HHS Public Access

Author manuscript

Bone Marrow Transplant. Author manuscript; available in PMC 2013 February 01.

Published in final edited form as:

Bone Marrow Transplant. 2012 August ; 47(8): 1067–1074. doi:10.1038/bmt.2011.234.

Osteonecrosis in Children after Allogeneic Hematopoietic Cell Transplantation: Study of Prevalence, Risk Factors, and Longitudinal Changes Using MR Imaging

Shelly Sharma, MD[1], **Wing-Hang Leung, MD, PhD**[2], **Pei Deqing, MS**[3], **Jie Yang, PhD**[3], **Richard Rochester, PA**[2], **Lunetha Britton, RN**[4], **Michael D. Neel, MD**[4], **Kirsten K. Ness, PhD**[5], and **Sue C. Kaste, DO**[1,2,6]

[1]Department of Radiological Sciences, St. Jude Children's Research Hospital, Memphis, TN

[2]Department of Oncology, St. Jude Children's Research Hospital, Memphis, TN

[3]Department of Biostatistics, St. Jude Children's Research Hospital, Memphis, TN

[4]Department of Surgery, St. Jude Children's Research Hospital, Memphis, TN

[5]Department of Cancer Epidemiology and Cancer Control, St. Jude Children's Research Hospital, Memphis, TN

[6]Department of Radiology, University of Tennessee Health Science Center, Memphis, TN

Abstract

Osteonecrosis after hematopoietic stem cell transplantation (HCT) has seldom been addressed in pediatric populations. At our institution, since January 2002, children undergoing allogeneic HCT (alloHCT) receive yearly follow-up magnetic resonance imaging (MR) of hips and knees. To estimate the prevalence, longitudinal changes and associated risk factors for osteonecrosis after alloHCT, we reviewed MRs for children who underwent single alloHCT during the study period. We analyzed 149 of 344 patients who had post HCT MRI imaging performed [84 males; median age11 years (range, 0.5–21years)], median follow-up time was 32.6 months (range, 2.8–97.2 months). Forty-four (29.5%) developed osteonecrosis of hips and/or knees; of those, 20 (45%) had at least 30% epiphyseal involvement. In 23 (52%) osteonecrosis lesions were identified in the first, and 43 (98%) by the third yearly scan. Knees were more frequently involved than hips; severity of osteonecrosis was greater in hips. Those who had pre-alloHCT osteonecrosis, two patients' hips and six patients' knees resolved completely; three patients' osteonecrosis lesions regressed after alloHCT. On risk factor analysis, age at time of alloHCT (p=0.051) and osteonecrosis identified by MRs before alloHCT (p=0.001) were the primary risk factors. This analysis shows that preventive strategies for osteonecrosis in this population should focus on measures to minimize risk factors before alloHCT.

Corresponding author: Sue C. Kaste, DO, Department of Radiological Sciences, St. Jude Children's Research Hospital, 262 Danny Thomas Place, MSN 220, Memphis, TN 38105-3678, Telephone: (901) 595–3347, Fax: (901) 595–3962, sue.kaste@stjude.org.

Keywords

Hematopoietic stem cell; transplantation; osteonecrosis; children; graft versus host disease

Introduction

The increased use of hematopoietic stem cell transplantation (HCT) among children, coupled with an increase in survival, has led to a rise in the number of young HCT survivors.[1,2] Osteonecrosis, a debilitating skeletal morbidity[3,4] is one complication that can compromise quality of life among these survivors. Osteonecrosis is a challenge to treat in this population because it is often identified in advanced stages, and in multiple joints, when the only available treatment is joint replacement. Surgery can be accompanied by high rates of infection because of immunosuppression, and often requires revision because of hardware failure in these young patients.[5,6]

Although published reports describe osteonecrosis in adults or mixed populations,[2,3,7–11] studies describing osteonecrosis exclusively in pediatric population are few.[12–16] A wide range of incidence rates, 3.9–44.0%, following pediatric HCT is reported. Among adults, the incidence of osteonecrosis is higher in allogeneic than in autologous HCT survivors[3,7,11] Previously reported risk factors for osteonecrosis include acute and chronic graft-versus-host disease (GVHD) requiring steroids, older age at transplantation, and a primary diagnosis of leukemia or aplastic anemia[2,3,9,11,12]. Limiting understanding of osteonecrosis in pediatric HCT patients are the diverse diagnostic criteria used in previous studies[3,8,11,12,17,18], ranging from symptom-based diagnosis and plain radiographs to magnetic resonance studies (MR).

We reviewed prospectively acquired serial MRs in children who underwent a single alloHCT at our institution from December 2000 to September 2007. We sought to assess the prevalence, associated risk factors, and longitudinal changes observed over time in the development of osteonecrosis after alloHCT. This knowledge provides an assessment of the magnitude of this problem and an understanding of the timing of onset of osteonecrosis in this vulnerable young population.

