of this year in Luxembourg, on the transposition af the directive into national law, a requirement the member states have to comply with before 13 May 2000.

A quick analysis of the text revealed that, in the context of this directive, the term radiation protection needed to be interpreted in the broadest possible sense: not only the physical conditions preventing occupational hazards and environmental contamination, but the protection of the patient against undue exposure and, as far as radiotherapy is concerned: the delivery of the appropriate dose to the patient. The directive touches upon format education and training requirements, accreditation of individuals and departments, minimal infrastructural requirements, staffing, recommendations for continued medical education and the implementation of quality assurance measures.

Is the European Radiation Oncology ready for this? Did we do our homework?

Whereas some other medical associations were pressing for European examinations and diplomas ESTRO has chosen for bottom-up approach by patiently and carefully working at a grassroots level on a convergence of European standards through its quality assurance, education, exchange and mobility programmes. Besides, the newly created European Board of Radiotherapy in which the scientific community (ESTRO) and the professional bodies (UEMS) are represented on a parity basis, started tackling the issues the profession needs to face up to in order to provide a solid basis for the guaranteed freedom of movement of its members within the European space: the harmonisation of basic and continued education, guidelines for the length and content of the practical training in radiotherapy (logbook system), and minimum standards for the accreditation of teaching departments. A European examination and diploma were only envisaged to come at the end of the road. However, with the European directive in mind these long term objectives have now gained momentum and. If ESTRO is to play a role in building a European consensus around the legal framework which will govern the future functioning of Radiation Oncology in Europe, it will have to come up quickly with solid data and creative and thorough discussion documents for entering the debate at the national level.

13

TOTAL BODY IRRADIATION

Ann Barret, Glasgow, Wielka Brytania

Introduction

The potential of systemic irradiation for the treatment of disseminated malignant disease was recognised almost immediately after the discovery of radioactivity by Madame Curie in 1897. By 1905, a German physicist, Frederick Dessauer, had designed an arrangement of x-ray sources, which would give a homogeneous dose of irradiation to the whole body. The treatment of 3 patients with leukaemia was reported by Adalar Eifer in a Hungarian journal in 1907. In 1923, Chaoul & Lange from the University Clinic of Surgery in Munich treated 12 patients with Hodgkin's disease, of whom 8 showed responses which lasted at least 7 months (1).

Special equipment for total body irradiation was installed at the Memorial Hospital, New York, in May 1931 and by June of the next year, Heublein reported results with 185 KV x-rays given at a dose rate of 0,67 to 1,26 cGy per hour to patients at distance of 18-14 feet (5.5-7.5 meters). He concluded that the safe whole body dose was 25% of an erythema dose (7.5 Gy measured in air) and noticed "encouraging improvement" in 3 out of 10 patients, but nó pronounced "beneficial clinical manifestations: (2). Nevertheless, this work continued and in 1942, an analysis of 270 patients was presented by Medinger and Craver (3).

Doses were limited to 3 Gy because of haematological toxicity and research soon started to find ways of overcoming this limitation. Thomas et al. (4) reported the use of intravenous infusion of bone marrow to patients receiving radiation and chemotherapy. The discovery of leuco-agglutinating antibodies by Dausset (5) stimulated much research, which led to the recognition of leukocyte histocompatibility antigens. An understating of these was essential for the initial development of safe bone marrow transplantation (BMT), which removed the dose limiting toxicity of total body irradiation (TBI) and permitted the use of much higher doses. Increasing experience has led to better ways of preventing graft versus host disease (GvHD) and enabled rescue after high dose therapy to be extended to the majority who do not have compatible sibling. (6)

From the early 1970s, the pioneering work of Donal Thomas, mostly in Seattle, has led to the increasing use of total body irradiation as a therapeutic method for many different conditions. Initially patients with the most radiosensitive tumours such as leukaemias and lymphomas were treated (7), but subsequently, systemic irradiation has been tried with many other types of cancer and the indications for treatment have been greatly extended. Patients with haematological or congenital metabolic diseases, where bone marrow transplantation may correct the underlying abnormality, have also been irradiated, although preparation for transplantation in these cases is more usually given by chemotherapy alone.

A scientific basis for total body irradiation has been difficult because interacting factors affect outcome of treatment. The effect of high doses of 8 Gy or more to the whole body on systems other than the bone marrow cannot be studied unless fatality is prevented by bone marrow transplantation or other stem cell support. However, BMT produces problems, (of which graft versus host disease is the most severe), which may influence complications such as interstitial pneumonitis in which radiation plays an important part. It is also difficult to determine how much radiotherapy contributes to control of diseases in a multi – modality treatment and it is unsatisfactory to compare results between centres where many aspects of patient management may differ. However, over the last 10 years, our understanding of how to improve TBI schedules has increased, particularly because of the studies undertaken in the large number of patients recorded by the International and European Bone Marrow Transplant Registries and through the continuing pioneering work of the Seattle Group (8,9).

Aims of Total Body Irradiation

At doses of 6 to 15 Gy, total body irradiation will produce bone marrow ablation. For benign disease, the intent of such treatments is provide enough immuno – suppression to allow an infused marrow or stem cells to engraft satisfactorily so that the underlying defect can be corrected. For patients with diffuse malignancies, the aim is to eradicate malignant cells by high dose systemic radiotherapy (in conjunction with chemotherapy) and to rescue the patient from the inevitable bone marrow toxicity by bone marrow transplantation or stem cell infusion.

Thus, in the first situation, the therapeutic agent is the transplant and in the second, it is the high dose therapy which includes total body irradiation. Obviously, the optimal scheduling of total body irradiation for the two situations may be different. Broadly speaking chemotherapy alone is often adequate to permit marrow engraftment in patients with benign diseases, although increased immune suppression immune suppression obtained by adding total body irradiation is sometimes necessary after rejection of a first graft or when HLA matching is less close. For those with malignant diseases however, the search for ways of intensifying treatment continues because in many situations relapse of the initial remains the major problem, and many regimens still include TBI as well as high dose chemotherapy.

For each disease treated the following should be defined:

1. The target cell population for the treatment (that is part of the normal immune system or a malignant cell population).
2. The biological behaviour and radiation response characteristics of the target cell population.
3. The dose needed to achieve the planned effect.
4. The most appropriate schedule of irradiation.
5. The interaction of radiation with other elements of the management of the patients.
6. The complications likely to occur.

