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DONNER LABORATORY AND DONNER PAVILION BERKELEY, CALIFORNIA 94720

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John O. Archambeau, M.D.
Director, Radiation Therapy
Nassau County Medical Center
2201 Hempstead Turnpike
East Meadow, New York 11554

Dear Dr. Archambeau:

Thank you for your letter of February 8th regarding the use of high-energy protons in cancer therapy. We cannot agree with you more that these beams should be fully explored. In fact, there has been a continuing effort by us and by others to study various aspects of their therapeutic potential for many years. Perhaps a discussion of heavy particles in general might help to clarify some of your questions. A review of the status at present and the problems to be solved in the future is presented with regard to the following aspects:

1. PHYSICAL CHARACTERISTICS

The unique Bragg peak ionization curve of heavy ions and the negligible scattering give rise to an ideal spatial dose distribution in radiotherapy. The possibility to irradiate a tumor with the high-LET peak component and the intervening normal tissues with the lower-LET plateau component is another attractive feature. Furthermore, in contrast to fast neutrons, a charged,heavy-particle beam can be readily focused or defocused and collimated to any desired size and shape. The ease in shielding and the absence of tritium hazard also make it superior from the standpoint of radiation protection. In addition, the dosimetry is not complicated by gamma contamination nor limited by enhanced energy deposition in fatty tissues.

There are more than half a dozen cyclotrons in this country and about an equal number abroad that are capable of producing protons or alpha particles with sufficient energy and penetration for medical use. As far as beam diameter and dose rate are concerned, most have an output more than adequate for therapeutic purposes. The fixed horizontal beam is a minor disadvantage, but should not be a major deterrment in limiting its usefulness in most situations. Plateau dosimetry has been fairly well standardized. However, the technique of Bragg peak therapy is much more complicated. To ensure accurate placement of the peak in a deep-seated tumor, it is necessary to know the exact three-dimensional boundaries of the target volume, and also the thicknesses of different intervening tissues or any air gap at each treatment position. Having done that an appropriate correction factor has to be applied for the differential stopping power of each layer of tissue and the absorber thickness adjusted accordingly before the beam enters the patient. The half-width of an unmodified Bragg peak is only a few millimeters. In order to cover a tumor of moderate size the peak has to be spread out by using wedge filters which decelerate the particles to varying degrees. Naturally, this is done at the expense of lowering the peak to plateau ratio as well as the average LET. Our current work includes the construction of a rather sophisticated treatment positioner for better precision; effort to refine the technique of transverse tomography or ultrasonics for anatomical studies; testing of a pencil-beam proton scanner to gauge stopping powers; and installation of a computerized dosimeter with a pulse modulator to ensure homogeneous dose delivery; and the incorporation of an automatic adjuster of absorber thickness for rotational peak therapy. For more efficient use of the beam time, a simulator will be a valuable adjunct in the future.

In the past, ions heavier than helium have been produced by heavy ion linear accelerators. Valuable information has been obtained with respect to their physical parameters and in vitro biological effects. Unfortunately, the maximum energy attainable is only around 10-MeV per nucleon which does not permit much in vivo animal study, not to mention any therapeutic applications. An exciting recent development is the success in accelerating high-LET heavy ions such as nitrogen and oxygen in the BeV range by modification of the Bevatron. The biggest handicap at present is the low particle flux. The beam intensity only amounts to a few rads per minute over a one square centimeter area. However, the physicists are very optimistic that this problem can be overcome in the near future.

2. RADIOBIOLOGY

The plateau portion of proton or alpha beam is comparable to x rays in terms of biological effects. Recent studies in our laboratory on T, renal cancer cells exposed in vitro and on marrow and gut tissues in vivo suggest that a modified 5 cm. wide peak is significantly more effective in cell killing, is associated with a reduced oxygen effect, and causes more irreparable damage compared to the plateau. Whether a small component of high-LET radiation might be responsible for the observed differences awaits further confirmation with in vivo tumor systems and other normal tissues. The greater RBE and smaller OER and recovery factor noted are not as marked as those of fast neutrons. The differential response between the tested tumor and normal tissues is also less apparent. Although it is doubtful that the therapeutic gain would compare favorably with that of fast neutrons or negative π-mesons, we feel that further exploration is justified in view of the dosimetric advantages. The Uppsala group, using single doses of protons, have found that the damage to many normal tissues is comparable to that after x-ray exposure. Further testing with fractionated doses is already underway. The Russians have also embarked on a series of pretherapeutic and therapeutic investigations on their cyclotron beams. Of course, we shall continue to extend our experimental program along similar lines.

Based on known radiobiological knowledge, we would predict that higher LET radiations such as the Bevatron-produced heavy ions appear the most promising in the future. RBE values for the Bragg peak should be near maximum, but it remains to be ascertained whether there will be a relative gain with respect to the effectiveness of peak vs plateau and to the response of tumor vs normal tissues. A greater safety margin between the tumorocidal dose and normal tissue tolerance would be particularly advantageous in situations where there are critical vital structures within the treatment volume. The mean LET of these ions is expected to be high enough to obliterate the oxygen effect almost completely which will further enhance the therapeutic gain ratio if there is a significant component of hypoxic cells inside a tumor. If cellular repair is essentially absent, as predicted, then the fractionation schedule would have to be adjusted accordingly. Presumably, there should be very little cell-age dependent variation of radiosensitivity. This would be beneficial until techniques of in vivo cytokinetic analysis become available when it might be feasible to synchronise the administration of increments of lower-LET radiation with the most sensitive phase of the tumor cell cycle and the most resistant phase of the normal cell cycle with high-LET radiation. The same probably holds true with regard to chemical radio-modifiers. Preliminary work has already begun, but all the above parameters will be evaluated systematically before final therapeutic trial will be instituted.

