CHAPTER

18 Total Body Irradiation

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Total body irradiation (TBI) is a radiotherapy technique that has been applied to treat various benign and malignant diseases over the past century. The technique has evolved in parallel with an increase in the knowledge of the biologic response to ionizing radiation and improvements in radiation dosimetry and treatment delivery. TBI remains an important component of hematopoietic stem cell transplant (HSCT), with the goal of eradicating residual malignant cells or modulating the immune system of the transplant recipient. In the context of HSCT, TBI is advantageous because biologic effects can be exerted uniformly, without the sparing of "sanctuary" sites such as the nervous system or tests or interference from metabolic or resistance processes.

HISTORY OF TOTAL BODY IRRADIATION

Only a decade after Roentgen described the "x ray," German biophysical engineer Friedrich J. Dessauer[1,2] first described a "new technique of radiotherapy" that involved homogenous irradiation of the entire body. In his initial report describing the technique in 1905, he proposed irradiating a supine patient using three simultaneously active, low-voltage roentgen-ray sources (Figure 18-1). In 1907, Aladár Elfer,[3] a medical professor in Hungary, reported his experience using a TBI technique that spared the head in three patients with leukemia. Although there is a paucity of data regarding the early use of the technique, some have speculated that untoward hematologic toxicity probably limited its application.[4]

Early success using TBI to treat hematopoietic and lymphoid malignant tumors in Europe (there named the Teschendorf method) prompted development of the technique in the United States.[5-7] Arthur C. Heublein, in collaboration with Gioacchino Failla, is credited with the development of the first TBI unit in North America, located at Memorial Hospital in New York City. In the United States, the technique became known as Heublein therapy.[8] A specially constructed treatment ward was designed to treat four patients at extended distance (5 to 7 m) simultaneously at an exposure rate of 0.7 roentgen (R)/hour, for about 20 hours/day, typically over 1 to 2 weeks, using a 185-kV x-ray tube at 3 mA, with a 2-mm copper filter. The goal was to deliver 25% of the erythema dose (750 R).

Remarkably, in Heublein's initial report, no hematopoietic toxicity was noted with this treatment schedule. Seven of 12 patients (58%) with advanced lymphomas and leukemias and 2 of 8 patients (25%) with metastatic breast, melanoma, and kidney cancers were noted to demonstrate some form of improvement after treatment.[9,10] A later report of the experience with 270 patients with cancer from Memorial Hospital treated with TBI between 1931 and 1940 confirmed that the technique was more successful in patients with hematopoietic and lymphoid cancers compared with those with carcinomas or sarcomas, for whom it was ineffective. The authors emphasized that the technique was safe if doses were prescribed cautiously. They did not recommend exposures greater than 300 R and noted hematopoietic and gastrointestinal toxicity with exposures as low as 50 to 100 R.[8]

In the early 1940s, World War II prompted an initiative to develop nuclear weapons, known as the Manhattan Project. Part of this endeavor sponsored research into the human biologic response to ionizing radiation, including TBI. The military's interest in TBI was primarily to help understand human tolerance for radiation exposure during occupational duties and warfare and to develop radiation biodosimetric assays. Several research studies coordinated through the Manhattan Project were initiated in patients with advanced cancers,[11-13] as well as patients with benign diseases.[13] For example, studies of dose escalation, radiation biologic dosimetry, and cognitive and psychomotor function were carried out at the M. D. Anderson Hospital for Cancer Research.[14] A detailed report of 30 patients treated at the maximum exposure level (200 R) in the initial study concluded that side effects primarily consisted of nausea, vomiting, and myelosuppression, and that intervention was necessary in 10% of patients treated with this dose of TBI.[15] At Baylor University College of Medicine, studies using 25 R to 250 R of TBI with 250 kV to 2 MV photons were performed to find a biologic dosimeter, as well as to study acute effects of radiotherapy.[16] The Sloan-Kettering Institute for Cancer Research also participated in similar studies of at least 20 patients, although the results were never published. The military conducted similar studies at the Naval Hospital in Bethesda, Maryland, and reported palliation of patients with radiosensitive diseases treated with fractionated TBI.[17] The most recent research study of TBI sponsored by the U.S. Department of Defense was conducted at the University of Cincinnati. It focused on identifying biochemical markers in the urine that predicted response to TBI. Later, studies of the neuropsychiatric effects of TBI were initiated. Ultimately, only results regarding the palliation of advanced cancers were reported.[18] Patients with advanced metastatic radioresistant malignant tumors, for whom chemotherapy was unavailable, were often treated with TBI in the absence of any clear anticipated benefit. Patients treated with TBI in this manner were included in research studies, often without consenting to participate. The ethics of this practice was called into question by a report written in 1995 by the U.S. Department of Energy's Advisory Committee on Human Radiation Experiments,[19] which may have contributed to the public's general uneasiness regarding radiation.[20]

TBI was not only used in malignant diseases, but it was also considered the critical immunomodulator in the first successful solid organ transplant. In 1959, a kidney was successfully transplanted between dizygotic twins after TBI at exposures of up to 450 R (given to the recipient).[21] Around the same time in France, successful kidney transplants after TBI were being reported.[22,23] Of the first seven patients who underwent kidney transplant following TBI or pharmacologic immunomodulation worldwide between 1959 and 1962, the two who did not experience kidney failure were treated with TBI alone (without chemical immunosuppression) before transplant, and each survived for more than 20 years after transplant.[21-23] However, successful preclinical studies with pharmacologic therapy prompted the use of chemical immunosuppressants (corticosteroids, 6-mercaptopurine, and azathioprine) for solid organ transplantation after 1963.[24]

With an increased understanding of the human response to TBI and a rapidly growing body of preclinical in vivo studies

of TBI, therapeutic protocols were developed to maximize benefit in patients with malignant diseases. In 1957, Nobel laureate E. Donnall Thomas[25,26] first reported the use of bone marrow infusion in humans following whole body irradiation or chemotherapy, and less than 1 year later he published his experience in using TBI with exposures up to 600 R followed by bone marrow transplantation. In the series of the first five patients with leukemia treated with TBI, who then received intravenous infusion of normal donor marrow, Thomas et al[26] noted the difficulty of acute myelosuppression and resultant hemorrhage and infection during the period leading up to engraftment. The report also commented that low dose rates (delivery over 2 to 3 days) appeared preferable to higher dose rates, for metabolic and immunologic reasons. In addition, patients receiving 200 R to 300 R fared better than those receiving 400 R to 600 R. The problem of delivering an adequately homogenous dose was raised, and suggestions about using higher-energy photons were proposed. Thomas et al[27] later reported on syngeneic bone marrow transplantation in two children after 850 R to 1140 R was delivered in a single fraction over 22 to 25 hours, using cobalt-60 (^{60}Co) sources. The authors concluded that 1000 R of TBI did not produce "troublesome" acute radiation sickness, did produce remission of leukemia, but did not cure the disease. The first report of successful cure of a patient with leukemia with allogeneic transplantation after TBI was reported in 1969. The technique involved opposed ^{60}Co sources, which operated at 5.8 R/minute, to a total exposure of 1620 R, calculated to be 954 rad at midline. With appropriate supportive care, no major acute radiation sickness was noted, but the patient died of overwhelming cytomegalovirus infection, without evidence of leukemia.[28]

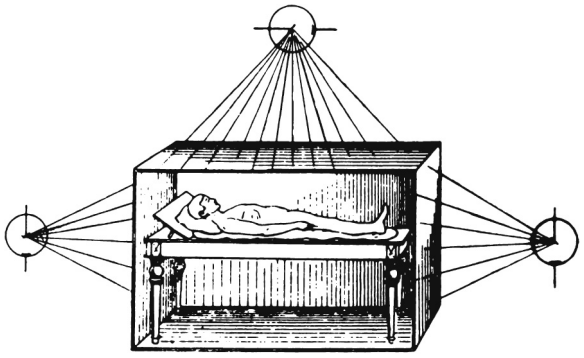

Figure 18-1 Diagram demonstrating the total body irradiation technique proposed by Dessauer in 1905.
Reprinted from Wetterer J editor: Handbuch der Röntgentherapie nebst Anhang. In Die radium therapie, Leipzig, 1908, Otto Nemnich.

Over the next several years, techniques of combining chemotherapy and TBI were developed and refined, with promising results.[29,30] Success in the treatment of advanced leukemias and severe aplastic anemia was achieved. Departure from the use of TBI alone was primarily fostered by the development of more effective cytotoxic chemotherapeutics and immunologic therapies, which when combined with TBI, yielded fewer leukemic recurrences.[29] Although the use of TBI without HSCT has largely been abandoned, primarily for fear of inducing secondary malignant tumors and limiting later therapeutic options, some question the validity of this fear and still contend that low dose TBI (1.5Gy to 2 Gy in 10 to 20 fractions over several weeks) is a viable option for initial therapy in advanced indolent lymphomas.[31] Figure 18-2 demonstrates how the use of TBI during HSCT has changed over a recent 15-year period.[32]

HEMATOPOIETIC STEM CELL TRANSPLANT

HSCT has evolved into a highly complex clinical discipline, firmly rooted in immune system and cancer biology, the details of which are beyond the scope of this chapter. When HSCT was initially performed (see History of Total Body Irradiation section), bone marrow was extracted from the donor and infused intravenously into the recipient. Later, peripheral blood stem cells, instead of bone marrow, were collected from the donor as an alternative to bone marrow grafting. For this reason, bone marrow transplants are now more appropriately termed *hematopoietic stem cell transplants* because the critical component of the graft is the hematopoietic stem cell (HSC), independent of the source. The peripheral blood stem cells

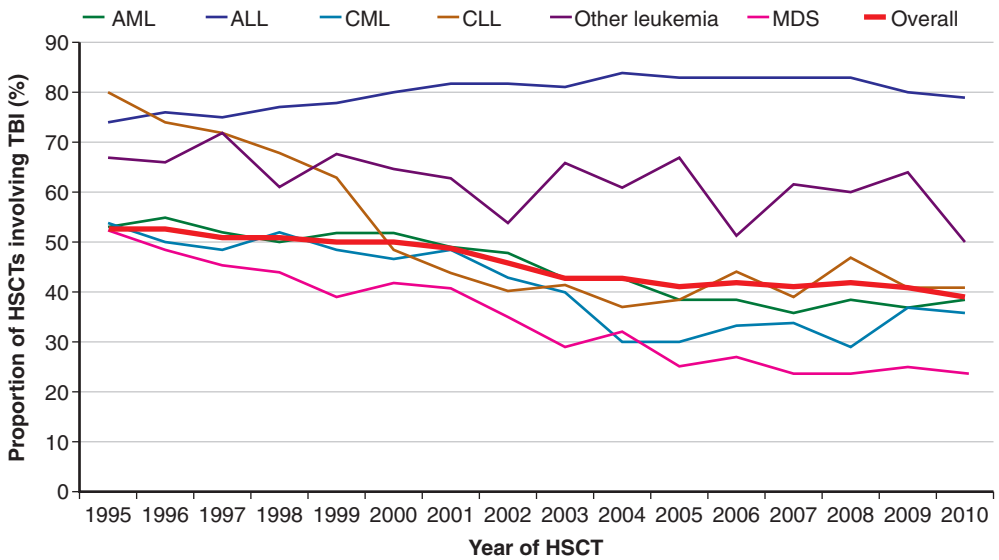

Figure 18-2 Temporal trends in the five diseases most frequently involving TBI as part of allogeneic HSCT, and overall. *ALL*, Acute lymphoblastic leukemia; *AML*, acute myelogenous leukemia; *CLL*, chronic lymphocytic leukemia; *CML*, chronic myelogenous leukemia; *HSCT*, hematopoetic stem cell transplant; *MDS*, myelodysplastic syndrome.
Data from Hong S, Barker CA, Klein JP, et al: Trends in utilization of total body irradiation (TBI) prior to hematopoietic cell transplantation (HCT), worldwide. Biol Blood Marrow Transplant 18(2 Supplement 2):S336–S337, 2012.

are often "mobilized" from the donor using hematopoietic growth-stimulating factors and are removed from the donor by apheresis. In addition, recent success using HSCs derived from human umbilical cord blood has been described. Depending on the source of HSCs, various postcollection processing measures (e.g., cell selection and depletion) may be undertaken to optimize the outcome of the transplant.

When transplant occurs between different individuals, the hematopoietic graft is said to be an *allogeneic graft.* This is in contradistinction to reinfusion of native HSCs back into the donor in an *autologous transplant,* more appropriately termed an *autoplant,* because nothing is being transferred between different individuals.[33] A rare but alternative situation is when an organ from a genetically identical twin of a patient is transplanted *(syngeneic transplant).* Of these three methods of HSCT, autologous and syngeneic transplantations are generally associated with less risk because issues related to immunocompatibility are minimized. Allogeneic transplantations require the "matching" of donor and recipient and are typically carried out through identification of human leukocyte antigen (HLA) compatibility. The donor may be related to the recipient or may be identified through registries of volunteers, such as the National Marrow Donor Program.