Types of "rescue "after high dose therapy

In the early of high dose therapy, bone marrow was used for "rescue" and could be obtained from a number of sources. Identical twin grafts (syngeneic bone marrow) offered apparent advantages in being well tolerated by the recipient. However, these grafts may be associated with a higher rate of relapse because of loss of a "graft versus leukaemia" effect which offsets the advantage of a lower incidence of transplant related complications. Allogeneic grafts from a fully compatible family member are usually preferred when available, although these may cause graft versus host disease. The scope of high dose therapy has been widened by using partly compatible family members or fully compatible unrelated donors, although graft versus host disease and rejection are major problems with these type of grafts. T cell depletion of allogeneic "mismatched" or unrelated grafts reduces graft versus host disease, but leads to a higher incidence of graft rejection and leukaemic relapse.

Reinfusion of autologus marrow (harvested during remission) has been widely used. The risk of persisting malignant cells being returned to the body and leading to relpse may be "purging" the marrow in – vitro to remove tumour cells and has been reported to improve outcome in a number of situations. (10) A major clinical problem however remains the failure to eliminate all tumour cells from the patient rather than from the marrow for reinfusion.

More recently, peripheral blood progenitor cells (PBPC) have been harvested after stimulation by appropriate colony stimulating factors. This procedure, which can be undertaken on a out – patient basis, appears to be satisfactory for ensuring engraftment. Early results suggest that allogeneic peripheral blood stem cells from a sibling donor may also be used satisfactorily (11). Manipulation of PBPC may be used to improve outcome further, either by purging autologous PBPC or by attempting to expand particular progenitor cell populations in vitro before reinfusion (12). Though some success has been reported, such manipulation always leads to an increased risk of graft failure. Another potential source of stem cells for engraftment is cord blood.

Indications for high dose therapy with TBI

Leukaemia

Most intensive treatments with haemopoietic support are undertaken for leukaemia.

Acute lymphocytic leukaemia

Children with acute lymphocytic leukaemia at high risk of relapse should be considered for treatment in first complete remission. This group includes those who fail to remit by day 28 of standard therapy, those with biphenotypic leukaemia or who have Ph+ cells, infants with MLL gene rearrangement and those with high hazard scores. Allogeneic matched related donors should be used when available, but allogeneic unrelated matched or related partially mismatched grafts may be considered for those at highest risk. Other children in the standard risk group should be considered for transplantation if they relapse after second complete remission has been obtained. In this group long – term survival may be expected in 50-70% of patients (13). Relapse remains a major problem and attempts to intensify preparation regimens have largely resulted in increased toxicity without significant survival rates.

In adults, results are less satisfactory because of high relapse and complication rates, (four – year actuarial survival of 30-40%) and BMT is reserved for those with Ph+ disease or who are in second remission (14).

Acute non lymphocytic leukaemia (ANLL or AML)

Patients with acute myeloid leukaemia (AMT) may be transplanted in first remission if they have a matched sibling donor. Relapsing patients should be considered for autologous bone marrow or PBPC, or unrelated matched donor bone marrow support after high dose therapy in second remission. Disease free survival rates of 50-80% at 5 years can be expected in a selected young group of patients (15).

Chronic myeloid leukaemia

Allogeneic bone marrow transplantation after high dose therapy is the only curative option for patients with CML, although it is only feasible in younger patients (aged<55). Patients with chronic phase disease are treated with hydroxyurea, busulfan or interferon alpha to obtain complete remission with disappearance of Ph+ cells. Conditioning before bone marrow transplantation is usually with cyclophosphamide/busulfan or cyclophosphamide and TBI. In patients transplanted in chronic phase within 1 year of diagnosis, 5 year survival rates between 40-70% may be obtained. If the transplant is delayed to later in the chronic phase, the survival rate falls and in accelerated phase disease, the survival after bone marrow transplantation is less than 30%. This approach is ineffective in patients who are treated in blast crisis. Autologous transplantation is being investigated and may prolong survival, although elimination of Ph+ cells is unlikely. At the onset of the disease, marrow purging may be possible since there will be a residual population of normal Ph- cells which declines as the disease progresses. Attempts are being made to select benign primitive progenitor cells from marrow obtained early in the disease to use for marrow reconstitution after conventional induction of remission (16).

Non-Hodgkin's lymphoma

High grade

A large number of patients with lymphoma have been with autologous bone marrow transplantation at different stages of their disease. A sub-set of patients with poor prognosis after conventional therapy can be intensified at presentation and should be considered for high dose therapy. This includes patients with intermediate r high grade disease with poor prognostic features (bone marrow or CNS involvement and high LDH levels) who may be considered for transplantation in first CR. Patients in second remission, but whose disease remains sensitive to chemotherapy may also be transplanted with good results. This approach has improved long term survival in these groups from 20% to 50% overall (17). Relapse appear to be higher when autologous rather that allogeneic support is used, but this disadvantage is offset by the higher transplant related morbidity seen with allogeneic transplants. Allogeneic procedures may also offer the advantage of a graft versus host disease (GvHD). Because f the toxicity of this approach, it is more suitable for young patients (<55) (18).

Low grade

Patients with short or second remissions from chemotherapy or those in whom only partial remission can be obtained may have improved survival after high dose therapy and autografting (19). However, this should not be the first approach because of the risk of myelodysplasia after transplantation and the long natural history of the disease. There is no clear evidence of benefit from purging the graft. Allogeneic transplantation may improve control rates (20).

Hodgkin's disease

Patients with high risk or relapsed. Hodgkin's disease may also be appropriately treated by high dose chemotherapy with or without TBI (21). Early transplantation is recommended to avoid drug resistant disease developing and to minimize cumulative toxicity.

Multiple myeloma

Young patients (<55) with good initial response to chemotherapy should be considered for high dose therapy with PBPC or autologous bone marrow, or allogeneic transplant following high dose therapy with malphalan alone or with TBI. This approach improves 5 – year survival rates and, using allogeneic marrow, a plateau in survival at approximately 40% has been reported. Regimes containing TBI appear to give better results than those using chemotherapy alone. This plateau in survival has not been seen in patients treated with PBPC. Even in those patients who relapse after high dose therapy with TBI, survival after relapse may be prolonged (22).

Other tumours

Neuroblastoma

Only 12-20% of patients with stage 4 disease will survive for more than 2 years after conventional chemotherapy. Lon term survival rates of up to 40% may be obtained with intensive initial therapy, appropriate local surgery or radiotherapy, and early atologous or allogeneic bone marrow transplantation after high dose melphalan alone or with TBI.

Patients over the age of 1 or with n-myc amplification should be considered (23). Purging of autologous marrow or PBPC has been shown to reduce relapse rates. Current studies are looking at ways of incorporating I^{131} MIBG therapy, conventional chemotherapy and high dose chemotherapy with TBI to improve outcome in this group of patients.

Patients with disseminated Ewing's sarcoma, PNET or rhabdomyosarcoma (23), where conventional treatment has a low chance of producing cure, are now being transplanted in well defined research protocols.

