

Ionizing Radiation Exposure due to Medical Imaging in Hematopoietic Stem Cell Transplant Recipients

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ABSTRACT

Introduction: The study aimed to quantify the ionizing radiation exposure of patients with hematologic malignancy who underwent hematopoietic stem cell transplantation (HSCT).

Methods: This was a retrospective evaluation of the adult patients who underwent allogeneic or autologous HSCT for hematologic malignancies in a single center between January 2016 and September 2020. All radiological imaging procedures involving ionizing radiation screened study participants. The study period covered both the pre- and post-transplantation phases. A typical cumulative effective dose (CED) was used to calculate the exposed ionizing radiation in units of millisieverts (mSv).

Results: A total of 120 patients (females 38.3%, mean age: 52.2±15.6 years) were included. Autologous HSCT was performed in 66 patients (55%), whereas 54 patients (45%) underwent allogeneic HSCT. Patients with acute myeloid leukemia and acute lymphoblastic leukemia comprised 53.7% and 31.5% of allogeneic HSCT, respectively. Autologous HSCT was mainly performed in patients with multiple myeloma (47%) and non-hodgkin lymphoma (34.8%). The median total CED was 11.85 mSv (interquartile range: 4.08-19.78). The median CED of allogeneic HSCT patients was significantly higher than that of the autologous HSCT group. The vast majority of the total CED (92.3%) comes from computed tomography imaging procedures. In the entire groups, 92 patients (76.7%) received a low dose (<20 mSv), whereas 26 patients (21.7%) received a moderate dose (>20-50 mSv) ionizing radiation.

Conclusion: One-third of all HSCT patients received a moderate ionizing radiation dose. Allogeneic HSCT patients had significantly higher median CED than autologous counterparts.

Keywords: Computed tomography, cumulative effective dose, ionizing radiation, radiation exposure, hematopoietic stem cell transplantation

Introduction

Hematopoietic stem cell transplantation (HSCT) is a therapeutic modality which is used in hematologic malignancies and several other disorders, including but not limited to aplastic anemia, sickle cell disease, and immunodeficiency syndromes (1). Advances in supportive therapy along with transplantation techniques have enabled a steep increase in the number of eligible patients for HSCT (2). For many hematologic malignancies, HSCT is the sole means of attaining a cure. However, despite providing a probable cure chance, HSCT has serious morbidities both in the peritransplant phase and in the long term (3). In a countless retrospective evaluation, between 2002 and 2015, the cumulative death rate among patients who underwent allogeneic HSCT for acute myeloid leukemia was 51% at five years. Although it changed according to when it occurred, the major causes of death were relapse of leukemia, graft-versus-host disease (GVHD), and infection, among others (4).

Both solid cancer and hematologic malignancy incidence increases after HSCT. One study spanning a 27-year-period reported that, among 3,372 patients who underwent HSCT, 137 patients (4%) developed a malignancy (5,6). Several risk factors impact the risk of developing a second malignancy after HSCT, such as myeloablative total body irradiation, younger age at the time of transplantation, chronic GVHD, and duration and intensity of immunosuppressive treatment (7-9). The causal association between low-dose radiation exposure from medical imaging studies and malignancies is more problematic to demonstrate. However, a large study involving 400,000 radiation workers revealed that 1-2% of deaths were from cancer was attributable to radiation exposure even at doses between 5 and 50 mSv (10).

HSCT patients undergo a host of radiological imaging procedures starting from the diagnosis of the primary malignancy for purposes of staging, preparation for HSCT, and after the transplantation for several complications. The cumulative dose of radiation exposure has been



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shown to be significantly increased in HSCT patients compared with the radiation exposure level in several solid organ transplant populations (11-14). However, there is a scarcity of knowledge regarding radiation exposure due to diagnostic imaging procedures in HSCT patients, and to the best of our knowledge, to date only one study evaluated the total cumulative radiation in patients who underwent HSCT (15). Thus, we retrospectively evaluated the ionizing radiation exposure of allogeneic and autologous HSCT patients in a single center.

Methods

This was a retrospective evaluation of the adult patients who underwent allogeneic or autologous HSCT for hematologic malignities in a single center between January 2016 and September 2020. During the specified period, we included all HSCT patients. Patients who underwent imaging procedures before admitting to our hospital were excluded because of the lack of data used to calculate the total radiation exposure.