Before undergoing HSCT, most patients will require intensive antineoplastic or immunomodulatory therapy, often referred to as *conditioning,* in preparation for HSCT. Conditioning can involve cytotoxic chemotherapy, immunomodulators, antibody therapy, or radiation therapy. The nature of the conditioning regimen can be referred to as of high or reduced intensity or as myeloablative, submyeloablative, or nonmyeloablative, to carry out conventional or mini-(ature) transplants.[33] Although agreed-on formal definitions of these regimens do not exist,[34] the goal of high-intensity/myeloablative/conventional transplant is to completely eliminate the recipient's native HSC compartment, which necessitates HSCT (autologous or allogeneic) for survival. High-intensity, myeloablative, and conventional transplants may or may not involve TBI to high doses (>5 Gy in a single fraction, >8 Gy in multiple fractions). Reduced-intensity, nonmyeloablative, minitransplant conditioning regimens are often used for older patients or those with medical problems, for whom a high-intensity, myeloablative, and conventional transplant would cause excessive morbidity or mortality and may or may not involve TBI to lower doses. During and immediately after conditioning, the transplant recipient is at significant risk for infections and other hematologic complications. For this reason, the supportive care of HSCT recipients is complex and should only be undertaken in specialized facilities. Nonetheless, some groups have developed reduced-intensity and myeloablative HSCT regimens, including TBI, which have been safely undertaken on an outpatient basis.[35,36]

After undergoing conditioning and HSCT, the major challenges are related to engraftment, the permanent reconstitution of the recipient's hematopoietic system, and prevention of graft rejection and associated postengraftment complications. The former process can be facilitated through the use of hematopoietic growth-stimulating factors, and the latter can be mitigated with chemical and biologic immunomodulators. Once the graft has successfully taken, the recipient is at risk of developing graft-versus-host disease (GVHD), in which engrafted HSCs recognize the host's native, non-HSC tissues as foreign and attack them. Specific organs at risk are the skin, gastrointestinal tract, and liver. The risk of GVHD is only present in patients undergoing allogeneic HSCT. Moreover, it has been recognized that part of the beneficial effect of transplant is the graft-versus-tumor (GVT) effect, a fundamental component of the therapeutic effect of HSCT, which can occur in autologous or allogeneic transplants.

According to data summarized by the Worldwide Network for Blood and Marrow Transplantation in 2006, the diseases most commonly treated with HSCT are lymphoproliferative disorders (54.5%, most often multiple myeloma [MM], non-Hodgkin lymphoma [NHL], and Hodgkin lymphoma [HL]), leukemias (33.8%, most often acute myelogenous leukemia [AML], acute lymphocytic leukemia [ALL], myelodysplastic syndrome [MDS], chronic myeloid leukemia [CML], and chronic lymphocytic leukemia [CLL]), solid tumors (5.8%), and nonmalignant disorders (5.1%).[37] The 2014 National Comprehensive Cancer Network (NCCN) guidelines for therapy indicate that allogeneic or autologous HSCT may be a treatment option for testicular cancer, AML, MM, MDS, CML, HL, and NHL, depending on the clinical situation. HSCT with or without TBI-based conditioning has also been described in the treatment of solid tumors, including breast cancer, germ cell tumors, renal cell carcinoma, melanoma, neuroblastoma, and other pediatric cancers. Detailed discussion of these diseases and their management is beyond the scope of this chapter, and the reader is referred to other chapters in this text and other reviews.[38-41] The role of TBI in nonmalignant diseases will be discussed in subsequent sections of this chapter.

RADIOBIOLOGY

Experimental radiobiologists have described much of what is known regarding the fundamental biologic effects of TBI, and clinicians have applied these principles to optimize the therapeutic benefit for patients. The essential rationale for TBI in the context of HSCT is to eradicate malignant or dysfunctional cells or modulate immune system function. Therefore, the critical radiobiologic in vitro data related to efficacy of treatment deal with normal and malignant hematopoietic cells.

Preclinical studies have helped define some of the fundamental radiobiologic properties of the normal lymphocytes. The D_0 (see Chapter 5) of normal lymphocytes has been reported to be 0.5 Gy to 1.4 Gy,[42-45] depending on the in vitro or in vivo model used to calculate this parameter. This D_0 suggests that normal lymphocyte cells are sensitive to ionizing radiation. A small shoulder on the radiation cell survival curve has been noted,[46,47] suggesting little repair between fractions of radiation. Clinical data have revealed similar findings in patients undergoing hyperfractionated TBI, with lymphocyte survival demonstrating an effective D_0 of 3.8 Gy, according to one study.[48] Other radiobiologic phenomena have been ill defined in other normal hematopoietic cells. Radiobiologically relevant levels of hypoxia are unlikely in the hematopoietic compartment. Repopulation is not likely to influence hematopoietic cell survival, given the short duration of most TBI regimens (1 to 5 days), although given the variable life span of leukocytes (days to years), it may be of some relevance. Redistribution would appear to be of significance, given the time scale for TBI; however, this has been difficult to assess.[49]

The radiobiology of malignant hematopoietic cells has been described. The D_0 of leukemic cells generally ranges from 0.8 Gy to 1.5 Gy; however, compared with normal hematopoietic cells, a wider range of radiosensitivities have been described.[50,51] Many have cited the technical nuances and variations in assay technique for this great range.[49,52] Similar to normal hematopoietic cells, their malignant counterparts are thought to demonstrate little sublethal damage repair,[53-57] although split-dose-rate and low-dose-rate experiments have demonstrated the capacity of leukemic cells to repair radiation-induced damage.[58-64] Generally, leukemic cells are thought to have a cell survival curve with a minimal shoulder or no shoulder, although this varies across cell types and cell lines.[47,61-63,65] For example, Cosset et al[52,66] summarized preclinical and clinical findings, concluding that AML demonstrates

little repair, whereas CML does demonstrate repair; ALL, myeloma, and lymphomas have not been well studied but appear to demonstrate a wide range of repair capacity.

Similar to normal hematopoietic cells, reoxygenation is unlikely to be radiobiologically relevant to malignant hematopoietic cells during TBI. Redistribution and repopulation, however, may be relevant but have not been systematically studied. Recent molecular studies suggest a significant effect of TBI on peripheral blood mononuclear cell immune-related gene expression in patients.[67]

In vivo preclinical research laid the foundation for the first successful HSCT in humans. Studies in rats,[68] dogs,[69] and nonhuman primates[70] demonstrated that reconstitution of the hematopoietic system was possible after TBI with supralethal doses of radiation. Later work in animals revealed that delivering TBI in several fractions required a higher total dose relative to the biologically isoeffective dose given in a single fraction.[71,72] Another model demonstrated no significant difference in the effect of a low-dose-rate (0.04 Gy/minute), single-fraction of TBI compared with a hyperfractionated course of TBI given three times a day to the same total dose.[73]

Although the hematopoietic system is the target of TBI, normal tissues effectively limit the dose that can be safely delivered. The sparing of normal tissues with fractionated TBI was proposed by Peters et al[53,54] and was subsequently supported by preclinical data in mice[74,75] and dogs[76] that showed that less lung injury occurred with fractionated TBI regimens.

IMMEDIATE TOXICITY AND MANAGEMENT IN TOTAL BODY IRRADIATION

Although a good deal of what has been learned about the acute in vivo biologic effects of TBI has been derived from laboratory-based animal studies, whole-body irradiation also has been studied in people exposed during accidental or wartime nuclear events.[77,78] These large-scale studies are valuable because they deal with apparently normal subjects; however, the retrospective nature limits the quality of the data. The reader is referred to several excellent reviews of acute and fatal radiation syndromes (gastrointestinal, hematopoietic, and cerebrovascular syndromes) that can be caused by TBI in an uncontrolled setting.[79-81]

Acute side effects of therapeutic TBI can be difficult to distinguish from other HSCT-related morbidities. However, Chaillet et al[82] conducted an informative prospective clinical study of the symptoms and signs that occur in patients after TBI, before the initiation of any other HSCT-related therapy. Thirty-one patients, 4.5 to 55 years of age, were treated using parallel-opposed anteroposterior 18-MV photons from a linear accelerator. Shielding was used to limit the lung dose to 8 Gy. A total dose of 10 Gy was given as a "single dose" as six discrete fractions of 1.6 Gy each given over 15 minutes, with a 30-minute break between fractions, for a mean dose rate of 0.04 Gy/minute and an instantaneous dose rate of 0.11 Gy/minute to 0.12 Gy/minute. Symptoms and signs were assessed regularly during the 4-hour TBI and for 20 hours after the completion of TBI. Antiemetics, but no chemotherapy or steroids, were given before the start of TBI. Table 18-1 displays the symptoms and signs experienced by patients during the 4 hours of TBI and within 24 hours of starting TBI. Fever was a common finding, and a maximum of 40.8° C (105.4° F) was noted in one patient. Tachycardia frequently paralleled febrile episodes; a maximum rate of 130 beats/minute was noted. Drowsiness was noted only in patients who received sedating antiemetics. Parotid gland pain was common, and bilateral parotid swelling was noted in 29% of patients. Marked lacrimation was noted in 6% of patients, whereas 16% of patients experienced ocular dryness. Two patients experienced mild conjunctival edema. Hypertension was noted only during TBI. The results of a similar study conducted by Buchali et al[83] of patients who were treated with a fractionated course of TBI delivered mostly to a total dose of 12 Gy using 2 Gy per

TABLE 18-1 Signs and Symptoms in Patients after Single-Dose or Fractionated TBI

	Single-Fraction TBI		Fractionated TBI
Symptom/Sign	Percentage of Patients Experiencing during TBI	Percentage of Patients Experiencing after TBI	Percentage of Patients Experiencing during 3 Days of TBI
Nausea	90	45	43
Vomiting	80	23	23
Parotid gland pain	26	74	6
Xerostomia	61	58	30
Headache	42	33	15
Fatigue	N/R	N/R	36
Ocular dryness	None	16	N/R
Esophagitis	N/R	N/R	4
Loss of appetite	N/R	N/R	16
Indisposition	N/R	N/R	25
Erythema	None	None	41
Pruritus	None	None	4
Diarrhea	None	None	4
No symptoms	N/R	N/R	17
Fever (>38° C)	42	97	N/R
Hypertension	42	None	N/R

Data from Chaillet MP, Cosset JM, Socie G, et al: Prospective study of the clinical symptoms of therapeutic whole-body irradiation. Health Phys 64(4):370–374. 1993; Buchali A, Feyer P, Groll J, et al: Immediate toxicity during fractionated total body irradiation as conditioning for bone marrow transplantation. Radiother Oncol 54(2):157–162, 2000.

N/R, *Data not reported;* TBI, *total body irradiation.*

fraction, twice daily, 8 hours apart, with lung doses limited to 10 Gy, are also summarized in Table 18-1.

A prospective clinical study showed that fractionation of TBI can reduce acute nausea, vomiting, mucositis, diarrhea, and parotitis, although the differences were not statistically significant. Late cutaneous eruptions were more common in patients undergoing fractionated TBI, although the numbers were not statistically significant. The same study, which randomized patients to either high- or low-dose rate TBI, revealed no differences in the acute toxicities mentioned when comparing dose rate.[84] Another randomized controlled trial (RCT) reported that fractionating TBI revealed "no apparent difference in acute toxicity" compared with single-fraction TBI, with both regimens being "well-tolerated."[85]

Older studies cite nausea and vomiting as frequent side effects of TBI. These symptoms have been substantially lessened with the advent of more effective antiemetics, such as the 5-hydroxytryptamine (serotonin) receptor-3 (5-HT3) antagonists. Several small but high-quality controlled clinical studies support the prophylactic use of 5-HT3 antagonists to reduce nausea and vomiting during TBI[86-90]; they are summarized in eTable 18-1. The use of corticosteroids in conjunction with 5-HT3 antagonists is supported by a trial listed in eTable 18-1. However, given the toxicity associated with this approach, consensus regarding routine administration in conjunction with TBI is lacking.[91-93] Of note, less nausea and vomiting have been noted in myeloablative conditioning regimens involving TBI compared with those that use chemotherapy alone, even with modern antiemetics.[94]

Oral mucositis is a side effect of TBI in up to 75% of patients undergoing myeloablative TBI, causing mouth pain and odynophagia and necessitating intensive supportive care such as total parenteral nutrition and opioid analgesics.[95] In one study, intensive dental hygiene conferred a reduction in the rate of moderate and severe mucositis, although the authors thought the rate to be clinically insignificant.[96] Topical oral agents, such as chlorhexidine digluconate and neutral calcium phosphate in conjunction with topical fluoride treatments can decrease pain duration and severity of oral mucositis, as well as pain and need for opioid analgesics.[97-99] Similarly, prophylactic oral sucralfate and clarithromycin have reduced moderate and severe oral mucositis rates.[100,101] One study showed that when given prophylactically, amifostine limited the duration of mucositis, with an associated decrease in the rate of moderate and severe infections, with no effect on HSCT outcome.[102] Low-level laser (650 nm) therapy has been reported to reduce the incidence of oral mucositis in a RCT.[103]

In one study, researchers noted that short-term intravenous recombinant granulocyte-macrophage colony–stimulating factor decreased rates of moderate to severe mucositis,[104] but in another study, no effect was found when this agent was delivered topically.[105] Recently, Spielberger et al[106] reported the results of a trial of the recombinant human keratinocyte growth factor palifermin, given before and after conditioning with 12 Gy of fractionated TBI. Palifermin reduced the rate and duration of moderate and severe mucositis by 35% and 3 days, respectively, and decreased mouth and throat pain, as reflected in reduced morphine usage and decreased need for total parenteral nutrition (by 24%). This study dealt only with patients undergoing autologous HSCT; however, in the setting of TBI for allogeneic HSCT, palifermin may also confer a protective effect on the mucosa, although studies suggesting this have been small and inadequately designed.[107]

Skin erythema may also be noted toward the end of a course of TBI; desquamation is rare. Hyperpigmentation may be noted in the long term. Alopecia typically occurs 7 to 14 days after TBI, and hair typically returns 3 to 6 months after treatment.[108] Changes in the color or texture of regrown hair have been noted. Of note, myeloablative conditioning regimens using chemotherapy alone have produced a significantly higher incidence of permanent alopecia.[109]