Very selected young patients with breast cancer may also benefit from high dose therapy. Patients with high grade brain tumours such as these, radiotherapy is used for local control rather than as part of the conditioning for high dose therapy.

Techniques for total body irradiation

To obtain a large enough field to encompass the whole body using a conventional treatment unit, the machine must be used with an extended source – patient distance as the largest field size available at normal working distances is usually of the order of only 40 cm^2. Under these working conditions, data must be obtained by direct measurement in a finite phantom at the extended distance used. The flatness of the beam at extended source-patient distance must be determined. Scatter contributed from walls, floor and treatment couch must also be directly measured and will be different for each treatment room. Dose distributions can be calculated from tissue air ratios or computerised tomographic density measurements. Special TBI planning systems have been developed which incorporate anatomical information from CT scanning with parameters of dose calculation such as depth backscatter, tissue thickens, thickens of inhomogeneity, off axis distance and source to skin distance to give accurate predictions of dose distribution (24, 25).

In vivo dosimetry can be performed with thermoluminescent lithium fluoride monitors, diodes or other different levels, differences between individual patients, the effect of positioning of the body with regard to the beam and the loss of internal scatter because the field is larger than the patient.

The maximum field sizes that can be obtained depend on the size and geometry of the treatment room and are often unsatisfactorily small, even when the patient is treated lying along the diagonal of the beam to increase the effective field size. Many centres ill have no choice of machine for total body irradiation and will have t use either cobalt or linear accelerator equipment chosen primarily by the characteristics of the room in which it is situated. The patient may need to be confined within the available field size be a device such as a specially designed treatment chair or a perspex box of the same dimensions as the field size (26, 27, 28).

With the patient in the supine position and treating with lateral fields, a more homogenous dose distribution may be obtained using higher energies of photons, such as 18 MV. If lung shielding is used and the clinical evidence of a difference in outcome of treatment whether a cobalt machine or linear accelerator at various energies is used (30).

Homogeneity

By analogy with conventional radiation treatment, it has been assumed that the aim of total body irradiation should be to obtain as homogenous a dose as possible to the whole body. If open and unmodified beams are used, inhomogeneities of up to 15% may be found. In thinner regions of the body such as the neck and ankles, doses may be larger than mid-abdominal doses by up to 15%. Doses in the lung are variable, but may be up to 10% higher because of increased transmission in air. Doses to the head may be low because they may be within the penumbral region if the field size is small or because of loss of internal scatter. The patient's position also affects dose distribution. For example, flexion of the neck to bring the chin onto the chest will reduce doses to the neck, and lung doses may be modified by varying the position of the arms.

Many centres use compensators to decrease doses to the lung or lower limbs or bolus around neck or ankles to act as compensators. Lung shields are used either as compensators to limit the lung dose to that received elsewhere in the body or to reduce the dose even lower to minimise pulmonary complications of total body irradiation. Some centres have considered applying shielding to the kidneys or liver to limit late toxicity (31).

Boosts

The assumption that homogeneity is desirable may be questioned. The most effective treatment may be one which delivers the highest dose feasible to the areas most likely to contain disease. In practice, this approach has been used when boosts are given to various parts of the body known to harbour residual disease or to areas at high risk because of poor chemotherapy access.

Testicular irradiation

Prophylactic testicular irradiation after the induction of remission in acute lymphatic leukaemia is not considered beneficial. Although isolated testicular relapse may occur, it is often the herald of systemic relapse for which further chemotherapy is indicated. However work from North American centres such Seattle and Memorial Sloan Kettering Hospital have shown that the incidence of testicular relapse can

be reduced by giving an additional dose to the testes before total body irradiation. This does not influence the overall survival rate. Since doses of 24 Gy are needed to prevent testicular relapse after testicular involvement, attempts have been made to boost testicular dose so that when given in conjunction with total body irradiation, doses are high enough to ensure local control. Doses of 4-6 Gy fractionated over 2-4 days re most commonly used. we have recommended 3 doses of 1.8 Gy on sequential days immediately prior to cyclophosphamide and total body irradiation.

Central nervous system

Similar boosts have been used in some centres to minimise the risk of CNS relapse. There are insufficient data to establish whether this approach is effective, although, as for the testicular boosts, a dose of 1.8 Gy given on 3 successive days before total body irradiation has proved safe and apparently effective in minimising CNS relapse.

Splenic irradiation

Patients with massive splenomegaly from chronic myeloid leukaemia may be left with residual splenic enlargement after chemotherapy and additional radiation may be given to the spleen. This is best localised by ultrasound and its position marked on the skin immediately before treatment. Treatment should be avoided if possible when platelet counts are low and daily fraction sizes are usually of the order of 0.5 to 1.5 Gy per day (32).

Nodal areas

With the increasing use high dose therapy in the treatment of lymphomas, additional treatment to initial or residual areas of nodal disease may be considered advisable since after bone marrow transplantation, most lymphoma relapses occur in sites of previous disease. Local radiotherapy may be given before or after high dose chemotherapy or TBI. Full therapeutic doses (35 Gy) have been reasonably well tolerated after bone marrow transplantation, although leukopenia and mucositis may be troublesome (33). It may be more convenient to plan to deliver boosts to local nodal areas before TBI using doses of 20 Gy to involved sites. Particular care should be taken when irradiating the mediastinum which may result in pneumonitis (34). If local treatment and TBI are given close to one another,it is safest to restrict total cumulative doses to 35 Gy.

Shielding

Lung shielding

Lung shielding is used by approximately 80% of European centres (27) undertaking total body irradiation. Lead blocks are usually made individually for each patient from suitable planning films or from CT measurements to cover the lung from the clavicle to the dome of the diaphragm following the inner contour of the chest wall. This arrangement shields only approximately 60% of lung tissue and also unavoidably 5% of bone marrow (35). Some techniques shield the lung for the main part of the TBI treatment and then add a boost to the bone-marrow-containing ribs using electrons (36). This is a complex arrangement and additional lung dose from the electron boost is inevitable. Scattered irradiation within the lung may also be significant, but it is difficult to quantitate.

Shields are placed either close to the machine head, which may make alignment with the patient difficult, or in direct contact or very close to the patient. Positioning may then be more accurate, but may cause some discomfort to the patient. It is difficult to ensure the accuracy of shielding especially if treatments are prolonged or if patients are restless or uncooperative; the proximity of the mediastinum, liver and spleen to which full doses must be given, makes accuracy very important. However, from the work of Dutreix it can be seen that shielding is only effective for at most 60% of the lung volume; 30% lies within the mediastinal fields and 5% in the apex where shielding is difficult, although lung doses may be highest. For this reason and because of concerns about accuracy in placing shields, some centres prefer to use no lung shielding, but to restrict lung doses to those known to be within tolerance.

