FAST-NEUTRON RADIOBIOLOGY AND RADIOTHERAPY

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Abstract

The application of fast neutrons, negative pions or heavy ions will only provide an advantage for the radiotherapy of cancer if, in comparison with conventional radiations, e.g., X-rays, gamma rays and electrons, better depth-dose and collimation characteristics or specific radiobiological dose response relationships result in greater local control probabilities for tumours without increased frequencies of severe normal tissue damage. Differences in intrinsic radiosensitivity and the presence of hypoxic cells are considered to be the main factors which can cause values of the relative biological effectiveness (RBE) for responses of tumours to be larger than RBE values for normal tissue tolerance. Clinical studies on lung metastases irradiated with single doses of 15 MeV neutrons indicate that RBE values for tumour growth delay can vary between 1.2 and 4.0, while RBE values for damage to several normal tissues are estimated from corresponding animal data to be approximately 2.5.

1. Introduction

The achievement of high rates of local control of cancer is frequently limited by the tolerance of normal tissues in the treated area. After treatments, normal tissues must be capable of restoring their integrity and function, i.e., late damage such as ulcers to skin, mucosa and intestine or paralysis due to spinal cord irradiation, must be limited to a very small fraction of the cases.

Interest in the biological effectiveness of beams of particles generated by large accelerators, stems for a considerable part from the possibilities of their application to the treatment of cancer. In principle, improvements in the control rates of cancer due to irradiation with various particles, in comparison with the rates presently attained with conventional treatments using high energy X-rays or gamma-rays, might be obtained on account of two factors which can lead to more destruction of neoplastic cells without exceeding the tolerance of normal tissues. These factors are a better spatial distribution of the radiation dose in and around the tumour in patients and a larger relative biological effectiveness (RBE) of the radiation for damage to the proliferative capacity of tumour cells as compared with the RBE for damage to the dose limiting normal tissues.

With negative pions and all types of heavy ions, quite favorable spatial distributions of dose can be attained, but with fast neutrons the depth dose and collimation characteristics are not better and frequently somewhat inferior to those of high energy X-rays. With respect to the radiobiological characteristics, fast neutrons, negative pions and heavy ions at Z-values in excess of about 10, might yield RBE-values for specific types of tumours in man in excess of RBE values for late effects on normal tissues, because of a smaller dependence of the effectiveness on accumulation of damage and on the conditions of irradiated cells, e.g., hypoxia. It is evident that except with respect to hypoxia, studies of normal tissue reactions are of equal importance as studies of tumour responses.[1,2,3]

2. Causes of Failure to Eradicate Tumours Locally

In cases where the treatment of cancer with ionizing radiation is successful, it can be concluded on the basis of radiobiological insights obtained during the past two decades, that complete impairment of the proliferative capacity of all tumour cells has been attained at a dose whereby the critical normal tissues are capable of restoring their integrity and function. If a local recurrence is observed after a dose equal to the tolerance dose of the limiting normal tissue, then it can be concluded that some of the tumour cells have retained the capacity for unlimited proliferation. For this reason studies of survival of cells with various systems, using their capacity for proliferation as a criterion for survival, are of great importance for an analysis of the radiosensitivity of tumours. Studies of this type with animal tumours have shown that a failure to eradicate all tumour cells by a given radiation treatment can be ascribed to several factors.

Firstly, the normal tissue tolerance may sometimes be particularly small for specific locations, especially depending on the size of the volume irradiated. This may render it impossible to administer a tumoricidal dose.

A second cause of failure to attain local tumour control is that the lethal effect on tumour cells is not large enough even with the relatively large doses tolerated by several normal tissues, e.g., total doses of 6000 rad of ^{60}Co gamma rays, applied in a schedule of 200 rad per day, 5 fractions per week. Factors which are known to influence responses of cells in tumours, rendering irradiation treatments less effective, include the intrinsic cellular sensitivity, as derived from the shape of a cell survival curve, repair of sublethal damage and of potentially lethal damage, the presence of hypoxic cells and inadequate reoxygenation, and the proliferation status of cells.[3]

The presence of hypoxic cells in tumours and the observation that the oxygen enhancement ratio (OER) of radiations which deposit their energy at high linear energy transfer (LET), e.g., fast neutrons, is smaller than the OER of X-rays, has frequently been considered as the principal rationale for the use of high-LET radiations in radiotherapy.[4,5] Various studies have shown, however, that differences in intrinsic radiosensitivity as expressed in shapes of survival curves of cells from various tumours, can be at least equally important. A general feature of the dose-effect relationships obtained with high-LET radiations is that the responses are less dependent on many conditions of the cells. As a consequence treatments of tumours with these radiations might render results less variable than with X-rays.