Methods

Study population

We retrospectively reviewed medical records and MRs of children who underwent a single alloHCT at St. Jude Children’s Research Hospital between December 2000 and September 2007. Only patients for whom post-HCT MRs of hips, knees, or both were available were included in the cohort. To assess the representativeness of the study sample, clinical characteristics of the cohort were compared with those of the excluded population.

Since January 2002, patients undergoing alloHCT at St. Jude have undergone baseline MR of the hips and knees at the time of alloHCT and follow-up protocol-driven imaging of hips and knees annually afterward. If bone marrow transplantation must be performed urgently, then pre-alloHCT MR imaging may be omitted. If the second follow-up MR is normal and

the patient is asymptomatic, then no further imaging is done. If the study is abnormal or symptoms persist during the second annual imaging study, then the patient is followed until imaging findings peak or symptoms resolve.

Institutional review board (IRB) approval was obtained for this study, and data were managed in accordance with the Health Insurance Portability and Accountability Act of 1996. All patients underwent IRB-approved treatment for their primary disease under institutional or cooperative group protocols.

Osteonecrosis

Patients being evaluated for osteonecrosis had coronal noncontrast T_1-weighted and short tau inversion recovery (STIR) imaging of the hips and/or knees and sagittal fast low angle shot MR 2-D imaging of the articular surfaces. MRs were performed with either a Siemens 1.5-T Symphony or a Vision MR unit (Siemens, Inc., Erlangen, Germany). MRs were reviewed and interpreted by an experienced pediatric radiologist (SCK) blinded to presence or absence of clinical symptoms. As described previously [5,19,20], osteonecrosis was defined as a geographic area of decreased signal on T1-weighted and increased signal on STIR images.

Osteonecrosis locations were classified as epiphyseal, metaphyseal, or diaphyseal.[19] Because the extent of epiphyseal involvement is an important predictor of joint outcome,[5] we categorized the extent of epiphyseal involvement as ≥30% or <30% of the weight-bearing surface. Thus, hip joint involvement was coded according to the involvement of the capital femoral epiphysis, and knees were coded as involved if an osteonecrosis lesion was present in either the distal femoral or the proximal tibial epiphysis. For patients who underwent multiple MRs after alloHCT (N=91), the MR revealing the most severe osteonecrosis was used for calculating prevalence and analyzing risk factors. We also evaluated the distribution and pattern of multiple joint involvement.

Longitudinal changes in osteonecrotic lesions

Serial MRs were evaluated to assess the evolution of osteonecrosis over time. Longitudinal changes were documented separately for knees and hips by comparing annual MRs after alloHCT and by comparing pre- and post-alloHCT MRs for patients for whom pre-alloHCT MRs were available.

Any case that resolved completely over time (hip or knee) bilaterally was classified as “resolved;” any decrease in size of the osteonecrosis lesion was categorized as “regression.” Patients with negative pre-alloHCT MR who had osteonecrosis lesions after alloHCT and those identified with osteonecrosis after alloHCT for the first time were considered “new cases.” Cases with an increase in the size of existing osteonecrosis lesions were labeled as “progression.” We also collected information about surgical interventions for osteonecrosis during the follow-up period.

Transplantation

All patients underwent alloHCT on IRB-approved protocols. Grafts were obtained from human leukocyte antigen (HLA)-identical siblings, matched unrelated donors (matched for five or six HLA loci), or mismatched family members. Patients with hematologic malignancies were conditioned with myeloablative total body irradiation (TBI)-based conditioning (12 Gy in 8 fractions over 4 days in doses of 150 cGy per fraction) or with reduced-intensity fludarabine-based conditioning (40 mg/m^2 for 5 days). Patients with non-malignant conditions were given busulfan-based conditioning (8–16 mg/kg). All recipients received either a calcineurin inhibitor or mycophenolate mofetil for GVHD prophylaxis.

GVHD was graded according to standard criteria.[21,22] Patients with grade 2 to 4 acute GVHD were treated with methylprednisolone (1–2 mg/kg daily). If GVHD remained at grade 2 or more for more than 7 days or progressed, secondary agents were started, such as a calcineurin inhibitor or mycophenolate mofetil that the patient was not receiving.