A reduction in the incidence of interstitial pneumonitis when shielding was introduced has been claimed by many groups, but often this change coincided with a reduction in effective whole body

doses by fractionation or more careful measurement of lung doses. It is not clear whether the development of interstitial pneumonitis can be provoked by high doses to part of the lung only or whether partial protection is effective. The role of lung shielding except to provide compensation if homogeneity of treatment is being sought therefore remains unclear. Similar rates of interstitial pneumonitis are reported by groups using techniques with and without lung shielding (30).

Specific techniques

Most groups giving total body irradiation treatments use a standard Cobalt unit or linear accelerator (4-18 MV) operating at a source skin distance (SSD) of approximately 4 meters which will usually give sizes from 128-160 cm. Within this field size, patients may lie supine, on their side or be seated with knees bent up on a special chair.

Perspex of up to 2 cm in thickness is usually placed next to the patient, both on beam side (entry) to prevent skin sparing, which would occur with high energy radiation and is undesirable because leukaemic cells may infiltrate the skin, and on the exit side to absorb backscatter from walls which increases skin dose without adding usefully to mid plan doses (24).

Special total body irradiation units have been installed in a number of centres. In Toronto, a single source wide angled collimator unit permits large field irradiation at a short treatment distance. Dual source treatment facilities have been available for many years in Seattle, where 2 opposing cobalt sources are mounted on floor rails to allow adjustment of treatment distances as sources decay (7). The patient is placed between the 2 horizontal beams. At the Royal Marsden Hospital (RMH) in London dual cobalt sources are mounted vertically and provide field sizes of 2 x 0.65 m. at m. SSD; in Boston, Massachusetts, two 4 MV linear accelerators similarly mounted give field sizes of 80 x 220 cm^2. These special facilities provide the possibility for varying. These special facilities provide the possibility for varying the parameters of treatment which are fixed with most single source units because of field size constrains (28,37).

Where there is no room large enough for total body irradiation, some centres have used a scanning cobalt beam, to cover the whole body. This has the theoretical disadvantage that not all the malignant cell population is being irradiated at the same time and that the incident dose rate is higher than when whole body treatments are given at extended distances. In practice, there is little evidence to suggest that this technique is less effective, although a higher incidence of interstitial pneumonitis has been reported with a sweeping beam technique than with a static beam (38).

Most patients are treated with postero-anterior and antero-posterior fields because the increased thickness of the body when lateral fields are used leads to less satisfactory dose distributions. This effect is less obvious in children. High energy linear accelerators (~18MV) may give a better dose distribution if lateral fields are used to treat supine patient. If vertical treatment units are used with the patient supine, it is possible to place lung shielding more accurately. With the patient lying on his side, careful positioning of the arms may contribute to compensation for increased lung transmission.

Some centres in the United States and Europe have adopted the technique first developed at the Memorial Hospital in New York where patients are treated standing supported by a modified bicycle seat and arm supports, with lung shields suspended from their shoulders. Additional boost treatments are then given with electrons to the chest wall to increase the dose to bone marrow bearing ribs (36).

From analysis of treatment results notified to the International and European Bone Marrow Transplant Registries, there is no evidence for superiority of one treatment technique over another and factors such as the dose given and the scheduling of total body irradiation are likely to be much more important (30).

Total lymphoid irradiation

Total lymphoid irradiation (TLI) was proposed by Slavin et al. (39) as a way of producing immumo – suppression without the lung toxicity of total body irradiation. It permitted stable chimerism after bone marrow transplantation and was widely used to facilitate organ engraftment. Initially, beneficial symptomatic response in auto – immune diseases such as systemic lupus erythematosus and rheumatoid arthritis was reported (40), but these responses may not be long – lasting and a relatively high incidence of secondary B-cell malignancy has indicated that this approach should be used with caution. TLI has been used for conditioning patients with aplastic anaemia after graft rejection, but it is a complicated technique and appears to offer little advantage over low dose total body or thoraco – abdominal irradiation. WithTLI, doses of 20 – 34 Gy with conventional daily fractionation have been

used. It has also been used in some centres before or after total body irradiation to produce additional immune suppression for patients receiving T – cell depleted marrow grafts.

Shaped fields such as a mantle and inverted Y (used more commonly in the treatment of Hodgkin's disease) or thoraco – abdominal fields with lung shielding may be used to deliver doses of 5 – 6 Gy.

Scheduling of total body irradiation

In conventional radiotherapy, regimens can only be considered isoeffective if they produce the same degree of tumour control for the same level of toxicity to normal tissue. In practice, the acute tolerance of normal tissues is likely to limit the doses that can be given, although late damage may be more critical. For total body irradiation, three endpoints must be considered if regimens are to be compared.

1. Effect on cells of the immune system.
2. Control of leukaemic or other tumour cell population.
3. Effect on normal tissues other than the bone marrow (whose function can be effectively replaced by the transplant procedure).

After bone marrow, the next most sensitive organ to damage from total body irradiation is the lung, with liver and kidney also at risk from similar or higher doses. For proper comparison of one schedule with another the question must be asked, do these two regimens produce equal rates of engraftment, control of initial disease and incidence of interstitial pneumonitis (and other normal tissue toxicity)? One treatment can only be proved to be better than another if it can be shown that, for equal rates of normal tissue toxicity, tumour control or engraftment (whichever is the most significant clinical factor) is improved. Unfortunately not all studies are constructed in this way and it may be difficult to conclude that a particular schedule is better then another if only one of the parameters is reported.

Analysis of treatment results is further complicated by the time scales of the different endpoints. Failure of engraftment will be obvious within 2 to 3 weeks and interstitial pneumonitis occurs most commonly up to 100 days after total body irradiation. Leukaemic or other tumour cell relapse however may occur at any time up to several years after treatment. Because patients who have died early with interstitial pneumonitis will be lost to the total analysis of tumour relapse, its true incidence with that schedule will be impossible to determine. Because of these problems, rates of interstitial pneumonitis have commonly been used as the single endpoint for comparison of schedules of total body irradiation.

However, using data from large reported series of TBI treatment alpha beta ratios for each of the normal tissues and the tumour population at risk (in so far as these can be determined from the literature) it should theoretically be possible to calculate an optimal schedule for TBI. In practice, because tumour cell populations and normal tissues vary in radiosensitivity both within patients and in different organs as well as between patients, it may not be possible to demonstrate a single "best treatment". Most of the currently used schedules have been shown empirically to be reasonably well tolerated. Differences in tumour cell population control are difficult to demonstrate since quantitation of residual disease after induction chemotherapy has not been possible up till now and there may be considerable variation in total tumour cell numbers in different patients who are apparently in complete clinical remission. Quantitative PCR of bone marrow may help to elucidate this situation.

