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Radiation Exposure from Diagnostic Procedures following Allogeneic Stem Cell Transplantation – How Much Is Acceptable?

Minoo Battiwalla¹, Farhad Fakhrehani¹, Natasha A Jain¹, Jeffrey K. Klotz¹, Priyanka A Pophali¹, Debbie Draper¹, Janice Haggerty¹, Zachariah McIver¹, James Jelinek², Kamna Chawla¹, Sawa Ito¹, and John Barrett¹

¹Hematology Branch, National Heart Lung and Blood Institute, NIH, Bethesda, MD

²Washington Hospital Center, Washington, D.C.

Abstract

Patients receiving allogeneic stem cell transplants (SCT) can remain acutely sick for many weeks and incur repeated diagnostic radiology procedures which may significantly increase radiation exposure. This retrospective cohort study was conducted to determine the cumulative radiation dose from diagnostic studies following SCT. Sixty-four consecutive patients with hematologic malignancies in a single tertiary care institution underwent total body irradiation-based myeloablative conditioning followed by 6/6 HLA-identical sibling allogeneic stem cell transplantation. The median follow up was three years. The cumulative effective dose in mSv from diagnostic radiologic studies in the peri-transplant period from day –30 to day +200 was calculated for each patient and its impact on overall survival and nonrelapse mortality was determined. The median cumulative radiation exposure from diagnostic radiologic procedures was 92 mSv (range 1.2–300), representing about 30× the normal annual background radiation for the population and 10% of the 1200cGy total body irradiation (TBI) dose used in conditioning. Sixty-five percent of the cumulative radiation exposure was delivered between day +1 and day 100 and CT scans contributed 88%. While radiation exposure from diagnostic procedures did not impact clinical outcomes the risk of second cancers in long term survivors is likely to be increased. Our results indicate that patients who are acutely ill for prolonged periods can receive clinically significant radiation doses during their hospital care. Our findings should prompt attempts to limit radiation exposure from diagnostic procedures in post-SCT recipients.

Keywords

HSCT; diagnostic; radiation; CT; outcome

Corresponding Author: Minoo Battiwalla, MD, MS, Hematology Branch, NHLBI, NIH., Address: Rm 5-3581, Bldg 10 CRC, 10 Center Drive, Bethesda MD – 20892. Phone: 301-827-0939; Fax: 301-827-3228; minoo.battiwalla@nih.gov.

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INTRODUCTION

Outcomes in allogeneic hematopoietic stem cell transplantation (HSCT) are compromised by high complication rates attributable both to the underlying disease as well as to the treatment. Transplant recipients undergo rigorous evaluation prior to transplant to determine transplant eligibility. Clinical evaluation frequently takes the form of diagnostic radiology procedures such as CT scans, X-rays, nuclear medicine studies and fluoroscopy. Following transplant many patients experience prolonged hospitalization and repeated diagnostic radiological procedures and may incur a significant cumulative radiation exposure. The health impact of incidental radiation exposure from diagnostic studies, particularly delayed cancer risk is becoming more widely appreciated. Since allogeneic SCT conditioning regimens including total body irradiation incur an increased risk of second cancers, [1] it is important to determine the contribution that radiological diagnostic procedures add to the total radiation dose received.

Frequent medical imaging is commonplace in oncology and recent studies are beginning to raise concerns about radiation risks [2, 3]. Late malignancies are already a documented problem in allogeneic stem cell transplant survivors, with the magnitude of risk of secondary malignancies after SCT ranging from four- to eleven-fold that of the general population[4]. The frequency of utilization of diagnostic radiology procedures in allogeneic HSCT has not been well characterized and the attendant risk of radiation exposure is completely unknown. We conducted a single-institute retrospective study of radiation exposure in the peritransplant period extending from day-30 to day 200 to define this risk.

PATIENTS AND METHODS

PATIENTS

64 consecutive patients (age 13–68 years) underwent myeloablative 6/6 HLA-matched sibling allogeneic HSCT for hematologic malignancies at our center between October, 2006 and September, 2011. All patients gave written informed consent for National Institutes of Health protocols, approved by the National Heart, Lung, and Blood Institute Institutional Review Board (protocol 06-H-0248 (NCT 00378534, FDA IDE #13058) and protocol 07-H-0136 (NCT00467961, FDA IND #13305). 06-H-0248 and 07-H0136 are contemporaneous protocols with comparable clinical outcomes for overall survival, relapse and nonrelapse mortality[5].