Risk factors

We considered associations between osteonecrosis after alloHCT and the following risk factors: sex, race, age at time of alloHCT (i.e., <10 years or ≥10 years), age at primary diagnosis, primary diagnosis (lymphoid malignancies and aplastic anemia vs. others), body mass index (BMI) at time of alloHCT (normal and underweight vs. overweight and obese), donor type (related vs. unrelated), conditioning regimen (TBI vs. non-TBI), acute GVHD (none vs. grade 1 or higher), chronic GVHD (none vs. limited, none vs. extensive), and physis status at the time of HCT (open vs. closed). BMI at the time of HCT was calculated only for patients older than 2 years, per Centers for Disease Control and Prevention (CDC) criteria (www.cdc.gov/healthyweight/assessing/bmi/childrens_bmi/about_childrens_bmi.html).[23] Since physeal development was bilaterally similar (correlation coefficient>0.95 with $p<0.0001$; results not shown) and there were only minor differences between hips and knees (correlation coefficient around 0.85 with $p<0.0001$), we used a majority rule to combine all six physis statuses into one status value. For patients with more than half physis statuses as “closed,” we defined the physis status as “closed.”

As previously described, [19] malignant conditions were categorized as lymphoid (i.e., acute lymphoblastic leukemia, non-Hodgkin lymphoma [NHL], and Hodgkin disease) or non-lymphoid (malignant conditions other than described as lymphoid). Because statistical power for eliciting the effect of individual treatment regimens was limited and individual cumulative doses of steroids received by each patient were unavailable, primary diagnoses were categorized on the basis of contemporary treatment protocols to assess the potential effect of steroid exposure. Diagnoses were grouped as follows: lymphoid malignancies and aplastic anemia vs. other conditions (i.e. non-lymphoid malignancies and sickle-cell disease, immunodeficiency syndromes, osteopetrosis, I-cell disease, Hurler disease, thromboasthenia, and Glanzmann disease).

Statistical analyses

Descriptive statistics were used to describe the study population by sex, race, primary diagnosis, age at the time of MR; age, BMI and physis status at the time of HCT,

conditioning regimen, product type, donor type, donor match type, acute and chronic GVHD grades and duration of chronic GVHD.

Osteonecrosis prevalence rates were calculated for epiphyseal involvement of any of the four lower extremity joints and for hips and knees separately. Time to development of osteonecrosis after alloHCT was calculated only for children with negative or undetected osteonecrosis before alloHCT. The pattern and distribution of joint involvement was examined by evaluating the number of lower extremity joints involved at the time when the earliest MR showed the highest grade of osteonecrosis. Cumulative incidences of osteonecrosis after alloHCT were estimated with death as the competing event.

We used a generalized estimating equation (GEE) models[24] to estimate the incidence of osteonecrosis over time. Independent variables with a significance level of 0.01 in univariate analysis were included in the multivariate GEE model. Because sickle cell anemia[25] is highly correlated with black race, the analysis was repeated with and without sickle cell patients in the model.

Data were analyzed by using SAS (Version 9.13; SAS Institute, Inc., Cary, NC). Statistical significance was set at a p-value of 0.05.

Results

Demographic characteristics of the study population

Of the 344 consecutive patients who underwent allogeneic HCT at St. Jude Children's Research Hospital from December 2000 to September 2007, 149 (84 males) children (median age at time of alloHCT 11 years (range, 0.5–21 years)) underwent at least one post-alloHCT MR of hips and/or knees irrespective of symptoms, and had undergone a single alloHCT (Figure 1). Demographic characteristics of the cohort are shown in Table 1. 116 patients had alloHCT for malignant diseases and 33 for non-malignant conditions. Median time to follow-up from the date of alloHCT was 32.6 months (range, 2.8–97.2 months). When compared to excluded patients, the study population was older at the time of alloHCT, had fewer males and more often received total body irradiation (TBI). Patients older than 10 years of age were more likely to have undergone pre-alloHCT MR than those younger than 10 years ($p<0.0001$) at time of bone marrow transplantation.

Prevalence, severity and time to development of osteonecrosis

When considering all four joints, the prevalence of osteonecrosis was 29.5% (44/149); 45.5% (20/44) had ≥30% epiphyseal involvement. The prevalence of osteonecrosis in the knees was 28.2% (40/142), greater than the prevalence of 9% (13/143) in hips. Fourteen of the 40 patients with osteonecrosis of the knees, 14 had ≥30% epiphyseal involvement. Twelve of the 13 patients with hip osteonecrosis had ≥30% epiphyseal involvement Cumulative incidence plots (Figure 2) show that 52.3% (23/44) of osteonecrosis cases were identified in the first and 97.8% (43/44) by the third annual scans.

Among the 44 children with osteonecrosis after alloHCT, 14 had evidence of osteonecrosis on pre-alloHCT MR. The median times to development of osteonecrosis in any joint in

children with unknown pre-alloHCT osteonecrosis status (n=16), and in children with negative pre-alloHCT status (n=14), were 12.4 months (0.2–38.7 months) and 12.2 months (0.2–24.4 months), respectively.

Pattern of joint involvement

Of the 44 patients with osteonecrosis, 30 (68.2%) had multiarticular involvement; most commonly, bilateral knee involvement (21/44). Three of these patients had bilateral hip coupled with uni- or bilateral knee involvement. Of the 14 of 76 children who had both pre- and post-alloHCT MR, nine were found to have multiarticular involvment.

