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DOSIMETRY AND RADIOBIOLOGY OF NEGATIVE PIONS AND HEAVY IONS

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INTRODUCTION

Historically, radiation therapy development has been directed toward obtaining more and more penetrating radiations so that the high dose region can be confined to the treatment volume while minimizing the dose to surrounding normal tissue. While the introduction of fast neutrons in radiotherapy was a step forward in development because of their higher radiation quality, it was a step backward in terms of dose localization. Because of the inherent nature of fast neutrons, their dose localization characteristics may never be truly comparable to current megavoltage x rays used in radiotherapy.

It is clear from presentations of clinical results using fast neutrons during this conference that their poor dose localization may be a limiting factor, especially for deep-seated tumors. In principle, negative pions and heavy ions have radiation qualities similar in certain respects to fast neutrons and, at the same time, have dose localization characteristics superior to even megavoltage radiations because of their Bragg ionization characteristics. Unlike fast neutrons and x rays, negative pions and heavy ions confine dose in the third dimension (at-depth), also because of their Bragg ionization characteristics. The ability to control beam depth necessitates applying inhomogeneity corrections precisely. The availability of CAT scanners allows precise measurement of beam inhomogeneities, at least in principle, taking advantage of the Bragg ionization characteristics of negative pions and heavy ions (Smith et al.).

Progress in the application of negative pions and heavy ions since the last neutron conference at The Hague has been phenomenal. Pion radiotherapy programs are currently in progress at three centers: Los Alamos, Vancouver, and Zurich. The Stanford University group pioneered the development of a large solid-angle pion-collecting device that permits simultaneous multiport irradiation (Fessenden et al.). The Zurich group is incorporating the Stanford design in their therapy facility (Von Essen et al.). The Los Alamos and Vancouver groups are using conventional pion-collecting devices. The Los Alamos facility provides a fixed vertical beam and the Vancouver facility a fixed horizontal beam. A clinical program is in progress at Los Alamos and is expected soon at Vancouver and Zurich where pretherapeutic radiobiology programs are being conducted.

Unlike the pion therapy programs, Berkeley currently is the only location for heavy ion therapy programs, although there are plans to develop heavy ion

facilities in Dubna (USSR) and Saclay (France). At Berkeley, a helium-ion beam from the 184-in. "synchrocyclotron" and heavy ion beams (carbon, neon, argon) from the BEVALAC are being used in radiotherapy as fixed horizontal beams.

There are 18 papers in the poster session, approximately half of which cover negative pions and the other half heavy ions. Although the poster contributions represent only a fraction of the recent experimental data on these radiations, they do provide data of interest in therapeutic applications and also show how negative pions and heavy ions compare with fast neutrons. In this brief survey, an attempt will be made to present some aspects of the poster contributions on negative pions and heavy ions and the current status and prospective and retrospective views. Such a view naturally reflects the personal opinion of the rapporteur.

NEGATIVE PIONS

Production of pion beams with intensities adequate for therapy (compared to fast neutrons) is further complicated by the requirement that the energy of the primary beam to produce pions (proton beams are usually used because of their good production cross section for pions) must be much higher than 400 MeV, compared to the energy of the primary beam (15 to 50 MeV D^+) used for neutron production by cyclotrons. The primary beam intensity used for pion production must also be very high (~ 20 to 500 μA). The production and collection of pions for radiotherapy applications, although technically achieved, have turned out to be more complicated than originally envisioned.

The depth dose distribution of pion beams has not been found superior to protons in spite of formation of stars near the end of the range and their Bragg ionization. This is due to enhancement of the dose near the end of the range, compared to the beam entrance from Bragg ionization, being higher for protons than for pions. Star formation near the end of the range for pions approximately compensates for this difference, thereby making the depth distributions of pions and protons comparable (Raju). Early biophysical measurements at Berkeley, CERN (Geneva), and NIMROD (United Kingdom) were very helpful in making the expectations for pions realistic.

Pion radiation quality at the plateau region is comparable to conventional low-LET radiations, and radiobiology results also indicate RBE values close to unity (McEwan et al.; Fessenden et al.; Raju et al.). In the pion stopping region, the radiation quality increases considerably because of π^- star products. Radiobiology data for negative pions at the Bragg peak position clearly indicate the increase in RBE and the reduction in OER (Baarli et al.; Tremp and Rao; Fritz-Niggli and Blattman). Although the high-LET dose fractions due to charged particles from negative π^- stars are reduced, with increasing Bragg peak width, fast neutrons from π^- stars become important and account for approximately 50% of the high-LET dose (Dicello et al.). Raju et al. also reported that, although the RBE values for negative pions at the peak centers decrease considerably with increasing peak width, OER values are nearly identical for different peak widths. The results by Baarli et al. are also consistent with this finding. Even at the Bragg peak position, passing negative pions deposit a large fraction of dose at much lower LET values compared to fast neutrons; hence, the average LET of negative pions is lower (Menzel et al.). As expected, pion radiobiology data have indicated lower RBE values and higher OER values compared to fast neutrons (McEwan et al.; Raju).

