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Complications of total-body irradiation in allogeneic bone marrow transplantation: A review article

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Abstract

Hematopoietic stem cell transplantation commonly known as bone marrow transplantation (BMT) or allogeneic BMT is the preferred therapeutic option for numerous blood-related conditions, both malignant and non-malignant. It is often the sole therapy strategy and essential for relapsed and refractory hematologic malignancies. There have studies regarding BMT on regimen containing total body irradiation (TBI) and a regimen without TBI. It is expected that TBI-based conditioning regimens provide better antitumor effects than chemotherapy regimens. The primary objective of TBI is to eradicate the recipient's bone marrow, facilitating the successful engraftment of donor bone marrow. Acute lymphoid leukemia (ALL) is the principal indication for TBI in bone marrow transplantation. Other diseases including Hodgkin's lymphoma, chronic myeloid leukemia (CML), acute myeloid leukemia (AML), and etc may benefit from TBI-based regimens; however, TBI use is associated with many side effects.The main complications of patients who underwent TBI-containing conditioning regimens in bone marrow transplantation are vomiting and nausea, with frequencies of approximately 66% and 35%, respectively. However, these events are easily managed. Acute complications include stomatitis, diarrhea, temporary loss of taste and appetite, and rash. Moreover, veno-occlusive disease, lung side effects, growth hormone deficiency, neurological side effects, cataracts, renal toxicity, endocrine impairments, and infertility are other complications in patients who underwent TBI-containing conditioning regimens in bone marrow transplantation. In review article, complications of TBI in allogeneic bone marrow transplantation were assessed.

Keywords: Allogeneic bone marrow transplantation, Complication, Total-body irradiation

Introduction

Hematopoietic cell transplantation is frequently the primary therapeutic approach for hematologic malignancies that are refractory or have relapsed (1). Research has been conducted on allogeneic bone marrow transplantation (BMT) with regimens incorporating total body irradiation (TBI) and those without TBI. The aim of treatment is increased survival through a combination of chemotherapy, TBI, and allogeneic immune responses (2).

Radiotherapy in bone marrow transplantation was introduced by E.D. Thomas. Since that time, TBI has been used in bone marrow transplantation. This constitutes a main part of conditioning protocols for bone marrow transplantation in hematologic malignancies. Immunosuppression is induced by TBI to prevent the rejection of donor marrow.

Although TBI is an effective part of bone marrow transplantation conditioning therapy, it is responsible for various complications.

It eradicates malignant cells in the same areas as chemotherapy and sanctuary organs that do not receive chemotherapy drugs. It appears that regimens containing TBI have better outcomes compared to regimens not containing TBI (3).

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It is appears that regimens containing TBI have better outcomes compared to regimens not containing TBI (3). However, TBI application is associated with side effects (3, 4).

Allogeneic Bone marrow transplantation (BMT)

Allogeneic bone marrow transplantation has emerged as the preferred treatment for numerous blood-related conditions, encompassing both malignant and non-malignant diseases. Frequently serving as the exclusive therapeutic approach, it plays a crucial role in addressing relapsed and refractory hematologic malignancies.

It is well-established curative therapy for acute lymphoblastic leukemia (ALL) and myeloid leukemia (AML) (5). In addition, allo-BMT remains the only therapy for chronic lymphocytic leukemia (CLL) with therapeutic potential (6). Stem cell transplantation (SCT) for the treatment of chronic myelogenous leukemia (CML) was initiated by Bookner et al., and subsequently by Goldman et al (7).

Adverse effects of BMT include hepatic sinusoidal obstruction syndrome, immune reaction called graft-versus-host disease (GVHD); and fungal, viral and bacterial infections. Risk factors for therapy-related mortality involve HLA mismatch, myeloablative conditioning regimen, age, and comorbidities (8-11).

Peripheral blood stem cell transplantation (PBSCT) has seen growing use as an alternative to bone marrow transplantation, yet evidence supporting PBSCT has equivalent outcomes to BMT is lacking (1).

Research findings underscore that bone marrow remains the preferred donor source for pediatric hematologic malignancies. However, the landscape is evolving, with an increased prevalence of PBSCT, constituting up to 70% and 30% in adult and pediatric hematopoietic cell transplantations, respectively (1, 12).

The disadvantage of PBSCT is higher treatment-related mortality and more frequent chronic GVHD (13-15). A systematic review compared PBSCT and BMT in adults with hematologic malignancies and demonstrated that the incidence of overall survival (OS) and relapse were similar between BMT and PBSCT (16).