Longitudinal changes

Among the 149 patients, 58 had only one post-HCT imaging study available for review, 32 had two, and 59 had more than two. Pre-HCT imaging studies were available for 76 children (Figure 1).[19]

During the first year after alloHCT, hip MRs were available for 124 and knee MRs for 129 patients (Table 3). Of the 129 patients with first annual hip MRs, 58 also had pre-alloHCT MRs; two showed complete resolution, and seven new cases of osteonecrosis were identified. For knees, 57 of 129 had pre-alloHCT MRs; two showed complete resolution, one regressed, and 25 new cases were identified.

During the second year after alloHCT, 124 patients had hip MRs for both the first and second year, and 129 had knee MRs for both years. On comparing serial MRs, regression was observed in one hip and one knee and complete resolution in four knees (Table 4). The four patients with complete resolution of lesions ranged in age from 2 years 8 months to 14 years 8 months at primary diagnosis and 3 years 2 months to 6 years 6 months at time of alloHCT. Three of the four were skeletally immature as evidenced by physeal patency at time of alloHCT and were shown to have epiphyseal involvement of < 30%. The patient with closed physes had epiphyseal involvement of at least 30%. Three of the four patients had a primary diagnosis of acute lymphoblastic leukemia; one had acute myelogeneous leukemia. All four patients were of healthy body weight; all had received total body irradiation. Two received 6/6 HLA matched sibling and two HLA 6/6 matched unrelated donor cells. Three patients developed acute grade 1 GVHD; one developed no acute GVHD. All four developed chronic GVHD (two limited, two extensive and all four with duration of less than 6 months).

New cases of osteonecrosis were identified in one hip and five knees as (Table 4). Among the 13 involved hips identified during follow-up, four have undergone total hip arthroplasty (THA). Two of these had THA before alloHCT and two afterward. In one patient, transient improvement in symptoms was documented after alloHCT, but subsequent progression required THA. All of these patients underwent core decompressions of the involved joints before THA.

Risk factors

Among the various risk factors studied, only pre-alloHCT osteonecrosis status (OR 13.50; 95% CI 2.64–68.92) and age ≥ 10 years at the time of alloHCT (OR 4.00; 95% CI 1.00–16.67) were associated with greater odds of osteonecrosis in the 3 years following alloHCT (Table 5). Black race was found to be significant on univariate analysis p=0.0431, but was not significant in models when patients with sickle cell disease were excluded. Other risk factors studied were not associated with an increased risk of osteonecrosis.

Discussion

Our analysis of prospectively acquired longitudinal MRs of hips and knees revealed a prevalence of osteonecrosis in almost 30% of the children in the first 3 years after a single alloHCT. Although knees were more often involved, hip involvement was more extensive. We observed complete resolution of osteonecrosis after alloHCT in two patients' hips and six patients' knees. Of those, one had osteonecrosis lesion involving more than 30% of the epiphyseal surface before alloHCT.

The prevalence of 30% is higher than previously reported rates that have been based on symptoms or less sensitive diagnostic techniques, but approach rates reported in MR-based studies;[12–16,26–30] symptom-based studies may underreport early-stage osteonecrosis. As we focused only on epiphyseal lesions of hips and knees[3], our findings may underestimate osteonecrosis-associated skeletal morbidity.

Aplastic anemia and ALL are well recognized risk factors for osteonecrosis following HCT[2,9]; we found no association in our post-alloHCT cohort. Our results conflict with those of our previous study, [19] where we evaluated risk factors for osteonecrosis before alloHCT and found some indication that a primary diagnosis of aplastic anemia or lymphoid malignancies may be a risk factor. As none of the published studies considered pre-alloHCT status, this discrepancy may be attributable to our risk factor analysis model adjusted for pre-alloHCT status.

The median time to development of osteonecrosis in our MR-based study was 12.3 months, a much shorter time period than reported in previous studies[3,7,8,10,12,31]. We found that only age older than 10 years and pre-existing osteonecrosis were predictive of an osteonecrosis in the 3 years following alloHCT. When future interventions that target early detection and prevention of osteonecrosis in the first 3 years following transplant are available, older children and children with existing lesions will be prime candidates for screening.

Older age has been consistently recognized as a risk factor for osteonecrosis [4,8]. White race has also been implicated as a risk factor for osteonecrosis [32]. We found no such association in our study population. Race was found to be statistically significant on univariate analysis but as sickle cell disease is strongly associated with black race, [25] we repeated analysis after excluding sickle cell patients and found no such association. Our cohort included 16 sickle cell patients, of whom eight were found to have osteonecrosis. Osteonecrosis is a well-known morbidity of sickle cell disease that has been positively

associated with the frequency of vaso-occlusive pain crises and elevated hematocrit [33]. This morbidity has been reported in 10–16% of symptomatic patients assessed radiographically [30,34,35] and in up to 40% of patients radiographically examined regardless of symptoms [29]. The high 50% prevalence of osteonecrosis we found in our sickle cell patients is similar to the MR-detected incidence of 65% reported after a follow-up period of 4 to 5 years [36].