HEAVY IONS

Curtis reported dose average LET calculations for heavy ions of carbon, neon, and argon at various points for 10-cm wide Bragg peaks. These calculated values,

along with values for helium, fast neutrons, and negative pions, are shown in Table I. The radiation quality of fast neutrons is in between that of carbon

TABLE I. Dose Average LET Values for Heavy Particles

Particle	Dose Average LET (keV/μm)			
		Peak Region (10 cm width)		
	Plateau	Proximal Peak	Central Peak	Distal Peak
Neutrons	75	75	75	75
Negative Pions	6	15	30	60
Helium	5	8	16	30
Carbon	12	30	40	130
Neon	30	70	100	300
Argon	100	200	300	1500

and neon ions at the peak region and that of neon ions at the plateau is lower than for fast neutrons. Although dose average LET values are helpful in comparing the radiation quality of particles, it should be stated that this may be an incorrect physical parameter in comparing radiobiological data. For energetic heavy ions, a significant fraction of the dose is deposited by energetic delta rays (low-LET); hence, the microstructure of the track should also be taken into consideration in interpreting the radiobiological data.

The dose average lineal energy of helium ions ranges from 4.4 keV/μm at the plateau to 22.3 keV/μm at the distal end of a 5-cm wide Bragg peak (Chemtob). Thus, the mean LET value, even at the distal end of the peak, is lower than for fast neutrons. Radiobiology results reported by Van Dam et al. and Raju are consistent with LET considerations.

As expected, dose localization of heavy ions has been found to decrease slowly with increasing charge of the heavy ion due to the increasing cross section for nuclear reactions. One of the pleasant surprises was that the dose localization advantage of heavy ions is still maintained even for neon and argon ions for ranges not exceeding 15 to 20 cm. This is because nuclear secondaries from heavy ion nuclear interactions proceed in the same direction as primary heavy ions with nearly the same velocity and come to rest near the vicinity of the primary beam. Thus, nuclear secondaries were not found to diminish the usefulness of heavy ions considerably.

From studies with 12-day-old spheroids (V79), Luecke-Huhle et al. concluded that the intercellular contact that protects cells after exposure to low-LET radiations is not detected after exposure to heavy ions.

Goldstein and Phillips reported an extensive series of measurements on survival of intestinal crypt cells for carbon and neon ions with single and fractionated doses. They found that single and fractionated doses of heavy ions produce dose-response curves with reduced shoulders but with similar slopes when compared to gamma rays. As expected, they have found the greatest recovery in the plateau regions. Recovery at the mid-peak region is considerably reduced compared to the plateau but is greater than at the distal end of the peak. These results are consistent with LET values at those respective points. Goldstein and Phillips concluded that fractionated treatments of heavy ions produce an enhanced effect in the peak region compared to the plateau region and could lead to a substantial gain in therapeutic ratio.

Curtis et al. reported a series of tumor (rhabdomyosarcoma) measurements after exposure to carbon, neon, and argon ions. Using some of these results, they calculated a factor of merit defined as the efficiency of killing for hypoxic cells at the peak region compared to oxygenated cells at the plateau region. They found that carbon and neon ions have nearly the same merit for 15-cm penetration. These results indicate that the gain in dose localization for carbon ions compared to neon ions is approximately counterbalanced by the reduction in OER for neon ions compared to carbon ions. For ranges greater than 15 cm, carbon ions are slightly more advantageous than neon ions. Hermans et al. compared the cell proliferation kinetics of rhabdomyosarcoma tumor cells after exposure to neon ions (6 Gy) with 300-kVp x rays (20 Gy) and concluded that the rate of cell-cycle progression of surviving cells after exposure to neon ions is not significantly different than that from x rays.

COMPARISON OF HEAVY PARTICLES

Raju reported a series of radiobiological measurements for heavy particles of interest in radiotherapy (p, He, C, Ne, Ar, π^-, n) using the same biological systems. For this comparative study, the depth dose distributions of all heavy charged particles were modified to 10-cm wide Bragg peaks. The OER for protons was not significantly different from that for x rays. The OER values for negative pions, helium ions, and carbon ions were larger, for neon ions similar, and for argon ions smaller when compared to fast neutrons. It was disappointing that heavy ions have OER values much higher than the expected values of unity. This could be due to a large delta-ray penumbra associated with energetic heavy ion tracks.