LATER TOXICITY AND ITS MANAGEMENT IN TOTAL BODY IRRADIATION

Hematopoietic Toxicity

As previously mentioned (see Radiobiology section), the hematopoietic system is particularly sensitive to TBI, and lymphopenia is often seen with doses of 0.5 Gy and can be seen with doses of 0.3 Gy. Lymphopenia is typically followed by neutropenia, thrombocytopenia, and finally anemia. Soon after a TBI dose of 4 Gy to 6 Gy has been given, lymphocytosis can be seen, but it typically is followed by neutropenia within 1 week. Three to 4 weeks after TBI, neutrophils fall to their minimum[110] (Figure 18-3). Regeneration of the HSC compartment depends on the total dose used because higher doses cause more rapid myelosuppression of greater duration. Administration of hematopoietic growth factors after TBI have the theoretical potential to alter hematopoietic system reconstitution, although reports in the setting of allogeneic HSCT have demonstrated an increased risk of GVHD and compromised survival,[111] and therefore, routine use is controversial.[112,113] Of note, hematopoietic growth factors have only been used in the period following TBI, given the concerns raised by a trial in lung cancer, where growth factors increased pulmonary toxicity and thrombocytopenia when given concurrently with chemoradiation therapy.[114]

Oral Toxicity

As noted before, the salivary glands frequently are affected by TBI. Although acute parotitis is typically self-limited and can be managed with antiinflammatory medicines, long-term salivary gland dysfunction can result in xerostomia, which may lead to dental caries. In a study of children who underwent allogeneic HSCT, the risk of developing impaired salivary function was 22% in those who received TBI as part of conditioning versus 1% in those who did not.[115] Salivary flow can improve up to 1 year after the completion of TBI.[116] Fractionated TBI was shown to reduce salivary dysfunction by 54% in one study.[117]

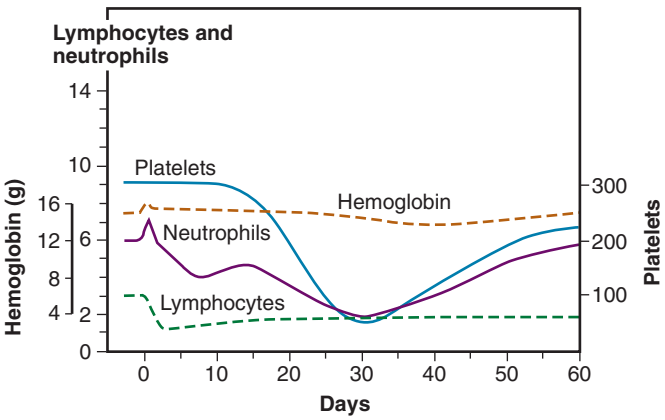

Figure 18-3 Representative hematologic response to total body irradiation, given as a single fraction of 200 cGy on day 0.
Data from Andrews GA: Radiation accidents and their management. Radiat Res Suppl 7:390–397, 1967; Figure 1, with permission from Radiation Research Society.

eTABLE 18-1 Randomized Controlled Trials of Prophylactic Antiemetics in Patients Undergoing TBI

Author	No. Patients	Total TBI Dose/ No. Fractions	Experimental Antiemetic	Control of Antiemetic	Outcome
Tiley et al.[86]	20	10.5 Gy/1	8 mg oral ondansetron at start of TBI + standard (metoclopramide, dexamethasone, lorazepam)	Placebo + standard (metoclopramide, dexamethasone, lorazepam)	Significantly fewer emetic events with ondansetron (60% vs. 10%, $p < 0.03$) during TBI
Spitzer et al.[87]	20	13.2 Gy/11 (in 4 days)	8 mg oral ondansetron 1.5 hr before TBI tid	Placebo	Significantly more patients had two or fewer episodes of emesis with ondansetron (60% vs. 10%, $p < 0.03$): significantly longer time to first emetic episode ($p < 0.005$) and significantly fewer episodes of emesis during the first 24 hours and over the entire study period ($p < 0.05$) with ondansetron
Prentice et al.[88]	30	7.5 Gy/1	3 mg IV granisetron 1 hr before TBI	Metoclopramide, dexamethasone, and lorazepam 1 hr before TBI	Significantly higher rates of complete control of emesis within first 24 hr with granisetron (53% vs. 13%, $p = 0.02$) and significantly longer duration of emesis control ($p < 0.005$) with granisetron
Okamoto et al.[89]	58	74% of patients received TBI: 6-12 Gy/1-6	40 μg/kg IV granisetron twice daily 30 min before TBI	Various	Significantly higher rates of complete control of emesis within the first 24 hr with granisetron (92% vs. 44%, $p < 0.01$) and throughout the duration of HSCT (68% vs. 0%, $p < 0.001$) with granisetron in patients receiving TBI
Matsuoka et al.[90]	50	64% of patients received TBI: 12 Gy/4-6	4 mg IV dexamethasone + 40 μg/kg granisetron bid 30 min before treatment	40 μg/kg IV granisetron twice daily 30 min before treatment	Significantly higher (100% vs. 63%. $p = 0.02$) rates of complete emesis control within the first 24 hr with dexamethasone in patients receiving TBI; insomnia, headache, flushing, and hyperglycemia were more common in patients with corticosteroid

TBI, *Total body irradiation.*

Myeloablative conditioning regimens with and without TBI have been associated with abnormalities in tooth development in children.[117-119] In one series, myeloablative conditioning regimens using chemotherapy alone were associated with significantly higher rates of tooth developmental abnormalities than those involving TBI, although rates of salivary gland dysfunction were highest among the patients treated with single-fraction TBI.[120] Because of the increased risk of oral pathology associated with TBI, careful pretransplant evaluation by a dental specialist is recommended to minimize the risk of serious morbidity.[121] Pilocarpine has been noted to help relieve symptoms of xerostomia in patients treated with TBI.[122]

Pulmonary Toxicity

The major dose-limiting toxicity of TBI is pneumonopathy (restrictive or obstructive lung disease), which can manifest early as pneumonitis or later as pulmonary fibrosis. In the setting of HSCT, radiation pneumonopathy can be difficult to distinguish from other causes of lung pathology; moreover, lung damage is likely multifactorial, with the risk of acute lung complications estimated to be 30% to 60%, depending on factors such as infection, conditioning regimen, GVHD, age, and diagnosis.[123] Likewise, late pneumonopathy occurs in 10% to 26% of patients and is associated with underlying lung dysfunction, type of conditioning regimen, acute and chronic GVHD and prophylaxis, donor and recipient age and immunocompatibility, stage of disease, and genetic predisposition.[124] TBI is a risk factor for idiopathic pneumonia syndrome,[125] as well as for diffuse alveolar hemorrhage.[126] Although rates of pneumonopathy in patients receiving TBI vary widely (10% to 84%),[127] some series have reported pneumonitis in up to 20% of patients undergoing HSCT who never received TBI.[128] In the modern era, with appropriate TBI techniques, the risk of pneumonopathy in patients treated with TBI may not be increased at all.[129] Nevertheless, the significance of the problem is clear, given that mortality related to interstitial pneumonitis in patients treated with TBI can be 60% to 80%.[128,130,131]

Several TBI-specific factors (e.g., total dose, fractionation, dose rate, and use of lung shielding) have been shown to have a significant bearing on the development of pulmonary complications. The total dose used during TBI has frequently been cited as a major factor influencing lung complications.[127,132,133] In two prospective RCTs using 12 Gy versus 15.75 Gy, higher rates of mortality were noted within the first 6 months in patients treated with 15.75 Gy, although pulmonary complications were not specifically cited as the cause of excess deaths.[134-137] In a retrospective dosimetric study, a mean lung dose of more than 9.4 Gy was found to be an independent predictor for lethal pulmonary complications in patients receiving TBI to a total dose of 10 Gy in three daily fractions, at 0.055 Gy/minute using parallel opposed lateral fields.[138] Two RCTs have demonstrated that fractionated TBI can reduce pneumonitis compared with single-fraction TBI, although only one study showed differences that were statistically significant.[85,139,140] A retrospective study found no difference in pneumonitis rates when comparing a single fraction of 6 Gy and three daily fractions of 3.33 Gy, suggesting that total doses of less than 10 Gy may not require fractionation to prevent toxicity, although no randomized data support this.[141] The necessity of hyperfractionation to prevent lung toxicity is unclear: A comparison of two prospective single-arm trials at the same institution revealed that conventional fractionation given with anteroposterior fields and lung blocks to a total dose of 12 Gy in daily three-Gy fractions may not be any different than hyperfractionated TBI given twice daily with 1.7 Gy per fraction to a total dose of 10.2 Gy over 3 days, using parallel opposed lateral fields and no blocks.[142] An RCT suggested that the angiotensin-converting enzyme inhibitor, captopril, may mitigate pulmonary toxicity associated with TBI.[143]

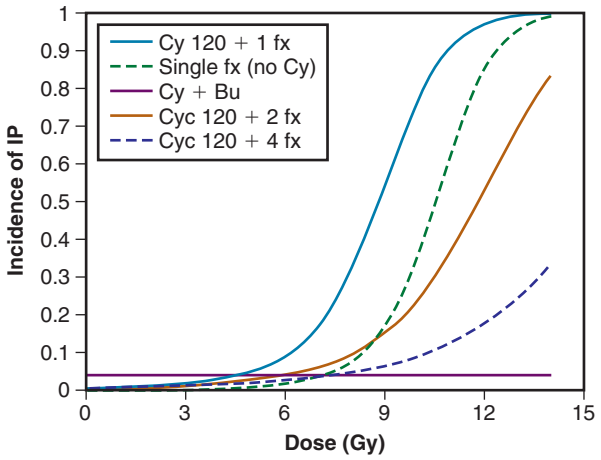

Figure 18-4 Incidence of pneumonitis based on dose-response model accounting for TBI fractionation, as well as chemotherapy effects. *Bu*, Busulfan; *Cy and Cyc*, cyclophosphamide; *fx*, fraction(s). *Data from Sampath S, Schultheiss TE, Wong J: Dose response and factors related to interstitial pneumonitis after bone marrow transplant. Int J Radiat Oncol Biol Phys 63(3):876–884, 2005; Figure 2, © 2005, Elsevier, with permission from Elsevier.*

Sampath et al[144] reviewed 26 studies involving 1096 patients to create a dose-response model for predicting the risk of pneumonitis from TBI while taking other factors into consideration. Although unable to estimate the risk of pneumonitis for hyperfractionated regimens, they were able to determine the effect of fractionation, cyclophosphamide, and busulfan on the risk of developing pneumonitis, in a dose-response model, as seen in Figure 18-4.

Pneumonitis rates were not significantly different in a trial that randomized patients to high- or low-dose-rate TBI.[84] However, there is an abundance of retrospective clinical data suggesting that lowering the dose rate (<0.025 to 0.09 Gy/minute) does decrease the likelihood of pulmonary complications,[127,133,137,145,146] especially if TBI is delivered as a single fraction.[147] If TBI is fractionated, some report that a low dose rate (<0.069 Gy/minute) is not necessary,[131] whereas others found a beneficial effect.[148,149] Studies of patients receiving fractionated TBI with lung shielding have demonstrated a reduction in pneumonopathy[150,151]; however, one RCT found no difference in pneumonopathy rates if the shielding allowed a lung dose of either 6 Gy or 8 Gy in a single fraction.[152]

Pulmonary function tests (PFTs), such as spirometry and diffusion capacity, are often helpful in the assessment of patients with pulmonary symptoms or radiographic abnormalities. Studies of PFTs in patients treated with HSCT have demonstrated a deleterious effect on spirometry and diffusion capacity, which often resolves in the absence of other complicating factors[153-155] and is related to the TBI dose.[156] A retrospective study found that lung shielding had a small but significantly beneficial effect on PFTs 1 year after HSCT, especially in patients with abnormal function before HSCT.[157] In one study, busulfan and not TBI, was associated with a negative effect on PFTs.[158] There is no evidence that obtaining PFTs improve pulmonary outcome after HSCT in adulthood, and for this reason they are not recommended.[159] However, some groups recommend baseline PFTs as part of long-term follow-up care for children treated with TBI.[160] Counseling regarding smoking cessation is of critical importance for all patients, especially those who are at increased risk of developing lung injury. In the event of acute pneumonitis, high-dose

steroids (30 mg to 60 mg of prednisone/day) typically alleviate symptoms within 24 to 48 hours.

Cardiovascular Toxicity

Cardiovascular toxicity in adults as a result of HSCT is relatively rare, given the stringent selection criteria for patients treated with this aggressive therapeutic modality. Nevertheless, in adult patients who survived autologous or allogeneic HSCT, cardiac events were responsible for 2.4% and 3% of deaths, respectively; this represents a greater than expected occurrence.[161,162] Most of the recent literature has identified no association between TBI and the development of cardiovascular disease in adults.[163,164] In several detailed prospective analyses using plasma cardiac troponin and brain natriuretic peptide levels, electrocardiography and echocardiography revealed no evidence of cardiac dysfunction in previously healthy individuals treated with TBI.[165,166] However, a prospective study of children who underwent allogeneic HSCT found a 12% and 26% cumulative incidence of abnormalities in ejection fraction (<30%) on echocardiography before HSCT and 5 years after HSCT, respectively. This study revealed that TBI was associated with abnormalities in cardiac function on univariate analysis but not multivariate analysis; the 5-year cumulative incidence of cardiac abnormality was 26% or 2% in children treated with TBI, with or without prior anthracycline therapy, respectively.[167] Recent data from large studies of survivors of childhood cancer suggest that the risk of cardiac mortality is significantly elevated for children who receive heart doses of 5 Gy, although it should be noted that anthracycline doses of more than 360 mg/m^2 similarly increased the risk.[168] Importantly, the rate of death from recurrence or progression of cancer exceeds the rate of death from cardiac disease by approximately a factor of 7.[169] The reason for excess late cardiovascular toxicity in TBI in children is probably because of the association of TBI with the premature development of cardiovascular disease risk factors (e.g., hypertension, dyslipidemia, diabetes) that result in deleterious consequences rather than direct radiation cardiotoxicity.[170-172] Therefore it is prudent to screen patients who have undergone HSCT for cardiovascular disease risk factors, whether treatment involved TBI, to minimize late morbidity and mortality.