Unlike other investigators, [10,13], we found no significant increase in risk for osteonecrosis among those who received TBI, possibly because our patients received very small doses of radiation per fraction (150 cGy/fraction twice daily).

The findings that pre-alloHCT osteonecrosis status was a risk factor for post-alloHCT osteonecrosis, and that GVHD was not an important risk factor during 3 years of follow-up supports the multiple hit theory of osteonecrosis; [37,38] steroid exposure imparts secondary rather than primary insult on the osteonecrosis pathway. Previous investigations, primarily conducted in adult populations, have identified an association between higher grade or longer duration of GVHD (acute or chronic) and osteonecrosis [2,3,7,8,11,39,40], attributing risk to prolonged exposure to steroids. We found no such association. Prolonged exposure to steroids was not a prominent characteristic of our population. In our study, only 12% of children developed GVHD that required steroid therapy treatment for longer than 6 months. As our population was followed for only 3 years post-alloHCT, it is possible that children in our cohort with chronic GVHD who eventually experience prolonged steroid exposure will develop osteonecrosis. Our analysis underscores the importance of pre-alloHCT therapeutic exposures, and the likelihood of osteonecrosis following alloHCT, and encourages us to explore novel options to curtail the compounding osteotoxic effect of glucocorticoids[41].

Another compelling finding in our study was regression or resolution of post-alloHCT osteonecrosis in several children. Of the patients whose osteonecrosis resolved completely, one initially had more than 30% epiphyseal involvement. As a standard of care at our institution, all children with osteonecrosis are managed conservatively until pain or restricted movement develops. At that time, analgesics and/or surgical options are offered. Whether these osteonecrosis regressions were the natural course of disease, a response to joint protection measures instituted in physical therapy[42], or a result of a protective effect of alloHCT is unknown.

Our data preclude us from making definitive conclusions about osteonecrosis recovery due to alloHCT. However, limited evidence[43–46] suggests that stem cells have a role in regenerative medicine. This reparative phenomenon may in part be attributed to mesenchymal stem cells or primitive hematopoietic cells with osteoblastic potential[43] engrafted during alloHCT. Increased chemotaxis by cytokines released from the necrosed bone may also facilitate mesenchymal stem cell homing and vascular proliferation[47,48].

Our findings should be interpreted with caution since the diverse primary diagnoses limited our ability to estimate the effect of disease pathophysiology or its treatment on the evolution of osteonecrosis. Because our study population was slightly older than patients who did not receive imaging, and because older age has been consistently associated with development

of osteonecrosis, our estimated incidence for osteonecrosis in the first 3 years following alloHCT may be inflated. Finally, although the lesions we detected in this cohort developed during the first 3 years after alloHCT, our study results do not provide information needed to ascertain delayed onset osteonecrosis in this population. Despite these limitations, we provide information about the prevalence and risk factors for development of osteonecrosis during the first 3 years after alloHCT among children.

Our results lead us to conclude that future screening and preventive strategies for osteonecrosis in children undergoing alloHCT should focus on pre-alloHCT risk factors among children who are older than 10 years of age. We recommend prospective controlled trials to determine the roles of physical therapy, mesenchymal stem cell therapy, and other novel interventions for treating early osteonecrotic lesions.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

This work was supported in part by grant number P30 CA-21765 from the National Institutes of Health, a Center of Excellence grant from the State of Tennessee, and the American Lebanese Syrian Associated Charities (ALSAC).

