

RESEARCH PLAN

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I. OBJECTIVES

To prepare for and evaluate heavy-ion therapy of human cancers. This evaluation would be conducted by:

1. organizing a group of university and community radiotherapists to plan for and carry out controlled clinical trials in helium/heavy-ion therapy;
2. designing and carrying out an initial trial of large-field, fractionated, extended Bragg peak helium-ion therapy;
3. evaluating such radiobiological and physical parameters as are necessary prior to heavy-ion therapy in humans;
4. initiating a trial of heavy-ion beams as soon as feasible.

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II. BACKGROUND

Physical Considerations

Helium and heavy ions have important physical attributes for potential use in cancer radiotherapy. By appropriate ridge filter construction the narrow Bragg peak may be extended so that the high-dose region covers a larger range of depth. A useful characteristic is a sharp falloff at the distal end of the beam. Additionally, in tissue these particles travel in nearly straight-line trajectories. Ionization from secondaries causes a relatively low background outside the beam for most energies, although above neon ($Z = 10$), the contribution from secondaries may become more important.

In radiotherapy, these penetration properties and the sharp falloff of beam distal to the extended Bragg peak allow the production of advantageous depth-dose distributions tailored to the dimensions of the tumor, and minimizing the dose to important adjacent normal structures. These advantageous dose/distributions should permit delivery of a higher dose to critical treatment volumes than currently available with conventional megavolt techniques.

High-LET Oxygen Effect

While the possibility of significantly decreased OER^{**} with helium ions is minimal, at the very high LET of heavy-ion beams there should be a significant decrease in OER.

It has been recognized that tumor cells often require less oxygen than normal cells and that many tumors exist with necrotic regions where the milieu is hypoxic or anaerobic (1). For low-LET radiations the OER is about 3; this means that a lethal dose of gamma rays for these tumor cells is about three times as great as the usual dose for normal oxygenated cells (2). Using human kidney cells as a test object, fast neutron and pi meson OER's have been measured at about 1.6, while the helium OER at the Bragg peak of 930-MeV particles is between 1.9 and 2.3 (3). These OER ratios are improvements over the OER for X rays; however, based on research with low-energy heavy ions and initial studies with high-energy oxygen ions, we know that the OER for heavy particles of appropriate atomic number can be considerably less than that of other radiations.

In 1966, Tobias and Todd suggested that high-energy neon might produce the required OER (4). It is possible, however, that the optimum therapeutic particle is heavier than neon. It is a major goal of our "pretherapeutic use of accelerated heavy ions" project to quantitate the cellular and tissue effects of heavy ions as a function of atomic number and velocity so as to optimize the desired heavy ion for therapy.

Clinical Experience

Work has been carried on in Sweden (5) on a variety of tumors and at the Harvard cyclotrons with small-field-directed, proton-beam therapy primarily for pituitary tumors (6). Recently an extensive program with large-field proton therapy has been started in Russia at the Institute for Theoretical and Experimental Physics in Moscow, the Laboratory for Nuclear Research at Dubna (7). About 250 patients have been treated

* Linear energy transfer.

** Oxygen enhancement ratio.

with large-field proton therapy, although detailed results of treatment are not available.

At Lawrence Berkeley Laboratory and Donner Laboratory, considerable experience over a number of years has been gained with high-energy protons and helium ions. The first therapeutic human exposure to high-energy deuterons was performed here in 1955; (8) since that time several hundred patients have been treated with small field, high dose low fraction-number helium-ion therapy, particularly for lesions of the pituitary. These treatments have proven particularly effective in acromegaly and Cushings' Disease therapy (9). A few patients in the past have been treated with small-field, high-dose, single fraction irradiation of small pulmonary metastatic nodules, or for brain malignancies (10).

There are available in the Bay Area a variety of sophisticated radiotherapy centers including the University of California at San Francisco Division of Radiation Oncology, Stanford University Medical School Division of Radiotherapy, the Zellerbach-Saroni Tumor Institute Department of Radiation Oncology, and numerous other radiotherapy centers listed in the Appendix. A number of these centers have interest in particulate radiotherapy, including Stanford University Medical School, where work is progressing on development of a pion radiotherapy beam. There has been substantial work done in the Radiobiology Laboratory of the Division of Radiation Oncology at the University of California, San Francisco on the radiobiological properties of neutron beams, both with external beams and Californium 252. These university and community radiotherapists have been invited to participate in a clinical trial of helium-ion and heavy-ion therapy through the formation of the Bay Area Heavy-Ion Association, (see Appendix B); their combined new cancer patient population is in excess of 5,000 cases per year. This group also includes radiotherapists from Northern California including the University of California at Davis and the Sutter Radiation Center in Sacramento, California, which has an interest in the development of an external neutron beam clinical trial; thus the Bay Area Heavy Ion Association will afford an interaction for all groups interested in particulate radiotherapy. The background for this clinical trial has been developed at Lawrence Berkeley Laboratory and Donner Laboratory through the assistance of Dr. Max L. M.Boone, Chairman of the Department of Radiation Oncology at the University of Arizona, Dr. Theodore L. Phillips, Professor & Director of Radiation Oncology UC San Francisco, and Dr. Malcolm Bagshaw, Professor & Chairman of the Department of Radiology at Stanford Medical Center. The organizational framework will be expanded to assure development of protocols for a controlled clinical trial, as well as the concomitant development of technical expertise in large-field, fractionated, extended-Bragg-peak therapy and the development of the appropriate clinical facilities to conduct an extended clinical trial of heavy-ion beams. The Association has already had indications from its present members of strong interest in participation in the clinical trial, both in treatment of the study patients as well as control patients and is open to any qualified radiotherapist who wishes in the future to participate in this endeavor.

