Whole Body Irradiation and Infection Prevention
—a Therapeutic Concept for
Patients with Generalized Metastasis

W. FINCK and D. HAMANN

Department of Radiology, Division of Nuclear Medicine and
Division of Radiation Therapy, Wilhelm-Pieck-University Rostock, GDR

Dr. Sasaki, Mr. Chairman, dear colleagues,

Let me first give my thanks to the authorities of the Tokai University School of Medicine for the kind invitation, giving us the opportunity to participate in this symposium. We are continuing the cooperation in the field of research on infection prevention which we started 3 years ago with the symposium “Applied gnotobiology for infection prevention in the immunocompromised host” organized by the Wilhelm-Pieck-University Rostock at Ahrensboop together with the Gnotobiotic Project Group of the European Organization on Research and Treatment of Cancer (EORTC). We were glad to have Prof. Ozawa and Prof. Nagao with us in 1983, and I hope that colleagues from Tokai University will be our guests next year, October, when a further symposium will be held at the Rostock University on “Problems in infection control in the immunocompromised host, interaction between the microflora and the patient”, again organized together with the Gnotobiotic Project Group of EORTC.

I am feeling somewhat like an outsider as I have to start from quite a different point of view than my colleagues, but I hope that I will be in touch with the general topic at the end.

The reaction of bone marrow to irradiation has been investigated over a long period of time, and we know a lot of experimental data concerning immune suppression caused by irradiation in great detail. Moreover, clinicians are experienced in estimating the infection risks for patients treated with radiotherapy. Under these conditions—with some restraints—overall accepted rules and principles do exist according to which therapeutic application of ionising radiation is handled. Nevertheless, in both types of application, in percutaneous radiation with gamma- or X-rays as well as in oral or intravenous application of radioisotope-labelled pharmacon, experimental results and theoretical considerations have produced new ideas in treatment of generalized metastases, and, in the case of percutaneous radiotherapy, clinical results have been reported already for over a decade.

The experiences in radiotherapy are closely associated with the development of accelerators, which allow, with a photon energy of more than 12-15 MeV, almost homogenous radiation absorption all over the body by one ventral and one dorsal field. This is tolerated undoubtedly better than irradiation with lower energy photons, permitting higher doses at lower risk.

In the case of radiopharmaceuticals, a new concept (and really it has only been a concept up to now) has evolved from the introduction of microdosimetric ideas into radioisotope therapy. In total or hemibody irradiation as well as in application of radiopharmaceuticals for therapeutic purposes, bone marrow function and infection prevention are the central considerations as they are the main dose limiting factors. Looking with appreciation at the results obtained from selective decontamination of patients during therapy for leukemia, we
must consider that this might be useful in radiation therapy as well. What are the fundamental facts? Cells with reproductive capacity are killed by radiation in a way which may be described in a semilogarithmic plot as a straight line dose-effect response, at least in simple systems. In more complicated ones in which more than one hit must be delivered to the sensitive volume, this line is bowed into a sigmoidal form. It is known from very old investigations that mitotic active bone marrow cells follow this type of dose-effect response as it is known from different cell cultures. Semilogarithmic dose-effect-relation means: even with high doses, cells will survive with mitotic capacity, but in very small numbers. In principle, mitotic delay responds in the same way as mitotic death—the dose-response curves being some what steeper—caused by the higher sensitivity of mitotic delay to radiation. That means: the question is not whether the cells will survive, but whether there will be enough time for recovery without fatal accidents during the immunocompromised period, the duration of which is dependent upon the dose.

This problem is closely associated with the problem of cancerostatic therapy of leukemia. Unfortunately, we are still far away from clinical applications and results as they have been reported by hematologists. Hence, that which we have to report is still in the state of conception and of basic research.

**WHOLE BODY AND HEMIBODY IRRADIATION**

The reaction to single short time whole body irradiation is well known: At below 0.2 or 0.3 Gy, we are able to avoid critical situations. After 1 Gy we have to expect radiation illness in all cases and some patients will die. During the last few years whole body irradiation has been abandoned in favor of hemibody irradiation. But we have as result, from older investigations, such as from Saenger's group (2), the 9 fatalities out of 85 following 1-3 Gy whole body irradiation (fractionated, of course), which should be due to the treatment. You will surely remember the report given by Gale during the conference on "Basic and Clinical Problems in Bone Marrow Transplantation" held by Tokai University Medical School at Copenhagen 2 years ago (1). Gale used 3 Gy in single short time whole body irradiation before bone marrow transplantation in addition to cyclophosphamide with the result of reduction of graft rejection to 5%. This morning Dr. Masaoka reported on the use of about 2 Gy/day.