This study approval by the Istinye University Clinical Research Ethics Committee [approval number: (2017-KAEK-120)/2/2021.G-102, date: 23.06.2021].

The necessary consent were obtained from our patients at their first admission to the hematology service so that their clinical data could be used for studies during treatment and follow-up.

All radiological imaging procedures involving ionizing radiation were detected from the patient charts and hospital radiologic imaging database system. These procedures included computed tomography (CT), direct X-rays, fluoroscopic examinations, and nuclear medicine imaging. The study period covered the time frame starting 30 days before transplantation and until the death of the patient or 60 days post-transplantation in surviving patients.

For each imaging procedure, a typical cumulative effective dose (CED) was used to calculate the exposed ionizing radiation in units of millisievert (mSv). Data reported by Mettler et al. (16) and Hart and Wall (17) were used to calculate CED for common radiology procedures such as CT and direct radiography. In case of missing and/or unavailable data, which allow the calculation of the CEDs, known minimum effective dose in mSv to calculate the total radiation dose was used by means of literature (18).

We categorized CEDs into the following groups as recommended by Nguyen et al. (13): low dose (0-20 mSv), moderate dose (20-50 mSv), high dose (50-100 mSv), and very high dose (>100 mSv).

HSCT Protocols (Conditioning Protocols)

- **For autologous HCT:** Multiple myeloma patients were treated with melphalan, and non-Hodgkin lymphoma (NHL) patients were treated with busulfan, etoposide, melphalan.

- **For allogeneic HCT:** Acute leukemias were treated with myeloablative chemotherapy (busulfan, cyclophosphamide) or nonmyeloablative therapy (fludarabine, busulfan, anti-thymocyte globulin) total body irradiation was not used in any conditioning regimen.

Statistical Analysis

To check the data in terms of distribution, Kolmogorov-Smirnov test and QQ plots were used. Non-normally distributed numeric variables were given as medians [interquartile range (IQR)]. Mann-Whitney U test was used to compare the two groups in terms of numeric data. Categorical variables were presented as numbers and percentages. To compare categorical variables, we used chi-square test. SPSS 24 (SPSS Inc., Chicago, IL) statistical software package was used for statistical analyses. Statistical significance was determined at p-value <0.05.

Results

General Characteristics of the Patients

A total of 120 patients (females 38.3%) were included in the study. The mean age of the patients was 52.2±15.6 years (minimum-maximum: 20-74 years). The most common primary hematologic diseases for which HSCT was performed were multiple myeloma (27.5%) and acute myeloid leukemia (25.8%). Of all HSCTs, autologous HSCT was performed in 66 patients (55%), whereas 54 patients (45%) underwent allogeneic HCT. Patients with AML and ALL constituted 53.7% and 31.5% of allogeneic HSCT, respectively. Autologous HSCT was mainly performed in patients with MM (47%) and NHL (34.8%).

Twenty-one (17.5%) patients had acute GVHD during the posttransplant phase. Overall, at 60 days post transplantation, 43 patients (35.8%) died. The mortality rate was significantly higher in the allogeneic HSCT group (53.7%) relative to the autologous HSCT group (21.2%) (p<0.001). The most common causes of death were infection (41.9%) and a combination of infection and GVHD (16.3%). Table 1 summarizes the general characteristics of the whole study group.

Radiologic Procedures and Cumulative Effective Radiation Dose

The median duration of the pre-transplantation phase was 122 days. During this phase, the median number of CT for each patient was 4 [(IQR), 1-6]. The maximum number of CTs for one patient was 37 in a patient with NHL; 20 before and 17 after the transplantation. The most common site for which CT was performed was thorax, followed by CT angiography. During the preparatory phase, the median number of chest X-rays was 12. During the first 60 days of the post-transplantation period, the median number of CTs and chest X-rays for one patient was 1 and 4, respectively (Table 2).

The median total CED was 11.85 mSv (IQR: 4.08-19.78). The median CED of allogeneic HSCT patients was significantly higher than that of the autologous HSCT group (Table 3 and Figure 1). The vast majority of the total CED (92.3%) comes from CT imaging procedures. Of all study patients, 40 (60.6%) had a total CED greater than 3 mSv. Only 2 patients had a total CED >50 mSv. In the entire group, 92 patients (76.7%) received a low dose (<20 mSv), whereas 26 patients (21.7%) received a moderate dose (>20-50 mSv) ionizing radiation. CED groups according to allogeneic and autologous HSCT groups are shown in Figure 2.

