PRINCIPLES OF TOTAL BODY IRRADIATION

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Total body irradiation delivered prior to bone marrow transplantation remains an important component of the conditioning regimen.

Proper engraftment of autologous or allogeneic bone marrow is possible because of the multifarious effects of high doses of ionising radiation on tumour cells and the host immune system. We will broadly outline the techniques used to deliver total body irradiation, and the effects of ionising radiation on normal and tumour cells from a biological and molecular point of view. Finally we will report the results of randomised clinical trials that have been conducted in our institution during the last ten years.

TOTAL BODY IRRADIATION TECHNIQUES

Total body irradiated (tbi) is delivered to patients using an 18 MV linear accelerator. Patients are placed within a single irradiation field lying on their left or right side 4 meters from the radiation source. Irradiation is given with horizontal beams using the anterior-posterior technique.

Three different types of total body irradiation have been performed during the last two decades in our institution. The golden standard established by the Seattle team was the first to be used and consisted in delivering 10 Gy in a single dose over 4 hours. The instantaneous dose rate was 12.5 cGy/min. and the average dose rate was 4 cGy/min. The dose was delivered to the midplane of the abdomen at the level of the umbilicus.

Due to new clinical and radiobiological assumptions, new techniques were devised to deliver total body irradiation.

A hyperfractionated schedule was started for it was assumed to be able to reduce the incidence and severity of acute and late normal tissue complications. Hyperfractionated total body irradiation delivered 11 fractions over 4 days, 3 fractions a day (total reference dose = 14.85 Gy). More recently for practical reasons, fractionated total body irradiation was introduced. This fractionated schedule delivers radiation in 6 fractions over 3 days; 2 fractions a day (total reference dose = 12 Gy).

The lungs are partially protected during total body irradiation for lung complications are one of the main causes of complications and death during bone marrow transplantation. The dose given to lungs is usually 8 to 9 Gy.

Radiation doses delivered to various parts of the body are monitored with in vivo dosimetry using diodes and thermoluminescent detectors. Diodes give immediate monitoring of the doses delivered. Radiation doses to various parts of the body are subsequently verified by thermoluminescent detectors. Diodes and thermoluminescent detectors are placed anteriorly and posteriorly on various parts of the patient.

The dose delivered using this techniques is uniform and most parts of the body receive +/- 10% of the dose delivered to the abdomen.

RADIOBIOLOGICAL BASES OF TOTAL BODY IRRADIATION

Total body irradiation given prior to bone marrow transplantation intends to fulfill three goals.

The first is to reduce the number of neoplastic cells so that disease can be eradicated. Recently experimental and clinical studies have shown that tumor cells may well repair the radiation-induced DNA damage (Uckun F.M. et al, 1993). As a more efficient repair of DNA damage leads to a higher survival a single dose total body irradiation is therefore more likely to achieve a greater reduction in the number of neoplastic cells than a fractionated schedule.

The second goal is to allow successful bone marrow engraftment by eradicating the recipient bone marrow cells and inducing immunossupression. Immunosuppression is of paramount importance when allogeneic bone marrow transplantation is performed.

Some experimental and clinical data seem to suggest that fractionated total body irradiation may be less immunosuppressive than a single dose schedule (Storb R. et al, 1994).

The third goal is the sparing of normal tissues, as lungs, liver and kidneys. Fractionated tbi seems to be better tolerated than a single dose of tbi (Cosset J.M. et al, 1989).

TOTAL BODY IRRADIATION AND BIOLOGICAL PARAMETERS

Early in the course of a single dose of tbi, a transient but large increase occurs in granulocytes occurs in the peripheral blood. This massive increase is due to their release from bone marrow (Dutreix J. et al, 1987). Concomitantly blood lymphocyte numbers rapidly plummet with all lymphocyte subsets being equally affected (Girinsky T. et al, 1991). Changes in the blood level of various hormones coincide with changes in white blood cell counts when high doses of radiation are delivered. Cortisol, adrenocorticotropic and corticotropin-relasing factor blood levels increase dramatically a few hours after the end of the tbi.

There is also a concomitant increase in interleukine 6 and tumor necrosis factor blood levels. These findings suggest that cytokines may be activating the hypothalamo-pituitary adrenal axis (Girinsky et al, 1994).

MOLECULAR BASES OF TOTAL BODY IRRADIATION

Two distant mechanisms account for the efficient manner in which total body irradiation reduces the number of neoplastic cells and begets immunosuppression.

It has long been thought that ionising radiation kills cells by a so called reproductive failure (inhibition of their ability to divide). Reproductive death seems to be mainly due to unrepared DNA double strand breaks. However, during the past few years, it has been demonstrated that ionising radiation is also able to kill neoplastic and normal cells through apoptosis or a so called programmed cell-death. The molecular events of apoptosis are in the process of being deciphered and p53, along with many other proteins seems to play an important role. Apoptosis can be triggered either by DNA or cell membrane damage (Haimovitz-Friedman A. et al, 1994). Preliminary data suggest that there may be a correlation between the magnitude of the immediate apoptotic response and radiocurability (Little J.B., 1994).

CLINICAL RANDOMIZED STUDIES TESTING RADIOBIOLOGICAL TENETS

During the last 10 years, 3 randomised studies have been conducted in our institution to study the acute toxicity on normal tissues of different total body irradiation schedules.

In our institution 3 randomized studies have been conducted to study in the last ten years. The first randomized study compared two different (6 Gy versus 8 Gy) given to the lungs to decrease the incidence of fatal lung complications without augmenting the risk of graft rejection or leukemia recurrences. The results suggested that the lower dose might increase leukemia recurrence rates (Girinsky T. et al, 1994).

The second randomized study compared two different total body irradiation dose rates (4 cGy/min. versus 2.7 cGy/min.). There were no obvious differences between the two groups in terms of lung complications and leukemia recurrences (Girinsky T. et al, submitted).

The third randomized study analyzed the impact of fractionation (total body irradiation given in a single dose of 10 Gy versus 11 fractions over 5 days) on acute complications, graft rejection, and leukemia recurrences. Preliminary data demonstrate no significant differences between the two types of fractionation.

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