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3. Radiobiological Characteristics of high-LET Radiations

3.1. General radiobiological features in relation to LET.

With thin layers of tissues, e.g., 10 μm at unit density, and with mono-energetic heavy charged particles, energy can be deposited in cells with a well defined small spread in linear energy transfer. Experiments with such conditions have shown that to a first approximation three regions of LET can be distinguished. At less than 10 KeV/μ m of tissue, cell lethality is mostly due to accumulation of damage from two or more ionising particles, it can be influenced by repair of sub-lethal damage and it is strongly dependent on the presence of oxygen and on other conditions. Between 10 and 100 keV/μ m of tissue, the RBE increases with LET, accumulation of damage is of less importance, but damage is still dependent to a considerable extent on the presence of oxygen and on other cell conditions. At LET values in excess of 100 keV/μ m of tissue, the cross-section or probability of cell lethality per particle, is to a large extent independent of accumulation of damage, of fractionation, as well as of cell conditions, e.g., hypoxia. In this region of LET, the RBE reaches a maximum with a subsequent decrease of LET values in excess of about 200 keV/μ m of tissue.[1)]

3.2. Energy deposition in tissue and RBE values of fast neutrons.

Fast neutrons deposit energy in biological medium by different types of interactions, including elastic scattering, inelastic scattering, capture processes and nuclear interactions. These processes result in a number of secondary charges particles, such as recoil protons, alpha particles and heavy nuclei. The energy deposition patterns of these secondary charged particles are dependent on the energy spectrum of the incident neutron beam and can be characterised by LET spectra with LET values from 1 to 800 keV/μ m of tissue. For a considerable part of the spectrum, the LET exceeds the LET values of X-rays. As a consequence, the RBE of fast neutrons is larger than that of X-rays. The relation of RBE as a function of neutron energy has been studied for various types of cells.[1,2)] In table 1 a number of RBE values of 15 MeV neutrons is given, showing that the RBE depends on the dose and the type of cell investigated. The differences in RBE values among various types of cells could be even larger for neutrons of lower energies. Similar differences may be observed for negative pions and heavy ions.

Table 1.

RBE VALUES DERIVED FROM SURVIVAL CURVES OF DIFFERENT TYPES OF CELLS

	at 50% survival	at 10% survival	at 100 rad of 15 MeV neutrons	at 200 rad of 15 MeV neutrons
mouse haemopoietic stem cells	1.5	1.1	1.3	1.1
mouse lymphocytic leukaemia cells L5178Y	2.1	1.6	1.8	1.6
cultured cells of human kidney origin	2.7	2.0	2.5	2.2
rat rhabdomyosarcoma cells	2.6	2.0	2.5	2.2
mouse intestinal crypt stem cells	1.8	1.6	1.9	1.8

3.3. RBE values of fast neutrons for responses of tumours and normal tissues.

Numerous studies with experimental tumours and different normal tissues have shown that the RBE values of fast neutrons increase generally with decreasing doses or doses per fraction and with decreasing neutron energy. Large differences have been observed, however, depending on the type of tumour or normal tissue irradiated.[7,8)] It has been concluded that if RBE values for responses of human tumours show a similar spread as observed for experimental systems, then large variations in RBE values by a factor of at least 2 must be expected. These variations are not caused by differences in the presence of hypoxic cells, but must be due to differences in intrinsic sensitivity of the cells. These variations imply that for some types of tumours the radiobiological properties of fast neutrons or heavy particles might not provide an advantage over X-rays with respect to the therapeutic margin, while for other types of tumours the gain might be significant. It should be a main object of radiobiological and clinical studies to obtain information about the types of tumours for which a useful gain can be obtained.

3.4. The influence of hypoxic cells in tumours.

The presence of hypoxic cells in tumours, and the observation that oxygen enhancement ratios (OER) of heavy particles and of fast neutrons are smaller by a factor 1.3 - 1.8 than the OER of X-rays, has long been considered to constitute the main rationale for the use of high-LET radiations in radiotherapy.[4,5)] The ratio $(OER)_x/(OER)_n$ has been denoted "gain factor" for neutrons, but more detailed examination of the influence of hypoxic cells in tumours has led to the conclusion that this ratio represents a maximum gain factor which would apply only if all cells in a tumour were severely hypoxic and remained hypoxic throughout a fractionated treatment course of several weeks. However, the effective gain factor associated with the low OER of heavy particles and fast neutrons is always considerably smaller than the maximum gain factor, because not all cells in a tumour are severely hypoxic and because in fractionated treatments, reoxygenation may occur. As a consequence the gain factor due to a reduction in OER alone might be only 1.1 to 1.2, instead of the value of 1.6 to 1.8 derived for large single doses.

4. Dose Distributions in and around Tumours

Fast neutron beams deposit energy in tissue with spatial distributions on a macroscopic scale which are similar to those of photon beams, i.e., the dose initially increases beyond the surface and subsequently decreases approximately exponentially. For a given neutron energy the relative depth dose is a function of the source-to-surface distance and field size. The neutron spectrum and the proportion of the dose due to gamma radiation varies with field size and depth in scattering medium. Consequently,

the biological effectiveness may also vary with field size and depth.