Hepatic Toxicity

Hepatotoxicity from TBI manifests primarily as venoocclusive disease (VOD), also known as sinusoidal obstructive syndrome (SOS), of the liver. This clinicopathologic phenomenon was first described in 1977 by Shulman et al,[173] who noted the onset of weight gain from ascites, painful hepatomegaly, and jaundice from centrilobular liver acinus necrosis 1 to 4 weeks after HSCT. Up to 70% of patients who undergo HSCT can be affected by VOD. TBI, along with many other risk factors, has been implicated in the development of VOD.[174] An RCT and a meta-analysis found that patients treated with busulfan instead of TBI were significantly more likely to develop VOD.[175,176] Two RCTs have concluded that fractionated TBI reduces the incidence of VOD compared with single-dose TBI.[139,140] Another RCT found no difference in the rate of VOD when the dose rate was either 0.06 Gy/minute or 0.15 Gy/minute,[84] although a retrospective study of single-dose TBI found that dose rates of 0.07 Gy/minute were associated with less VOD than dose rates of 0.18 Gy/minute to 1.2 Gy/minute.[177] A TBI dose greater than 13.2 Gy has been reported to be associated with higher rates of VOD on univariate analysis,[178] although a dose greater than 12 Gy was not associated with VOD in another retrospective study.[179] Lawton et al[180] reported a nonstatistically significant 10% decrease in the rate of fatal VOD in patients treated with TBI as part of HSCT when a 10% attenuation liver block was employed. Ursodeoxycholic acid was effective in preventing VOD in an RCT of patients undergoing TBI followed by HSCT,[181] although another RCT did not support this finding.[182] Reduced-intensity conditioning regimens may also prevent VOD. Treatment of VOD can include the fibrinolytic antithrombotic agent defibrotide; decompressing the sinusoids by a transjugular intrahepatic portosystemic shunt and liver transplantation is another, more invasive, option for the management of severe disease.[183]

Visual Toxicity

Cataracts are one of the most common complications of TBI. Patients may present with painless vision loss and may be noted to have opacification of the lens on examination. In one series of patients treated with TBI in one or two fractions, severe visual impairment was noted in about half of patients.[184] This problem has been noted to arise in a large proportion of patients treated with TBI, depending on the total dose, use of fractionation, and the dose rate. When considering risk factors associated with HSCT, steroid use,[185-187] prior cranial irradiation,[188,189] and the development of GVHD[187] have been shown to predispose to cataractogenesis, whereas heparin use appears to be protective.[190]

Delivering TBI in a single fraction is the single biggest risk factor for developing a cataract after HSCT.[190-195] High-dose-rate (>0.035 Gy/minute to 0.048 Gy/minute) TBI also appears to increase the risk of cataract formation.[188,190,193,196] A prospective study that randomized patients to high- or low-dose rate TBI found that the incidence of cataract 5 years after treatment was 12% and 34% in the low- and high-dose rate arms, respectively, with 13% and 39% of the cataracts, respectively, occurring in patients who received fractionated or single-dose TBI.[197] Kal[198] and van Kempen-Harteveld[199] recently reviewed the subject of TBI-induced cataracts and concluded that a biologically equivalent dose of 40 Gy yields a 10% chance of developing cataracts, using linear-quadratic modeling that included corrections for dose rate, with an α/β of 0.65 for late effects on the lens. On the basis of this, they suggest considering lens shielding for single-fraction TBI regimens,[198] although this is controversial in the setting of malignant disease.[199] Given the frequency of cataracts occurring after TBI, patients should be monitored for the development of this complication.[200] Management of cataracts that impair vision or degrade quality of life may involve phacoemulsification and extraction; recent data suggest that these procedures are safe, with an adverse event rate of 0.1% for experienced surgeons,[201] and effective, with a 90% chance of 20/40 vision postoperatively.[202]

Renal Toxicity

Kidney dysfunction occurs in approximately 17% of survivors of HSCT[203] and can manifest in a number of ways, with the most to least frequent syndromes being idiopathic chronic kidney disease, nephrotic syndrome, thrombotic microangiopathy (thrombotic thrombocytopenic purpura and hemolytic uremic syndrome), and acute renal failure.[204] The syndrome most associated with TBI is thrombotic microangiopathy, which can manifest as nephritis, hypertension, proteinuria, or anemia 6 to 12 months after HSCT. HSCT-related risk factors for nephropathy can include GVHD, infections with cytomegalovirus or BK virus, nephrotoxic medications such as cytotoxic chemotherapeutic agents (cytarabine, cyclophosphamide, ifosfamide, cisplatin, retinoic acid, carmustine, actinomycin D, melphalan), antibiotics (acyclovir, ganciclovir, foscarnet, vancomycin, amphotericin, aminoglycosides), and

immunosuppressants (cyclosporine, tacrolimus, methotrexate). The larger and more contemporary studies of chronic kidney disease after HSCT have not demonstrated an association with TBI.[205-209]

Total dose has been implicated as the most important factor in predicting renal morbidity from TBI; a retrospective study found that GVHD and high-dose TBI (13.5 Gy) were associated with elevated serum creatinine levels.[210] A prospective evaluation of renal function using radioisotopes found that early nephropathy was associated with age of younger than 40 years, use of kidney blocks (possibly related to nephrotoxic contrast media given during simulation), and nephrotoxic drug use, whereas late nephropathy was associated with nephrotoxic drug use but not TBI dose.[211] The benefit of kidney shielding has been assessed in two retrospective studies, both of which demonstrated significant improvement in long-term kidney function, with no evidence of dysfunction when the hyperfractionated dose was limited to 9.8 Gy to 10 Gy.[212,213] Two recent dose-effect modeling studies have demonstrated that nephropathy is unlikely after a biologically equivalent total dose of 16 Gy (calculated using a linear quadratic model, with corrections for dose rate and an α/β of 2.5 Gy) and that fractionating TBI and delivery of a low dose rate (<0.10 Gy/minute) prevent kidney dysfunction.[198,214] Monitoring blood chemistry and counts, as well as blood pressure and urine studies, is advised given the prevalence of kidney disease after HSCT.

Although no therapies have been proven to treat HSCT-related nephropathy, medication therapies (antihypertensives, corticosteroids), plasma exchange, hemodialysis, and renal transplant are possible options for management.[204] The angiotensin-converting enzyme inhibitor captopril prevents chronic nephropathy in patients with diabetes[215] and may reduce the risk of radiation nephropathy from TBI in preclinical studies.[216,217] A small RCT in which captopril was given to mitigate chronic renal failure in patients undergoing 12 Gy of fractionated TBI (with a kidney dose of 9.8 Gy) before HSCT revealed less nephropathy; however, the results were not statistically significant.[218]

Endocrine Toxicity

Hypothyroidism is the most common endocrinopathy after HSCT.[219] Most cases are overt and primary in nature, but subclinical and autoimmune thyroid dysfunction have also been noted. Hypothyroidism has been reported in up to 90% of patients after TBI delivered with a single dose of 10 Gy[220] and in up to 15% of patients treated with hyperfractionated TBI to 15 Gy.[221] These findings demonstrate the benefit of fractionation in avoiding this complication. One of the largest studies with a lengthy follow-up of children treated with or without TBI before HSCT revealed that TBI was not a risk factor for developing hypothyroidism when compared with equivalent conditioning with busulfan. In this study, the risk of hypothyroidism was higher in children undergoing HSCT before 10 years of age, and the risk continued to increase until 28 years after HSCT.[222] A recent study demonstrated that reduced-intensity conditioning with lower doses of radiation during TBI was not associated with lower rates of hypothyroidism,[223] suggesting that there is no dose threshold effect. Nevertheless, this complication should be monitored with assessment of thyroid hormones and can be easily managed with thyroid hormone replacement and monitoring.

Gonadal and reproductive endocrine functions can be altered by HSCT and TBI, as reviewed by Chemaitilly and Sklar.[219] In males, Leydig cell function is typically preserved, given the dose of radiation delivered during full-dose TBI.[224] However, in patients who have received prior testicular radiation or who will have a testicular boost during conditioning, Leydig cell function may be threatened. Germ cells are typically thought to be exquisitely sensitive to radiation. A recent study demonstrated that fertility is significantly reduced among boys treated with a radiation dose of more than 7.5 Gy to the gonads, although it should be kept in mind that other antineoplastics, such as alkylating agents, also profoundly reduce fertility.[225] Although there have been case reports of men being treated with TBI and later having children, most men are rendered sterile by HSCT with full-dose TBI; most will experience azoospermia with reduced-dose TBI, but some may also be rendered sterile. With this in mind, male patients should be counseled regarding gamete cryopreservation before initiation of therapy. Likewise, postpubertal women are likely to experience ovarian failure as a result of intensive conditioning, including TBI, and should be counseled about this before treatment. However, about half of prepubertal girls who are treated with fractionated TBI will experience normal reproductive development.[226] As reviewed by Schmidt et al,[227] several fertility-preserving options may be available to women who wish to bear children after HSCT. In a longitudinal prospective study, TBI was reported to be associated with worse sexual functioning among men (but not women) who underwent HSCT.[228]

Hypothalamic-pituitary function appears to be unaffected by TBI of adults to doses of 12 Gy.[229] However, if additional brain radiotherapy is delivered, this complication could be encountered. Growth dysfunction may be caused by TBI through a variety of mechanisms, including growth hormone deficiency and skeletal dysplasia; other factors, including GVHD, liver dysfunction, and busulfan-based conditioning, may also contribute. Younger patients are more likely to be affected by growth impairment. In addition, children treated with single-fraction TBI (as opposed to fractionated TBI) are more likely to experience growth impairment.[230] Growth hormone replacement therapy has been recommended to correct this deficiency,[231] although RCTs have not shown proven benefit[232] and treatment is associated with significant toxicities.

Bone Toxicity

Bone health is another concern after HSCT. Although TBI has been shown to be a risk factor for avascular necrosis of bone,[233] a prospective study found no association between bone metabolism and conditioning with TBI; corticosteroid use is probably the major factor in HSCT causing bone health problems.[234] Monitoring bone health with growth assessments, biochemical hormone assessments, and dual-energy x-ray absorptiometry (DEXA) scans is appropriate, and consideration of counseling, weight-bearing exercise, and use of calcium and vitamin D supplementation or antiresorptive agents (bisphosphonates) should be given in patients with evidence of abnormalities.

Nervous System Toxicity

Mild to moderate neurocognitive impairment has been noted in up to 60% of adults undergoing HSCT with TBI.[235] However, these findings have not been consistent, and several studies have documented no impairment at all.[236,237] As recently confirmed in a prospective multicenter study,[238] TBI-based conditioning (compared with non–TBI-based conditioning) has not been associated with neurocognitive impairment in adults who received full-dose[239] or reduced-intensity conditioning.[240] Children treated with TBI may experience mild neuropsychologic effects.[241] The effects are more prominent in young children,[242] especially those younger than 3 years of age.[243] Similar to adults, no difference in neurocognitive function has been

associated with TBI and non–TBI-based conditioning regimens in older children.[244] However, in young children, TBI-based regimens appear to exert more of a negative effect than non–TBI-based regimens.[245] The magnitude of the deficit has been described as statistically, but not clinically, significant (i.e., a deficit of 3 points in IQ) in recent investigations.[246]

Beyond generally mild cognitive effects of TBI on the nervous system, other types of toxicity are rare. Myelopathy is uncommon, but it has been reported to occur with TBI in conjunction with involved radiation therapy fields, even at cumulative doses considered to be "tolerable" (e.g., 45 Gy).[247] Similarly, severe and fatal neurologic toxicity was reported in a series of children treated with TBI and was generally associated with prior whole-brain radiotherapy to 18 Gy; therefore the cumulative radiation dose in this approach must be considered carefully.[248] Other neurologic toxicity has not been associated with TBI in adults[249] or children.[250]

Risk of Secondary Malignant Tumors

Beyond organ-specific toxicities, the risk of developing secondary malignant neoplasms is increased in patients who have undergone HSCT. Typically, three groups of secondary malignant neoplasms after HSCT are described, and they follow a distinct pattern of development[251] (Figure 18-5): myelodysplastic disease (MDS) and acute myelogenous leukemia (AML), posttransplant lymphoproliferative disorder (PTLD), and solid tumors.[252] There are multiple risk factors that may predispose a patient to the development of a secondary malignant tumor after HSCT, including, but not limited to, genetic aberrations, therapy given before HSCT, conditioning regimen, graft source and processing, posttransplantation immunosuppression, and GVHD[38]; only the association of TBI with secondary malignant neoplasms will be discussed here.

Secondary MDS or AML after HSCT has been reported to occur at rates between 1.1% at 20 months and 24.3% at 43 months. The World Health Organization classifies secondary MDS and AML as alkylating-agent or radiation-related disease, typically occurring 4 to 7 years after treatment, or topoisomerase-II inhibitor–related disease, typically occurring 6 months to 5 years after treatment.[253] Several studies have attempted to quantify the risk of developing secondary MDS or AML after undergoing TBI, with conflicting results. Studies from research groups from Minnesota,[254] Newcastle,[255] the City of Hope,[256] and France[257] have demonstrated no increase in rates of MDS or AML after myeloablative HSCT using TBI. Other studies from Nebraska,[258] the European Group for Bone Marrow Transplantation (EBMT),[259] Paris,[260] Barcelona,[261] and France[262] have found weak associations of borderline or no statistical significance. One study found an association of secondary MDS or AML with TBI on multivariate analysis when TBI was used with etoposide and cyclophosphamide.[263] A recent, detailed study of this subject found that among 4000 patients treated with autologous HSCT for lymphoma, 57 developed MDS or AML, with a cumulative incidence rate of 3.7%, 7 years after HSCT. A case-control analysis revealed a weak association of TBI and the subsequent development of MDS or AML that was not statistically significant. In a small subgroup analysis, a TBI dose of 13.2 Gy was associated with MDS or AML, but the authors cautioned that this group of patients may have shared other non–TBI-related factors that could have contributed to leukemogenesis. Older age also appeared to increase the risk.[264] The dose threshold effect was not supported by a more recent study that found no differences in the rate of MDS or AML after TBI, whether 12 Gy or 14 Gy of TBI was given.[265]

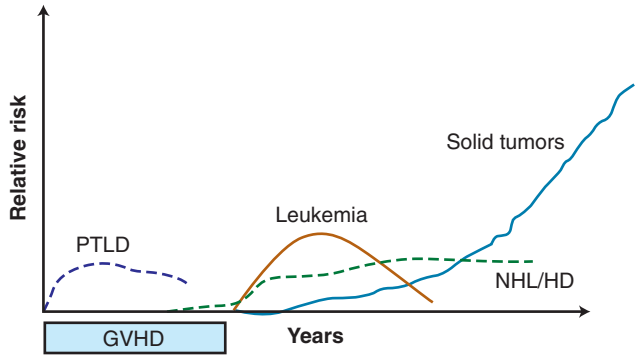

Figure 18-5 Relative risk and chronology of second malignant tumors after allogeneic hematopoietic stem cell transplant (HSCT). *GVHD*, Graft-versus-host disease; *HD*, Hodgkin disease; *NHL*, non-Hodgkin lymphoma.
Data from Ades L, Guardiola P, Socie G: Second malignancies after allogeneic hematopoietic stem cell transplantation. New insight and current problems. Blood Rev 16(2):135–146, 2002; Figure 1, © 2005, Elsevier, with permission from Elsevier.