Discussion

The salient findings of this study can be summarized as follows: First, the median CED for HSCT recipients was 11.8 mSv. Second, only 2 of our

Table 1. Clinicodemographic characteristics of the entire study population

| | Patients (n=120) |
|--------------------------------|------------------|
| Age (years) | 56.5 (41-64.8) |
| Sex; (n, %) | |
| Female | 46 (38.3%) |
| Male | 74 (61.7%) |
| BMI median (IQR) | 26.5 (23.6-30.8) |
| Diagnostic; (n, %) | |
| Multiple myeloma | 33 (27.5%) |
| Acute myelogenous leukemia | 31 (25.8%) |
| Non-Hodgkin lymphoma | 25 (20.8%) |
| Acute lymphoblastic leukemia | 21 (17.5%) |
| Hodgkin's lymphoma | 6 (5.0%) |
| Myelodysplastic syndrome | 1 (0.8%) |
| Mycosis fungoides | 1 (0.8%) |
| Plasma cell leukemia | 1 (0.8%) |
| T-cell lymphoblastic leukemia | 1 (0.8%) |
| The type of HCT; (n, %) | |
| Allogeneic HCT | 54 (45%) |
| Autologous HCT | 66 (55%) |
| GVHD; (n, %) | 21 (17.5%) |
| Number of deaths; (n, %) | 43 (35.8%) |
| Cause of death | |
| Infection | 18 (41.9%) |
| GVHD + infection | 7 (16.3%) |
| Relapse | 5 (11.6%) |
| GVHD | 4 (9.3%) |
| Engraftment failure | 2 (4.6%) |
| Unknown | 7 (16.3%) |

IQR: Interquartile range, HCT: Hematopoietic cell transplantation, GVHD: Graft-versus-host disease

patients had a high dose, which was defined as a CED between 50 and 100 mSv. Third, the vast majority of the CED originated from computed tomographic imaging procedures. Fourth, patients who underwent allogeneic HSCT had significantly higher CED compared to patients who underwent autologous HCT.

Although recently several studies evaluated the amount of ionizing radiation exposure in various patient groups (19-22) along with the general population, some of the most vulnerable patient groups in terms of secondary cancer development, including transplant recipients, have been ignored to some extent. Some authors have even discussed the potential radiation dose for a middle-aged person just from cancer screening procedures and advised caution in this regard (23).

This relative negligence in terms of lack of studies investigating ionizing radiation exposure in transplant recipients may be due to the already increased mortality risk of these patients from more readily apparent causes such as infection and GVHD. These multiple and more palpable threats to the well-being of the transplant recipients might delegate the awareness of the harmful effects of radiation to a lower point in the list of priorities.

Table 2. Number of radiological imaging procedures involving ionizing radiation and cumulative effective doses in the whole patient group

| | Patients (n=120) |
|---|--------------------|
| Duration of the HCT preparation phase (days) | 122 (64.3-174.5) |
| Number of procedures involving ionizing radiation | |
| Pre-transplantation | |
| Computed tomography | 4 (1-6) |
| CT angiography | 1 (1-1) |
| Thorax | 2.5 (1-4) |
| Upper abdomen | 0 (0-1) |
| Lower abdomen | 0 (0-1) |
| Cranial | 0 (0-0) |
| Neck | 0 (0-0) |
| Chest X-ray | 12 (7-21) |
| PET | |
| Vertebra | - |
| Post-transplantation | |
| Computed tomography | 1 (0-3) |
| Chest X-ray | 4 (2-8) |
| Cumulative effective dose from computed tomography (mSv) | 10.50 (3.36-18.31) |
| Cumulative effective dose from conventional radiography (mSv) | 0.84 (0.49-1.38) |
| Total cumulative effective dose (mSv) | 11.85 (4.08-19.78) |

HCT: Hematopoietic cell transplantation, PET: Positron emission tomography, mSv: Millisieverts

Several studies of solid organ transplant recipients such as heart and kidney revealed much higher doses of ionizing radiation exposure than normally allowed and that of patients who had chronic medical conditions (14,24-27). Solid organ transplantations also entail a preparatory phase during which several radiological procedures are undertaken to evaluate the disease burden and make necessary plan for the transplant procedure. However, HSCT differs from solid organ transplantation crucially; that is HSCT requires conditioning, which is carried out in some patients with the use of whole-body irradiation in addition to myeloablative chemotherapy (28). This therapeutic irradiation significantly increases the CED of a patient in a very short period. In our study, none of the patients had total body irradiation as part of the conditioning regimen. Thus, the lack of radiation in conditioning might account in part for relatively lower CED values in our patients.