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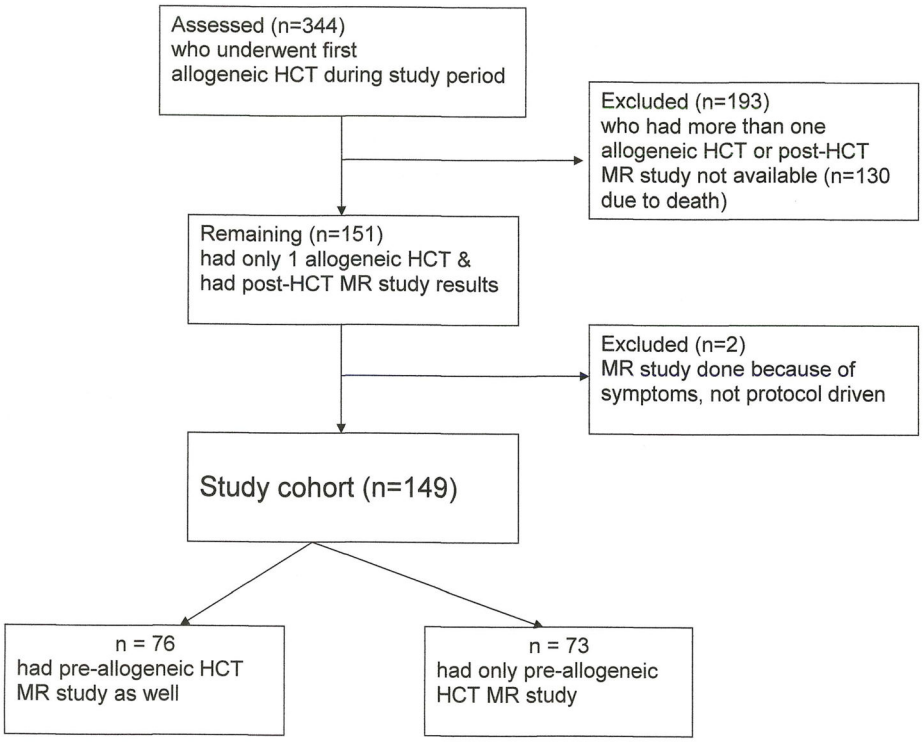

Figure 1. Study cohort description

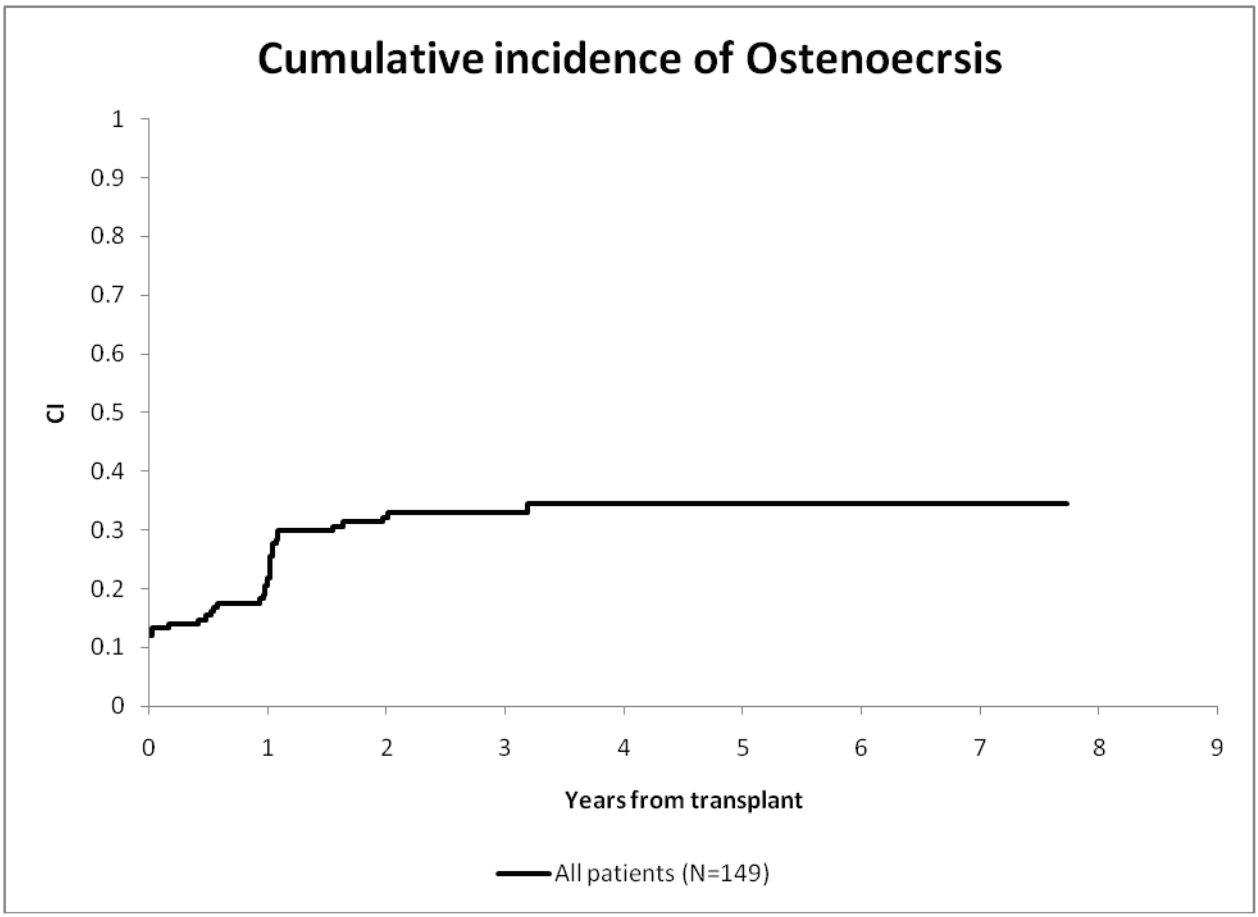

Figure 2. Cumulative incidence of osteonecrosis

Note: The intercept (in red) has been shown to be 12% (SE 2.68%), to emphasize that 14 patients were already known to have osteonecrosis at the time of alloHCT because of magnetic resonance imaging done prior to alloHCT.

