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REVIEW ARTICLE

Total body irradiation prior to bone marrow transplantation; some aspects of fifty year experience

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Summary

There has been a remarkable growth in the use of bone marrow transplantation (BMT) in the past 30 years. The rapid expansion of BMT reflects its increasingly important role in the treatment of several life-threatening diseases of the hemopoietic system. The first BMT in human patients was performed after conditioning with total body irradiation (TBI). As an important part of BMT protocols, TBI has an established role in many preparative regimens used before BMT in the treatment of hematological diseases.

Historically, TBI schedules varied during the last 30-year period with regard to different radiation source used, treatment technique, beam modifiers, actually delivered total dose, dose rate, and fractionation schedule.

The aim of this review article is to discuss the 50-year experience in the field of TBI, as well as radiobiological, technical and dosimetric requirements and especially effects of total dose, dose rate and fractionation schedules on the prognosis of transplanted patients.

The radiobiological and radio-oncological requirements demand special TBI treatment techniques quite different from usual radiotherapy. The technique needed depends extremely on the prescribed values of treatment parameters and on the local technical possibilities. TBI dosimetry has to account for the physical situation of treatment with very large field sizes at extended distances and should be performed under TBI conditions close to the real treatment situation. The effects of total dose, dose rate, fractionation schedule on the leukemia cell killing, immunosuppression, and sparing of normal tissues are considered in detail. Their effects on overall survival, leukemia recurrence, acute and chronic graft versus host disease (GvHD), late radiation-induced injuries to normal tissues or organs as well as incidence of interstitial pneumonitis, renal dysfunction and cataract development are analyzed.

The definition of currently used TBI procedures is so different in different centers that retrospective analyses remain futile, under better definition and normalization of dose, fraction size, and endpoints occur. There are a lot of difficulties to evaluate, compare or understand clinical results from so different treatment regimens, often with an irregular set of parameters. In order to establish clinical trials and to evaluate clinical results, we need comparable schedules, uniform specification, and complete reporting of all relevant parameters.

After 50-year experience in the field of TBI, we are beginning to understand the relationship of TBI dose, dose rate and fractionation. However, 20 years after Glasgow we will repeat his persuasion that, however, many questions remain unanswered.

Key words: bone marrow transplantation, dose rate, fractionation schedule, radiobiological, total body irradiation, total dose

Introduction

There has been a remarkable growth in the use of BMT in the past 30 years. More than 23,000 transplantations have been carried out worldwide in 2001, 15,882 of them autologous and 7,272 allogeneic. The rapid expansion of BMT reflects its increasingly important role in the treatment of several life-threatening diseases of the hemopoietic system.

The first BMT in human patients was performed

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after conditioning with TBI. As an important part of BMT protocols, TBI has an established role in many preparative regimens used before BMT in the treatment of hematological diseases. For example, in France a total of 10,630 TBI have been documented, with 850 to 900 TBI each year since 1995 [1].

Historically, TBI schedules varied during the last 30-year period with regard to different radiation source used, treatment technique, beam modifiers, actually delivered total dose, dose rate, and fractionation schedule. Other variables in BMT, e.g. high dose chemotherapy, are more difficult to quantify and model than TBI, and will be more difficult to optimize. TBI delivered in many different ways can be analyzed for many different endpoints.

The aim of this review article is to discuss the 50-year experience in the field of high dose TBI, as well as radiobiological, technical and dosimetric requirements and especially effects of total dose, dose rate and fractionation schedules on the prognosis of transplanted patients.

Historical data

TBI is an important technique, an integral part of a life-saving, relatively new therapeutic maneuver. Actually TBI is applied for the treatment of disseminated malignant diseases since the beginning of the 20th century. Since the early days of radiotherapy, physicians have used TBI and half body irradiation (HBI) to treat advanced systemic and disseminated diseases. Simultaneous irradiation of the entire body with multiple sources was proposed by Dessauer in 1905. In 1923, Chaoul and Lange, using four large fields, treated a patient's lymphogranulomatosis with "Roentgenstrahlen" [2]. Early analyses of the effects of "accidental" TBI led to the discovery of the possibilities of BMT [3,4]. The benefits of TBI (in the 1950s in the dose range of 5.0 to 12.0 Gy) and BMT are that they offer a chance for curing previously lethal bone marrow disorders. The logical consequence of these new insights was the design of treatment protocols in which patients were given deliberate or "therapeutic" TBI by an infusion of unaffected bone marrow cells.

In 1959 Webster reviewed the physical consideration of irradiators that would produce a uniform TBI dose and concluded a minimum of four radiation sources would be necessary to achieve a uniform total body dose [5]. Three separate multiple source irradiators with exposure rates from 1.5-40 R min^{-1}, containing 5-8 ^{60}Co or ^{137}Cs sources, were used at the Oak Ridge National Laboratory in the mid 1960's and early 1970's to study the radiation effects in mammals and to treat some patients. Two track mounted mobile, parallel opposed ^{60}Co sources with specially designed collimators, were used by Lam et al. for BMT at the Fred Hutchinson Cancer Research Center in Seattle, Washington and by the Munich Cooperative Group for BMT [6,7]. Surmont et al. performed TBI at Gustave Roussy Institute using twin opposed ^{60}Co sources separated by a movable concrete wall [8]. From 1960-1974, a ^{60}Co moving field technique was used for TBI at the Princess Margaret Hospital in Toronto [9]. With the advent of linear accelerators, which provide higher energies and higher dose rate, a technique using lateral 25 MV X-ray beams was employed between 1975 and 1977 [10]. In 1977 a special ^{60}Co unit was designed and constructed specifically for the treatment of very large fields (50x160 cm) at relatively short, only 90 cm source-to-skin distance (SSD) [11,12].