TRANSPLANT CONDITIONS

Recipients received conditioning with fludarabine 125 mg/m², cyclophosphamide 120 mg/kg and total body irradiation (TBI) of either 12 cGy (age <55 years) or 4 cGy (age ≥ 55 years).

G-CSF mobilized peripheral blood grafts underwent CD34⁺ selection by the Miltenyi CliniMacs system, with infusion of a target CD34⁺ dose of 6×10^6 /kg (range 3 to 10×10^6 /kg) and a fixed CD3⁺ dose of 5×10^4 /kg.

24 patients (PD cohort) received 5×10^6 CD3+/kg donor lymphocytes selectively depleted of alloreactivity by ex vivo photo depletion (Kiadis) [6] while the remaining patients (TCD cohort) received a prophylactic unmanipulated donor lymphocyte infusion of 5×10^6 CD3+/kg on day 90 in the absence of GVHD.

Low dose cyclosporine (100–200ng/mL) till day 21 was the sole GVHD prophylaxis.

RADIATION EXPOSURE

All 66 patients were evaluated for diagnostic radiology exposure. Diagnostic radiology procedures (X-rays, CT Scans, fluoroscopy, and nuclear medicine (NM)) were extracted from the electronic medical record and documented for each individual in three periods (day –30 to 0, day +1–100 and day +101–200). Pretransplant studies in the 30 days prior to transplant were included to capture diagnostic radiology for restaging and eligibility determination, which includes a routine CT scan of the chest, abdomen and pelvis at our center. Radiation exposure was calculated using the “effective dose” (ED) in mSv. The effective dose is a means of converting a non-uniform (or localized) radiation dose to a dose that would be equivalent to a whole-body exposure in a reference patient. Given the considerable variations in effective dose based on machine characteristics, the majority of common diagnostic studies had their effective dose computed by direct measurements conducted by NIH Radiation Safety. For infrequent studies, values were assigned from literature review. Since no standards were found for interventional radiology procedures, they were assigned an ED equivalent to 5 minutes of fluoroscopic exposure. [Supplementary table I] ED is defined as total body absorbed dose (whole body equivalent) required to achieve an adequate diagnostic image. The biological effects vary by the type and energy of the radiation and the organism and tissues involved. The unit of effective dose is the Sievert (1 Sievert (Sv) = 1 joule/kilogram (J/kg)).

All patients received therapeutic TBI in their conditioning regimen. The unit of the absorbed dose of radiation in therapeutic radiation is the gray (1 Gy (Gy) = 1 joule/kilogram (J/kg)). 48 patients who were < 55 years old received 12 Gy (divided in 8 fractions with lung shielding to 600 cGy) and 16 patients who were ≥ 55 years old received 4 Gy (divided in 8 fractions without lung shielding).

The relationship between the dose equivalent and the absorbed dose is given by: dose equivalent (Sieverts) is the product of dose (grays) and the Quality Factor (Q). The quality factor (Q) for X-, gamma, or beta radiation (covering all forms of radiation exposure from diagnostic radiation) is 1.[7] For comparison purposes in this study, 1Sv (radiation equivalent) = 1Gy (radiation absorbed) = 1J/Kg.

STATISTICAL ANALYSIS

Nine patients failed to survive >200 days and were excluded from study of the impact of diagnostic radiation exposure on clinical outcomes. Overall survival (OS) and nonrelapse mortality (NRM) were evaluated in the remaining 55 subjects who survived >200 days in univariate analysis (Kaplan Meier estimate)[8] and multivariable Cox proportionate hazard models[9]. In order to compensate for the confounding association between diagnostic radiology procedures and patient morbidity, serum albumin and serum creatinine (as

alternative surrogates for patient complexity) were introduced into the multivariable models. All variables were tested for the proportionate hazards model. The variables for the cumulative and the periodic ED were forced into the multivariable models at all steps of model building regardless of statistical significance. A backward and forward stepwise model building approach was used. Statistical analysis was performed using SPSS (IBM, PASW 18, version 18.0.3). Variables that attained a p-value ≤ 0.05 were held in the final multivariate models.