The Northern California Cancer Program, a nonprofit corporation formed by the major organizations interested in cancer research, therapy and related activities has applied for designation as the comprehensive cancer center for Northern California and Northwestern Nevada. The University of California (Berkeley, San Francisco Medical Center, and Davis campuses), Stanford University Medical School, and Zellerbach-Saroni Tumor Institute among others are represented in this organization. To co-ordinate radiotherapy research in particulate irradiation, a high-LET committee has been formed by the NCCP under the chairmanship of Malcolm Bagshaw. Other current members include T. L. Phillips, J. R. Castro (UCSF); C. Tobias LBL; A. Raventos, S. Silverman (UC Davis); D. Pistenma, and R. Kallman (Stanford).

This committee will endeavor to co-ordinate clinical trials in Northern

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California including possible neutron trials (UC Davis), pion trials (Stanford) and helium/heavy-ion trials (LBL). Considerable common information can be shared and duplication avoided in treatment planning, compensation for inhomogeneities, and development of treatment protocols.

It will be a particular aim of this project to maintain close communication and liason with other groups involved in particulate radiotherapy including on-going neutron trials at the university of Washington, TAMVEC and MANTA, the proton trial at Massachusetts General Hospital (Harvard Cyclotron) and the pion radiotherapy trial at the Los Alamos Meson Physics Facility.

There are already existing links to these on-going trials through many of the investigators on this project; in addition, Dr. Tobias is a member of the North American Particle Committee which is chaired by Dr. Bagshaw.

We will be especially interested in possible coordinated and/or cooperative clinical trials in order to develop answers from the available patient pool at the earliest opportunity.

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III. RATIONALE

The change from orthovolt to megavolt radiotherapy techniques provided the ability to deliver an increased radiation dose to deeply embedded structures together with diminution of dose to uninvolved normal tissues. This improved dose distribution has led to an increase in local control rates and decreased normal tissue reactions and morbidity in a number of human tumor sites. Nevertheless, local and regional failures still account for a sizable proportion of instances where radiotherapy fails to control the tumor. Two possible advantages exist in heavy-ion radiotherapy which may improve the tumor control ratio:

1. A clear improvement in the ability to deliver a higher dose to both tumor and treatment volume with a decreased dose to normal tissues lying near or surrounding the treatment volume.
2. An improved chance of tumor control secondary to the physical properties of heavy ions, particularly the decrease in oxygen enhancement ratio shown to be present with increasing LET.

The use of helium-ion therapy for the first phase of this study will have its potential advantage primarily in the ability to better deliver a more localized dose to the treatment volume and minimize the dose to adjacent normal structures. There may be a small advantage in terms of decreased OER compared with conventional radiotherapy, however. Potential advantages therefore are found mainly in two clinical situations: 1) Ability to deliver a higher dose, where in the past doses have been limited by virtue of normal structures to 5,000 rads in 5 weeks with conventional low-LET radiotherapy. A higher tumor control may be the result of the ability to raise this dose level to the equivalent of 6,000 to 7,000 rads in 6 to 7 weeks with low-LET radiotherapy. 2) Where it has been possible to deliver doses on the order of 7,000 rads in seven weeks or its equivalent, an increase in local control may be small if present, but there may be a reduction in the incidence and severity of normal tissue reactions by virtue of the better localization of dose.

Information thus gained from fractionated, helium-ion, Bragg peak therapy will be of considerable value in developing treatment techniques with heavy ions as well as a control group for comparison with heavy-ion therapy, where both the advantages of better dose localization and significantly lowered OER are expected.

In previous considerations we have suggested the following possibilities for tumors that will be considered for heavy-ion therapy: 1) tumors that have necrotic regions and are known to contain anoxic cells; 2) tumors that can be precisely localized, with dimensions that are known; 3) tumors inaccessible to surgery; 4) tumors adjacent to radiosensitive structures which cannot be avoided easily using conventional radiation; 5) tumors possessing cells sensitive to heavy ions; 6) tumors which do not metastasize rapidly; and 7) very small tumors.

We felt that heavy-ion therapy might be contraindicated for: Tumors locally controlled) than 75% by chemotherapy or conventional radiation, with acceptable morbidity levels; 2) tumors known to metastasize rapidly; 3) tumors which cannot be properly localized.

