotherapy could benefit from heavy charged particle treatment, either with light ions such as protons or helium ions or heavier ions such as carbon. With approximately 200,000 cancer patients treated definitively with radiotherapy per year in the United States, this suggests that as many as 10,000 patients per year could benefit from charged particle therapy.

As a national need for 4-6 such centers might exist in the United States, we propose continuation of the heavy charged particle radiation oncology program in the form of a Biomedical Heavy Ion Center at LBL for continued studies in heavy ion medicine and biology. Using the existing space, shielding, and local injector, a strong-focused synchrotron could be realized for less than the cost of a proton center alone at a new off-site facility. This would provide both proton and heavy ion research capabilities with an in-place, experienced team of physicians, physicists, biologists, biophysicists, accelerator engineers, computer scientists and other personnel. Such a center would be hospital-optimized and benefit from the highly sophisticated medical resources in this area. In addition to medical studies, important biological and physical research could also be accomplished such as studies of effects of cosmic particles which would be encountered in manned space flights.

Similar proposed heavy ion facilities at NIRS, Japan, GSI-Heidelberg, Germany and/or EULIMA (European Community) would be vital for continued study of heavy ion medicine. A comprehensive program, berefiting from expertise in such fields as medicine, biology, biophysics, accelerator physics and engineering, radiation chemistry, genetics, computer science and biostatistics is needed. Only through multidisciplinary research can we determine the most effective use of heavy ions in medicine and biology.

Summary

1. Protons and helium ions are highly effective in irradiation of many locally advanced, unresectable tumors adjacent to critical structures.

2. High LET ions such as carbon or neon ions have important biological properties in addition to dose localization parameters which may make them more effective in treating some human tumors.

3. A new Biomedical Heavy Ion Center is proposed at UCLBL to continue the biophysical and clinical studies in heavy ion medicine.

Table 3

Phase I-II Neon Ion Trial Results

Site	Neon	Results with Standard Therapy UCSF
Glioblastoma Brain	Med Survival-13.7 mos (n=13 pts)	Med Survival-9-12 mos
Nasopharynx, Paranasal Sinus	Loc Con-16/24 (67%) Med Follow=18 mos (4-85 mos)	Loc Con-21%
Salivary Gland	Loc Con-11/14 (79%) Med Follow=13 mos (5-91 mos)	Loc Con-28%
Prostate	Loc Con-12/13 (92%) Med Follow=28 mos (11-60 mos)	Loc Con-60%
Sarcoma	Loc Con-21/36 (58%) Med Follow=15 mos (3-76 mos)	Loc Con-28%
Pancreas, Stomach, Biliary Tract	Loc Con-10/78 (15%) Med Survival-8 mos	Loc Con-20%

Loc Con = Local control in irradiated area. Med Follow = Median followup from time of radiotherapy. Med Survival = Actuarial medial survival (Kaplan-Meier method).

Appendix

Definitions

Heavy Ion - Electrically charged nuclei of chemical elements. The term "Heavy" is somewhat arbitrary but it typically implies an ion heavier than protons or helium.

LET - Linear Energy Transfer refers to the rate at which energy is deposited as it passes through tissue. It does this by ionizing (stripping electrons from) the atoms that it encounters. LET depends on the type of radiation and its energy. In general, the more massive the particle and the greater its charge, the higher its LET. Xrays, protons and helium ions are characterized by low LET whereas carbon, neon and silicon ions are examples of high LET radiations.

RBE - Relative Biological Effectiveness is a term that compares the effects of different types of radiation, generally with the standar being Xrays. Radiations that have high LET also have high RBE for effects on human tissues or tumors.

Heavy Charged Particles - These particles are the electrically charged nuclei of chemical elements. They may range in mass from light elements like hydrogen (protons) or helium to nuclei many times heavier like carbon, neon, silicon or iron.

Treatment Planning - Process of using tumor imaging studies such as CT (computer tomographic scans) and a powerful computer to map out the radiation dose distribution in the body. Such plans are optimized to find the best way to irradiate a patient's tumor.

MRI - Magnetic Resonance Imaging scanning makes use of magnetic fields to image structures within the body.

PET - Positron Emission Tomography scanning images radiation produced by certain trace radiochemicals injected into the body and gives both an anatomical and physiological picture of the imaged organs.

Megavoltage Irradiation - (Low LET) Irradiation produced generally by linear accelerators for hospital use in treating human tumors, in ranges from 4-20 MeV. These are usually Xrays but electron beam therapy in similar energy ranges may be employed for relatively superficial treatment.

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