Radiosensitivity of cells of the normal haemopoietic and immune systems

Early work by Till and McCulloch (41) using the exogenous spleen colony assay system in mice showed that bone marrow stem have a limited capacity to repair sub-lethal damage. Similar radiation survival curves have been obtained with human bone marrow cells cult5ured in-vitro (42). Because of these typical cell survival curves, little effect is expected from changes in radiation schedule and this has been confirmed in a number of experimental systems. However, Tarbell et al. (43) have shown D_0 values of 80 cGy for single fraction high dose rate treatment, 85 cGy for low dose rate single fractions and 55-65 cGy for fractionated regimens, suggesting increased sensitivity to fractionated treatment. Nevertheless, overall it seems reasonable to conclude that the effect of variations in dose rate and fraction are insignificant for the killing of normal bone marrow cells which represent a very radiosensitive population.

The LD_{50} for man from bone marrow ablation is 4 Gy and in patients with non – malignant disease undergoing bone marrow transplantation, doses of 6 Gy appear necessary to ablate host marrow adequately to allow engraftment of donor marrow. This is below the level at which lung damage will occur and scheduling therefore is not critical if killing normal stem cells is the only consideration.

The complication of graft versus host disease after bone marrow transplantation can be greatly reduced by the in-vitro manipulation of harvested bone marrow to reduce T cell numbers. The use of T cell depleted bone marrow however results in a markedly increased rate of graft rejection as well as of leukaemic relapse. The mechanism for the failure of engraftment after T cell depletion is not clear, although host natural killer cells and T lymphocytes have been implicated. Empirical intensification of conditioning for bone marrow transplantation with T cell depleted marrow has resulted in increased rates of graft versus hostdisease. There are differences in radiosensitivity in-vitro forthe various lymphocyte subsets (T,B, OKT_4, OKT_8) which may be responsible for these outcomes (44). Further studies are needed to determine which cell is responsible for graft rejection and to elucidate the role of increased doses of total body irradiation in the abrogation of graft failure.

Radiosensitivity of leukaemic and other malignant cells

O'Donoghue in his review of the literature of the in-vitro radiosensitivity of human leukaemic cell lines has found descriptions of 8 different lines (including 3 lymphomas) and measurements of bone marrow or peripheral blood leukaemic progenitor cells from 20 patients (45). These studies confirmed that leukaemic cells are highly radiosensitive with a low capacity for the accumulation and repair of sub-lethal damage. As for normal stem cells, little effect of changes in dose rate or fractionation would therefore be expected. However for this cell population, the doubling time must also be considered. This would be likely to be insignificant for continuous low dose rate irradiation, but if a doubling time 2,5 days is considered, fractionation over a period of 5 days could result in a reduction in log cell kill of 0.6. Direct studies of the effects of various schedules of total body irradiation on leukaemic cell in – vitro have not been reported. There is some evidence of increased survival of leukaemic cell in-vitro when radiation is given as a split course compared with continuous radiation to the same total dose.

For control of leukaemia and other malignancy, it can be assumed from general experience in radiotherapy that increasing dose of radiation will produce increased tumour cell kill. This can be shown using the same technique and scheduling of total body irradiation, by demonstrating reduction in rates of relapse as the dose is escalated and has been confirmed by studies from various groups. In a study of escalating single fraction low dose rate total body irradiation in 238 patients at the Royal Marsden hospital, London, a lower relapse rate was noted after 10.5 gy than 9.5 gy although at a higher dose of 11.5 Gy any benefit in preventing leukaemic relapse was offset by a high early death rate from lung damage. Similarly the Seattle Group have shown a lower rate of leukaemic relapse with 15.7 Gy compared with 12 gy, although at the expense of a higher transplant related morality (9). However, for other tumour types whose radiobiological characteristics will be different, dose should not be considered in isolation (40).

In addition, other biological factors such as total body burden of tumour may outweigh any possible advantage of increasing dose within the range feasible because of normal tissue damage.

Normal tissues

A direct effect of increasing the total irradiation dose on the incidence of damage to normal tissue can also be demonstrated. For the lung, the dose limiting tissue in total body irradiation the response curve using upper half body irradiation for disseminated malignant disease shows an apparent threshold below which lung damage is not clinically apparent, with a steep increase in incidence with dose over the range 9-10 Gy (47). For single fraction low dose treatments in the RMH experience , the incidence of interstitial pneumonitis rose from 30% with 10.5 Gy to 69% with 11.5 Gy. Similar steep responses have been seen with high dose total body irradiation of the range of 7-8 Gy. (Work from Seattle suggest that when fractionated total body irradiation with 2 Gy fractions is used , maximum tolerated lung dose is of the order 14-15 Gy.

Isoeffective schedules of total body irradiation for the endpoint of clinical lung damage manifested as interstitial pneumonitis are reasonably well established as 7.5 Gy single fraction treatment by lowering the dose rate, 10.5 Gy single fraction low dose rate and 14-15 Gy with fractionated TBI.

Several experimental and clinical studies have now suggested that although considerable sparing of normal tissue damage may be achieved in single fraction treatment by lowering the dose rate, regimens using small dose fractions are likely to be best, since for equivalent toxicity, dose rates for a single fraction would have to be very low leading to very prolonged treatment times which are not feasible in practice. Fractionated TBI is therefore now widely used, although there is great variation in the dose given per fraction.

The response of the lung to fractionated radiotherapy is dependent much more on fraction size than duration of treatment. The half time for repair of lung is estimated to be approximately 1.5 hours and a minimum of 6 hours is needed between fractions to ensure that repair is complete. Many groups report a reduced incidence of pneumonitis is with fractionated total body irradiation but in many cases all that has been accomplished effectively is a reduction in overall dose. If fractionated radiotherapy is to be used, it is likely that the most benefit will be obtained using relatively small doses fraction (<2 Gy) although even lower fraction sizes (1.2 Gy) maybe beneficial in terms of lung sparing and clinically feasible and effective (36). Within the range of dose used per fraction, little additional benefit is gained using low dose rate as opposed to the standard output of most machines, although, additional sparing with very low dose rates has been reported experimentally. Similar dose response curves and a beneficial effect of fractionation in reducing late damage have also been demonstrated for liver, kidney and lens.

In summary therefore, toxicity to normal tissue, efficacy against the tumour population and feasibility in term of delivery must all be considered, as well as overall treatment time and tim between fractions. Regimens such as the Seattle, UK MRC and Memorial Sloan Kettering regimens all offer the advantages of high dose, low dose per fraction and reasonable overall treatment time and therefore appear to be the most satisfactory at present. Clinical trials from Seattle have recommended a total dose of 14.4 Gy in children and 13.2 Gy in adults and this corresponds very well with the UK experience with the MRC protocol of 14.4 Gy (maximum lung dose in 8 fractions of 1.8 Gy given over 4 days) (48).Further experience with treating patients with treating patients with others tumours may lead to a change in these recommendations, but this is unlikely since the parameters of normal tissue toxicity will not vary.