In the 1970s the most commonly used TBI schedule was a single fraction of about 10 Gy administered at a low dose rate. In the 1980s, some authors recommended fractionating the dose in daily or twice daily sessions with a goal of improving the therapeutic ratio, particularly by reducing treatment morbidity [13,14].

Initially, therapeutic tests were carried out in clinically advanced stages of panmyelopathy, immunodeficiency and leukemia [15], but consequently TBI had become a widely used conditioning regimen for BMT or peripheral blood stem cell transplantation (PBSCT) in patients with hematological malignancies [16,17], multiple myeloma [18], Hodgkin's or non-Hodgkin's lymphomas [19].

The result of the last 50 years of progress is a very powerful set of clinical tools. At present, the main indications for autologous or allogeneic BMT are severe panmyelopathy, severe combined immunodeficiency, aplastic anemia, acute lymphoblastic leukemia (ALL), and acute (AML) and chronic myelogenous leukemia (CML). Autologous BMT is carried out in ALL, malignant lymphomas and some solid tumors.

Total body irradiation: radiobiological, technical and dosimetric requirements

Radiobiological requirements

High dose TBI, combined with intensive chemotherapy, is a part of a general concept of aggres-

sive treatment in the management of systemic malignancies. Both are highly toxic to normal tissues. For bone marrow rescue, subsequent transplantation of compatible bone marrow is required. The goal of TBI in this setting is threefold: destroying residual neoplastic cells; cleaning the host marrow to allow repopulation with donor marrow cells; providing sufficient degree of immunosuppression to avoid allograft rejection by immunologically active cells in the host [20-22].

The advantages of using TBI over chemotherapy in the conditioning of patients are well known. TBI is the most effective immunosuppressive conditioning agent [23]. Moreover, all cells in the body will be treated (irrespective of vascular supply or sanctuary sites, i.e. body compartments where effective chemotherapy levels cannot be reached, such as of the testes); cells in S-phase are sensitive to radiation; parts of the body can receive more or less radiation by changes in the TBI technique (e.g., field within a field, or partial shielding); irradiation is not crossreactive with any other agents and prior treatment will not have induced resistance to radiation in tumor cells [23,24].

The complex radiobiological situation of combined chemoradiotherapy and BMT is not yet clearly understood [25-29]. We know that TBI reduces the number of malignant stem cells by a factor of 10 for each 1.5 to 2 Gy. Thus the total reduction rate for leukemic stem cells is still of the order of 10^{-6} if doses 8 to 14 Gy (usually 10 to 12 Gy) are delivered in a few fractions.

The number and distribution of target cells depends on the type and stage of disease. In the stage of complete remission or in the chronic phase, respectively, no target cells can be detected. But their number may still be of the order of 10^{-6}. This indicates the necessity to treat patients in an early complete remission. A homogeneous distribution of dose is required to achieve a uniform probability of target cell kill within the whole body. Consequently, the whole body including the skin has to be regarded as a target volume. In the case of treatment in a later stage of disease, regions of higher concentration of malignant stem cells, such as testis, mediastinum, lymph nodes, pelvic bone marrow or the central nervous system, are possible to need a higher dose given for instance by additional beams. The lungs, as the most critical vital organ, can be spared by reducing the local dose (via shielding of the lungs) or the average lung dose rate and by fractionation [30-32]. It has to be emphasized that the risk of interstitial pneumonitis (IP) is increased by many interacting factors such as dose, dose rate, and treatment time; type, dose and time schedule of chemotherapy; age and physical findings in the lungs; infections; or toxicity related to bone marrow engraftment [30-34].

Technical requirements

TBI always is a compromise. It is well known that optimal irradiation of the entire body encompasses contradictory requirements. There are many different kinds of weighting these requirements, reflecting the complexity of the situation. The radiobiological and radio-oncological requirements demand special TBI treatment techniques, quite different from the usual radiotherapy. The technique needed depends absolutely on the prescribed values of treatment parameters and on the local technical possibilities. The local technical conditions often limit the choice of a TBI technique. The TBI methods vary from center to center in patient positioning, in the prescribed dose regimen and in machine orientations. Large fields are usually achieved at extended SSD. While there are some centers that perform TBI on specially designed machines in dedicated treatment rooms, the vast majority of TBI are performed on standard therapy equipment in standard treatment rooms. The normal radiotherapy treatment room has to be used in more than 90 % of the radio-oncologic centers [35]. But only little children can directly be treated by an unmodified vertical photon beam, lying prone and supine close to the floor. For adults a distance of about 4 m is needed to produce a sufficient large uniform beam, enabling to position the patient along the diagonal (70%) or main axes (20%) of the field. The production of very large radiation fields with standard radiotherapy equipment is a difficult task requiring careful planning and a considerable physics effort. The constraints imposed on the desired treatment by the design of the treatment room and by the treatment machine itself must be considered to achieve the optimum treatment method. Tumor dose rate, beam energy, uniformity of dose distribution in the patient, as well as patient's comfort during treatment are-in addition to the large field size-important parameters of a TBI technique.

All high energy photon beam qualities have been utilized for TBI. Photon energies above 1 MeV are suitable for anterior (a) posterior (p) /pa TBI, providing for sufficient dose homogeneity. Higher energy X-ray beams, at least 6 MV, are used for bilateral irradiation. Occasionally, higher energies up to 25 MV have been used, especially in Europe. When energies higher than ^{60}Co are to be used, one must use a tis-

sue equivalent material (beam spoiler) in front of the patient. This allows for adequate build up of dose at the patient's surface and prevents skin under dosage.