Abbreviations: CI, cumulative incidence; ON, osteonecrosis

Table 1

Demographic data for patients who received magnetic resonance imaging after allogeneic HCT

Demographic variable	Frequency (n=149)	Percentage (%)
Sex		
Male	84	56
Female	65	44
Race		
Other	29	20
Black	28	19
White	92	62
Diagnosis		
Nonmalignant	33	22
Malignant	116	78
Primary diagnosis		
Others	87	58
Lymphoid malignancies & aplastic anemia	62	43
Survival status		
Dead	28	19
Alive	121	81
BMI at alloHCT*		
Normal & underweight	96	67
Overweight & obese	47	33
Age at MR**		
<10	51	34
≥10	98	66
Age at alloHCT		
<10	65	44
≥10	84	56
Conditioning regimen		
Total body irradiation	101	68
No-total body irradiation	48	32
Physis status at allo HCT		
Closed	42	28
Open	107	72
Acute GVHD maximum Overall grade		
No acute GVHD	30	20
Grade 1, 2	81	54
Grade 3, 4	38	26
Chronic GVHD grade		
No chronic GVHD	92	62
Limited	26	18
Extensive	31	21

Demographic variable	Frequency (n=149)	Percentage (%)
Donor type		
Unrelated	57	381
Related	92	62
Donor match type		
HLA-matched siblings	49	33
Matched unrelated donors	57	38
Mismatched family members	43	29
Product type		
HPC-A	47	32
HPC-C	1	1
HPC-M	101	68
Duration of chronic GVHD		
No prior chronic GVHD	92	62
Duration ≤ 6 months	39	26.
Duration > 6 months	18	12

* BMI calculated only for children more than 2 years old.

** Age at the first peak osteonecrosis, if a patient did not have any positive imaging result; age at the last imaging date was used.

Abbreviations: alloHCT, allogeneic hematopoietic stem cell transplantation; BMI, Body mass index; GVHD, Graft vs. host disease;; HPC-A, Hematopoietic stem cell from peripheral blood; HPC-M, Hematopoietic stem cell from Marrow; HPC-C, Hematopoietic stem cell from cord; MR, magnetic resonance imaging

Table 2

Characteristics of study cohort (*N* =149) versus those who were excluded (*N* = 195)

Characteristics		Total *n* (%)	Excluded *n* (%)	Study Cohort *n* (%)	P value
Gender	Male	216 (63)	132 (68)	84 (56)	**0.0332**•
	Female	128 (37)	63 (32)	65 (44)	
Race	White	213 (62)	121 (62)	92 (62)	0.8501
	Black	68 (20)	40 (21)	28 (19)	
	Other	63 (18)	34 (17)	29 (20)	
Diagnosis	Non-malignant	68 (20)	35 (18)	33 (22)	0.3422
	Malignant	276 (80)	160 (82)	116 (79)	
Primary Disease	Others	212 (62)	125 (64)	87 (58)	0.3143
	Lymphoid Malignancies + Aplastic Anemia	132 (38)	70 (36)	62 (42)	
Age at alloHCT	Age at alloHCT <10	174 (52)	109 (56)	65 (44)	**0.0294**•
	Age at alloHCT >=10	170 (49)	86 (44)	84 (56)	
Donor Type	Unrelated	113 (33)	56 (29)	57 (38)	0.0650
	Related	231 (67)	139 (71)	92 (62)	
Conditioning regimen	Total Body Radiation	204 (59)	103 (54)	101 (68)	**0.0103**•
	No TBI	137 (40)	89 (46)	48 (32)	

• Values depicted in bold were statistically significant

Abbreviations: alloHCT, allogeneic hematopoietic stem cell transplantation; TBI, Total body irradiation

Table 3

Longitudinal changes in the osteonecrotic lesions in children observed with magnetic resonance imaging during the first year after alloHCT.

