

RADIOBIOLOGICAL AND CLINICAL BASES OF PARTICLE THERAPY (REVIEW)

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1200, Bruxelles (Belgium)**Introduction**

Application of new types of ionizing radiations is today one of the most promising approaches for improving the efficiency of radiotherapy. However, there are still controversies concerning the conclusions which can be drawn from the available clinical results with fast neutrons, and thus concerning the future of high-LET radiation in cancer therapy. This in turn raises controversies about the priority level which should be given to rather large and costly investments, such as those implied in heavy-particle therapy programs.

When discussing the place of non-conventional ionizing radiations, one has to distinguish :

- particle beams which only improve the physical selectivity of the irradiation, i.e. the dose distribution (e.g. proton beams or helium ion beams);
- high-LET radiations which produce different types of biological effects, and which aim at improving the differential effect between tumour and normal tissues (e.g. : fast neutrons);
- the two approaches can be combined and one could seek after a high physical selectivity with high-LET radiation (e.g.: heavy ions).

Improvement of the physical selectivity with proton and helium ion beams

Historically, the major improvement in the efficiency of radiation therapy was the replacement of conventional X-rays (200 kV X-rays) by high-energy photons or electrons. The clinical benefit was rapidly evident for all, or for the majority of the patients. This illustrates the importance of the physical selectivity in radiation therapy.

We are now close to make a further step : the introduction of proton beams. The characteristics of the proton beams make them superior to high-energy photons from the point of view of the physical selectivity. On the other hand, no advantage has to be expected from the biological point of view : for the high energy required to the protons in external irradiation, we stay in the field of low-LET radiations. For the present discussion, we can assume that helium ion beams are similar to proton beams.

The clinical benefit of proton beams has been demonstrated for several well selected tumour types or sites for which a physical selectivity is essential. The best example is the uveal melanoma, which has been treated since 1974 by proton beams at the Harvard cyclotron [1].

The high physical selectivity of the proton (and helium ion) beams can be exploited for other localisations : radioresistant tumours close to critical organs such as chordomas or chondrosarcomas of the base of the skull, paraspinal tumours, and meningiomas (Suit in [18]; Castro in [19]).

There is an increasing number of projects which aim at treating with protons many other tumour types, and larger proportions of patients. One of the most impressive is the Loma Linda project at Los Angeles. Once all treatment rooms will be fully operational, the centre is expected to have a capacity of 1 000 new proton beam patients per year [14]. This kind of project really aims at systematically substituting proton to photon beams; it raises a least 3 types of problems :

- 1) to what extent will the clinical benefit justify the increased cost and efforts involved;
- 2) such program will imply, in a more or less near future, a redefinition of the radiotherapy network, and a progressive replacement of several small photon therapy units (or departments) by huge proton therapy facilities;
- 3) finally, the benefit of the high physical selectivity of the proton beams will be fully exploited only to the extent that the accuracy in patient-beam positioning and in dosimetry would reach the same level as with photons. The proton beam generators should also be as reliable as the modern linear accelerators.

It is at present the task of the teams who have access to high-energy cyclotrons to provide a clear, and quick, response to that problem. It would be indeed a significant improvement to be able to deliver high-doses (60-70 Gy) to bronchus or oesophagus tumours, or to treat a Hodgkin patient, with a (nearly) full sparing of the spinal cord.

The differential effect and the potential advantage of fast neutrons and high-LET radiations**1. Radiobiological data**

Historically, fast neutrons were introduced in therapy because of the existence of hypoxic cells and the reduction in OER when increasing LET. However, high-LET radiations exhibit other differences in their biological properties, when compared to low-LET radiations:

- a reduction in the differences in radiosensitivity from cell line to cell line (i.e. "intrinsic radiosensitivity") [2]. On the other hand, Fertil et al. [7], comparing the responses of 6 cell lines to X-rays and neutrons, observed a modification in their relative radiosensitivities (i.e. a given cell line more resistant to X-rays could be more sensitive to neutrons another cell line).
- a reduction in the differences in radiosensitivity related to the position of the cell in the mitotic cycle [5].
- less repair phenomena (in general), and as a consequence less difference between the responses of the cell populations to fractionated irradiation.

From the above arguments, it can be concluded that all cell populations, in all conditions, tend to respond in a more similar way when exposed to neutrons compared to photons. From that point of view, a reduction in OER can be considered as a particular aspect of a more general phenomenon, i.e. a reduced difference in radiosensitivity between cell populations [17].

Two practical consequences can be derived from the above radiobiological considerations :

1. The importance of patient selection. An absence of (or a wrong) selection of the patients could worsen the clinical results and lead to erroneous conclusions about the value of fast neutrons. This could maybe explain a least some of the reported discrepancies in clinical results.
2. The need for a high physical selectivity with high-LET radiations, which proceeds from the reduced differences in radiosensitivity. When large differences in radiosensitivity are observed between the cancer and normal cell populations, a poor physical selectivity is of limited consequence. In typical cases, such as seminomas or lymphomas, the dose prescribed to

the target volume is below the tolerance dose, and irradiation of a few additional cm^3 of normal tissue would be of little clinical importance (in chemotherapy, there is obviously no physical selectivity at all, and the potential therapeutic gain depends only on a biological selectivity). By contrast, when the differences in radiosensitivity are reduced with very high-LET radiation, the therapeutic efficiency mainly rests on a high level of physical selectivity; sparing a few cm^3 of normal tissues then becomes of real importance.