Total Body Irradiation (TBI)

TBI constitutes a pivotal element in the comprehensive management of extensively spread malignancies, primarily those related to hematopoietic diseases. According to findings, it is expected that TBI based conditioning regimens provide better antitumor effect than chemotherapy regimens (17).

The primary objective of TBI is to eliminate the recipient's bone marrow, allowing for the successful engraftment of donor bone marrow.

ALL is the primary indication for TBI in bone marrow transplantation. Other diseases, including Hodgkin’s disease, CML, AML, and MM, may potentially benefit from a TBI-based regimen; however, the indications remain controversial (3).

D0 values (the dose needed to decrease survival cells to 37%) of bone marrow cells range from 0.3 to 1.6 Gy, indicating a high radio-sensitivity (3). The anti-leukemic effect of TBI was assessed by evaluating leukemia cells, revealing a wide range of heterogeneity in radio-sensitivity. D0 values of leukemia cells fall within the range of 0.8–1.5 Gy, making them as radiosensitive as bone marrow cells. Other studies have reported extreme D0 values ranging from 0.3 Gy to 4 Gy.

Based on the results, variations in hypersensitivity appear to exist among different leukemia cell lines. Nevertheless, it is important to consider that these discrepancies could be influenced by biases arising from variations in the cloning procedures employed during the experiment

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Side-effects and complications of TBI

The main complications experienced by patients undergoing TBI as part of the conditioning regimen for bone marrow transplantation were vomiting and nausea, with frequencies of 66% and 35%, respectively. However, these events were easily managed using oral ondansetron and granisetron. Acute complications also include stomatitis, diarrhea, temporary loss of taste and appetite, rash, and asthenia (3). In this article, we briefly review the most important complications of TBI.

TBI and Hepatic sinusoidal obstruction syndrome (Veno-occlusive disease)

Veno-occlusive disease (VOD) is a life-threatening complication of TBI, but its diagnosis can only be confirmed through biopsy. According to a meta-analysis study, the mean incidence of VOD in stem cell transplantation was found to be 13.7% (18). A higher incidence of VOD was associated with male gender and conditioning chemotherapy that solely included cyclophosphamide. Kumar et al. also reported a higher incidence of VOD among transplant recipients who received TBI (19). Additionally, various fractionated schedules of TBI were associated with a lower risk of VOD. Furthermore, extending the interval between cytotoxic therapy and TBI may decrease the risk of VOD (19).

TBI and lung side effects

Kelsey et al. reported that severe pulmonary complications were prevalent after TBI-based myeloablative conditioning regimens and occurred in approximately 33% of patients (20). Singh et al. reported that reducing the lung dose during TBI remarkably improved survival (21).

Torr et al. reported that patients undergoing TBI suffered from acute respiratory distress syndrome and lung complications, which were associated with poor clinical outcomes (22). Thomas et al., assessed long term complication of TBI and observed pulmonary late complications 3 to 6 months after external radiotherapy (18 to 20 Gy). Furthermore, this complication was more common in prone and supine positions vs. lateral position (23).

TBI and growth hormone deficiency

Growth impairment and growth hormone deficiency are other side effects of TBI (24, 25). Darzy et al. reported that radiation and TBI can induce growth hormone deficiency (25). The principal site of radiation damage is the hypothalamus, although the latter may be affected directly. Sanders and colleagues showed that growth hormone treatment substantially contributes to the stature of children by the age of 10 years (24).

TBI and neurologic side effects

Neurological side effects, including peripheral neuropathy, encephalopathy, were observed in 11% to 59% of patients who underwent hematopoietic stem cell transplantation. Encephalopathy was predominantly associated with sepsis and the use of sedative drugs (26).

Peper and co-authors investigated the neurobehavioral effects of TBI in individuals who received 50 mg/kg of cyclophosphamide, hyperfractionated TBI (14.4 Gy, 12 × 1.2 Gy over 4 days), and autologous bone marrow transplantation. They found no indications of neurological deficits in the patients post-TBI, with only one exception. As a result, they concluded that the occurrence of long-term neurobehavioral toxicity was minimal (27).