Patients with HSCT have a relatively high mortality rate after the transplantation procedure (4). Secondary cancer development is as common in HCT patients as in solid organ recipients (29). Despite the high vulnerability of this special population, as far as we know, only one study to date has investigated the amount of ionizing radiation in HCT patients.

Battiwalla et al. (15) evaluated 66 allogeneic HSCT patients in a retrospective cohort study. The authors covered a period of 230 days; 30 days pre-transplantation and 200 days post-transplantation. The

Table 3. Cumulative effective doses in the allogeneic and autologous HSCT groups

| | Groups (n=120) | | |
|---|------------------------|------------------------|---------|
| | Allogeneic HSCT (n=54) | Autologous HSCT (n=66) | p-value |
| Duration of the HCT preparation phase (days) | 120 (90.8-247.8) | 127.5 (46.8-173.5) | 0.316* |
| Cumulative effective dose from computed tomography (mSv) | 13.9 (9.2-22.23.0) | 5.6 (0-14.1) | <0.001* |
| Cumulative effective dose from conventional radiography (mSv) | 1.2 (0.8-1.9) | 0.6 (0.4-1.0) | <0.001* |
| Total cumulative effective dose (mSv) | 15.8 (10.2-25.0) | 6.3 (0.6-14.6) | <0.001* |

*Mann-Whitney U test, HCT: Hematopoietic cell transplantation, HSCT: Hematopoietic stem cell transplantation, mSv: Millisieverts

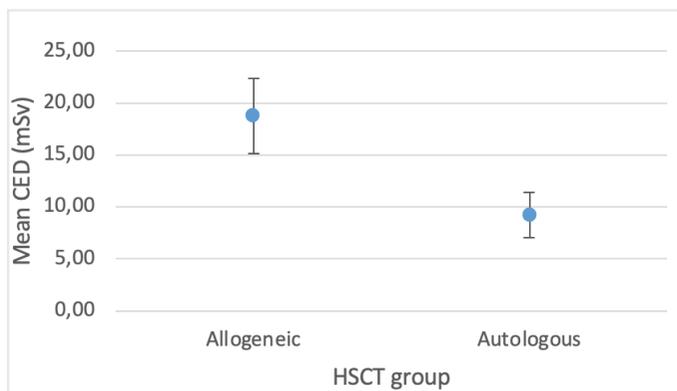


Figure 1. Simple error bars showing the mean cumulative effective dose in allogeneic and autologous hematopoietic stem cell transplantation. Error Bars: 95% confidence interval
CED: Cumulative effective dose, HSCT: Hematopoietic stem cell transplantation, mSv: Millisieverts

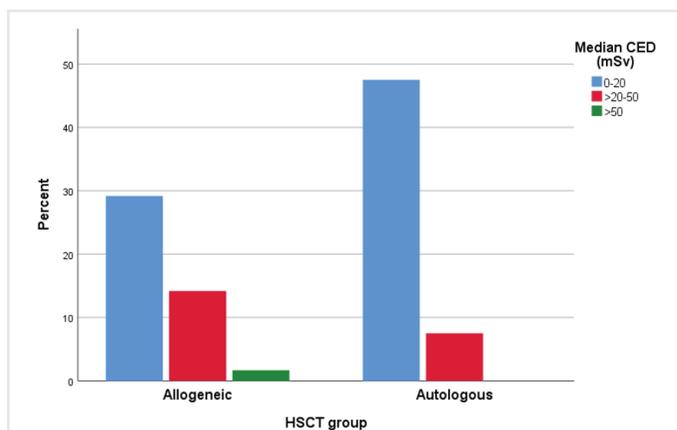


Figure 2. Clustered bar chart depicting median CED groups in allogeneic and autologous HSCT patients
CED: Cumulative effective dose, HSCT: Hematopoietic stem cell transplantation, mSv: Millisieverts