3. CLINICAL EXPERIENCE

The Harvard cyclotron has been used mostly for pituitary irradiation. They have employed Bragg-peak therapy exclusively with single-dose multiportal technique and obtained high success rates in some pituitary disorders. However, the low incidence of complications they have reported has been challenged by others.

At Uppsalla, proton therapy has been applied to small groups of pelvic and nasopharygeal cancers. Unfortunately, some of these patients also received prior x-ray therapy and no definite conclusion can be drawn. Recently, they have extended this work to a larger scale clinical trials on various cancers. Naturally, one awaits anxiously for their findings.

The Russians, within the last two years, have also initiated cyclotron therapy for several types of malignancies, first at Dubna, later at Moscow, and more recently at Gotchina. They seem very optimistic about their progress.

We understand that the NASA Cyclotron in Virginia will also be in operation for medical use soon, and we are looking forward to seeing your group start a clinical program in the near future.

At Berkeley, the overall treatment results of pituitary irradiation have been remarkable. The number of patients treated has almost doubled in the last few years. Most of these patients were treated with the plateau portion of the helium ion beam from the 184-inch synchrocyclotron. Therapy usually consists of six equal increments given over an eleven-day period. The entrance and exit doses are practically identical so that biplanar rotational technique is necessary for better dose geometry. We are experimenting with additional saggittal fields to minimize the lateral dose contribution to structures such as the cranial nerves and temporal lobes. Data are being collected to optimize the total dose and fractionation schedule for each pituitary disorder. Side effects have been minimal, especially among the more recently treated patients, since we have improved our radiodiagnostic techniques, and adopted a more conservative tolerance limit for normal brain tissues. Initial trial of Bragg peak therapy in 1963 and on several acromegalic patients with large hypophyseal tumors has demonstrated more satisfactory tumor suppression. Unfortunately, the damage to neural tissues may be also more severe. Since accurate beam penetration is so critical, further refinement is in progress to avoid any under or over-shoot of the Bragg peak.

As a preliminary study before a definitive clinical trial of cancer therapy, we have treated several patients with brain tumors and several with pulmonary metastases. Postmortem analysis of the brain tumor patients who were irradiated several years ago has uniformly shown complete absence of residual neoplastic cells inside the treated volume which received over 5,000 rads in eleven days. However, in each case tumor recurrence was noted elsewhere. Hemispheric irradiation for gliobastoma multiforme is being contemplated. Pulmonary metastase serve as an excellent model for comparing different types of radiation. In fact, the Dutch group at Ryswijk are also using it in a pilot study with fast neutron therapy. Our accumulated cases are too few for statistical analysis. The preliminary impression is that Bragg-peak alpha-particles are more effective than equivalent cobalt-60 gamma rays in causing tumor regression. These patients are being followed to check whether damage to the lungs and other tissues is also more excessive.

For future definite clinical trials with protons, alpha particles, heavier ions, or π-mesons, we are faced with the same problems that confront radiotherapists involved in fast neutron therapy. These were discussed by Drs. Kaplan, Kligerman, and Withers at some length during a recent symposium in Holland. In essence the following criteria should be followed for valid statistical evaluation. A large number of patients is needed, especially where the expected improvement in salvage rate is not too large. For each stage of each category of cancers treated, there should be a corresponding matching group of control patients who are to be treated with equivalent technique. The types of malignancies chosen should have a high enough frequency so that a sufficient number of cases can be collected over a relatively short period of time. Here close collaboration among centers would certainly help to expedite the study. However, this would necessitate mutual agreement on some standardized dosimetry and treatment techniques. Initial selection should be confined to those cancers which have a high incidence of rapid local recurrense after x- or y-irradiation, presumably due to the presence of relatively radioresistant hypoxic cells inside the tumor or to critical normal tissues in the vicinity which limits the tumor dose. Distant metastases should not be so frequent as to invalidate the analysis of survival data. Cancers which can be eradicated efficiently by x- or y-ray therapy would not be suitable for ethical reasons. On the other hand, the prognosis of some cancer types(s) to be tested with newer modalities or radiotherapy should not be so short in duration to prohibit evaluation of the long-term effects on normal tissues. Finally, the feasibility of combined therapy should be considered. Perhaps high-LET radiation given only as the initial and/or final increments is adequate to achieve optimal results.

Some may question a priority whether the probably benefit will out-weigh the expense involved in such a study and the continued devotion of so many personnels over a long time, but, as long as radiation remains a major tool in the conquest of cancer, we feel strongly that any possible salvage of human lives deserves all the effort that we have and shall put in.

We hope that this communication will help you get a clearer perspective of our views. If we can be of any further assistance, please write to us again.

Sincerely yours,

John H. Lawrence, M.D.

By Claude Y. Chong, M.D.

CYC:df

Dr Chong an able colleague did a good job on this letter I think and I made a few changes in it but in general I agree!

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