The patient's position depends on the beam incidence and on the useful field length. Mostly the sufficiently (≤ ± 5%) flattened part of the field is not large enough, even if the diagonal of the field is used. Many techniques of irradiation of the entire body have been developed enabling to fit the patient's body into the flattened part of the photon beam. In 75% of treatments, the legs have to be bent or specially designed chairs or positioning support are needed. Many centers have treated patients in the standing position utilizing special treatment stands, which are of great value for accuracy and reproducibility.

Successive irradiation of the whole body is performed in 65-85% by two opposing photon beams (a/p or bilateral TBI) and in 15% by four beams (combined ap/pa and bilateral TBI). As it is easier to realize bilateral TBI often (35%) these techniques are required. The largest lateral separation of the beam quality determines the dose in homogeneity [35-37]. Bilateral irradiation alone cannot provide for sufficient uniformity of dose. Such a procedure does not permit to shield the lungs without under dosage of important parts of the target volume. If bilateral TBI has to be used, tissue equivalent moulages, the size of which can easily be planned, are required to equalize the irregular lateral body surface. However, they can never improve the depth dose homogeneity in beam direction. Most authors prefer a/p TBI more and more frequently due to physical considerations [35,38,39]. A/p irradiation is possible with horizontal beams if a semi embryonic position, the patient lying on his side, comfortable for him, is used. But accurate treatment requires much time for localization, repositioning, alignment and verification of lung shielding under these TBI conditions. A prone and supine position, combined with vertical beam incidence, permits ap/pa TBI providing for good dose homogeneity as well as for easy and exact lung shielding. Sufficient large vertical treatment distances or wide aperture irradiation are not common (5%). Very large effective field sizes are realized by sector scanning or by linearly moving beam techniques. For instance, linear patient translation with present constant velocity through a vertical beam can provide a/p TBI in an ideally flattened photon beam with 2 m length. Historically, examples of ap/pa-TBI techniques are the Toronto technique (utilizing a very broad vertical l□ ^{60}Co gamma ray beam, flattened by a specially designed filter for TBI in a short distance in prone and supine position), the Boston technique (utilizing two opposing vertical accelerator photon beams for TBI in supine position in a dedicated TBI-room), the Montreal technique (utilizing a sweeping ^{60}Co gamma ray beam), or the Essen technique (utilizing patient translation with a specially dedicated flat coach moved computer controlled with constant calculated velocity through a fully open, unmodified vertical ^{60}Co gamma ray beam).

There is no ideal technique to irradiate the whole body homogeneously and precisely and to shield the lungs optimally. In order to realize TBI and to guarantee optimal treatment, several technical and physical modifications, performed in different ways, have been utilized by some centers [35,40,41]. They prefer to optimize the dose distribution by means of extensive *in vivo* dosimetry. Instead of dose calculations they use the results of the first TBI fraction or of a test irradiation for optimization [42]. Dose modifying corrections are done by weighting the different beams ap/pa combined with bilateral irradiation.

It is obvious that the irradiation technique strongly determines the amount of dosimetry and individual treatment planning and of confirmation, verification and documentation. Thus a TBI technique should be chosen to allow for precise and reliable TBI as good as reasonably achievable (APARA-concept) [43]. Criteria for selecting a TBI technique are reliability of irradiation, homogeneity and accuracy of dose delivery, exactness and reproducibility of lung shielding, and comfort for patient and staff [44]. However, there is no evidence that the technique of treatment is strongly relevant for the clinical results – as long as sufficient dose is delivered to the target cells and/or as the organs at risk are spared sufficiently. Many other factors seem to be much more essential as well as the prescribed dose, fractionation, dose rate or timing and other parameters.

Dosimetric requirements

As TBI treatment planning has to regard the radio-oncological, technical and physical requirements, TBI dosimetry has to account for the physical situation of treatment with very large field sizes at extended distances. An extrapolation of routine small field dosimetric data for the treatment matching to data for large fields at extended SSD is not acceptable because of different conditions that affect the large-field parameters.

As mentioned by Van Dyk et al. in an AAPM report of 1987, the dosimetric problems of TBI are well illustrated [37]. The contour of the human body, tissue inhomogeneities in the human body, and beam off axis factors are the major contributors to wide

differences in dose within a single patient, between patients and most importantly, between institutions.

Since 1985, according to Podgorsak et al. the three basic dosimetric parameters that should be known for each TBI technique are the following: the dose rate at depth dose maximum in the patient (sometimes referred to as machine output), the central axis percentage depth dose and beam profiles along the two field axes [44]. These parameters should be measured in suitable phantoms for each TBI technique.

As have been stated by Quast, TBI dosimetry should be performed under TBI conditions close to the real treatment situation [43]. The absorbed dose to water must be determined. The dose monitor should be calibrated against dose measurements central in a water equivalent phantom of TBI equivalent size and typical thickness. Photon fluency profiles have to be measured with small phantoms. Influences on the local dose must be investigated systematically. A reproducible ap/pa technique should be used. The TBI dose shall be specified to mid-abdomen reported in Gy. The single and total dose and the dose-rate to the lungs, the number of fractions and the treatment time schedule must be stated. *In vivo* dosimetry is required if non-reliable TBI technique is used.

Unfortunately, dosimetric studies are not performed or reported in sufficient detail by the great majority of transplant centers to allow for a prospective or retrospective dose determination in the most important subsections of the body and comparisons with other centers.

Total body irradiation: effects of total dose, dose rate, and fractionation schedule

Effects of total dose

To fulfill the therapeutic and conditioning tasks of TBI, the specified radiation dose has to be delivered at certain timing conditions. As long as it is not possible to fit the special distribution of dose to the local concentration of target cells, the whole body has to be irradiated in a sufficiently homogeneous and exact way.