MR results before alloHCT		MR results one year after alloHCT			Total
		Not Involved	ON; < 30% Epiphyseal involvement	ON; ≥ 30% Epiphyseal involvement	
Hips:	Not done/Missing	63	0	3∞	66
	Not Involved	49	0	4∞	53
	ON; < 30% Epiphyseal involvement	1•	1	0	2
	ON; ≥ 30% Epiphyseal involvement	1•	0	2	3
	Total	114	1	9	124
Knees:	Not done/Missing	59	8∞	5∞	72
	Not Involved	34	7∞	5∞	46
	ON; < 30% Epiphyseal involvement	2•	7	1	10
	ON; ≥ 30% Epiphyseal involvement	0	1±	0	1
	Total	95	23	11	129

Abbreviations: alloHCT, allogeneic hematopoietic stem cell transplantation; MR, magnetic resonance imaging; ON, osteonecrosis

•Cases that showed complete resolution;

∞New lesions identified during first year

±Cases that showed regression of the osteonecrosis lesion

Table 4

Longitudinal changes in the osteonecrotic lesions in children observed with magnetic resonance imaging during the second year after alloHCT.

One year post alloHCT MR imaging results		Two year post alloHCT MR imaging results				Total
		Not done/Missing	Not Involved	ON; < 30% Epiphyseal involvement	ON; ≥ 30% Epiphyseal involvement	
Hips:	Not done/Missing	12	2	0	0	14
	Not Involved	58	55	0	1∞	114
	ON; < 30% Epiphyseal involvement	0	0	1	0	1
	ON; ≥ 30% Epiphyseal involvement	3	0	1±	5	9
	Total	73	57	2	6	138
Knees:	Not done/Missing	6	2	0	1∞	9
	Not Involved	53	38	4∞	0	95
	ON; < 30% Epiphyseal involvement	7	4•	11	1	23
	ON; ≥ 30% Epiphyseal involvement	2	0	1±	8	11
	Total	68	44	16	10	138

Abbreviations: MR, magnetic resonance imaging; ON, osteonecrosis

∞New cases identified with osteonecrosis during second year after allogeneic HCT

±Case that showed regression in the size of the osteonecrosis lesions after allogeneic HCT

•Cases that showed complete resolution

Table 5

Risk factor analysis for osteonecrosis after alloHCT

Univariate analysis using GEE model			
Clinical Variables	**Clinical Level**	**95% CI of OR**	**P Values**
BMI at alloHCT	Normal Underweight	0.86(0.40 to 1.83)	0.6925
	Overweight Obese		
Gender	Female	1.81(0.87 to 3.74)	0.1108
	Male		
Race	Black	2.09(0.87 to 5.05)	0.1011
	Other	0.49(0.06 to 4.25)	0.5138
	White		
Diagnosis type	Malignant	1.04(0.43 to 2.50)	0.9283
	Non-malignant		
Primary Diagnosis	Lymphoid Malignancies + Aplastic Anemia	1.40(0.68 to 2.88)	0.3662
	Others		
Age at alloHCT	Age at alloHCT <10	0.15(0.06 to 0.37)	<.0001
	Age at alloHCT >=10		
Chronic GVHD grade	Extensive	1.33(0.55 to 3.21)	0.5302
	Limited	1.33 (0.48 to 3.64)	0.5819
	No chronic GVHD		
Acute GVHD Maximum Overall Grade	No acute GVHD grade ≥ 1	0.82(0.32 to 2.12)	0.6834
Physis Status	Closed	3.33(1.55 to 7.15)	0.0020
	Open		
Donor Type	Related	1.78(0.82 to 3.89)	0.1465
	Unrelated		
Conditioning regimen	NO TBI	1.16(0.54 to 2.51)	0.7020
	TBI		
Duration of Chronic GVHD, 6 months	No prior chronic GVHD		
	Duration <= 6 month	1.29(0.56 to 2.95)	0.5455
	Duration > 6 month	1.42(0.44 to 4.58)	0.5546
Pre-alloHCT MR	Involved	14.19(3.52 to 57.27)	0.0002
	Not done/Missing	0.75(0.33 to 1.74)	0.5074
	Not involved		
Multiple GEE model analysis[#]			
Variable	**Clinical Level**	**95% CI of OR**	**P Values**
Pre-alloHCT MR	Involved	13.50(2.64 to 68.92)	0.0018
	Not Involved	0.86(0.30 to 2.51)	0.7867
	Not done/Missing		
Physis	Closed	1.42(0.41 to 4.94)	0.5827
	Open		
Age at alloHCT	Age at HCT <10	0.25(0.06 to 1.01)	

Univariate analysis using GEE model			
Clinical Variables	**Clinical Level**	**95% CI of OR**	**P Values**
	Age at HCT >=10	4.00 (1.00 to 16.7)	0.0518
Race	Black	2.64(0.82 to 8.52)	0.1046[#]
	Other	0.53(0.05 to 5.44)	0.5925[#]
	White		
Gender	Female	1.10(0.42 to 2.86)	0.8462
	Male		

Abbreviations: alloHCT, allogeneic hematopoietic stem cell transplantation; BMI, body mass index; GVHD, graft vs. host disease; TBI, total body irradiation; MR, magnetic resonance imaging

[#]Only factors significant (0.1 significant level) from univariate GEE model were included in this model

[#]For race analysis sickle cell patients were excluded.