Accordingly, our initial efforts in helium-ion therapy will be directed towards conducting a controlled clinical trial of helium-ion therapy and gaining experience applicable to heavy-ion therapy when it becomes available. For example, initial suggestions for trial sites for fractionated, large-field, helium-ion therapy include: 1) periaortic lymph nodes in such tumors as carcinoma of the uterine cervix, prostate, bladder, ovary and/or rectum; 2) gliomata of the brain; 3) soft

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tissue sarcomas; 4) localized pancreatic tumors and/or renal tumors; 5) pelvic tumors where dose localization and avoidance of normal tissues may be important, such as certain prostate, bladder or rectal tumors.

A detailed consideration of physical and biological factors in radiotherapy with high-LET radiations was made earlier by Drs. Tobias, Lyman and Lawrence (10). The radiobiological and physical factors in favor of high-LET radiations for therapy of human cancer were evaluated. It was expected that heavy-ion beams would show high LET with low OER. Experimental analysis of heavy-ion beams including carbon, oxygen, and neon have been underway at LBL for some time using first low-intensity beams of the Bevatron (C, N and O) and more recently the high-intensity and heavier beams of the Bevalac (Ne and Ar). The Bevalac project, financed by ERDA, has as one of its major aims the applications of high-LET radiobiology for the purposes of radiology.

Physical Properties of Heavy-Charged-Particle Beams

As heavy charged particles penetrate matter, collisions with atoms result in multiple, small-angle scattering. Since heavy charged particles are many times heavier than electrons, a heavy-ion beam will scatter less than an electron beam, *i.e.*, the angle of scattering is reduced approximately by the ratio of the masses. Particles such as helium ions can be used to produce sharply defined beams with very little side scattering. The scattering and straggling of heavier ions is even less than that of helium. This allows the heavier beams to be shaped with greater precision than is possible with photon or electron beams.

Heavy-charged-particle beams also have definite range of penetration: this range depends upon the energy. As the particle beam penetrates matter, the rate of energy loss by the particle increases with decreasing particle velocity, resulting in delivery of a relatively large dose to a small region (the Bragg peak region) just before the particle comes to rest (see Figure 1, curve A).

These properties make possible intense irradiation of a small, strictly localized tumor within the body while maintaining a relatively low skin dose.

The helium-ion beam from the 184" Cyclotron (11) (12) has a range of approximately 32 cm in water. In order to obtain a beam of different range, a degrader is placed in the beam path; this degrader absorbs energy from the beam as the beam passes through it. With careful choice of a degrader of appropriate material and thickness, shorter ranges may be obtained. To treat a volume with thickness greater than width at the 80% level of the Bragg peak, it is necessary to combine irradiations of particles with different ranges. One technique for accomplishing this is to use a ridge filter, a carefully-shaped degrader of nonuniform thickness. When the treatment volume is increased in such a manner, the surface dose will approach the treatment dose. An example of extended Bragg-peak, depth-dose distribution is shown in Figure 1, Curve B.

There is some skin sparing, due to finite thickness of absorber necessary to establish secondary electron equilibrium. This vanishes if a solid bolus is used adjacent to the skin. The biological effect somewhat increases with depth, due to increasing RBE. Beyond the treatment volume, the dose will drop very rapidly. For a small treatment volume, dose drops from 80% to 20% within about 4 mm. With a large treatment volume, the same decrease in dose occurs within 5 mm, and the exit dose is less than 3% maximum. Beams from accelerators tend to be tightly focused and have small cross-sectional areas. Larger beam areas are generally obtained through the use of magnets or scattering foils (13), or by magnetically scanning the beam over the desired area. Large treatment volumes can also be irradiated by appropriately scanning a patient across a beam with small area. Technical difficulties with these methods seem to favor scattering as the most

reliable and most easily accomplished method. The technique of double scattering, developed by workers at the Harvard Cyclotron Laboratory (14), is also a suitable method for obtaining a large, uniform, helium-ion treatment field of sufficient intensity to be clinically useful. Figure 2 indicates an example of lateral dose distribution of a wide helium-ion beam at the 184" cyclotron.

Dosimetry of the helium-ion beam is performed primarily with ionization chambers of both transmission type and tissue-equivalent probe type(14). Ionization chambers are referenced to Faraday cup and calorimeter measurements. The large beam is shaped to the final desired cross section by a Cerrobend alloy collimator.

Patients will be treated either sitting, standing, or lying, depending upon the area to be treated and entry portals. Each position will require some patient immobilization to minimize patient motion during simulation, setup, and treatment. Immobilization methods which may be employed are head masks, biteblocks, head and body casts (light cast) and velcro straps.

Treatment planning will be done using the best available data on cross-sectional, stopping-power distributions. Residual range of the beam will be determined by the maximum depth of penetration needed for each entry portal, taking into account inhomogeneities in the beam path. Compensation in various areas of the field will be provided when it is possible to spare a significant amount of normal tissue beyond the treatment volume or to avoid irradiation of a vital structure. Compensation will not be attempted for small structures where patient motion might incorrectly alter the position of the compensator so as to underirradiate the intended treatment volume.

We have measured the stopping power for particle beams as a function of the atomic number (15). These allow calculation of the stopping power of wet bone and of other tissue inhomogeneities, as long as the atomic composition is known. Relative stopping power of bone/soft tissue for high-energy helium ions is about 1.2, as a slowly varying function of the particle energy.

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