In addition, with low-LET radiations, where repair phenomena play an important role, differences in repair capacity between the normal and cancer cell populations can be exploited by selecting appropriate fractionation regimen. This possibility is reduced with high-LET radiations since repair phenomena are in general smaller. Consequently, from a radiobiological point of view, high-LET radiations then appear to be a treatment modality with limited possibility of enhancing an eventual differential effect by selecting the optimum fraction sizes.

2. Clinical data

Fast neutrons therapy is applied today routinely in more than 17 centres throughout the world [13]. Locally extended salivary gland tumours are the first type of tumours for which the superiority of fast neutrons was recognized. A survey of the results of the non-randomized clinical studies as well as the results of the RTOG/MRC prospective randomized trial overwhelmingly support the contention that fast neutrons offer a significant advance in the treatment of inoperable and unresectable primary or recurrent malignant salivary gland tumours [8] [15].

Remarkably good results have also been reported with neutron therapy for locally extended tumours of the paranasal sinuses. In the series treated at the Hammersmith Hospital, 86 % (37/43) of the patients showed complete remission and relief of symptoms was noticed in all cases [6]. The value of fast neutrons, for tumours in the head and neck area, is questioned [9].

For soft tissue sarcomas, the results reported from the different centres indicate an overall local control rate after neutron therapy of 53 % for inoperable tumours, which is higher than the 38 % control rate currently observed after low-LET radiation for similar patients series. For primary bone tumours and differentiated chondrosarcomas, better results have also been observed after neutron therapy compared to the current photon therapy results (reviewed in [10] and [19]).

Prostatic adenocarcinomas, having in general a long doubling time, should be a good indication for neutron therapy taking into account the available radiobiological data [3]. Excellent results were achieved in Hamburg, Louvain-la-Neuve and Chiba [11] [15]. The most convincing data are the result of a randomized trial, initiated by the RTOG, on locally advanced (C,D1) adenocarcinomas of the prostatic gland [12]. The local control rate was 77 % for patients treated with mixed schedule (55 patients) and only 31 % for patients receiving photons alone (36 patients) ($P < 0.01$). Actuarial survival rates at 8 years ("determinantal" survivals, i.e. adjusted by exclusion of intercurrent deaths) were 82 % and 54 % respectively ($P=0.02$). The RTOG is now performing another randomized trial comparing neutrons only to conventional photon treatment.

The value of fast neutrons has been assessed in other tumour types or sites but no definitive conclusions can be drawn yet; some of the results are promising [13] [15]. In fact, the general conclusion which emerges from the review of the clinical results is in agreement with what could be expected from the radiobiological data : replacement of X-rays by neutrons - or more generally of low-LET by high-LET radiation - brings a benefit for some types of tumours and, on the contrary, a loss for other tumours. The tumours for which fast neutrons were found to be superior to conventional X-rays are, in general, slowly growing and well differentiated.

In contrast, negative results have been obtained for brain tumours [13].

As far as the proportion of patients, suitable for neutron therapy is concerned, figures ranging from 10 to 20 % have been suggested. They correspond to the percentages of radiotherapy patients for which neutrons were shown to be superior than conventional X-rays. These percentages are probably at the lower limit since they were often obtained with low energy cyclotrons and poor physical selectivity. It is likely that with high-energy, hospital based modern cyclotrons, neutron therapy will be found to be useful for a larger proportion of patients. In addition, neutrons could extend the field of the indications of radiation therapy by allowing to envisage the treatment of groups of tumours "traditionally" considered to be radioresistant (e.g. adenocarcinomas).

The rationale for heavy ion therapy

The heavy-ions combine the advantage of a high physical selectivity with the potential advantage of high-LET radiation for the treatment of some tumour types. As far as the physical selectivity is concerned, heavy ions are similar to protons or helium ions. Heavy ion beams have even a smaller penumbra, but it is questionable whether this could be of clinical relevance. More important is the fact that, with heavy ions, the higher RBE at the level of the spread out Bragg peak further improves the advantage of the dose distribution. As far as the high-LET advantage is concerned, the LET at the level of the spread out Bragg peak depends on the type of particle, and on the width of the spread out Bragg peak. These factors then also influence the RBE, OER, etc...

From the radiotherapy point of view, the use of heavy ion beams is justified by 3 sets of arguments [16] :

- 1) the radiobiological and clinical data indicating that, for the treatment of some tumours types and/or sites, high-LET radiations could be superior to low-LET radiations;
- 2) the fact that a high physical selectivity is even more important with high- than with low-LET radiations, due to a general reduction in the difference of radiosensitivity between cell populations ;
- 3) the encouraging results reported from Berkeley, which are an additional argument, although they were obtained on a limited, selected, group of patients [4].

Only a few heavy-ion therapy facilities are planned in the world : the facility at the NIRS in Japan which is under construction, the LIBRA project in the USA, and in Europe the GSI project in Darmstadt-FRG and the EULIMA project. Due to their high cost and complexity, an international cooperation is necessary in

order to ensure the appropriate patient recruitment and a rapid exchange of information. Patient recruitment should aim in principle :

- at selecting for heavy ions tumour types or sites for which there is evidence that better results could normally be expected than with conventional treatments;
- at initiating randomized trials designed to answer specific questions of great relevance in radiobiology and/or therapy.

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