It is well known that the initial intensive chemotherapy sterilizes the proliferating leukemic cells. Radiotherapy is required to eradicate the leukemic stem cells that survive in sanctuaries less accessible to chemotherapy. The antileukemic effect of TBI requires higher doses than the conditioning effect [45,46]. Thus the leukemic stem cells alone have to be considered as the target cells for dose planning. However, the doses needed to reduce the number of leukemic stem cells to a survival rate of 10^{-4} to 10^{-6} as necessitated by radiobiologic considerations [45-47] reach or exceed the tolerance of vital organs at risk. Although increasing the TBI dose may have improved relapse-free survival, toxic deaths have been more frequently reported [48,49].

Relatively small dose differences are biologically significant. It is well known from experimental animals as well as clinical studies of TBI that the dose/effect curves for most endpoints are steep. Fraction sizes from 1.1 to 9.0 Gy have been used with total dose up to approximately 10.0 Gy for single fraction TBI and 12-16 Gy for fractionated TBI. Small fractions (2.0 Gy) are suspected to cause fewer late effects. Their introduction in TBI procedures is probably not warranted, as late effects (with the exception of lung) are not dose- limiting. Immunosuppressive and tumoricidal effects of TBI decrease with fraction size and the logistics of small repeated TBI fractions are unduly complicated [47]. According to Vriesendorp et al. different TBI procedures using a different total dose and fraction size cannot be compared without extensive radiobiological "normalization" as well as normalization formulas will be different for different endpoints [50].

However, the optimal dosage for radiation treatment for hematological malignancies with the highest probability of uncomplicated care is not yet known. A large variety of TBI schemes have been used [51-55], e.g. TBI doses of 5 to 16 Gy, lung doses of 6 to 15 Gy, delivered in 1 to 13 fractions on 1 to 6 days at lung dose rates of ≤ 0.01 to ≥ 1 Gy/min. Clinical and experimental data indicate that the time pattern of dose may affect the incidence of side effects while the cure rate is less influenced [23,45,51,56]. The achieved spatial distribution of dose seems to be relevant for both effects, not the technique applied. These facts should dictate the choice of treatment regimen and the parameters to be reported.

Total dose and malignant cell eradication

At multivariate analysis, total dose emerged as an independent factor influencing significantly overall survival [39]. The observations indicate that dose escalation improves the results of TBI. The probability of 7-year survival is 74% if more than 9.9 Gy are administered and only 38% under 9.9 Gy [57-59]. These authors found that the incidence of relapse at 7 years was 55% in patients who received less than 9.9 Gy, compared with only 11% in patients who re-

ceived more than 9.9 Gy (p = 0.0005). Furthermore, a recent survey of long-term survival after allogeneic BMT has shown that conditioning regimens including single dose TBI of 10 Gy were associated with a higher risk of death non-related to relapse when compared with conditioning regimens including single dose TBI of < 10 Gy [59].

Increasing the TBI dose above 10 Gy is not necessarily associated with a better outcome in patients undergoing allogeneic BMT. According to Bieri et al. a total dose of 10 Gy may be at least as effective as 12 or 13.5 Gy in patients receiving a 3-day bifractionated TBI conditioning programme prior to BMT for hematologic malignancies [60]. Two randomized studies comparing two fractionated TBI regimes were reported in the early 1990s from Seattle [48,49]. Twelve Gy in 6 daily fractions of 2 Gy were compared with 15.75 Gy in 7 daily fractions of 2.25 Gy. A better relapse-free survival but a worse event-free survival was observed among both CML and AML patients randomized to the high-dose TBI regimen. Surprisingly, the inverse correlation of fractionated TBI dose with survival observed in the study of Bieri et al. was the disease-related rather than treatment-related morbidity. Paradoxically, the cause of death in almost two-thirds of patients dying after conditioning with the highest (13.5 Gy) TBI dose was disease progression [60]. The univariate analysis determined that in patients irradiated with dose rate less than 6 cGy/min, the probability of leukemia-free survival (LFS) was better for patients receiving the correct planned total dose (12 Gy) compared to patients receiving less than 12 Gy (p=0.01) [39]. According to radiobiological model, the two-fractionated regimens (12 Gy/6 fr/3 days and 9.9 Gy/3 fr/3 days) adopted by some institutions to condition lymphoblastic and myeloid leukemia, respectively, could be probably at a level of "threshold of efficacy" [61-63].

In patients allografted in first remission, the probability of LFS was higher in patients receiving 12 Gy compared with those receiving less than 12 Gy planned dose (86 *versus* 64%, p=0.05) [39]. Moreover, when patients did not develop chronic GvHD, the delivery of total dose of 12 Gy clearly improved leukemia relapse-free survival compared with patients receiving less than 12 Gy (50 *versus* 27%, p = 0.04) [39]. The impact of TBI dose (12 Gy or less) on LFS was not evident in patients allografted in second remission. New TBI schedules with higher total dose and/or different fractionation regimen should be designed and tested for patients allografted in second remission who are at higher risk for relapse [38,39].

Total dose and immunosuppression

Higher doses of TBI will be followed by a higher incidence of GvHD and less leukemia recurrence [64,65]. Calculations regarding tumoricidal effects of graft *versus* leukemia (GvL)/ GvH reactions indicate that less than 1 log of tumor cells are killed by severe GvH reactions [64]. The results of Socie et al. [61] appear to be predicted by prior studies i.e. more interstitial pneumonitis and GvHD after high single fraction and more leukemic recurrence after "biologically" lower dose fractionated TBI [56,61,64,65].