Drug-radiation interactions

As total irradiation is only one element of the conditioning regimen, drug-radiation interactions must be considered in assessing the effectiveness or toxicity of a particular treatment.For many years, the combination developed by the Seattle Group of cyclophosphamide 120 mg/kg given on days 4 and 3 before total body irradiation has been widely used (7). The continuing problem of leukaemic relapse after one marrow transplantation has led to attemptsto intensify conditioning before grafting in various ways. Radiation dose and fractionation may be modified (9) or more commonly alternative drugs or several chemotherapeutic agents have been used in combination. Unfortunately most of these studies have either found no improvement in relapse rates or have found that an improvement in relapse rate is offset by an increase in transplant related morbidity and mortality (49,50,51,52).

Attempts to replace total body irradiation with drugs have been made and the most widely used schedule is that developed by Santos of cyclophosphamide (60mg/kgx2) and busulfan (4mg/kgx4)(53). Results comparable with those from total body irradiation containing regimens are obtained. Both total body irradiation and busulfan are potent stem cell killers. The spectrum of morbidity is different and the optimum schedule must be determined taking these factors into consideration (54).

For the radiation oncologist directing TBI treatments, one of the persisting challenges is to assist in developing more effective, but less toxic preparatory regimens.

In many cases the effects of individual drugs given in conjunction with radiation are well know, and potentially toxic drugs such as cytosine arabinoside, methotrexate and cisplatin can be avoided. As new drugs are developed and added to conditioning regimens, constant vigilance and careful observation are needed to detect any unforeseen interactions.

Complications of total body irradiation

Acute effects

Nausea and/or Vomiting may be expected in most, but not all, patients after total body irradiation. After single fraction exposures at low dose rate, vomiting occurred in 75% of patients after a dose of 2-3 Gy had been received (55). When fractionated total body irradiation is used, Vomiting may be less marked, but occurs in most patients between ½ - 8hours after the start of treatment. It is difficult to separate the emetic effects of chemotherapy and radiotherapy in this situation when chemotherapy is given before TBI. Data from patients treated with cyclophosphamide after TBI suggest that this drug does play a major role in the nausea and vomiting that is seen with high dose therapy. Nausea and

vomiting may continue up to 4 days after irradiation and may be associated with diarrhoea related to direct toxicity on the gut. Children under 10 years of age may experience less vomiting than adults. Vomiting may be precipitated by movement and general discomfort and reduced by fasting and anti-emetics. The most effective anti-emetic prophylaxis appears to be with a combination of 5 hydroxy triptamine (5HT) antagonist such as ondansetron with dexamethasone (56).

Acute damage to the gut may be reflected by severe diarrhoea, anorexia and cramping abdominal pain occurring within 4 or 5 days of irradiation. Histologically, there is evidence of flattening of crypt epithelium and degeneration of crypt cells by 10 days after treatment. Repair occurs usually within 20 days. Damage to the villi may results in malabsorption, although complete recovery normally occurs.

Total body irradiation may also cause hypotension and pyrexia which may be worsened by the use of drugs such as chlorpromazine and ameliorated by steroids.

Bilateral parotitis is common after total body irradiation, but usually resolves within 24 hours. It is associated with a rise in the parotid iso-enzyme serum amylase with no change noted in pancreatic amylase (57). Values return to normal by 6 days there are normally no sequelae although xerostomia may persist for up to a year after treatment. Pilocarpine may help to stimulate saliva flow after treatment. Careful attention to dental hygiene is necessary if the mouth remains dry to prevent further complications. Graft versus host disease will exacerbate the oral sequelae of treatment (58).

In treatment uncomplicated by graft versus host disease or drug toxicity, no immediate changes in serum urea, electrolytes, liver function tests, calcium, phosphate or alkaline phosphate have been noted. There is a rapid fall in the lymphocyte count to 50% by the end of treatment with single fraction total body irradiation with a half time of 30 hours, and to 60% 13 hours after the first fraction of a fractionated course. Rises in granulocyte concentrations may be very marked (200-400% of initial value) after only 10 minutes of total body irradiation, although numbers then decline rapidly to initial values or lower. No changes in platelets or red cell numbers were noted up to 72 hours after the start of total body irradiation. No short term changes in concentrations of T3 or T4 are noted, although TSH values are lowered after 10 Gy in most cases.

Reversible alopecia would be expected from the dose levels used for total body irradiation. This factor cannot be separated from the effects of chemotherapy and permanent impairment of hair regrowth may occur Changes in colour or texture of regrowing hair are common.

Late effects

In radiobiological terms, effects on lung liver and kidney may be termed late, although in practice, damage to these organs from total body irradiation may manifest itself within 1 to 6 weeks of irradiation.

Lung

Interstitial pneumonitis and graft versus host disease are the two most important factors contributing to early death after bone marrow transplantation. Interstitial pneumonitis is characterised by fewer, dyspnoea, cough and hypoxia within the period up to 100 days after transplantation. Chest radiographs show characteristic bilateral changes of diffuse interstitial, and lung function testing shows a reduction in diffusing capacity. Histological changes of oedema, cellular infiltrates, alveolar exudation, type 2 pneumocyte proliferation and later collagen depositions are seen.

The clinical syndrome of pneumonitis is due to an accumulation of activated T cells in the lung with an associated population of macrophages and neuthropils (60). There is an increase in cells expressing messenger RNA for inflammatory proteins such as tumour necrosis fachtor alpha, interleukin 1 beta, and transforming growth factor beta (TGH beta). The host MLC class II expressing cells are increased in lung after TBI and this process is potentiated in patients undergoing allogeneic transplant or those with a lesser degree of matching whereas it is rare with syngeneic transplants or autologous grafts. These acute changes lead on to a process of type 2 pneumocyte plorifelation and collagen deposition with fibrosis.

In many cases specific etiological factors may be deteced. Up to 40% of cases are associated with cytomegalovirus or other infection. Cytomegalovirus infection. can be diagnosed by culture of lung tissue, by bronchial alveolar lavage or by identifying the characterisitic viral inclusion bodies in lung biopsies. The mortality from this condition is high. Others possible infective agents are pneumocystis (which may largely be prevented by prophylactic administration of trimethoprin-sulpha methoxasole), herpes simplex or zoster, aspergillus, candida and other fungi and a variety of bacteria.

In approximately 60% of patients with interstitial pneumonitis, no infectious agent can be detected and a diagnosis of idiopathic pneumonitis is made.