For therapy of metastases, whole body irradiation in single doses in the range of 1 Gy can not be accepted because of high risk. Hemibody irradiation with fractionated doses are used nowadays. If by this way the blood building system in the upper part of the body may recover after irradiation before the lower part is irradiated the problem of the sensitive organ will change: attention will turn to the lungs and to the gastrointestinal tract. Radiation induced pneumonitis is a severe complication, feared even in radiation of limited areas of the lungs in patients with bronchial carcinoma. It is the dose limiting organ for the upper part of the body. The pathogenesis of pneumonitis, especially the role of infection of the respiratory tract is not fully understood at present. We measured lung ventilation and perfusion with the methods of nuclear medicine and we are sure that functional disturbances are not the primary cause of death in these patients.

In the lower part of the body, the gastrointestinal tract is the crucial sensitive organ. We know this from H. Quastler's fundamental studies. The mitotic activity of the epithelial cells originating from the crypts of Lieberkuehn is suppressed and, if there is no recovery of mitosis, the gastro-intestinal tract will be nude after 3 to 4 days, when the life time of these cells is finished, free of epithelium, with loss of water, of electrolytes, and with bacterial invasion. In experiments, full recovery is possible if the animal survives this period by special treatment. It is identical to the situation which has been mentioned before in connection with the bone marrow cells: even with high doses, a small portion of the cells will retain mitotic capacity, but it will take too long to build up enough cells to cover the mucosa, thus the animals will die. We measured DNA synthesis of mucosal cells with labelled precursors in rats (Fig. 1) and obtained the typical course with rising specific activity during the labelling period, with constant activity during the period in which cells move along the mucosa, and decreasing activity, when cells are being reject-
ed at the top of the villi. Fig. 2 gives the dose-effect response 24 hrs. after irradiation, at the point of reaching maximum specific activity according to Fig. 1. The recovery of synthesis after 800 R is shown in Fig. 3. Synthesis starts at a remarkable rate after this radiation dose just before the gastro-intestinal tract becomes nude. The higher the dose, the longer the time until a measurable level of DNA synthesis is reached.

What happens with the gastro-intestinal function? We investigated the capacity of mucosal cells to transport glucose against a concentration gradient in in vitro experiments (Fig. 4). Concentration ratio 1 indicates equal concentration on both sides of the gut. Normally, in this experimental order the mucosal cells concentrate up to 2.2 fold against the gradient. The right part of the picture shows the active transport capacity after 800 R: it corresponds to the mitotic activity as shown by the DNA synthesis in Fig. 5. The left side of Fig. 4 is more relevant to our problem: there is a transient insufficiency of active transport. This effect is not strongly dose-dependent; it was repeated in all experiments without exception, and we have no idea why it happens.

There experiments were concerned with the time scheme of radiation fractionation in our patients given hemibody irradiation. We know from animal experiments that the intestinal radiation syndrome proceeds in an almost identical course in the mammalian species. If we assume, that the situation in man is somewhat similar, and if we take into account that it will take about another two hours to compensate for the changes caused by disturbances in active transport, and if we add another hour to be on the safe side, then the second dose should be administered to the lower part of the body 5-6 hours after the first dose (Fig. 5).

We have no experimental orders to investigate the reaction of the lungs. The irradiation schedule of the upper part of the body has been developed from step-by-step experience and from literature. We are not sure whether we may shorten the interval between irradiations of the upper of the body: we have not lost a single patient by pneumonitis since this schedule was adopted.

But the next step must be to shorten the interval between irradiation of the upper and the lower part of the body, and here, bone marrow depression and immune deficiency at the higher dose level applied become the predominant problems which we have to overcome.

Fig. 1 Specific activity of DNA and RNA in rat mucosal cells, after injection of labelled precursor; specific activity in arbitrary units.
Fig. 2 Dose-dependent suppression of DNA synthesis 24 hours after irradiation. Mean and standard deviation.