Patients receiving actually the fractionated dose of 12 Gy had a higher probability of developing chronic GvHD than patients receiving less than 12 Gy [39,66]. Chronic GvHD was the most significant factor at uni- and multivariate analyses preventing leukemia relapse occurrence after BMT and favoring overall survival. When patients received 12 Gy and persecuted chronic GvHD, a strong protection against relapse was obtained. These results obtained in ALL patients are similar to those observed in a group of 142 patients affected by acute and CML conditioned with cyclophosphamide and fractionated TBI (9.9 Gy/3 fr/3 days) and receiving HLA identical BMT [66]. The analysis strongly suggested that TBI dose more or less than 9.9 Gy was one of the major factors involved in the prevention of relapse after allogeneic BMT and was also an independent factor at multivariate analysis [58,59,66].

It has been reported that the incidence/ severity of chronic GvHD seems to be higher in complete chimerism as compared to mixed chimerism [67]. Some data seem to support the hypothesis that the correct delivery of total dose of TBI might favor sensibly complete hemopoietic chimerism in recipients and help develop chronic GvHD with less relapse occurring [39].

One other variable that deserves attention is the influence of changing the quality and quantity of the donor marrow inoculum. Lowering the donor stem cell content under 10^7 may necessitate an increase in TBI dose to achieve equivalent engraftment.

Total dose and normal tissue toxicity

It has long been known that high dose single fraction TBI (8 Gy) will lead to a high incidence of IP [68]. As Vriesendorp et al. mentioned [50], the median dose of 10 Gy documented in the Socie et al's article [69] appears to be dangerously high, even with lung shielding, and hard to justify for a single fraction

of TBI. Some authors postulate that it is possible to intensify TBI from a total dose of 10.2 Gy delivered in 6 twice-daily fractions to 12 Gy delivered in 4 once-daily fractions without significantly increasing the risk of pulmonary toxicity. The increased dose may contribute to a decrease in the recurrence rate in these patients [38].

Renal dysfunction after allogeneic BMT is strongly related to the delivered TBI dose (and dose per fraction) and to the presence of GvHD. Combining both variables, two risk categories were defined: low risk (i.e., 10 Gy TBI with/without GvHD and 12 Gy TBI without GvHD) and high-risk (i.e., 12 Gy TBI with GvHD and 13.5 Gy TBI with/without GvHD [70]. However, a negative influence of renal dysfunction on survival could not be ascertained [70]. Renal shielding should be recommended if a TBI dose greater than 12 Gy (fractionated twice daily over 3 days) is to be prescribed. Furthermore, in those cases with a high risk of developing GvHD (e.g. unrelated allogeneic BMT, absence of T-cells depletion), these data suggest that kidney doses greater than 10 Gy should be avoided.

Benyunes et al. compared the incidence of cataracts and the need for surgery, between single dose TBI (10 Gy) and two dose ranges of fractionated TBI [71]. There was an 85% incidence of cataracts in the single-dose group, compared with 50% for the more than 12 Gy and 34% for the less than 12 Gy of fractionated TBI groups. In the single-dose group, 59% required surgery, compared with only 33% in the more than 12 Gy fractionated group and 22% in the less than 12 Gy group.

Doses up to 14 Gy can be administered safely [72]. For total doses of ≥15 Gy with lung doses of 9-9.5 Gy, the risk of serious transplant-related complications cannot yet be finally assessed, but such higher doses should be considered with caution because of the possibility of increasing toxicity in organs other than the lung. This may be particularly relevant for patients older than 40 in whom a greater risk of dying after BMT was observed [59, 73-75]. The suggestion that higher TBI dose may even be deleterious remains to be confirmed by prospective trials.

Effects of dose rate

The parameter "dose rate" has to be defined more precisely in TBI dose specification according to its radiobiological relevance. Often the dose rate is determined at the dose specification point at mid abdomen, at the dose maximum inside the body or at a point free in air at the position of TBI treatment.

There are more problems associated with the definition of dose rate and the question which dose rate is essential, the momentaneous dose rate or the averaged dose rate, according to Quast [36]. Radiobiological experience indicates that the averaged lung dose rate, i.e. the lung dose per fraction divided by the lung irradiation time per fraction, is relevant while the instantaneous lung dose rate has less influence on the dose-response curve [76]. All experimental data show that the averaged lung dose rate is the essential parameter, which should always be reported (as long as the treatment time is smaller than the repair time). Data from Lehnert indicate that the instantaneous lung dose rate does not show a significant influence on lung toxicity (LD 50/180d in mice) if the averaged dose rate is kept constant, while there is a significant influence due to a variation of the averaged dose rate [77].

All experimental data demonstrate that there is no significant dose rate effect on bone marrow stem cells or other malignant stem cells, while a strong influence is found on normal tissue treated in a single fraction [76]. Thus as the lung is the most critical vital organ at risk, the TBI dose rate must always be specified to lung tissue [36].

Travis et al. and Peters and Travis investigated the influence of dose rate and fractionation [78,79]. The dose rate variation by a factor of 100 did not show a significant influence on bone marrow damage in total body irradiated mice, either irradiated in a single fraction or fractionated 1.8 Gy each 6 hours. However, in fractionated TBI there was a shift to a slightly higher tolerance doses for bone marrow damage, measured as LD50/30d. After BMT, the lung toxicity is determined as the LD50/9 month. These investigations indicated a good lung sparing effect if the dose rate is sufficiently low in single-fraction TBI or if the dose is given fractionated. However, there is no significant dose rate effect in hyperfractionated treatment. The question is still open if there is a dose rate effect in TBI with only a few fractions.