The risk of interstitial pneumonitist is increasedby the use of methotrexate rather than cyclosporin for immunosuppression after grafting, older age, presence of severe graft versus host disease, long interval from diagnosis to transplantation, poor performance status pretlansplant and high dose rate totaltotal body irradiation (61). In the IBMTR series , for patients with none of these factors, the probability of developing interstitial pneumonitist was 8% compared with 94% in patients with all these factors. There was on evidence from this study of anadvantage for fractionated radiation in reducing pneumonitist and no dose response relationship was detected for radiation doses to lung between 5,6 and 12,8 Gy (30).

Methotrexate appears to have more direct toxcity for lung than cyclosporin. This may be because of a potentiating effect of irradiation damage. The cyclosporin syndrome of adult respiratory distress (ARDS) may be seen after renal toxicity has developed from high dose treatment. Increasing age may increase risk of pneumonitist because there is a greater likelihood of prior infection with cytomegalovirus. Graft versus host disease also increase the risk of pneumonitis by immunological and infective processes.

The lack of correlation in the study above of pneumonitis with total dose contrasts strongly with data presented by Keane et al. (47) who showed a clear dose response relation over the range of 7-10 Gy. This may have been obscured in the date from the International Bone Marrow Transplant Registry by different ways of reporting doses or by the fact that some of the schedules were delivering doses below the threshold for lung damage.

Liver

Liver damage in recipients of bone marrow transplants may be related to the conditioning regimen, to graft versus host disease or to infection either previously or newly acquired. The clinical picture of radiation or chemotherapy associated liver damage develops within a few weeks of treatment with weight gain, jaundice abdominal pain, hepatomegaly, ascites andin severe cases, encephalopathy. This condition is asociated with a high mortality rate and is more often seen after prepariation of patients with busulfan than with TBI.

Histopathological changes are of veno-occlusive disease, where the terminal hepatic venules and sublobular veins are narrowed by sub-endothelial fibrosis and thickening with trapping of cells, including hepatocytes, withinthe lumenresulting in obstruction to sinusoidal blood flow. Although factors other than radiation are usually more important in its causation, the incidence is reported to be lower after fractionated than high dose rate single fraction TBI. Low dose heparin and tissue plasminogen activators such as alteplase have been used to try to to reduce the severity of this problem. Spontaneous resolution within 3 to 4 weeks may occur (62)

Kidney

There are many factors which may contribute to renal damage during the preparation for and recovery from bone marrow transplantation including the use of chemotherapeutic agents such as ifosfamide, antibiotics and cyclosporin.

Tests of glomerular function after bone marrow transplant/TBI usually show minor impairment. Tubular defects and haemolytic uremic syndrome are more likely to occur, but are more related to drugs than radiation exposure (63) Endothelia injury is characteristic of acute radiation nephropathy which is related yo dose of radiwtion. The dose used for TBI should be below the threshold for overt damage. Although renal failure is a common problem of multi- factorial aetiology after bone marrow transplantation, it is difficult to quantitate precisely the contribution of TBI. Mirabell however has shown a dose dependent effect in his patients (31).

Radiation nephritis is a well recognised entity after local field irradiation to doses in excess of 20Gy and may occur many years after exposure. The first report of radiation nephritis after total body irradiation was by Bergstein et al. (64). Two children developed hypertension, hameaturia and impaired renal function 6 months after treatment. Histologically the kidney showed expanded mesangial zones, thickening of capillary and arteriolar walls, focal areas of tubular atrophy and interstitial oedema and fibrosis. One of the patients had received cyclosporin and acyclovir, drugs with known renal toxicity. Tarbell et al. (65) found evidence of renal dysfunction in 11 out of 29 survivors of transplantation, for acute lymphoblastic leukaemia or neuroblastoma between 1980 and 1986.

Conditioning regimens had included drugs with renal toxicity such as cisplatin, teniposide and ifosfamide. Patients presented with anaemia, haematuria and a rising creatinine: biopsy in 2 patients showed changes consistent with radiation nephritis or the hemolytic uremic syndrome.

It thus appears that the tolerance of the kidney to radiation may be dinished when multi-agent chemotherapy is used concomitantly and than children may be especially susceptible. Because of the late onset of radiation nephritis, this problem may increase in severity with longer follow-up of bone marrow transplantation.

Eye

Marked changes are observed in transplanted patients who develop chronic graft versus host disease with keratoconjunctivitis and changes in lacrimal gland secretions. Retinitis may result from conditioning with cytosine arabinoside and TBI. in uncomplitated survival after total body irradiation the only change to be observed is the development of cataract. In the Seattle series reported in 1984 (66), the risk of developing cataract was 18% and 19% in patients treated with chemotherapy or fractionated total body irradiation and 80% in those receiving single fraction total body irradiation. All cases were bilateral and the risk increased for 3 years after transplantation before stabilising. Surgival excision was nacessary in half the patients. Chronic graft versus host disease and steroid therapy were also associated with a higher risk of developing cataracts. With low dose single fraction total body irradiation, the incidence is lower than after high dose single fractions treatments, but higher than with fractionated irradiation being of the order of 58% at 10 years (67).

Teeth

Disturbances in tooth development and size are seen after BMT with TBI with a sevsrity inversely proportional to age at the time of treatment (68).

Central nervous system damage

A syndrome of somnolence with lassitude, anorexia, and sometimes vomiting, may be expected at about six weeks after TBI. A similar picture is seen after cranial irradiation for ALL and is believed to be due to transient demyelination. No treatment is needed as the condition improves spontaneously (within seven to ten days). It does not correlate with any persisting or late damage.

Leukoencephalopathy may occur within days or months of transplantation and may be related yo drug administration (especially high dose methotrexate), radiation or viral infection. It is uncommon after total body irradiation unless previous cranial irraduation has been given and the incidence is inversely correlated with age. The charasteristic appearance on computerised tomographic scanning is of dilated ventricles, cerebralatrophy, hypodense areas and calcification.

Damage to the spinal cord has been reported anecdotally but is rare. By extrapolation from results of expected, although there are few detailed long term studies yet (69).

Quality of life

Quality of life after bone marrow transplantation may be impaired. In a study from Toronto, many patients reported low grade symptoms such as fatigue, pain, joint stiffness and sleep disturbance. Patients studied at less than 3 years from the time of transplant experienced considerable impairment, while longer term survivors were indistingishable from the normal population in most areas studied. However, 81% of patients overall were satisfied with the health related quality of life after treatment and 91% were prepared to recommend a transplant for somebody in similar circumstances (70).

Hormonal changes

Gonadal function

Gonadal function and fertility are known to be affected by high dose chemotherapy and total body irradiation. The degree of impaired function depends on age, sex and dose and type of therapeutic agent used.