RESULTS

PATIENT CHARACTERISTICS AND TRANSPLANT OUTCOMES

Pretransplant patient and donor characteristics are summarized in Table I. The median time to an ANC $>500/\mu\text{L}$ was 12 days and there were two episodes of secondary graft failure. The incidence of acute GVHD grades II–IV and III–IV were 18.8 and 4.7%, respectively. Limited and extensive chronic GVHD occurred in 29.1% and 27.2 % of transplant recipients. 55 subjects survived beyond the 200-day landmark and were evaluable for survival analysis. At a median follow up of 36 months, the Kaplan-Meier estimates for the cumulative incidence of relapse/progression, non-relapse mortality and overall survival were 19.4%, 34.3% and 56.2%.

DIAGNOSTIC RADIOLOGY PROCEDURES

Between day –30 and day 200, patients received a median of 11 diagnostic X-rays, 10 CT-scans, one fluoroscopic and zero nuclear medicine studies. The median cumulative radiation exposure from diagnostic radiology procedures was 91.6 mSv (range 1.2–300.1).

In terms of time frame, 29% of the cumulative ED was delivered between day –30 to 0, 65% between day +1–100 and only 6% between day +101–200. And in terms of diagnostic modalities, the relative contributions from CT scans, X-rays, fluoroscopy, and NM were 88%, 6%, 5% and $<1\%$, respectively. [Figure 1]

CUMULATIVE DIAGNOSTIC RADIATION AND CLINICAL OUTCOMES

Although a greater than median cumulative dose of incidental radiation from day–30 to +100 was significantly associated with NRM and overall survival ($p<0.03$) in univariate analysis. In multivariable analysis, cumulative doses of radiation lost significance and were displaced by serum creatinine and serum albumin in the final models for OS, and by albumin, acute GVHD and photodepletion for NRM. [Figure 2, Table II]

DISCUSSION

Most estimates of harmful effects of low dose radiation derive from studies of atomic bomb survivors in Japan. Radiation doses ranging from 5–150 mSv with a mean of about 40mSv produced a definite increase in cancer risk [10, 11].

Radiation impact from diagnostic procedures has been difficult to quantify epidemiologically, because of debate regarding the linearity of the dose response curves at low doses of radiation, recall bias, long latency till cancer development, nonuniform

exposure and marked differences in X-ray energies produced by diagnostic machines [12, 13]. However, a large cohort study involving over 400,000 nuclear radiation workers showed a 1–2% dose-related increase in cancer deaths from chronic exposure to low levels of radiation, even at cumulative doses as low as 5 to 50 mSv [14]. This data is consistent with the conclusion of Biological Effects of Ionizing Radiation (BEIR) VII, which showed “a linear, no-threshold dose–response relationship between exposure to ionizing radiation and the development of cancer in humans” [13]. Recurrent computed tomography (CT) scans have been singled out as a major concern and children are particularly vulnerable [15–17]. In one risk estimate, de Gonzalez, et al. estimate that approximately 29, 000 (95% UL, 15, 000–45, 000) future cancers could be related to CT scans performed in the US in 2007 [18]. In response, the FDA has developed a collaborative initiative to reduce unnecessary radiation exposure from medical imaging [19]. The initiative focuses on the three types of procedures that are the greatest contributors to the U.S. population’s total radiation exposure from medical imaging: computed tomography (CT), fluoroscopy, and nuclear medicine studies.

Our patients received a median of 92 mSv. This is 30× greater than the average annual radiation exposure from all sources in the US of about 3.0 mSv and double the accepted limit of 50 mSv per year for health care workers [20]. Furthermore some patients received radiation doses up to 100 fold greater than the annual radiation exposure. Between day +1 and day 100 post SCT, CT scans represented approximately 90% of the radiation exposure and peak exposure (65%). While excessive for a healthy individual, the median total radiation exposure from diagnostic radiation (92 mSv) represented around 10% of the myeloablative conditioning radiation dose given at our center. Consistent with this, cumulative dose of incidental radiation exposure did not affect NRM and OS multivariable analysis. Nevertheless, such excess radiation from diagnostic procedures would be more significant after reduced intensity regimens, popular for patients over the age of 55 who may receive conditioning regimens with no or very low dose TBI.