These comparative radiobiological results clearly indicate that there is no unique characteristic in any one particle that is not shared to some degree by other particles. For example, dose localization characteristics of all heavy charged particles are similar. Biological effects such as RBE and OER of fast neutrons appear similar to those for some of the heavy ions. If we are interested only in dose localization without significantly changing the radiation quality from conventional low-LET radiations, the particle of choice is the proton. Ongoing fast neutron therapy trials will answer the question as to whether high-LET is an advantage in treating certain types of resistant tumors. If the results are promising, neon and argon ions may be even more effective. Clinical results with mixed schemes of neutrons and gamma rays appear promising. If this is confirmed, negative pions, helium ions, and carbon ions may be very effective because the radiation quality of these beams is approximately similar to that of the mixed scheme of neutrons and x rays.

DISCUSSION

Authors of the poster contributions were asked to make specific comments that were not well covered by the rapporteur. Von Essen pointed out that there is a considerable penumbra for negative pions not particularly different from that of fast neutrons because of multiple scattering and nuclear interactions. He hoped that some of this problem could be overcome by using the 60-channel applicator in Zurich. Smith commented that, although the penumbra for large static beams of negative pions is comparable with Co-60 gamma rays, improvements comparable to the 60-channel applicator can also be made at Los Alamos where they are planning to scan a cylindrical beam through the patient.

Curtis cautioned about using dose average LET values because they may not be a correct physical parameter for comparing radiobiological results. He also mentioned that the dose average LET values at the distal end of a broad Bragg peak for heavy ions are point values not relevant for tumors of any significant size.

There was some discussion of LET distribution of negative pions compared to fast neutrons. Fowler concluded that, if high-LET is an advantage, neutrons are better than negative pions. Fessenden stated that, when multiple converging π^- beams are used, the biological effects in the plateau region decrease considerably, which may prove to be an advantage.

Goldstein pointed out the importance of RBE measurements for fractionated treatments and stated that the RBE value using the mouse gut system for carbon ions at the plateau region (30 keV/μm) is not significantly different from the peak region (130 keV/μm) for single doses but that, for fractionated doses, there are large differences due to considerable recovery at the plateau region but lack of recovery at the peak region. Dicello stated that the model he uses would be helpful in understanding Goldstein's data.

Kligerman stated that the biological effectiveness of negative pions for a broad peak they have chosen for therapy remains the same from the proximal to distal side of the peak for single and fractionated doses using multicellular spheroids. Clinical results are consistent with this finding. From these results, it appears to him that a small amount of the high-LET component mixed with the low-LET component interferes with repair of low-LET damage. He felt that these aspects should be taken into consideration.

In comments from the floor, Phillips disagreed with Raju's comment that argon ions may be a progressive form of neutron therapy. He stated that argon ions have disturbing qualities due to poor dose localization and reduction in RBE for aerated cells at the peak compared with the plateau. He also stated that carbon ions and negative pions have similar advantages and that neon ions are radiobiologically similar to fast neutrons but with better dose localization. He suggested that more study is needed before we can choose from these particles for radiotherapy applications. Raju responded that he was not proposing argon ions as the particle of choice for radiotherapy--that he just wanted to point out some of the radiobiological similarities with neutrons. Studies with cultured Chinese hamster cells (V79) using aerobic and hypoxic cells have indicated no significant differences in RBE for aerated cells all through the depth of penetration for the 10-cm wide Bragg peak, with the exception of the last few millimeters where the RBE is lower due to saturation effects. The RBE for hypoxic cells remains consistent with the entire depth of penetration. The dose localization advantages of heavy charged particles also is still maintained for argon ions with ranges up to ~ 15 cm.

There was extensive discussion regarding how the OER for fast neutrons compares with the OER for heavy ions. Hall stated that his impression, after seeing the posters, was that the OER for carbon and neon ions for spread-out Bragg peaks is nowhere near as good as for fast neutrons and for argon ions is not much better, while losing the dose localization. After some discussion, Fowler summarized by saying that the OER for neon ions is comparable and that for argon ions is lower compared to fast neutrons. There was some agreement on this summary. Alpen stated that his laboratory has biological data for about five different cellular systems and that there is no way we can make generalizations. For example, there is significant recovery for cultured cells at the neon plateau but no recovery for the gut system. Alpen agreed with Fowler's summary on OER. Broerse suggested that the appropriate way to compare OER data by different investigators is to compare the OER of a given particle with the OER for x rays by the same investigator.

(The references cited herein are the authors mentioned in Poster Session D.)