In adult women, the usual pattern seen after TBI ovarian failure with amenorrhoea, low plasma oestradiol levels with raised gonadotrophins, and infertility. Low androgen levels may be found,

probably also resuling from ovarian damage. A direct effect on the adrenal gland may occur although no abnormalities of plasma cortisol levels have been reported. Since androgen is needed to sustain increased muscle activity during exercise, low levels may help to explain the easy fatiguability reported by patients after TBI (71).

In very young but post-pubertal females, ovarian recovery may be seen in 10-25% at 2 – 7 years after BMT. Recovery is not affected by hormone replacement therapy and this may be temporality discontinued to assess whether recovery has occurred. It is possible that this group of patients may undergo early menopause (as has been reported after chemotherapy).

In men, the most common pattern is of infertility (due to a direct effect on the testes) but with normal testosterone and gonadotropin level. If additional radiation is given by a testicular boost so that total doses are greater than 20 Gy, testosterone levels may be low with raised gonadotropins and replacement therapy may be necessary.

Studies in pre_pubertal children suggest than manyboys and some girls receiving TBI may progress normally through puberty. Young age at the time of treatment may be relatively protective. Most boys will probably be azoospermic, but patients who progress through puberty with normal gonadotropin and sex hormone levels may be fertile.(72, 73).

Although the probablity of fertility cannot yet be accurately predicted, pregnancies have been reported after TBI given to males and females. No abnormalities in offspring of these patients have been reported although the rate of spontaneous abortion may be increased (74).

Thyroid function

The most common abnormality seen after BMT with TBI conditioning is compensated or over hypothyroidism with elevated TSH levels with or without low free serum thyroxine or tri-iodo thyroine levels. Thyroind abnormalities, which are commonly first detected between 12 and 60 months after treatment, have been reported in 2 – 56% of patients treated with TBI, but hypothyroidism may also occur in up to 10 of patients conditioned without TBI (75) Replacement therapy is given early to try to reduce the risk of induction of thyroid malignancy.

Growth

Growth may be affected by TBI in two ways.

1. By damage to the hypothalamus and pituitary gland leading to impaired growth hormone (GH) production.
2. By direct effect on the epiphyseal plate leading to early epiphyseal fusion.

Studies comparing effects of TBI with thoraco-abdominal irradiation have shown that the central effect is the most significant. Cranial irradiation given before TBI increases the risk of failure of GH production (76).

Normal levels of GH may be maintained after TBI, especially if this fractionated, or a pattern of normal plasma levels with low GH peaks after stimulation may be seen. Growth hormone should be administrated if GH levels are measured to be low, if there is a low GH peak after 2 stimulation tests and a loss of height SDS of 1 SD or more (shown by measurement of sitting rather than standing height). Low GH peaks have been reported in 20 – 70% of patients and graft versus host disease and poor nutritional status increase the risk of GH failure. Administration of growth hormone at an early stage as soon as growth velocity starts to fall off prevents further decrease in height, although "catch – up" growth does not occur.

Appropriate sex hormone administration is also essential to obtain the full growth potential of the pubertal growth spurt.

Heart

Cardiac toxicity is not a major problem after total body irradiation, although it has been observed after high dose cyclophosphamide therapy. Myocardial fibrosis and constrictive pericarditis are late effects occurring many years after conventional radiotherapy, and careful following-up of patients receiving total body irradiation is necessary to determine whether these same complications will develop. In one study of 28 patients with leukaemia, serial echo cardiography and radionuclide ventriculography showed abnormalities in only 4, in whom the resting ejection fraction was reduced after treatment. Animal studies have shown acute changes in the pattern of isoenzymes in mice after

total body irradiation and this enzyme changes may lead to functional alterations. On the basis of experience from conventional radiotherapy it seems possible that coronary artery disease or myocardial infarction may occur at an earlier age than normal in this patient population (77).

Second tumour induction

In the first year or two after bone marrow transplantation, the commonest malignancies seen are recurrence of the original disease or lymphoproliferative disorders which seem to be related to immune suppression and Epstein Barr virus infection (78).

A large study from the Seattle Group and the International Bone Marrow Transplant Registry has followed nearly 20,000 patients treated with bone marrow transplantation to determine the risk of the new solid cancer. 9,501 patients survived longer than 1 year and 73% of the patients had had TBI as part of the initial conditioning for BMT. 3,200 patients have survived for 5 years or more and in this group 80 second tumours were diagnosed These included 17 carcinomas of the buccal cavity or pharynax, 11 brain tumours, 11 melanomas, 8 thyroid carcinomas, tissue tumours. The overall risk of developing a second tumour was inversaly related to the age at the time of bone marrow transplant and directly related to time since treatment, original tumour type and dose of radiation (79).

Risk in children treated before the age of 10 was increased 36.6 times and as age 20-29 4.6 times, whereas over the age of 39 the risk was nearly the same as in a normal population. Cumulative incidence was 0.7% at 5 years, 2.2% at 10 years and 6.7% at 15 years. Patients with ALL were most likely to develop brain tumours whereas melanoma occurred more often in those treated for AML. Patients treated with thoracoabdominal or total body irradiation had a higher risk than those conditioned without radiation. No difference was seen whether TBI was given as a single fraction on in several fractions. The risk of brain tumours was highest in those who had received cranial as well as total body irradiation (4 of the 13 patients with brain tumours).

Other factors which are possibly associated with increased risk may be determined by immunological abnormalities: T cells depletion possibly related to melanoma induction, immune abnormalities with oral mucositis and chronic graft versus host disease for buccal cavity tumours, cyclosporin administration (for skin tumours), papilloma virus infection i squamous cell carcinomas of skin and buccal mucosa. Buccal cavity tumours observed were muco-epidermoid carcimonas – the type also observed in survivors of the atomic bomb.

It is interesting to compare this patteren of second tumour incidence with that seen after treatment of leukaemia without bone marrow transplant when the cumulative incidence of second tumours at 20 years is 2.9-4%. A similar pattern of brain, thyroid, skin, and connective tissue tumours occurs, but the greatest risk (27 times expected) is of brtain tumours in those treated with cranial irradiation (80).

These date underline the risks of radiation and the need for prolonged follow-up. Patients should be encouraged to avoid exposure to known carcinopgens (such as tobbaco) which may potentiate the effects of radiation.

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NEW ADVENCES IN BIOLOGY AND MODERN TREATMENT OF HODGKIN'S DISEASE

Volker Dieh

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LOCALISED AND ADVANCED HODGKIN'S DISEASE: TOWARD A COMMON STRATEGY? AN EORTC LYMPHOMA GROUP POINT OF VIEW

Patrice Carde

Paryż

In patients with localised Hodgkin's disease (HD), the EORTC initiated in 1975, with the H5 trial a completely new strategy consisting in adapting treatment intensity (NCI Monographs 6: 303-310,