Dose rate and malignant cell eradication

Leukemia-free survival was higher in patients receiving TBI at dose rate less than 6cGy/min, suggesting that higher leukemia cell killing might occur with lower dose rate [39]. The hypothesis that higher leukemia cell killing may occur with dose rate less than 6cGy/min, by an increased cell death mediated by apoptosis [80], needs to be verified by further experimental data. According to some authors, clinical evidence for higher leukemic relapse has already

emerged by the decrease in radiation dose rate [66]. However, although important at univariate analyses of combined TBI parameters, dose rate did not emerge at multivariate analyses as a significant factor affecting transplant-related mortality, leukemia relapse or overall relapse [39,81].

Dose rate and immunosuppression

Dose rate variation did not show an impact on acute and chronic GvHD occurrence. However, according to some authors, dose rate higher than 6cGy/min may increase acute GvHD grade and IP incidence and lower performance status of patients transplanted, thus worsening the prognosis [39]. According to Down et al. for allogeneic complete donor entgraftment TBI at 5 cGy/min required higher total doses [55].

Dose rate and normal tissue toxicity

Univariate analyses have shown that the dose rate is a significant factor affecting the incidence of IP. Higher probability of IP was evident in patients irradiated with dose rate more than 6 cGy/ min, compared to patients treated with lower dose rate [39]. This effect, clearly reported when single-dose TBI has been used, has not been proved to be true for fractionated TBI [82,83]. Gogna et al. [84] concluded that there was no statistically significant difference in the incidence of IP over the two sets of dose rates (6.9 and 8.9 cGy/min and 2.9 and 6.5 cGy/min, respectively). The study suggested that the incidence of IP using fractionated TBI is not influenced by dose rates below 8.9 cGy/min.

Dose rate has been supposed to influence cataract incidence [85-88]. Belcacemi et al. reported high instantaneous dose rate as a main risk factor for cataract development and the need for surgery [89]. Low dose rates of TBI seem to result in a lower cataract incidence [90]. Ozsahin et al. concluded that the TBI regimen (instantaneous dose rate and/or fractionation) might have an influence on the development of cataract following BMT [91]. The cataract incidence found by Ozsahin et al. [92] for fractionated low dose rate TBI with 6 cGy/min was only 2%, with a 5-year estimated incidence of 4%. The results of Zierhut et al. are comparable to the high dose rate group of Ozsahin with a 5-year estimated incidence of 22% [93]. On the other hand, ionizing radiation seems to have a predictive effect on posterior capsule opacification following extracapsular cataract extraction and intraocular lens implantation [94].

Effects of fractionation

Much of our knowledge about dose, dose rate and fractionation is based on LD 50/30 assays and spleen colony-forming units (CFU) assays in animals or *in vitro* cells studies [55,95]. Animal studies have demonstrated that the shoulders on the single fraction cell survival curves for the lung and gastrointestinal tract are wider than for the shoulder on the bone marrow stem cells survival curve [96]. These data support the hypothesis that low dose rate or fractionation will provide a protection and a therapeutic gain for the intestine and lung relative to the bone marrow [46].

For a long time the α/β ratio of leukemia cells has been considered as being "high" (i.e. about 10-15 Gy, or even more), mostly extrapolating from characteristics of the hemopoietic stem cells. However, some authors reported a broad initial shoulder of the survival curve for about half the leukaemia cells as they were able to study [97,98]. This would suggest that the α/β ratio could be in a proportion (to be determined) of leukemias, significantly lower than the "conventional" values.

An adaptation of the TBI technique should be based on the knowledge of the shape of the initial part of the dose-response curve of the leukemic cells. Unfortunately, this technique is not routine yet; maybe we should think of developing some types of "predictive assay" able to provide us with the precise value of the α/β ratio for a given leukemia cell-line as proposed by Cosset et al. [99].

Actually, the choice of TBI schedule would probably depend, at least in part, on the assessment of the repair capacity of the leukemic cells of a given patient. Should these leukemic cells be totally devoid of repair capacity, Cosset et al. agree with Turresson that a 12 Gy fractionated TBI (6×2 Gy) would be slightly more efficient and less toxic than the conventional "low dose rate" 10 Gy single dose TBI [99,100]. Conversely, if the leukemic cells exhibit a marked repair capacity and/or if their potential doubling time is short, a 12 Gy fractionated TBI (6×2 Gy) would possibly be expected to be less effective on leukemia than the standard 10 Gy single dose TBI. This could be explained either by some leukemic cell proliferation during the 3 to 6 days of the fractionated scheme and/or by a marked repair capacity of some leukemic cell lines [69].

Fractionation and malignant cell eradication

Cosset JM et al. [101] evaluated the specific influence of fractionation of TBI on the outcome of the subsequent BMT. Available experimental and clin-

ical data on the influence of fractionation in leukemia cell killing, immunosuppression, and sparing of normal tissues were analyzed. Review of the available data shows that the role of fractionation on leukemia cell killing may vary with the leukemia type. For ANLL a few experimental and several clinical studies show no or little fractionation effect; a 12-13 Gy fractionated scheme could, therefore, be more efficient than a conventional single dose TBI. For ALL, a high fractionation sensitizing effect was observed for some leukemic cell lines *in vitro* without indisputable clinical confirmation at the moment. For CML some sensitivity to fractionation is suggested, and an increase in total or fractional dose may be necessary in fractionated schemes to equate the efficacy of a 10 Gy single dose.