The association of TBI with the subsequent development of a PTLD has been described in several studies. Because it is thought to result from immune system dysfunction, PTLD occurs primarily in patients following allogeneic, not autologous, HSCT. The cumulative incidence of PTLD at 12 years varied by the number of risk factors the patient had and ranged from 0.2% to 8.1%.[266] Small early studies from Seattle[252] and the Center for International Blood and Marrow Transplant Research (CIBMTR)[267] suggested an association between TBI use during HSCT and subsequent development of a PTLD. However, later research from Minnesota,[254] Vancouver,[268] and Nebraska[269] suggested no association between TBI and PTLD. A follow-up study from the CIBMTR, the largest and most comprehensive study available, involving 26,000 patients who underwent allogeneic HSCT over a 30-year period, clearly demonstrated no association between PTLD and TBI, in contrast to their previous findings.[266]

The risk of solid tumors after HSCT involving TBI has been studied extensively.[270-280] The largest and most recently updated analysis from the CIMBTR suggests that among patients who undergo allogeneic HSCT, the cumulative incidence of developing a solid malignant tumor (including carcinomas in situ that are not of the skin) is 1%, 2.2%, and 3.3% at 10, 15, and 20 years after transplant, respectively, based on the competing risk analysis method.[281] The number of secondary solid tumors was double what would have been expected in this population; significantly higher rates of oral cavity and pharyngeal, liver, central nervous system, thyroid, bone, and soft-tissue cancers and melanomas were observed. TBI was found to be a risk factor for developing a secondary solid tumor, with the risk increased in those who survived more than 5 years from the HSCT and in those younger than 30 years old at the time of HSCT. Although a previous study found that TBI doses of less than 10 Gy were associated with fewer secondary solid tumors,[270] this dose association was not maintained in the subsequent analysis.[281] There was no difference in the rate of secondary solid tumors in patients treated with fractionated or single-dose TBI. There was no increased risk of squamous cell carcinomas in patients treated with TBI and no increased risk of secondary solid tumors in patients treated with TBI after age 30. Chronic GVHD and male sex were associated with the development of secondary solid tumors and squamous cell carcinoma, respectively.[281]

Given the increased risk of secondary malignant neoplasms after TBI, careful surveillance of long-term survivors is a desirable (but not yet proven effective) strategy for minimizing secondary morbidity and mortality. Guidelines published by

the American Cancer Society,[282] the National Comprehensive Cancer Network (NCCN; www.nccn.org), and the Children's Oncology Group[160] provide important references regarding assessing patients at higher risk of developing a secondary solid tumor.

PHYSICAL PRINCIPLES OF TOTAL BODY IRRADIATION

Although irradiating the entire body may seem like a simple exercise, TBI is a highly specialized technique fraught with unique challenges. Nevertheless, the physical aspects of TBI have not changed significantly over the last three decades. The American Association of Physicists in Medicine (AAPM) Report 17, Task Group 29, "The Physical Aspects of Total and Half Body Photon Irradiation," is still considered the authoritative reference for methodology and recommendations regarding the physical aspects of TBI.[283] More recently, the American College of Radiology created a practice guideline for TBI treatment delivery.[284] The reader is referred to these resources and others[285] for detailed information on this subject.

As with all radiotherapeutic techniques, TBI requires meticulous attention to the details of patient measurement, set-up, dosimetry, and quality assurance. Among institutions that perform TBI, most have a dedicated and specially trained team of physicians, dosimetrists, physicists, and therapists who participate in successful implementation because the technique is quite different than typical external beam radiation therapy. Backup systems are essential given the critical time- and situation-dependent nature of HSCT. Readers intending to develop a TBI program are encouraged to contact and learn from centers that have experience with the technique.

Comparison of Techniques of Total Body Irradiation

A report from 1980 highlighted several approaches that have been explored in TBI.[286] The common factor in the different ways of delivering TBI is the goal, which is to deliver the prescribed dose of ionizing radiation to the entire body in a uniform manner (±10% of the prescription dose). An opposed-parallel anterior-posterior (AP/PA) horizontal field setup was developed at Memorial Sloan-Kettering Cancer Center (MSKCC) many years ago.[287] In this technique, the patient is positioned upright several meters from the source with the support of a custom-designed stand. In this technique, high-energy photons are used to increase dose homogeneity although high-energy photons will reduce the dose in superficial structures (skin and subcutaneous tissues), and therefore a beam spoiler is used to increase the surface dose. The beam spoilers are affixed to the stand, which can also accommodate blocks for shielding, imaging equipment for field and patient position verification, and placement of dosimeters (Figure 18-6). When using shielding, compensatory electron boosts can be delivered to superficial tissues such as those of the chest wall (Figure 18-7).

An alternative to the AP/PA field arrangement is a lateral field arrangement, pioneered by Khan.[288] In this approach, the patient is able to recline in a comfortable position during treatment, typically with the knees drawn toward the chest and the arms by the side. As with the AP/PA technique, the patient is typically positioned several meters from the radiation source and the arms can provide shielding to the lungs from the lateral beams. However, as the lateral body thickness is quite disparate over the head-to-toe length of a patient, compensators (usually fixed to the gantry head) will often be required to reduce the dose to the head, neck, and legs. Positioning with this technique is critical; therefore performing and confirming several measurements as well as determining symmetry using in-room light fields and lasers are essential.

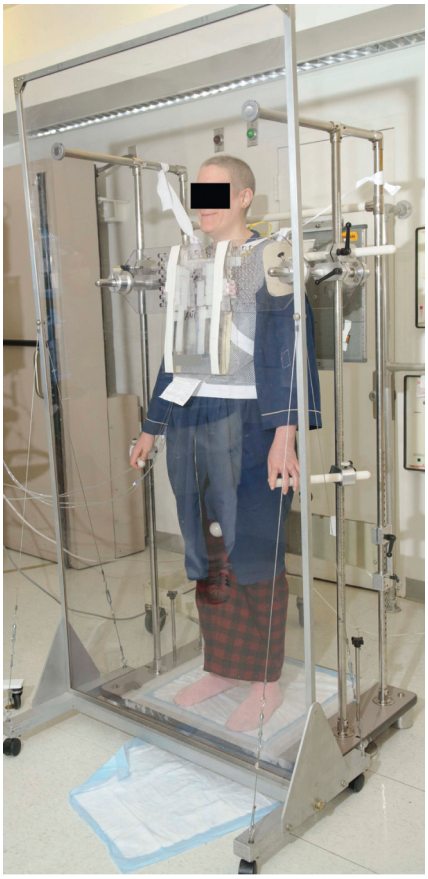

Figure 18-6 Patient in position for total body irradiation using anteroposterior beam arrangement, with lung blocks in place.

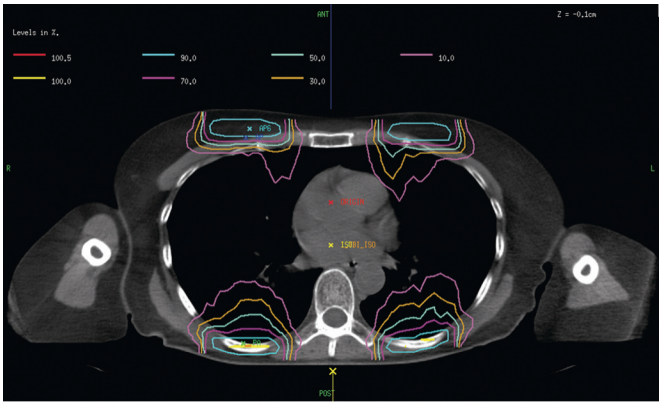

Figure 18-7 CT axial section demonstrating electron-boost dose distribution.

Although the AP/PA and lateral field arrangements are the most commonly employed TBI techniques, other methods exist. Children undergoing TBI may require conscious sedation during radiation therapy, making the previously described techniques impossible. In this situation, TBI can be delivered with the child lying on or near the floor with the gantry pointed down. The child's smaller body size often will facilitate this arrangement; however, in larger children it may be necessary to match two fields. An alternative would be

translating the patient or radiation source during treatment.[287] Logistic considerations largely prohibit this type of approach.

In recent years, several novel approaches to delivering radiation therapy to the entire body have been described. One of these approaches involves rotational intensity-modulated radiation therapy (delivered by a TomoTherapy unit). This approach appears dosimetrically advantageous because it could allow targeting and radiation dose escalation in the bone marrow, and for this reason, it is often referred to as total marrow irradiation (TMI).[289] Early phase clinical trials suggest the technique is tolerable.[290,291] However, sparing the circulating hematopoietic cells from radiation therapy might defeat the purpose of delivering radiation to the entire body. Another approach of delivering systemic radiation therapy is using radionuclides conjugated to monoclonal antibodies, commonly referred to as radioimmunotherapy, instead of external beam radiotherapy. The feasibility of this concept has been demonstrated by several groups, with encouraging results in allogeneic[292,293] and autologous HSCT.[286,287] The uncertainty in biodistribution and clearance of this form of radiotherapy is the major drawback.

Because there are no clinical data to suggest that one technique is advantageous over others, dosimetric benefits have largely dominated the choice of which TBI method to use. Because the AP/PA TBI technique is employed most frequently and is preferred under most conditions, the remaining discussion will focus on its application.

Simulation and Planning for AP/PA Total Body Irradiation

Patients undergoing TBI should be simulated in the treatment position, which is often most easily reproduced in the treatment room. For AP/PA TBI, height must be measured to ensure that the field will adequately encompass the entire patient; exceptionally tall patients might need to sit on the seat of the treatment stand. Other measurements of the AP thickness at the suprasternal notch, chest, abdomen, and pelvis are performed for dosimetric calculations.

While the patient is in the treatment position, radiographs of the thoracic cavity can be obtained to create lung shielding or other blocks. Careful attention should be paid to the size of the blocks so that they are produced in a manner proportional to the treatment field size and distance from the source; this often requires a magnification correction factor. For example, lung shielding is typically designed so that block edges are 1 cm to 2 cm from the bony thoracic periphery, diaphragm, and vertebral bodies. When shielding is used, some institutions choose to perform compensatory electron boosts matched to the blocks. In these situations, computed tomography (CT) can be helpful for planning purposes (Figure 18-7), although the obvious limitation is that CT cannot be performed when the patient is in the treatment position. Alternative imaging modalities (e.g., ultrasound) performed in the treatment position may be helpful in specific situations (e.g., chest wall boosts in patients with large, pendulous breasts).

Beam Energy, Angling, and Production

A wide variety of beam energies have been used for TBI. Most radiation oncology departments now use linear accelerators to generate ionizing radiation, although it should be noted that ^{60}Co generators, which typically produce lower-energy photons than linear accelerators, were the source for many of the early clinical studies. As noted previously, higher beam energies will achieve a more uniform dose distribution but may provide doses lower than desired to superficial structures, so beam spoilers may be needed. The thickness of the patient along the beam axis is the dominant factor dictating the choice of beam energy; typically, lateral field arrangements require higher beam energies than AP/PA field arrangements; however, this ultimately depends on patient size, beam spoilers, and source-axis distance. The source-axis distance can be up to 5 meters; it will often depend on the size of the treatment room relative to the size of the radiation field (dictated primarily by the size of the patient) and may restrict the application of some specific geometric approaches.

The central axis of the beam should be incident at the umbilicus; this usually requires around 5 degrees of gantry angling. The collimator is usually opened to its maximum size (40 × 40 cm) and is rotated to 45 degrees, maximizing the height of the field. The total dose can be prescribed to any anatomic point, but it is often prescribed in the midplane of the pelvis or at the umbilicus.

Compensation

As higher beam energies will reduce the dose delivered to the superficial structures, beam spoilers are often used. Typically an acrylic screen 1 cm to 2 cm thick is used to produce electrons that should increase the surface dose to at least 90% of the prescribed dose. If required, shielding is affixed to the plastic holder on the beam spoiler and placed using reference marks on the patient. For example, at MSKCC, a half-value layer block is employed for lung shielding. Electronic portal imaging can be used to confirm accurate placement of shields. Electron boost fields matched to the lung shields can also be set up using reference marks on the patient.

Calibration and Quality Assurance

Several groups recommend calibrating the treatment delivery unit for TBI using a dosimeter in a large water tank at the distance that will be used for treatment, in the treatment stand, if possible. Given the extended distance, large field size, and compensators used in this technique, a significant amount of scatter radiation will be produced and must be accounted for during calibration. For this reason, the typical percent depth dose (PDD) or tissue maximum ratio (TMR) measurements used for external beam radiation therapy should not be used for TBI; these measurements must be made specifically for the TBI setup. Moreover, variations in dose based on patient size and dose heterogeneity throughout the body should be anticipated and verified during the calibration process. In vivo dosimetry should be performed at several locations (i.e., along the central beam axis, under shielding blocks, and at distal extremities) to verify accurate dose delivery. Regular quality assurance checks should be undertaken according to AAPM guidelines.