Negative pions and heavy ions will deposit energy in tissue with various types of distributions on a macroscopic scale. With depth in tissue the dose will increase up to the Bragg peak. Because of the well defined range of these particles, the dose beyond the maximum range will be negligible. Due to the mass of the particles scattering effects will be relatively small. Finally with negative pions, star formation will increase the effect at the end of the range. All these features can be used to produce optimal dose distributions, especially taylored to spare specific normal tissues outside the prescribed treatment volume.

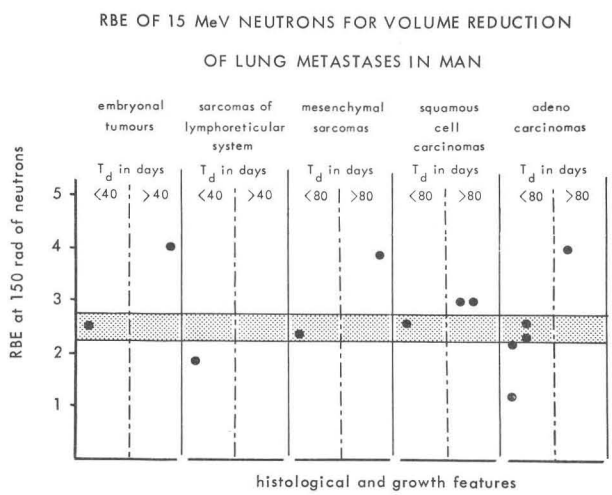
In the case of negative pions, star formation gives rise to α-particles but also to fast neutrons. If large volumes, e.g. of 1000 cm^3, are to be treated, the dose due to fast neutrons may increase to a considerable fraction, e.g., 0.2-0.4 of the total dose deposited. As a consequence the sharp boundaries of the treated volume are partly eliminated.

Improvements in local tumour control due to dose distribution properties will result only if the possibility is provided to give a larger effective dose to the tumour without increasing late complications. This depends evidently on the tumour location.

5. Quantitative Aspects of Applications of high-LET Radiations to Tumours in Man.

From the preceding discussion of variations of RBE values of fast neutrons in relation to various factors, it must be concluded that similar large differences might be expected with tumours in patients. Consequently, before large scale clinical application is started, it is evidently of great importance to obtain some numerical data about RBE values for a variety of types of tumours. This might lead to the elimination of some types of tumours from further trials if consistently low RBE values were obtained. For this purpose, volume changes of pulmonary metastases in patients were measured from serial chest radiographs after irradiation with single doses of 15 MeV neutrons or ^{60}Co gamma rays and 250 kVp X-rays.[9] The neutron generator at the Radiobiological Institute in Rijswijk, the Netherlands, producing 15 MeV neutrons through the D-T reaction, was used to deliver single doses ranging between 150 and 220 rad of neutrons to lung metastases from different types of tumours in patients. Comparison was made with doses ranging from 380 to 510 rad of ^{60}Co gamma rays or 250 kVp X-rays given to the same metastases after regrowth or simultaneously to other metastases in the same patient. RBE values were derived for growth delay of metastases in 13 patients. The values have been related to a standard dose of 150 rad of 15 MeV neutrons and ranged from 1.2 to 4.0. In general the largest RBE values were obtained for slowly growing metastases. The number of data is too small as yet to conclude that for specific types of tumours high-LET radiations might provide a significantly larger advantage than for other types. The mean value of RBE at 150 rad of 15 MeV neutrons for several normal tissues in experimental systems is about 2.5. Thus if this value were similar to that for normal tissues in man, for some tumours, e.g., with an RBE = 4, a significant advantage would be obtained in comparison with X-rays.
(compare figure 1)

Figure 1.



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DISCUSSION

J. MCKEE: All speakers this morning have made extensive use of the terms "cure" and "survival". Are there internationally accepted definitions of these terms?

G.W. BARENDSEN: Yes, cure is defined by a return of the life expectancy of the irradiated patient to the life expectancy of similar aged persons without cancer. The term survival is usually given at 5 years or 10 years after treatment.

G. BURTON: Is there any radiobiological evidence for a difference in performance in therapy using 15 MeV monoenergetic neutrons or a neutron beam of mean energy 15 MeV as is obtained from say a 30 to 40 MeV deuterons on beryllium reaction?

G.W. BARENDSEN: There are fairly accurate data suggesting that the mean energy is an adequate characteristic for the prediction of the best relative radiobiological effectiveness, but these are not sufficiently extensive to conclude that this is true for all types of neutron spectra.

G. SCHATZ: What is the optimum neutron energy for neutron therapy?

G.W. BARENDSEN: This choice depends on four factors:

a) The requirement of an adequate depth-dose characteristic;

b) The requirement of an adequate dose rate;

c) The increase in cost of the generator with increasing energy;

d) The possibility of changes in biological effeciveness and oxygen enhancement ratio with increasing neutron energy about which we know very little.

I would suggest that neutrons of average energy 15-25 MeV, e.g. produced with 50 MeV deuterons on a Be-target, might be adequate.