In the context of TBI for BMT, some authors reported no clear advantage of fractionated over single dose scheme, with a possible exception for children [101]. Indeed, the early results from clinical trials using fractionated TBI in leukemia are superior to the clinical trials using single fractions and the incidence of radiation pneumonitis is lower [102]. But the view of most of the contemporary authors is opposite: multivariate analyses showed that fractionation does not influence relapse-free and overall survival [59,61,82,103]. A TBI (fractionated) >10 Gy may not necessarily be associated with a better outcome in patients undergoing allogeneic BMT for hematological malignancies as proposed by Bieri et al. [59]. A randomized study comparing single 10 Gy *versus* fractionated 12 Gy (6 daily fractions of 2 Gy) TBI in patients with AML suggested an improved relapse-free survival without significant improvement in overall survival, for patients in the fractionated arm [61].

Conditioning the available clinical data several papers showed a trend (non-significant) for a higher rate of relapse after fractionated than after single-dose TBI [101]. Moreover, a number of studies have reported a particularly high incidence of relapse after fractionated TBI (most often 6×2 Gy) in a situation of T-cell depletion of the graft [104]. It remains unclear whether small fractions of TBI dose may affect relapse incidence via a reduction of leukemic cells below a critical level or whether they may influence the host-graft interaction; lower TBI dose may reduce the capacity of donor marrow to engraft securely either because of impaired immunosuppression or because of sparse residual host hemopoiesis (mixed chimerism) and this may be associated with increased risk for relapse [65].

However, some authors mentioned that the conclusion that there are no dramatic differences in clinical outcome between single or fractionated TBI, appears premature [50].

Fractionation and immunosuppression

Numerous experimental studies have demonstrated that the immunosuppressive effect of TBI, a major determinant of entgraftment, is highly fractionation-sensitive. According to Down et al., while 7 Gy as a single acute exposure was capable of inducing complete donor entgraftment, fractionated TBI at 2 Gy per fraction every 6 hours only allowed complete entgraftment at a total dose of 14 Gy [55]. Graft failures have been reported when T-cell depletion of the graft was associated to fractionated TBI schedules. Many reports indicated that higher TBI doses or the addition of total lymphoid irradiation (TLI) [105,106] may overcome such rejection in a large proportion of patients. However, decreased numbers of graft failures have not been consistently reported with either increased TBI dose or with the addition of TLI [107,108].

Fractionation and normal tissue toxicity

A large amount of radiobiological and clinical data has demonstrated that late radiation-induced injuries to normal tissues or organs are highly fractionation-sensitive. There are data suggesting that late pulmonary toxicity is reduced, dependent on the fractionation schedule [109]. Wara et al. [110] determined from the concept of effective dose to lung tissue, that increasing the number of fractions contributed more to reducing the damage to lung tissue than the increasing the overall treatment time. IP was one of the endpoints examined in the randomized study from Seattle [103,111], comparing single dose with fractionated irradiation in patients with AML in first remission. The incidence of IP was less with the fractionated regimen (15%) when compared with the single-dose regimen (26%). Vriesendorp created a Table of surviving target cells for a variety of different TBI schedules. The results show the impressive sparing of the lungs and intestine to be expected with more fractionated regimens [112,113]. According to Tait et al. a 14.4 Gy fractionated TBI resulted in less marked restricted ventilation and impaired gas exchange, which reverted to normal by two years, even when the lung dose was increased from 11.0 to between 12.0 and 13.5 Gy [114]. After exclusion of patients with GvHD (30% allografts) there were no significant differences in pulmonary function abnormalities between autograft and allograft recipients. Surprisingly, according to Ozsahin et al. multivariate analyses on 157 patients showed that fraction-

ation does not influence the incidence of IP [81]. The results from a retrospective non-randomized, multi-institutional study of Socie et al. show a sparing effect of fractionation for lung tissue that could be offset by a less effective leukemic stem cell kill. The results must be confirmed and clearly need additional data, ideally from a randomized study [69,112].

TBI is generally delivered with fractionated (i.e. 12 Gy/6 fractions/3 days) or hyperfractionated (i.e. 13.2 Gy/11 fractions/3.5 days) regimens in an attempt to increase the therapeutic ratio between leukemia cell killing and normal tissue toxicity [39]. Use of hyperfractionated regimes to minimize leukemia regrowth may be of great value in reducing the amount of late normal tissue damage for theoretical, radiobiological reasons. Several reports have demonstrated a beneficial effect of hyperfractionation for late-reacting tissues like the lung, but not for example the lens, when compared to standard fractionation [71,93,115]. Whenever hyperfractionation of TBI, which achieves similar tumor control rates as compared to standard regimens, leads to further reduction of late effects compared to standard fractionation is not clear at present [115].

Single-dose and high-dose rate TBI are the main risk factors for cataract development and need for surgery as stated Belkacemi et al. on a cohort of 1063 patients available for survival after transplant for ALL in first and second complete remission [89]. Comparative studies between single-dose and fractionated TBI show a dramatic reduction of cataract incidence in the fractionated group [71,90]. Although one might expect that hyperfractionation would further reduce cataract incidence, this effect was not seen in any study [93].

For total doses of ≥ 15 Gy (lung dose 9-9.5 Gy) given in 12 fractions over 4 days the risk of serious transplant-related complications cannot yet be finally assessed but such higher doses should be considered with caution because of the possibility of increasing toxicity in organs other than the lung [109].

The categorical opinion of Vriesendorp et al. that the potential therapeutic advantages of single fraction or multiple fractions TBI cannot be elucidated by comparing ill-defined doses and ill-defined fraction sizes without efforts to normalize and optimize such parameters [62], should be probably not neglected.