Our study is limited by the lack of organ specific measurements of radiation dose which was not available for all the diagnostic radiology procedures performed. Secondly, follow up was too short to examine impact on second cancers which are a concern in long-term SCT survivors [21]. Nevertheless, as discussed above, this possibly avoidable diagnostic radiation has the potential to adversely impact long-term outcome after SCT since the risk of second malignancies is directly related to cumulative radiation dose received.

While our study involved a largely adult SCT population it should be noted that children are the most vulnerable population for adverse events from radiation exposure. The effective doses of radiation in medical imaging are considerably greater in pediatric recipients for reasons that are not well understood [22, 23] and children’s hospitals are leading the way in reducing diagnostic radiation exposure. Growing awareness of the hazards of cumulative radiation exposure has stimulated efforts to reduce diagnostic radiation exposure by limiting clinically unnecessary restaging and duplicate studies (e.g. PET/CTs), eliminating multiphase studies (e.g. liver imaging) and diminishing image detail without reducing diagnostic accuracy.

In conclusion, although diagnostic radiology procedures can be expected to only modestly increase the overall radiation exposure of SCT any unnecessary radiation exposure is worth avoiding. Our findings should stimulate greater awareness of the large doses of radiation accumulated in post transplant recipients who can remain acutely sick for months and prompt efforts to minimize such exposure.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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FIGURE 1.

Effective Dose According to Transplant Period and Diagnostic Modality

A. Proportions of the effective dose received according to transplant period

B. Proportions of the effective dose received according to diagnostic modality

FIGURE 2.

Univariate Survival Analysis for the Cumulative Effective Dose of Diagnostic Radiation.

Univariate Kaplan Meier survival analyses show inferior outcomes for cumulative ED greater than the median for [A] overall survival (day -30 to day +200), [B] overall survival (day -3- to day +100) and [C] nonrelapse mortality (day -30 to day +100).

Table I

Patient Characteristics		
Number of subjects		64
Median Age (range)		48 (13 to 68)
Sex (F/M)		
Ethnicity	Hispanic/Non Hispanic	33/31
Diagnoses	Acute Myelogenous Leukemia	25
	Acute Lymphoblastic Leukemia	14
	Biphenotypic Acute Leukemia	2
	MDS/MPD	15
	NHL/CLL	5
	CML	3
Risk Status	High/Standard	35/29
Median CD34+ dose ($\times 10^6/\text{kg}$)		6.2
Performance status	KPS $\geq 90\%$ (ECOG 0)	61
	KPS $< 90\%$ (ECOG 1)	3
CMV serostatus (Donor/Recipient)		
	pos/pos	40
	pos/neg	8
	neg/pos	9
	neg/neg	7

Table II

Risk Factor	Hazard Ratio	p value
Multivariable model for overall survival		
Cumulative ED from day –30 to day 200	1.96	0.129
Cumulative ED from day –30 to day 100	1.68	0.235
Day 200 serum creatinine	4.01	0.001
Day 200 serum albumin	0.16	<.001
Excluded Factors (p>0.05)		
Photodepletion protocol, age, disease, disease stage, pre-transplant performance, CMV serology, year of transplant, CD34 dose, time to ANC>500, acute GVHD grade, chronic GVHD, day 30 creatinine, Day 100 creatinine, day 30 albumin, day 100 albumin		
Multivariable model for nonrelapse mortality		
Cumulative ED from day –30 to day 200	1.347	0.618
Photodepletion protocol	0.531	0.037
Acute GVHD grade III–IV	3.036	0.001
Day 200 serum albumin	0.355	0.027
Excluded Factors (p>0.05)		
Age, disease, disease stage, pre-transplant performance, CMV serology, year of transplant, CD34 dose, time to ANC>500, chronic GVHD, day 30 creatinine, Day 100 creatinine, day 30 albumin, day 100 albumin		

ANC, absolute neutrophil count; CMV, cytomegalovirus; GVHD, graft versus host disease.