ROLE OF TOTAL BODY IRRADIATION IN CONTEMPORARY HSCT

The role of TBI in HSCT has been refined over the last several decades. High-level evidence guides some of the rationale for using TBI, and in some situations, institutional and practitioner preference dictates the use of the technique. Major questions that have been answered deal with the necessity of using TBI during HSCT, as well as questions regarding dose, fractionation, shielding, and boosting.

Necessity of Using Total Body Irradiation in HSCT Conditioning

Although the earliest studies of HSCT for malignant hematopoietic diseases involved both chemotherapy and

radiotherapy (see History of Total Body Irradiation), in the 1970s several regimens using only chemotherapy (without TBI) were developed, largely for logistic reasons, because facilities adequate for performing TBI were not widely available.[294] Soon thereafter, the availability of conditioning regimens for HSCT *without* TBI (primarily involving busulfan and cyclophosphamide)[295] gave rise to several important clinical studies that investigated the necessity of TBI in HSCT in various hematopoietic diseases.

Acute Myelogenous Leukemia

There have been two RCTs comparing TBI-based conditioning regimens with non–TBI-based conditioning regimens for AML. In 1987, the Groupe d'Etude des Greffes de Moelle Osseuse (GEGMO) initiated a prospective multicenter RCT to evaluate whether TBI could be replaced by busulfan, in an effort to limit toxicity in allogeneic HSCT.[296] A similar single-institution study was initiated at the University of Minnesota, for patients receiving autologous HSCT, but accrual was poor and the study was terminated early.[297] As noted in eTable 18-2, superior rates of overall survival, disease-free survival, and fewer relapses were noted with the TBI conditioning regimen in both trials, with only the French trial demonstrating a statistically significant difference.[296,298] An updated analysis of three trials of allogeneic HSCT for AML that randomized patients to conditioning with or without TBI found marginally significant improvements in overall survival and disease-free survival rates. In patients treated with TBI, the estimated 10-year survival rate was 63%, and in those not treated with TBI, the rate was 51% ($p = 0.068$); patients treated with TBI had a 10-year disease-free survival rate of 57%, and untreated patients had a rate of 47% ($p = 0.051$). On multivariate analysis, TBI was associated with significantly less hair loss and no difference in the rates of GVHD, cataracts, avascular necrosis, or pulmonary complications.[299] A retrospective analysis by the CIBMTR revealed that TBI-based conditioning yielded fewer relapses (especially in extramedullary and central nervous system sites) and less hepatic VOD than busulfan-based conditioning.[300] This topic continues to generate controversy, with recent retrospective analyses of registry data demonstrating no difference in TBI and non-TBI, intravenous busulfan-based conditioning,[301] and other similarly designed observational studies suggesting improved outcomes with non–TBI based regimens.[302,303]

Chronic Myelogenous Leukemia

Two RCTs have compared the efficacy and toxicity of allogeneic HSCT in patients with CML, preceded by conditioning with either TBI with cyclophosphamide or busulfan with cyclophosphamide[305-307] (see eTable 18-2). Both studies showed no significant difference in rates of overall survival, event-free survival, or transplant-related mortality. The French study found more relapses in patients treated with TBI (especially fractionated TBI), but this was not seen in the study from Seattle, which used fractionated TBI exclusively. The Seattle trial did show significantly longer episodes of fever, more blood cultures revealing bacteria or fungi, more hospitalizations in the 100 days after transplantation, and a higher incidence of grades 2 to 4 GVHD in patients treated with TBI. An updated, combined analysis of three studies that randomized patients with CML to different conditioning regimens before allogeneic HSCT confirmed no significant difference in rates of survival (65% and 63%) and disease-free survival (52% and 42%) for patients treated with busulfan and cyclophosphamide or cyclophosphamide and TBI, respectively. There were no differences in the 5-year cumulative incidence of chronic GVHD (37% and 39%). However, cataracts were more common among patients treated with TBI.[299] Retrospective data also suggest that busulfan-cyclophosphamide–conditioning regimens before allogeneic HSCT for CML may be favored because of lower relapse rates,[308] although higher rates of GVHD, hepatotoxicity, and hemorrhagic cystitis have been reported with chemotherapy alone.[309]

Acute Lymphoid Leukemia

The Pediatric Blood and Marrow Transplant Consortium conducted the only RCT comparing the effect of preallogeneic HSCT conditioning using busulfan or TBI, in children with ALL. A central nervous system boost of 6 Gy was given to patients with a history of prior central nervous system disease but no prior central nervous system irradiation if randomized to TBI; if randomized to busulfan, patients with a history of central nervous system disease received 18 Gy of central nervous system radiation therapy before receiving busulfan. The study showed no difference in overall survival rates; however, longer event-free survival times were noted for patients treated with TBI. Patients 6 years old or younger, as well as those in their first complete remission, appeared to experience the most benefit from the TBI regimen.[310] A retrospective study by Davies[311] using the CIBMTR data of 627 children with ALL who underwent HSCT after conditioning with cyclophosphamide and TBI (CY/TBI) or busulfan and cyclophosphamide (Bu/CY) found that the risk of relapse was not significantly different in the two cohorts. However, the risk of treatment-related mortality was significantly greater in the Bu/CY group. The use of CY/TBI was associated with superior rates of overall survival and leukemia-free survival. Based on these data, the authors concluded that less treatment-related mortality in the CY/TBI group led to greater rates of overall survival and leukemia-free survival. A multivariate analysis of adults with ALL who underwent HSCT preceded by conditioning with fractionated TBI to 12 Gy (lung dose of 9 Gy) or busulfan found that shorter times of event-free survival and disease relapse were more likely among patients who did not receive TBI on multivariate analysis. There were no differences in the rates of transplant-related mortality, hepatic VOD, or GVHD.[312]

Multiple Myeloma

The Intergroup Francophone du Myelome conducted a trial (9502) that randomized 399 patients with newly diagnosed multiple myeloma to high-dose therapy in preparation for autologous HSCT, after three cycles of vincristine-Adriamycin-dexamethasone chemotherapy. High-dose therapy consisted of melphalan 200 mg/m^2 (HDM200) or melphalan 140 mg/m^2 and 8 Gy of TBI delivered in four daily fractions without lung shielding (HDM140). Overall survival rates were longer in the HDM200 group ($p = 0.05$); however, event-free survival rates were not different in the two groups. The authors speculated that the improved overall survival rate was attributed to the better salvage regimens available after initial therapy with HDM200 and suggested that the standard conditioning regimen for autologous HSCT for MM should be without TBI.[313]

Mixed Diseases

Two prospective trials of conditioning have been carried out in groups of patients with leukemias and lymphomas. Because these trials included a heterogeneous group of diseases, results should be interpreted with caution. Nevertheless, in 1988, the Nordic Bone Marrow Transplantation Group initiated a

eTABLE 18-2 Randomized Controlled Trials Comparing HSCT Conditioning Regimens with and without TBI

Disease	Author (Group)	No. Patients	Type of Transplant	TBI-Based Conditioning	Non-TBI–Based Conditioning	Total TBI Dose Number and Frequency of Fractions Dose Rate	Technique
ALL	Bunin (PBMTC)[298]	43	Allogeneic marrow, cord, or peripheral blood	TBI, etoposide 40 mg/kg in 1 day, then Cy 120 mg/kg in 2 days	Bu 16 mg/kg in 4 days, then Cy 120 mg/kg in 2 days	12 Gy 6 bid (dose rate not described)	Not described
ALL AML CML Lymphoma	Ringden (NBMTG)[107,171]	167	Allogeneic marrow	Cy 120 mg/kg in 2 days, then TBI	Bu 16 mg/kg in 4 days, then Cy 120 mg/kg in 2 days	10-12.7 Gy 1-7 given once or more daily 4 cGy/min-12.7 cGy/min	Varied; all had lung blocks limiting dose to 9 Gy-10 Gy
ALL AML CML	Blume (SWOG)[302]	122	Allogeneic marrow	TBI, then etoposide 60 mg/kg in 1 day	Bu 16 mg/kg in 4 days, then Cy 120 mg/kg in 2 days	13.2 Gy 11 tid (dose rate not described)	Not described
AML	Dusenbery (Minnesota)[291]	35	Autologous marrow	Cy 120 mg/kg in 2 days, then TBI	Bu 16 mg/kg in 4 days, then Cy 200 mg/kg	13.2 Gy 8 bid (4.5 hr apart) 10 cGy/min	6 MV-24 MV photons Bilateral parallel-opposed Head and neck, lung, lower extremity compensators
AML	Blaise (GEGMO)[290,292]	101	Allogeneic marrow	Cy 120 mg/kg in 2 days, then TBI	Bu 16 mg/kg in 4 days, then Cy 120 mg/kg in 2 days	10-13.5 Gy 1-6 given once or twice daily (6 bid†) 3 cGy/min-25 cGy/min (5 cGy/min†)	Varied; all had lung blocks (8.8 Gy^2)
CML	Clift (Seattle)[294,304]	142	Allogeneic marrow	Cy 120 mg/kg in 2 days, then TBI	Bu 16 mg/kg in 4 days, then Cy 120 mg/kg in 2 days	12 Gy 6 qd 6-7 cGy/min	Dual opposed ^{60}Co sources Geometry not described Blocks not described
CML	Devergie (SFGM)[295]	120	Allogeneic marrow	TBI, then Cy 120 mg/kg in 2 days	Bu 16 mg/kg in 4 days, then Cy 120 mg/kg in 2 days	10 Gy-12 Gy 1-24 given 1-8 times daily (bid†) 3-25 cGy/min (8 cGy/min†)	Varied; all had lung blocks (8.8 Gy^2)
MM	Moreau (IFM)[301]	282	Autologous peripheral blood	TBI, then Mel 140 in 1 day	Mel 200 in 1 day	8 Gy 4 qd (dose rate not described)	Not described No lung blocks

bid, *Twice daily;* Bu, *busulfan;* Cy, *cyclophosphamide;* EFS, *event-free survival;* HSCT, *hematopoietic stem cell transplant;* Mel, *melphalan;* mo, *month;* OS, *overall survival;* qd, *once daily;* RFS, *relapse-free survival;* TBI, *total body irradiation;* tid, *thrice daily;* TRM, *transplant-related mortality.*

All drug doses are given as mg/m^2 unless otherwise stated.

**Statistically significant difference.*

†*Observed incidence.*

‡*Median.*

Conditioning Regimen	OS	EFS	Relapse	Non-relapse Mortality	TRM	Other Findings
TBI Non-TBI	3 yr: 67% 3 yr: 47%	3 yr: 58% 3 yr: 29%*	43%[1] 36%[1]	24%[1] 9%[1]	— —	No significant difference in GVHD, or pulmonary, cardiac, or neurologic toxicity after HSCT The TBI group had significantly better EFS among patients who received unrelated donor stem cells, and who were under 6 years
TBI Non-TBI	7 yr: 63% 7 yr: 54%	7 yr: 62% 7 yr: 51%	7 yr: 29% 7 yr: 29%	— —	7 yr: 14%* 7 yr: 34%	No significant difference in immunosuppressant use, interstitial pneumonitis, or Karnofsky score, growth, renal, pulmonary or thyroid function at follow-up The TBI group had less hepatic VOD, hemorrhagic cystitis, chronic GVHD, death from GVHD, obstructive bronchiolitis, with more cataracts
TBI Non-TBI	3 yr: ~24% (7 mo[2]) 3 yr: ~28% (7 mo[2])	— —	— —	— —	— —	No significant difference in GVHD, hemorrhage, sepsis, lung complications, infections VOD, drug toxicity, relapse, disease-free survival
TBI Non-TBI	2 yr: 46% 2 yr: 35%	2 yr: 50% 2 yr: 24%	2 yr: 43% 2 yr: 70%	Reported as "not different" Reported as "not different"		No significant difference in time to engraftment, GVHD, time in the hospital, infection, hepatic VOD, hemorrhagic cystitis, pneumonitis
TBI Non-TBI	12 yr: 59%* 12 yr: 43%*	12 yr: 55% 12 yr: 35%	12 yr: 25% 12 yr: 37%	— —	12 yr: 16% 12 yr: 27%	No significant difference in time to engraftment, GVHD The TBI group had less chronic GVHD related mortality
TBI Non-TBI	9 yr: 65% 9 yr: 73%	9 yr: 48% 9 yr: 55%	9 yr: 22% 9 yr: 19%	9 yr: 25% 9 yr: 20%	— —	No significant difference in the rate of engraftment, GVHD, hepatic VOD, number of fevers, deaths from infection, mean duration of first hospitalization The TBI group did have significantly longer fevers, more blood culture revealing bacteria or fungi, more than 1 hospitalization in the 100 days after transplant, and higher incidence of grades 2-4 GVHD
TBI Non-TBI	5 yr: 66% 5 yr: 61%	5 yr: 51% 5 yr: 59%	5 yr STBI: 11%* 5 yr FTBI: 31% 5 yr: 4%*	Not reported Not reported	29%[1] 38%[1]	No significant difference in the rate of engraftment, GVHD, hepatic VOD, interstitial pneumonitis, hemorrhagic cystitis, GVHD
TBI Non-TBI	3.75 yr: 45.5%* 3.75 yr: 65.8%*	21 mo‡ 20.5 mo‡	— —	— —	3.6%[1] 0%[1]	No significant difference in growth factor use, cardiac, pulmonary, renal, liver toxicity, or response rates The TBI group had significantly higher rates of mucositis hospitalizations —

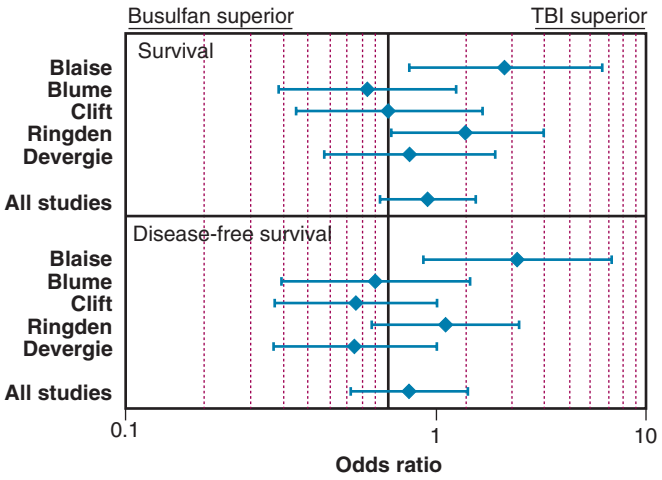

Figure 18-8 Odds ratio and 95% confidence intervals of survival and disease-free survival in a meta-analysis of TBI–based conditioning versus non-TBI–based conditioning in five randomized controlled trials (RCTs).
From Hartman AR, Williams S, Dillon JJ: Survival, disease-free survival and adverse effects of conditioning for allogeneic bone marrow transplantation with busulfan/cyclophosphamide vs total body irradiation. A meta-analysis. Bone Marrow Transplant 22(5):439–443, 1998; Figure 1, © 1998 Nature Publishing Group, with permission from Nature Publishing Group.

