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Total body irradiation in allogeneic bone marrow transplantation conditioning regimens: A review

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ABSTRACT

Hematologic malignancies may require, at one point during their treatment, allogeneic bone marrow transplantation. Total body irradiation combined with chemotherapy or radiomimetic used in allogeneic bone marrow transplantation is known to be very toxic. Total body irradiation (TBI) induces immunosuppression to prevent the rejection of donor marrow. TBI is also used to eradicate malignant cells and is in sanctuary organs that are not reached by chemotherapy drugs. TBI has evolved since its introduction in the late fifties, but acute and late toxicities remain. Helical tomotherapy, which is widely used for some solid tumors, is a path for the improvement of outcomes and toxicities in TBI because of its sparing capacities. In this article, we first review the practical aspects of TBI with patient positioning, radiobiological considerations and total dose and fractionation prescriptions. Second, we review the use of intensity modulated radiation therapy in bone marrow transplantation with a focus on helical tomotherapy TBI, helical tomotherapy total marrow irradiation (TMI) and total marrow and lymphoid irradiation (TMLI) and their dosimetric and clinical outcomes. Finally, we review the perspective of dose escalation and the extension to older patients and patients with comorbidity who do not benefit from a standard bone marrow transplantation conditioning regimen.

1. Introduction

Radiotherapy in bone marrow transplantation conditioning regimens was introduced in the late fifties by Nobel Prize Laureate E.D. Thomas (Ferrebee and Thomas, 1958). Since that time, total body irradiation (TBI) has been widely used in bone marrow transplantation. TBI induces immunosuppression to prevent the rejection of donor marrow. TBI aims to eradicate malignant cells in the same area that chemotherapy does (Bortin et al., 1992; Vriesendorp et al., 1991) and in sanctuary organs that are not reached by chemotherapy drugs, which are mainly the brain and testes.

TBI is an important part of conditioning regimens for bone marrow transplantation for hematological malignancies. Regimens containing TBI seem to achieve better outcomes than regimens not containing TBI (Hartman et al., 1998; Blaise et al., 2001; Dusenbery et al., 1995; Michel et al., 1994; Bunin et al., 2003; Clift et al., 1998; Ringden et al., 1994).

Even though TBI is an efficient part of bone marrow transplantation conditioning treatment, it is responsible for many side effects. The acute toxicities include nausea, vomiting, diarrhea, stomatitis, temporary loss of taste, parotitis and rash. The late toxicities include interstitial pneumonitis (IP), hepatic veno-occlusive disease (VOD), cataracts, infertility, hormone-related disorders, bone toxicity (osteoporosis), growth retardation and secondary malignancies (Bolling et al., 2011; Van Dyk et al., 1981; Blaise et al., 1992; Leiper, 1995; Shank, 1996; Ringden et al., 1999; Socie et al., 2001; Della Volpe et al., 2002; Schenken and Hagemann, 1975; Thomas et al., 1993; Curtis et al., 1997; Hasegawa et al., 2005).

In this article, we review the literature about TBI techniques in bone marrow transplantation, from two-dimensional to intensity modulated radiotherapy (IMRT) techniques.

2. Total body irradiation

^{60}C and linear accelerator based techniques were the first techniques of TBI that were described, and they are still widely used (Giebel et al., 2014).

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2.1. Patient positioning (Roberts et al., 2013) (Fig. 1)

Few dedicated systems exist, but, today, TBI is mostly performed with standard linear accelerators. The primary limitation of standard linear accelerators is the maximum field size of 40 × 40 cm at a standard source-surface distance (SSD). However, positioning patients at a superior SSD, generally 200–600 cm, allowed for an enlarging of the field size. If the size of the treatment room allows it, patients are treated by a single field. Otherwise, multiple fields are required. Two main techniques are used. 1) Antero-posterior directed fields are the simple technique. The patient is treated in alternative dorsal and ventral decubitus, and gantry remains at the 0° position. Patients are treated lying down in a couch or on the floor. This position is convenient for children or for those patients with a height that allows for it. It is also the position of choice for children who need anesthesia. 2) If this position is not usable or not optimal, lateral decubitus is an alternative set up, in which the gantry is turned at 90° with a collimator rotation of 45°. 3) The third position and the less used is that of a seated position, and irradiation is performed with parallel lateral fields. Shields are positioned relative to tattoos on the patient skin, and the shielding position is then verified by means of MV imaging on a photostimulable phosphor cassette. A hard copy of the radiography is printed and evaluated by the physician. This time consuming and poorly accurate procedure is being improved by direct imaging systems such as the Theraview TBI imager, which allows for real time shielding positioning, in which shielding positioning could be controlled faster before irradiation and during irradiation.

2.2. Radiobiological considerations

One of the aims of TBI is to eradicate the bone marrow in the recipient to allow for the donor bone marrow to engraft in the recipient. D_0 values (dose required to reduce survival cells to 37%) of bone marrow cells range from 0.3 to 1.6 Gy, demonstrating a high radiosensitivity (Hendry, 1985; Uckun and Song, 1989). The antileukemic effect of TBI has been explored by experiments on leukemia cells, which reported a wide range of heterogeneity of radiosensitivity. As reviewed by Cosset et al. (1994), leukemia cell D_0 values are in the range of 0.8–1.5 Gy, which make them as radiosensitive as bone marrow cells. However, some studies report extreme D_0 values, ranging from 0.3 Gy to 4 Gy. The most commonly accepted conclusion of those studies is that there are differences in hypersensitivity between the different leukemia lines. However, the authors stated that it could be a bias caused by differences in cloning techniques that were used in these experiments. Unexpectedly, leukemic cells certainly have a capacity for repairing sublethal lesions, and several studies demonstrated an increase in the survival of leukemic cells with fractionated irradiation schedules (Cosset et al., 1994). Animal studies reported a better immunosuppressive effect in an equivalent dose single-fraction regimen compared to that of fractionated schedules (Storb et al., 1989; Storb et al., 1994; Salomon et al., 1990).