median cumulative effective radiation dose from diagnostic radiological procedures was found to be 92 mSv (range: 1.2-300). This median value is much larger than the median value of our patients [11.85 mSv (IQR, 4.08-19.78)]. Several factors can explain this discrepancy. First, we calculated radiation exposure until the 60th day after transplantation. Second, none of our patients underwent total body irradiation as part of the conditioning regimen. Third, the mortality rate in our cohort was much higher compared to the cohort of Battiwalla et al. (15) hence limiting the additional doses of ionizing radiation. The authors did not find an impact of radiation exposure on the short-term clinical outcomes. We did not evaluate the clinical outcome and radiation

exposure association in our study with the presumption that radiation-induced cancer development is a late effect. We, are of course, aware of the fact that radiation exposure affects several other organ systems, including, the heart and immune system (30). Considering the increased burden of cardiovascular disease in HSCT recipients (31), new research should also explore the additional cardiac risk attained by ionizing radiation in HSCT patients.

It is well appreciated that as the dose of radiation exposure increases, the risk of secondary malignancy also increases well (32-35). Moreover, this association starts at relatively low doses of ionizing radiation exposure. Eisenberg et al. (33) reported that for every 10 mSv CED, cancer risk over 5 years showed a 3% risk increase. In a large multinational study that recruited radiation workers, Cardis et al. (10) found that workers were exposed to an average of 20 mSv ionizing radiation and there existed a positive correlation with cancer-related mortality and exposure dose. Interestingly, the cancer risk seemed to start at a dose as low as 5 mSv (36). Thus, even low-level radiation exposure might can contribute to secondary malignancy development; radiologic studies should be conducted cautiously.

Most of the total radiation dose (88%) has come from CTs in the study by Battiwalla et al. (15). Similarly, 92.3% of the total CED was due to CTs in our study. Thus, in our opinion, physicians should be particularly vigilant for the performance of repeated CT imaging in their patients if they limit the radiation exposure in their patients.

All patients in the study by Battiwalla et al. (15) underwent full-match allogeneic transplantation. However, we included both allogeneic and autologous HSCT patients in this study. Interestingly, the median CED was significantly higher in allogeneic HSCT patients compared with autologous HSCT patients. The duration of pre-transplantation phase was not different between the groups. The mortality rate was significantly higher in the allogeneic HSCT group relative to the autologous HSCT group (p<0.001). Since most of the ionizing radiation exposure comes from the pre-transplantation period, we think that the nature of the underlying hematologic diseases dictated the need for radiological procedures and thus created a significant difference between the groups in terms of median CED.

Study Limitations

First, this was a relatively small study conducted in a single center. Thus, our findings are difficult to extrapolate for other centers since conditioning regimens, and patient characteristics vary across different centers. Second, we could not obtain information regarding the exact timing of the radiological procedures. Though we knew that the imaging

procedures were certainly performed during the study period, we did not provide data with respect to the pre- or post-transplantation timing of the radiological procedures. Thirdly, during the follow-up of patients after the transplantation, we did not detect any malignancy but probably the time was probably not long enough to detect secondary malignancies.

Conclusion

This study was the second but the largest study investigating CED in patients who underwent HCT. Moreover, for the first time in the literature, we reported that patients who underwent allogeneic HSCT received significantly more ionizing radiation compared with patients who underwent autologous HCT. More studies are clearly needed to elucidate whether this increased exposure to ionizing radiation affects the future development of malignancy in HSCT recipients.

Ethics Committee Approval: This study approval by the İstinye University Clinical Research Ethics Committee [approval number: (2017-KAEK-120)/2/2021.G-102, date: 23.06.2021].

Informed Consent: The necessary consent were obtained from our patients at their first admission to the hematology service so that their clinical data could be used for studies during treatment and follow-up.

Peer-review: Externally peer-reviewed.

Authorship Contributions: Surgical and Medical Practices - S.H.A., A.T.; Concept - S.H.A., A.T.; Design - S.H.A., I.Y.; Data Collection or Processing - S.H.A., I.Y., A.T.; Analysis or Interpretation - S.H.A., I.Y.; Literature Search - S.H.A., I.Y., A.T.; Writing - S.H.A.

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