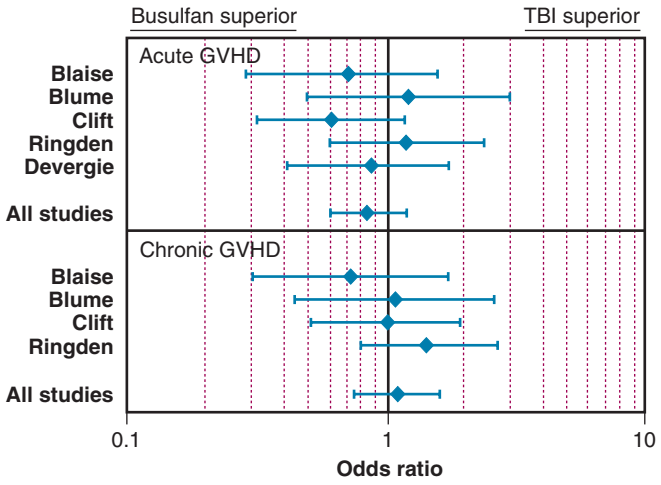

Figure 18-9 Odds ratio and 95% confidence intervals of acute and chronic graft-versus-host disease (GVHD) in a meta-analysis of TBI–based conditioning versus non-TBI–based conditioning in five and four randomized controlled trials (RCTs), respectively.
From Hartman AR, Williams S, Dillon JJ: Survival, disease-free survival and adverse effects of conditioning for allogeneic bone marrow transplantation with busulfan/cyclophosphamide vs total body irradiation. A meta-analysis. Bone Marrow Transplant 22(5):439–443, 1998; Figure 2, © 1998 Nature Publishing Group, with permission from Nature Publishing Group.

multicenter RCT of 167 patients (27 children and 140 adults); 68 patients had AML, 38 had ALL, 57 had CML, and 4 had lymphoma before allogeneic HSCT.[175] With 7 years of follow-up, the authors found a survival benefit in the TBI group among patients with "advanced" disease, with less toxicity compared with busulfan regimens; no differences were identified in the subset analysis of the different diseases that were treated.[109] The Southwest Oncology Group's RCT (SWOG 8612) also investigated the role of TBI before allogeneic HSCT for ALL ($n = 48$), AML ($n = 40$), and CML ($n = 34$) patients who were not in their first remission. This regimen substituted etoposide for cyclophosphamide in the TBI group only, making a meaningful comparison difficult. Although rates of overall survival and disease-free survival appeared to be superior for "good-risk" patients in the TBI group, the differences were not statistically significant.[314]

In the setting of allogeneic HSCT, a meta-analysis of the RCTs by Hartman and colleagues[176] summarized how TBI influences the outcome of conditioning regimens before allogeneic HSCT. As illustrated in Figure 18-8, overall survival and disease-free survival rates are slightly better with TBI-based regimens, although the results were not statistically significant. As shown in Figures 18-9 and 18-10, rates of GVHD were roughly equivalent, whereas hepatic VOD was clearly more common with busulfan-based regimens. The occurrence of interstitial pneumonitis also appeared similar in both groups. Another recent meta-analysis of 18 prospective and retrospective studies comparing TBI-based conditioning regimens with those not involving TBI (busulfan-based regimens) found that TBI improved disease-free survival rates in AML and ALL but not in CML. Growth and development problems, interstitial pneumonitis, and cataracts were more common with TBI-based regimens, but transplant-related mortality, VOD, and hemorrhagic cystitis were more common with busulfan-based regimens.[315]

There is much less data regarding the role of TBI before autologous HSCT. A non–TBI-based conditioning regimen is preferred for MM; however, no other trials have randomized

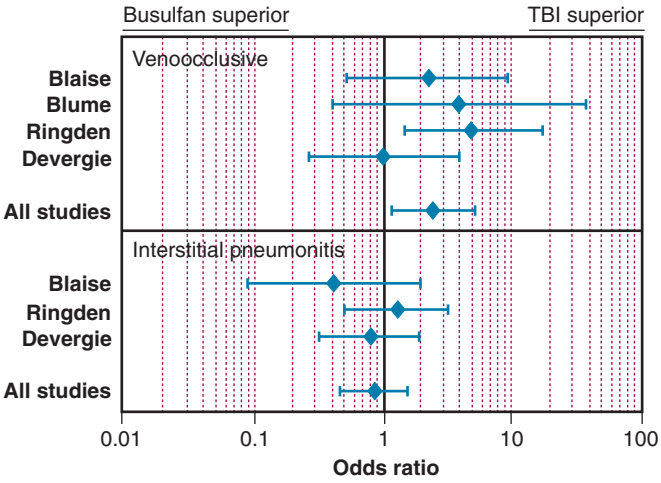

Figure 18-10 Odds ratio and 95% confidence intervals of hepatic venoocclusive disease and interstitial pneumonitis in a meta-analysis of TBI–based conditioning versus non-TBI–based conditioning in four and three randomized controlled trials (RCTs), respectively.
From Hartman AR, Williams S, Dillon JJ: Survival, disease-free survival and adverse effects of conditioning for allogeneic bone marrow transplantation with busulfan/cyclophosphamide vs total body irradiation. A meta-analysis. Bone Marrow Transplant 22(5):439–443, 1998; Figure 3, © 1998 Nature Publishing Group, with permission from Nature Publishing Group.

patients to a TBI or non-TBI conditioning regimen before autologous HSCT, and therefore, institutional preference primarily dictates choice of the technique in these situations.

Dose of Total Body Irradiation

The appropriate radiation dose to use during conditioning with TBI has been investigated by several groups. In 1985, researchers in Seattle conducted an RCT of two TBI regimens

as part of the HSCT for AML. Seventy-one patients were randomized to receive 12 Gy in six daily fractions (2 Gy/fraction/day) or 15.75 Gy in seven daily fractions (2.25 Gy/fraction/day). TBI was delivered using opposed ^{60}Co sources, at 0.06 Gy/min to 0.07 Gy/minute. The use of shielding was not described. Higher-dose TBI (15.75 Gy) was associated with higher rates of mortality in patients who did not relapse, although the authors note that this was limited to the first 6 months after transplant and to higher rates of grades 2 to 4 acute GVHD ($p = 0.02$). Patients receiving higher-dose TBI were less likely to receive adequate immunosuppression. Nonetheless, patients treated with lower-dose TBI (12 Gy) appeared to be more likely to relapse, although this finding was only marginally significant ($p < 0.06$).[134] A report of the long-term results (minimum follow-up of 7.5 years) of the trial revealed no difference in overall survival rates between the two TBI groups.[136]

In a similar trial, also from Seattle, 116 patients with CML were randomized to receive either 12 Gy or 15.75 Gy, as described previously. Higher-dose TBI (15.75 Gy) was associated with a superior relapse-free survival rate and with more grades 2 to 4 acute GVHD, although this was not statistically significant ($p = 0.15$). Initially, survival rates appeared to be superior in patients receiving lower-dose TBI (12 Gy). However, further follow-up revealed no significant difference in survival rates. Similar to the experience with AML, the authors concluded that higher-dose TBI was associated with greater relapse-free survival but at the cost of more acute GVHD, which likely led to transplant-related mortality that offset the survival benefit.[135]

Retrospective data suggest a benefit to higher-dose (>12 Gy) TBI in certain clinical scenarios. The highest doses of TBI reported in the literature are 20 Gy before autologous HSCT,[316] but at least one study has reported lower relapse rates and less transplant-related mortality in a subset of patients with ALL who received a TBI dose of more than 13 Gy.[317] Although modeling studies suggest that higher biologically effective doses are associated with lower relapse rates and longer overall survival times,[318] the finding of excess toxicity with higher doses in clinical dose-escalation studies does warrant caution.[319-322] For these reasons, fractionated TBI doses used before myeloablative HSCT typically range between 12 Gy and 15 Gy.

Reduced-intensity conditioning regimens have been used more often over the last decade for patients who might not be able to tolerate a myeloablative HSCT (because of advanced age or comorbidities) but could benefit from the graft-versus-tumor effects of allogeneic HSCT. A recent RCT suggested that reduced-intensity conditioning regimens (with TBI to 8 Gy in four fractions and fludarabine) offer fewer side effects than standard conditioning (with TBI to 12 Gy in six6 fractions and cyclophosphamide), but no difference in disease control or survival.[323] The role of TBI as part of reduced-intensity regimens is ill defined; however, a recent RCT compared reduced-intensity condition with busulfan or TBI (2 Gy in one fraction) and found inferior disease control, but lower nonrelapse mortality with TBI, and no difference in overall or progression-free survival.[324] Likewise, the optimal dose of TBI as part of reduced-intensity autologous HSCT has not been defined in an RCT. Several notable studies of allogeneic HSCT have employed TBI doses of 2 Gy to 8 Gy, often in conjunction with chemotherapy.[325-340] eTable 18-3, lists some representative allogeneic HSCT regimens using low-dose TBI.

Fractionation and the Total Body Irradiation Dose Rate

Laboratory-based radiobiologic data (see Radiobiology section) and clinical observations prompted trials investigating fractionation and dose-rate delivery in TBI. Thomas and et al were the first to conduct an RCT of single-dose or fractionated TBI in patients with AML. In this study, 53 patients with AML were randomized to receive TBI in a single 10 Gy dose or in a dose of 12 Gy in six daily fractions after receiving cyclophosphamide. TBI was delivered using opposed ^{60}Co sources, at a rate of 80 R/minute in air at midpoint (~0.06 Gy/minute). Disease-free survival times were significantly longer in the patients who were treated with fractionated TBI. There was no apparent difference in acute toxicity in the two treatment groups.[85] A follow-up report from the same institution described similar results using a slightly lower dose of single-fraction TBI (9.2 Gy using opposed ^{60}Co sources at 0.04 Gy/minute). Among the patients randomized, those who received fractionated TBI survived significantly longer than those receiving single-fraction TBI. Patients receiving single-fraction TBI experienced twice as many leukemic recurrences compared with those receiving fractionated TBI, although this was not statistically significant ($p = 0.09$). VOD of the liver was significantly more common in patients receiving single-fraction TBI ($p = 002$).[139]

Ozsahin et al[84] conducted a study investigating the effect of dose rate in patients undergoing single-dose or fractionated TBI as part of autologous or allogeneic HSCT for a variety of hematologic and lymphoid cancers. One-hundred fifty-seven patients receiving single-dose or multiple-fraction TBI were randomized to a low dose rate (0.06 Gy/minute or 0.03 Gy/minute, respectively) or a high dose rate (0.15 Gy/minute or 0.06 Gy/minute, respectively). Radiotherapy was delivered with ^{60}Co or 6-MV photons. Single-dose TBI was delivered to a total dose of 10 Gy with the lung dose limited to 8 Gy. Fractionated TBI was delivered to a total dose of 12 Gy in six fractions over 3 days, with the lung dose limited to 9 Gy. A variety of chemotherapies were used. The authors found no significant differences in rates of overall survival or relapse-free survival, pneumonitis, VOD, or GVHD. Cataracts were significantly more common among patients receiving single-fraction, high-dose-rate TBI. In a follow-up report, with a median follow-up time of 50 months, TBI in a single fraction or at a high dose rate was associated with the development of cataracts.[197]

Girinsky et al[140] conducted an RCT of 160 patients older than 15 years who were undergoing autologous or allogeneic HSCT for a variety of hematologic and lymphoid cancers. Patients were treated with a single fraction of TBI (STBI) with 10 Gy over 4 hours (average dose rate of 0.045 Gy/minute; instantaneous dose rate of 0.125 Gy/minute) or with hyperfractionated TBI (HTBI) with 14.85 Gy in 11 fractions over 5 days at a dose rate of 0.25 Gy/minute. A linear accelerator was used to deliver 18-MV photons with lung shielding; patients receiving STBI received a lung dose of 8 Gy, and patients undergoing HTBI received a lung dose of 9 Gy. After TBI, cyclophosphamide or melphalan was given, followed by HSCT. With a median follow-up of 8 years in 147 assessable patients, rates of overall survival and cause-specific survival were higher in the HTBI group; however, the differences were not statistically significant. A multivariate analysis that controlled for prognostic variables revealed greater cause-specific survival rates but not greater overall survival rates in patients treated with HTBI ($p = 0.04$). There was no significant difference in the rates of lethal pneumonitis, hepatic VOD, GVHD, graft failure, infection, or organ failure. However, the rate of hepatic VOD was significantly higher in the STBI group.