TBI and Cataract: Cataracts are a frequent late complication of regimens involving TBI. The estimated 10-year overall incidence of cataracts was reported to be 50%. Factors such as age greater than 23 years, steroid administration, higher dose rate, and allogeneic BMT are associated with a higher cataract rate, whereas fractionated TBI leads to a lower

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rate of cataract formation (3). Ozsahin et al. also reported that the TBI regimen, whether fractionated or instantaneous dose rate, may influence the development of cataracts following BMT (28). Liper et al. noted that the incidence of cataract development was 80% for a single fraction and 18% for fractionated total body irradiation (TBI), suggesting a significant protective effect associated with fractionated irradiation (29).

Pearlman et al., conducted a study about adverse effects of TBI and revealed that cataract was common with short onset time (30).

TBI and renal toxicity

Different studies have reported renal toxicity associated with TBI, with an incidence ranging from 3% to 43%, particularly observed at total doses of fractionated TBI ranging from 12 Gy to 14 Gy (3). Miralbell et al. reported a significant relationship between renal dysfunction and TBI dose (4). Borg et al., also reported that a dose of 12 Gy at 2 Gy/fraction led to nephritis in 1 patient among 59 patients, 2 years after the completion of TBI and BMT (31).

Safwat et al. emphasized the importance of evaluating patients treated with bone marrow transplantation (BMT) and TBI for potential long-term kidney damage. Additionally, the authors suggested that fractionation, especially hyperfractionation, could serve as a protective measure against TBI-induced renal damage (32). Lawton et al., also revealed a significant reduction in the incidence of renal nephropathy after lowering the TBI dose (33).

TBI and bone impairment

Bone impairment is another side effect of TBI-containing regimens, including osteoporosis (34, 35). Another study revealed that TBI causes polyostotic /generalized bone changes (36).

Another study revealed that adverse effects of TBI are musculoskeletal complications, including short stature, and slipped capital femoral epiphysis (37).

TBI and endocrinal impairments

After bone marrow transplantation, endocrine impairments, including thyroid dysfunction, are frequently reported. Hypothyroidism is associated with the use of TBIT (38). Thomas et al. assessed endocrine function in children who underwent TBI. Some patients received single-fraction TBI (9-10 Gy), while others received fractionated TBI over 3 or 4 days. They observed that the basal gonadotropin concentration was increased in 50% of patients in the single-fraction group and 30% of patients in the fractionated group. Pathological changes in thyroid function were seen in 73% of patients in the single-fraction group and 25% of patients in the fractionated group (39). Lettley et al., assessed the complications of TBI and observed thyroid dysfunction in 39% of patients, but there was no evidence of hypothalamic pituitary axis damage, directly (40).

TBI and infertility

Based on studies which were conducted about the effects of radiotherapy or TBI, the prepubertal uterus was more vulnerable to radiation than after puberty (41).

According to Claessens and colleagues, sexual relationship deterioration was observed in 59% of patients, with 47% of men reporting erectile dysfunction and 53% of women experiencing vaginal dryness (42). Bath et al., assessed the complications of TBI in women and revealed that ovarian failure after TBI is common (43). Another study showed that TBI with ovarian shielding decreased the dose of radiation to 2.4 Gy, and preserved fertility without enhancing the risk of relapse (44).

Lettley et al., also evaluated the complication of TBI and revealed gonadal failure needing estrogen replacement and severe impairment of fertility in women and men, respectively (40).

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TBI and teeth complications

TBI radiation to the neck and head can lead to permanent teeth impairment, growth impairment, and diminished secretion of saliva. Additionally, it has the potential to disrupt the formation of enamel and dentin, resulting in hypoplasia of the maxilla and mandible. Moreover, it can contribute to root and tooth shortening, and in certain instances, complete absence of tooth development, contingent on the patient's age at the time of irradiation .Tooth decay commonly manifests on usually resistant surfaces and characteristic sites (29). The sole administration of chemotherapy induces significant alterations in dental development, promoting decay, and the combined impact of both treatment modalities can substantially impact dentition.

TBI and quality of life

Studies have demonstrated that individuals undergoing TBI-containing conditioning regimens experienced a reduction in their quality of life. Claessens et al. reported in a study that quality of life was decreased in approximately 44% of patients who underwent TBI, with 35% of patients showing a reduction in intellectual capacity and 41% experiencing a deterioration in their job situation (42).

Conclusion

Although TBI was an efficient part of bone marrow transplantation conditioning therapy, it was associated with various side effects and complications.

Author Contribution

Kazem ansardi designed and edited the manuscript. Amer yazdan parast and pouya Baghi wrote and edited the manuscript.

Conflict of interest

None

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