Fig. 3 Recovery of DNA synthesis after 800 R.
Fig. 4 Active glucose transport by intestinal mucosa after 800 R (see text).

hemibody irradiation

upper part 4 Gy (2 + 2)
5 - 6 hours
2 Gy (1 + 1)
4 weeks

lower part 4 Gy (2 + 2)
5 - 6 hours
4 Gy (2 + 2)

Fig. 5 Time schedule of fractionated hemibody irradiation.
MICRODOSIMETRICAL ASPECTS OF RADIOISOTOPE THERAPY OF METASTASES

The second problem seems to be far removed from the first, but from the viewpoint of radiation sensitivity of tumors, metastases, and bone marrow, it is quite the same in spite of the different starting point.

We know of no specific metabolic activity of tumor cells, which could be used to transport radiopharmaceuticals into the tumor by its own metabolism, with the exception of thyroid carcinoma. Even carriage of isotopes by labelled monoclonal antibodies is far from a therapeutic level of concentration in or around the tumor cells. Some new aspects have been brought up by the introduction of microdosimetric calculations into tumor therapy with radioisotopes.

If we use isotopes with a range of rays which is short in comparison to the size of the irradiated object, we can no longer expect a homogenous distribution of radiation in the tissue of interest, as we normally do, and as we calculate with the help of Marinelli's formula or the MIRD concept. This is the case in isotopes with extremely weak photons, with weak beta-particles and with alpha-particles.

We worked on diphosphonic acids over some years, labelled with $^{99m}$Tc for bone scintigraphy. We could synthesize about 30 of these compounds and learned something about the relation between chemical structure and biodistribution (3).

Aminomethane diphosphonic acids and its derivatives are substances with high bone-to-body ratios of accumulation, with rapid drop of the body background, with strong binding to the skeleton, and with high concentration in pathological bone areas in comparison to normal bone. We considered, whether the introduction of sulfur into the molecule could result in a similar sufficient biodistribution and whether this could be used in therapy of bone metastases, by substituting the sulfur with $^{35}$S, a weak beta-emitter. Out of 5 S-containing diphosphonic acids, 3 seemed to be convenient from the viewpoint of synthesis and in vitro or in vivo behaviour (Fig. 6). Fig. 7 gives the typical biodistribution of one of these radiopharmacons. Fig. 8 the body retention, which compared well with bone accumulation.

The microdosimetrical aspect is demonstrated in Fig. 9. The left curve gives the beta range distribution of $^{35}$S in soft tissue, and the one on the right the distribution of the distance of spongiosa material surrounding bone marrow, assessed from microscopic pictures of human vertebra. It is to be seen, that the area of bone marrow surrounded by spongiosa is large in comparison to the range of the beta rays. This is quite another situation from that involved in the therapeutic application of $^{32}$P, which causes an almost homogeneous irradiation of the marrow zone and therefore is only used for palliative therapy.

Which amount of activity has to be applied for a therapeutic dose in the metastases? Fig. 10 gives the known formula describing dose per time DL$_\beta$ in dependency of the concentration of the radionucleide C and the mean beta energy $\overline{E}_\beta$ (upper part). By integration, we get the total dose, which can be described very simply, if we assume time to be long (last line). If we demand 100 Gy as an effective dose for the metastasis and take into account the data of biodistribution, we must apply 2.7 GBq. This means a dose of 8.5 Gy to the normal skeleton, which should be acceptable for an adult patient. Whole body irradiation is about 10m Gy. Bone marrow is partly outside the range of beta rays, but a period of bone marrow depression and immune insufficiency will result. We must overcome the period up to full restoration with therapeutic concepts such as selective decontamination. Further development of therapy of metastases with radiopharmacons depends to a high degree on further development of treatment of radiation-induced immune insufficiency.

The above are two lines of research which are still in progress. We have no final results, but I was encouraged to give this report by the fact that we were stimulated to start these investigations by the symposium on applied gnontobiology, held 3 years ago together with our colleagues from Tokai University.
Fig. 6 Diphosphonic acids with sulfur in mercapto- or thio- binding.

Fig. 7 Biodistribution of ethylmercaptomethane diphosphonic acid 1-6 hours after injection.
Fig. 8 Body retention of ethylmercaptomethane diphosphonic acid 1-6 hours after injection.

Fig. 9 Distribution of the range of $^{39}$S beta rays in soft tissue (left curve) and distribution of the distances of spongiosa material surrounding the bone marrow (right curve).
Fig. 10 Calculation of activity and radiation dose (see text).

REFERENCES