The necessity of hyperfractionation versus conventional daily fractionation has never been tested in a prospective trial. Investigators from the M. D. Anderson Cancer Center compared the outcome of patients in different prospective HSCT protocols and found that fewer patients in the conventionally fractionated group had recurrences of disease. These results

eTABLE 18-3 Representative TBI-Based Reduced-Intensity Conditioning Regimens for Allogeneic HSCT

Disease	Author (Group)	No. Patients	Total TBI Dose Number and Frequency of Fractions Dose Rate	Additional Conditioning Therapy	Technique	Type of Transplant
AML	Hegenbart (multicenter)[312]	122	2 Gy 1 0.07 to 0.20 Gy/min	84% received Flu 90 in 3 days, then TBI	Dual opposed ^{60}Co sources or linear accelerator Geometry not described Blocks not described	Allogeneic marrow (5%) and peripheral blood (95%)
AML	Stelljes (CGTSG)[313]	71	8 Gy 4 given bid 8.9-30 cGy/min	TBI, then Flu 120 in 4 days ±ATG	Not described	Allogeneic marrow (4%) and peripheral blood (96%)
AML	Hallemeier (Washington University)[199]	32	5.5 Gy 1 27.6-36.4 cGy/min	Cy 120 in 2 days, then TBI	6-MV photons from linear accelerator Parallel opposed lateral fields Arms at side for lung shielding	Allogeneic peripheral blood
CLL	Sorror (Seattle)[315]	64	2 Gy 1 7 cGy/min	83% received Flu 90 in 3 days, then TBI	Dual opposed ^{60}Co sources or linear accelerator Geometry not described Blocks not described	Allogeneic peripheral blood
CML	Kerbauy (Seattle)[316]	24	2 Gy 1 7 cGy/min	67% received Flu 90 in 3 days, then TBI	Dual opposed ^{60}Co sources or linear accelerator Geometry not described Blocks not described	Allogeneic peripheral blood
CML	Khoury (Washington University)[317]	30	5.5 Gy 1 26.4-36 cGy/min	Cy 120 in 2 days, then TBI	6 MV photons from linear accelerator Parallel opposed lateral fields Arms at side for lung shielding	Allogeneic peripheral blood
Hematologic malignancy	McSweeney (Seattle)[318]	45	2 Gy 1 7 cGy/min	None	Dual opposed ^{60}Co sources or linear accelerator Geometry not described Blocks not described	Allogeneic peripheral blood
Hematologic malignancy	Baron (Seattle)[319]	221	2 Gy 1 7 cGy/min	77% received Flu 90 in 3 days, then TBI	Not described	97% allogeneic peripheral blood
Lymphoma	Tomblyn (Minnesota)[320]	76	2 Gy 1 dose not reported	Flu + Cy, then TBI or Flu + Bu, then TBI or Bu + Clad, then TBI	Not described	Allogeneic marrow (10%), peripheral blood (46%), and cord blood (43%)
Mantle cell lymphoma	Maris (Seattle)[321]	33	2 Gy 1 7 cGy/min	Flu 90 in 3 days, then TBI	Linear accelerator Geometry not described Blocks not described	Allogeneic marrow (4%) and peripheral blood (96%)
MDS/AML	Schmid (Wiesbaden)[322]	75	4 Gy 1 dose rate not reported	TBI, then Cy 80-120 in 2 days, ATG	Not described	Allogeneic marrow (19%) and peripheral blood (81%)
MDS/MPD	Laport (multicenter)[323]	148	2 Gy 1 7 cGy/min	97% received Flu 90 in 3 days, then TBI	Linear accelerator Geometry not described Blocks not described	Allogeneic marrow (2%) and peripheral blood (98%)

Continued

eTABLE 18-3 Representative TBI-Based Reduced-Intensity Conditioning Regimens for Allogeneic HSCT—cont'd

Disease	Author (Group)	No. Patients	Total TBI Dose Number and Frequency of Fractions Dose Rate	Additional Conditioning Therapy	Technique	Type of Transplant
MPD/ secondary AML	Hallemeier (Washington University)[324]	51	5.5 Gy 1 25.3-37.2 cGy/min	Cy 120 in 2 days, then TBI	6-MV photons from linear accelerator Parallel opposed lateral fields Arms at side for lung shielding	Allogeneic peripheral blood
MM	Maloney (Seattle)[325]	54	2 Gy 1 7 cGy/min	17% received Flu 90 in 3 days, then TBI	Linear accelerator Geometry not described Blocks not described	Allogeneic peripheral blood
MM	Badros (Arkansas)[326]	31	2.5 Gy 2 given bid; dose rate not reported	TBI and Mel 100, then Flu 60 in 2 days	Not described	Allogeneic peripheral blood

AML, *Acute myelogenous leukemia;* ATG, *antithymocyte globulin;* Bu, *busulfan;* Clad, *cladribine;* CLL, *chronic lymphoid leukemia;* CML, *chronic myelogenous leukemia;* Cy, *cyclophosphamide;* Flu, *fludarabine;* MDS, *myelodysplastic syndrome;* Mel, *melphalan;* MM, *multiple myeloma;* MPD, *myeloproliferative disorder;* TBI, *total body irradiation.*

All drug doses are given in mg/kg unless otherwise stated.

should be interpreted with caution because this study was not randomized and other factors not related to TBI may have influenced the results.[142] Investigators in Seattle have conducted phase I/II studies of twice- and thrice-daily hyperfractionation protocols that did not suggest a significant benefit with hyperfractionation versus conventional fractionation when they were compared with historical results.[315,321]

Organ Shielding During Total Body Irradiation

The necessity of shielding to prevent normal tissue toxicity has been investigated in several studies; because pneumonopathy has been considered the dose-limiting toxicity of TBI, the studies have primarily been concerned with lung shielding. Labar et al[150] conducted a trial in 64 patients with AML, ALL, and CML who were undergoing TBI and cyclophosphamide conditioning. Patients were treated with 12 Gy of TBI in three fractions given once daily and were randomized to TBI with or without lung shielding after stratifying by age group (<20, 21 to 30, 31 to 40, >40 years), sex, underlying disease, GVHD prophylaxis, and donor-recipient sex combination. TBI was delivered using a ^{60}Co source, and blocks were used to limit the estimated lung dose to 9 Gy in the group of patients treated with lung shields. There was no difference in rates of leukemia-free survival or relapse. Although interstitial pneumonitis was more common in the group of patients treated without lung blocks (12%) compared with those treated with lung blocks (4%), this difference was not statistically significant.

Girinsky et al[152] conducted a similar study in a group of 85 patients with various lymphoid or hematopoietic cancers. Each patient received TBI with a dose of 10 Gy given in a single fraction over 4 hours (average dose rate of 0.04 Gy/minute; instantaneous dose rate of 0.125 Gy/minute). Patients were randomly assigned to receive a 6 Gy or 8 Gy lung dose. The authors observed no differences in rates of overall survival or lung complications. However, chronic GVHD and infections were significantly less common in the low lung dose group. Interestingly, there were significantly more leukemia relapses in the low lung dose group. The authors speculated that the additional lung shielding may have fostered survival of leukemic cells, which led to higher rates of relapse.

Retrospective data support the benefit of shielding. Weshler et al[151] reported a series of 44 consecutive patients who received 12 Gy of TBI; the first 23 patients were treated with opposed lateral fields and had no lung shielding in place, whereas the subsequent 21 patients had half-value layer transmission blocking after 6 Gy. Pneumonitis occurred in 26% of patients without lung shielding, whereas no pneumonitis was noted in those who had lung shielding. Investigators from Wisconsin have demonstrated sparing of renal and hepatic dysfunction with shielding.[180,212]

Boosting in Total Body Irradiation

There is scant high-level evidence for integrating a boost into the radiotherapy plan involving TBI. The EBMT conducted an RCT to assess the benefit of splenic boosting before allogeneic HSCT in patients with CML in their first complete remission. Two-hundred twenty-nine participants were enrolled and stratified based on age (25 years) and T-cell depletion. Patients were randomized to receive a 10-Gy boost to the spleen (given in one, two, or three fractions) within 14 days of HSCT. Overall, there was no difference in the groups. However, in subgroup analysis, it was determined that patients who did not undergo T-cell depletion and who had more than 3% circulating basophils before transplant demonstrated a statistically significant improvement in overall survival rates.[341] At MSKCC, the testes of males with leukemia undergoing myeloablative HSCT are boosted with 4 Gy in one fraction, based on the results of a retrospective series that revealed significantly lower rates of testicular relapse with this treatment strategy.[342] These findings have never been validated in a prospective study, but other institutions have incorporated the findings in their radiotherapy strategies, as discussed by Quaranta et al.[343] In other situations, investigators have reported success in delivering an involved field boost to the central nervous system (in leukemia)[344] or bulky nodal disease (in lymphoma),[345] although the efficacy of these approaches has never been validated in prospective trials.

Total Body Irradiation in Nonmalignant Diseases

Because radiotherapy is most commonly employed in the treatment of malignant diseases dealt with in other sections of this book, special attention will be paid to the role of TBI as part of HSCT for nonmalignant diseases. Although there are reports of using TBI as part of conditioning before HSCT for nonmalignant-acquired diseases such as severe aplastic anemia, paroxysmal nocturnal hemoglobinuria, systemic amyloidosis, and the acquired immunodeficiency syndrome caused by the human immunodeficiency virus, in general TBI is avoided in these situations.

Although no RCT data exist to support the use of TBI in the conditioning regimen of patients undergoing autologous HSCT for autoimmune conditions, several pilot studies have prompted the execution of phase III studies incorporating TBI. The basis for the role of TBI lies in preclinical studies of a rat model of autoimmune arthritis treated with pseudo-autologous HSCT. When the highest tolerable doses of TBI, cyclophosphamide, or busulfan were given, TBI was the most effective single conditioning agent.[346] Saccardi et al[347] summarized the results of phase I and II trials carried out by the EBMT using HSCT for multiple sclerosis (MS), which revealed stabilization or improvement of neurologic symptoms in 63% of patients, who generally had severe or progressive disease. Collectively, TBI was part of the conditioning regimen in 16 of the 178 patients. Statistical analysis revealed that busulfan, and not TBI, was associated with transplant-related mortality. Interestingly, Nash et al[348] studied 26 patients in a pilot study using high-dose myeloablative conditioning before autologous HSCT, including 8 Gy of TBI, and found that the 3-year progression-free survival rate was 73%, with a 91% overall survival rate, with minimal toxicity. Concerns about the use of TBI in HSCT for MS were brought up by Samijin et al[349] as well as Burt et al,[350] who speculated that radiotherapy may have contributed to axonal injury or caused dysfunction of neural precursor cells, although direct evidence of this was lacking. For these reasons, the ongoing RCT to compare autologous HSCT (ASCT) with mitoxantrone drug therapy for severe MS will not involve TBI (www.astims.org/). Similar concerns regarding the toxicity of radiotherapy in patients with inflammatory bowel disease have prompted investigators to omit TBI from ongoing RCTs of autologous HSCT in Crohn disease.[351]

As in studies of MS and Crohn disease, autologous HSCT has been explored recently for patients with systemic sclerosis (SSc, scleroderma) in several pilot studies. Binks et al[352] reported the results of a phase I/II trial of autologous HSCT for poor-prognosis systemic sclerosis, using a variety of conditioning regimens, some of which included TBI. In their initial report, two of nine patients who received 8 Gy of TBI died of interstitial pneumonitis 1 and 3 months after TBI. This prompted investigators to minimize the TBI dose during further investigations of HSCT in this disease.[353] After two of

the first eight patients in a study by Nash et al[354] died of pneumonitis, these investigators shielded the lungs with five half-value layers after patients received the first 2-Gy fraction. With shielding in place, no further TBI-related pulmonary mortality has occurred; however, two patients developed myelodysplastic syndrome and a former smoker was diagnosed with stage 1 lung cancer.[355] Autologous HSCT for systemic sclerosis is currently being studied in two RCTs; in the United States, the Scleroderma Cyclophosphamide or Transplantation (SCOT) trial, NCT00114530, will incorporate 8 Gy of TBI, whereas in the Autologous Stem Cell Transplantation International Scleroderma (ASTIS) trial in Europe (www.astistrial.com), TBI will not be used.

Several inherited diseases have been successfully treated with HSCT using TBI for conditioning; however, this approach is not desirable for children, who frequently need HSCT at a young age. HSCT for thalassemia has been carried out in several Italian centers and generally does not involve TBI. However, reduced-intensity regimens involving low doses of TBI have been used in a few small series of patients undergoing HSCT for thalassemia and sickle cell disease with favorable results.[356,357] Immunodeficiency syndromes are often treated with HSCT, but TBI is not commonly employed during conditioning, probably because these syndromes are commonly caused by impaired DNA damage repair by nonhomologous end-joining. Phagocytic disorders have been treated with HSCT using myeloablative doses of TBI.[358] HSCT is considered the only curative therapy for osteopetrosis, and the first successful case involved TBI.[359] Likewise, hundreds of patients have been successfully treated for lysosomal or peroxisomal storage diseases (i.e., mucopolysaccharidoses, mucolipidoses, leukodystrophies, glycoprotein and other disorders) with HSCT, often using TBI, although this approach is undesirable in younger children.[360-362] Recent studies have focused on non–TBI-based approaches in these diseases.[363] Fanconi anemia is a disease commonly treated with allogeneic HSCT. In favorable patients with an HLA-matched sibling donor, TBI can usually be avoided. However, in patients with evidence of MDS or AML, use of TBI should be considered. TBI is typically delivered in a single fraction, given the underlying defects in DNA repair and cell-cycle checkpoint regulation in patients with Fanconi anemia. Prospective dose-escalation studies have found no benefit of doses beyond 4.5 Gy.[364]

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