Discussion

Total body irradiation is an important element in the preparation of the patients for BMT. In treatment of disseminated malignancies TBI is applied more and more frequently with increasing success. Regarding the radiobiological requirements, the physical and technical possibilities and their limitations, as well as the reliability and reasonableness of treatment, treatment planning of TBI means a very special challenge for the medical physicist. The critical situation of treatment of disseminated malignancies is exacting all steps of TBI dosimetry, treatment planning and treatment.

The discussion between Vriesendorp et al. and Gale et al., concerning the postulated by Vriesendorp quantitative application of classical physics, radiation biology and radioactive oncology concepts in animal models and patients in contrast to the postulated by Gale new "qualitative" mechanisms responsible for important TBI effects such as tumor eradication or immunosuppression, represents a topic of interest among the scientific community [50,51].

Radiobiological models are helpful for developing less toxic TBI procedures but can only be effective after dosimetric control has been obtained and if the influence of other variables on the outcome of BMT are taken into account. Modeling attempts were initiated and can be verified by selecting the most promising TBI schedules predicted by the model for further *in vivo* testing [56,113].

There is no ideal way of performing TBI. The literature review reveals that treatment methods for TBI are highly heterogeneous and standardization would be desirable [116]. The large variety of techniques of TBI treatment dosimetry, treatment planning and repositioning make radiobiological evaluation of clinical results difficult. In treatment of disseminated malignancies, improvement of curability and reduced complication rates require high precision TBI. Better choice in TBI techniques and dosimetry has permitted better homogeneity of dose and, therefore, a significant sparing of critical tissues with maximum probability of uncomplicated cure. The inhomogeneity of dose can reach ± 30% or even higher values, depending on the technique of TBI [117] and on the individual anatomical situation. Observations suggest that the variations in homogeneity of dose distribution to patients might modify toxicity or efficacy of radiotherapy [35]. For realizing of optimal TBI treatment often dose modifying techniques are required. These have the common goal to raise or to lower the local dose, taking into account the retroactive influences on the distribution of dose in other parts of the body. Ideally one should deliver just enough radiation to obtain the required immunosuppression while maintaining a minimum in acute side effects and a maximum in tumor cell kill. Perhaps we must agree with Vriesendorp et al. [50] that in future cooperative TBI

efforts, radiation oncologists will have to suppress their small field radiation experience in which one wants to deliver homogeneous maximum dose. This is not the appropriate solution for the complicated TBI and BMT situation in which a deliberately inhomogeneous dose distribution is needed.

Normally, the goal of TBI, regardless of the treatment method, is to deliver, with a specific˜ dose-rate, a prescribed total dose, throughout the patients' body including the skin. Since the prescribed TBI dose approaches or actually reaches the tolerance dose of certain organs, possibly causing permanent damage or lethal complications (e.g. radiation-induced pneumonitis), it is important to know accurately the dose delivered by TBI. Available data suggest that very cautious attempts could be made to adapt TBI schedules to the potential normal tissue toxicity, T-cell depletion, and to the type of leukemia [118].

Advances of TBI over the past 30 years have greatly improved treatment results. It is well known that the main parameters influencing TBI are the actually delivered dose, dose rate and fraction size. In many of the studies it is difficult to separate the effects of fractionation from those of the total dose, as both changed in the regimens used.

The observations indicate that dose escalation improves the results of TBI. The probability of 7-year survival is 74% if more than 9.9 Gy are administered and only 38% under 9.9 Gy [57]. Increasing the TBI dose above 10 Gy is not necessarily associated with better outcome in patients undergoing allogeneic BMT. In patients allografted in first remission, the probability of LFS was higher in patients receiving 12 Gy compared with those receiving less than 12 Gy planned dose. The impact of TBI dose (12 Gy or less) on LFS was not evident in patients allografted in second remission. According to the radiobiological model, the two-fractionated regimens (12 Gy/6 fr/3 days and 9.9 Gy/ 3fr/3days) adopted in some institutions to condition lymphoblastic and myeloid leukemia, respectively, could be probably at a level of "threshold of efficacy". Higher doses of TBI will be followed by a higher incidence of acute and chronic GvHD. The severity of chronic GvHD seems to be higher in complete chimerism as compared to mixed chimerism. In multivariate analyses, dose rate did not emerge as a significant factor affecting transplant-related mortality, relapse-free and overall survival rates. Dose rate variation did not show impact on acute and chronic GvHD occurrence. Review of the available data shows that the role of fractionation on leukemia cell killing may vary with the leukemia type. In a context of TBI for BMT, no clear advantage of fractionated over single-dose scheme can be shown with a possible exception for children. However, the conclusion that there are no dramatic differences in the clinical outcome between single or fractionated TBI appears premature. Fractionated and single-dose TBI are probably of equal value when the dose and technique are optimal [118]. Fractionated treatment is more resource-intensive, but less burdensome for patients. The potential therapeutic advantages of single and multiple fraction TBI cannot be elucidated without efforts to normalize and optimize such parameters [50]. The immunosuppressive effect of TBI, a major determinant of entgraftment, is highly fractionation-sensitive. Side effects by delivered TBI are distinctly determined by total dose, fraction size and dose rate.

Conclusion

The definition of the currently used TBI procedures is so different in different centers that retrospective analyses remain futile until better definition and normalization of dose, fraction size, and endpoints occur. There are a lot of difficulties to evaluate, compare or understand clinical results from so different treatment regimens, often with an irregular set of parameters. In order to establish clinical trials and to evaluate clinical results, we need comparable schedules, uniform specification, and complete reporting of all relevant parameters.

After a 50-year experience in the field of TBI we are beginning to understand the relationship of dose, dose rate and fractionation in TBI. However, 20 years after Glasgow [97] we will repeat his persuasion that, however, many questions remain unanswered.

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