2.3. Total dose, fractionation and dose rate

As in many treatment plans, the total dose and fractionation have to be balanced between the relapse rate, side effects and complications. Ten grays in a single fraction TBI (STBI) has been the first widely used regimen (Thomas et al., 1975a, 1975b). To improve the outcomes of the TBI regimen, reducing relapse rates, graft versus host disease (GHVD) and toxicities, especially lung pneumonitis, were required. Since the early eighties, several studies comparing fractionated and hyperfractionated TBI regimens have been published. Thomas et al., in a prospective randomized trial, compared $STBI_{10Gy}$ with fractionated TB (FTBI) 12 Gy in six consecutive daily fractions of 2 Gy and demonstrated superiority of the FTBI schedule in terms of overall survival (OS). The two-year OS rate was 65% for the $FTBI_{12Gy}$ schedule, compared to 45% for the $STBI_{10Gy}$ schedule (p = .05). No acute toxicity difference was observed between the two treatments (Thomas et al., 1982). Shank et al. experimented, in a prospective non-randomized trial, $FTBI_{13.2Gy}$ in 11 fractions of 1.2 Gy three times a day during four consecutive days compared to $STBI_{10Gy}$. Even if it was not the primary endpoint of this study, the authors observed a lower incidence of IP with the hyperfractionated schedule, 24% vs. 70%. In acute non-lymphocytic leukemia (ANLL) patients, the authors found a significant difference in favor of the FTBI compared to the STBI schedule for one-year relapse-free survival (RFS) and OS rates at 53% vs. 17% (p < .001) and 61% vs. 17% in (p < .01), respectively (Shank et al., 1983). In another study using a large retrospective analysis in 21 French institutions, Socie et al. compared a $STBI_{10Gy}$ vs. several fractionated schemes of $FTBI_{12Gy}$, mainly 2 Gy twice daily (BID) for 3 days or 4 Gy once daily for 3 days (Socie et al., 1991). The study did not demonstrate a significant difference in OS, but the fractionation significantly reduced the incidence of chronic GVHD (41.3% vs. 22.2%; p = .01) and IP (37.5% vs. 1.7%; p = .02).

The Seattle team published a randomized trial evaluating another $FTBI_{15.75Gy}$ with 7 consecutive daily fractions of 2.25 Gy, which demonstrated to have a better RFS rate than the $FTBI_{12Gy}$ with 6 consecutive daily fractions of 2 Gy. The probability of relapse at 4 years was 0.25 for the 12 Gy arm vs. 0 for the 15.75 Gy arm (p = .008). There was not a significant difference in OS rates because of an increase of non-relapse mortality induced by acute GVHD complications, hepatic VOD or infection (Clift et al., 1998; Thomas, 1990; Clift et al., 1991). Others study reported a decrease of relapse with a higher TBI dose threshold, which ranged from 9.9 Gy to 13 Gy (Scarpati et al., 1989; Marks et al., 2006).

Several studies investigated the use of a reduced intensity conditioning regimen (RIC) in bone marrow transplantation for patients who were not eligible for a myeloablative conditioning regimen (MAC) due to age or comorbidities. Aoudjhane et al., in a retrospective registry based study including patients older than 50 years, compared MAC in combination with TBI with doses > 10 Gy or busulfan with doses > 8 mg/kg and others drugs and RIC combining fludarabine and TBI doses < 2 Gy or busulfan doses < 8 mg/kg. No significant difference in the 2-year RFS and OS rates were observed (Aoudjhane et al., 2005). Bornhäuser et al., in a prospective phase 3 trial with AML patients, compared an RIC consisting of $FTBI_{8Gy}$ (BID fraction of 2 Gy) and fludarabine with a $FTBI_{12Gy}$ (6 BID fractions of 2 Gy) and cyclophosphamide. No significant differences were observed in the OS, RFS and disease-free survival (DFS) rates (Bornhauser et al., 2012). In patients younger than 35 years, Sébert et al. compared MAC and RIC regimens in a retrospective study and did not demonstrate any significant differences in the OS and RFS rates between the two regimens (Sebert et al., 2015).

Ozsahin et al. evaluated the influence of low dose rate (6cGy/min) versus high dose rate (200cGy/min) in TBI. They did not find significant difference in OS, 4 years RFS, GVHD, 4 years IP and VOD incidence rate. However, 4 years cataract incidence was higher in patient treated with high dose rate STBI or FTBI (Ozsahin et al., 1992).

2.4. Indications of TBI

Acute lymphoid leukemia (ALL) remains as the main indication of a TBI based conditioning regimen in bone marrow transplantation. Several studies compared TBI containing regimens with non-TBI containing regimens in bone marrow transplantation. A prospective randomized study compared busulfan–cyclophosphamide (BuCY) and TBI–cyclophosphamide (CyTBI) in children. The results demonstrated a better event-free survival (EFS) rate from the TBI-CY regimen compared with the BuCY regimen, with a 3-year EFS of 58% vs. 29%, respectively (p = .03). Additionally, the OS rates were not significantly different between the two regimens (Bunin et al., 2003). Davies et al., in a retrospective study, demonstrated a better DFS from the CY-TBI regimen