Incidence of Severe Osteonecrosis Requiring Total Joint Arthroplasty in Children and Young Adults Treated for Leukemia or Lymphoma: A Nationwide, Register-Based Study in Finland and Denmark

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Purpose: The population-based incidence of severe osteonecrosis (ON) necessitating total joint arthroplasty (TJA) in patients with hematological cancer is unknown. This study assessed the incidence of ON requiring primary TJA in children and young adults treated for leukemia or lymphoma.

Methods: Patients diagnosed with leukemia or lymphoma before 31 years of age were identified from the Finnish and Danish Cancer Registries. These data were combined with those from the National Hospital Discharge and the Finnish Arthroplasty Registers. Data on the orthopedic procedures performed and the appropriate diagnosis codes given before the age of 40 were also retrieved.

Results: The estimated cumulative incidence of TJA was 4.5% at 20 years for patients treated for chronic myeloid leukemia, followed by 2.1% for patients treated for acute myeloid leukemia. It was considerably lower in patients with acute lymphoblastic leukemia (ALL; 0.4%). Multivariate analysis revealed that allogeneic stem cell transplantation (allo-SCT) increased the risk of TJA (hazard ratio [HR]=9.4; 95% CI: 5.3–16.9). The risk of TJA was higher in patients diagnosed with cancer at 10–19 and 20–30 years of age than in those diagnosed before the age of 10 (HR=24; 95% CI: 3.1–176 and HR=26; 95% CI: 3.6–192 respectively).

Conclusion: The incidence of ON requiring TJA was highest among patients with myeloid leukemias and lowest in patients treated for ALL. Allo-SCT and age ≥ 10 years at diagnosis were the most important risk factors for ON requiring TJA in hematological malignancies.

Keywords: osteonecrosis, total joint arthroplasty, chronic myeloid leukemia, acute myeloid leukemia, acute lymphoblastic leukemia

MORE THAN 80% OF CHILDREN and adolescents with hematological cancer are expected to be cured and become long-term survivors.^{1,2} Along with the rapidly growing number of long-term survivors, a major challenge is to reduce treatment-related late effects for this population. Osteonecrosis (ON) is an extremely rare disorder in the general population,³ but is an important late effect in children and young adults treated for leukemia or lymphoma. The pathophysiology of ON has not been well elucidated, but corticosteroid-induced apoptosis of osteocytes⁴ and ischemic insult to the bone and bone marrow⁵ have been suggested.

Although several factors are associated with the etiology of ON, exposure to glucocorticoids (especially prolonged treatment with dexamethasone^{6–8}) and diagnosis between 10 and 20 years of age^{9,10} have been consistently associated with higher risk of ON. There are only a few studies of patients older than 20 years of age, one of which found that individuals younger than 20 years of age are at higher risk of ON than patients older than 20.¹¹ Allogeneic stem cell transplantation (allo-SCT) across all ages^{12–14} and treatment with radiation in childhood have also been reported to increase the risk of ON.⁶

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The overall incidence of symptomatic ON in pediatric and adolescent cancer survivors is low, ranging from 0.4% to 1.4%.^{6,7} However, patients with hematological malignancies seem to have a remarkably higher incidence of ON. In patients with pediatric or adolescent acute lymphoblastic leukemia (ALL), the incidence of symptomatic ON has been reported to vary from 1.1% to 9.3%,^{7,9,10,15} but magnetic resonance imaging (MRI) screening has revealed that the incidence may actually range from 15.5% to 38%.^{16–18} MRI has been established as the most sensitive method for the early diagnosis of ON.^{19,20}

The majority (up to 70%) of pediatric cancer patients with ON identified by systematic MRI screening remain asymptomatic, do not require treatment, and improve with time.^{17,21–23} Among younger adults, especially cancer survivors, ON may be the cause of the destruction and collapse of the femoral head.⁵ However, the long-term consequences of symptomatic and asymptomatic ON are unknown, and the proportion of cancer survivors in need of total joint arthroplasty (TJA) has not been reported. TJA is performed on patients with symptomatic joint destruction. In the total hip arthroplasty procedure, the affected femoral head and damaged acetabular cartilage are removed and replaced with an implant.

The purpose of this nationwide, population-based study in Finland and Denmark was to assess the incidence of and risk factors for severe ON requiring TJA in patients treated for leukemia or lymphoma in children and young adults diagnosed before the age of 31 years.

Methods

Patients diagnosed with leukemia or lymphoma before 31 years of age were identified from the Finnish and Danish Cancer Registries. These data were combined with data from the Finnish and Danish National Hospital Discharge Registers and the Finnish Arthroplasty Registry. Data on the orthopedic procedures performed and the appropriate diagnosis codes given before the age of 40 were also retrieved.

Data sources

Finnish and Danish Cancer Registries. The population-based and nationwide Finnish Cancer Registry has collected data on all cancers diagnosed in Finland since 1953. The registry is more than 99% complete and very accurate.²⁴ The Danish Cancer Registry is a population-based registry containing data on the incidence of cancer throughout Denmark since 1943. Details of individual cases of cancer are available

according to the 7th revision of the International Classification of Diseases (ICD) for all years, and according to the ICD-O since 1978.²⁵ The patient population was identified from the two cancer registries: cancer diagnosed at 0–30 years of age in the period from 1975 to 2000 in Finland and from 1975 to 2006 in Denmark. Only patients who survived for at least 2 years after diagnosis were included.

Finnish and Danish National Hospital Discharge Registers. The Finnish National Hospital Discharge Register (FNHDR) is maintained by the National Institute for Health and Welfare and contains comprehensive healthcare records on inpatients, provided by all hospitals and municipal health centers in Finland. In the FNHDR, information about the discharge diagnoses, surgical procedures, dates of admission and discharge, and hospital code has been recorded since 1967. The coverage and accuracy of the diagnosis registration are approximately 90%.²⁶ During the study period, Finnish Procedure Coding 1983 and 1996, Classification of diseases 1969 and 1987, and ICD-10 were used in Finland, and ICD-8 and ICD-10 were used in Denmark.

The Danish National Hospital Discharge Register (DNHDR) has information on all discharges from Danish hospitals since 1977, and records 99.4% of all discharges from public somatic hospitals in Denmark.²⁷ The register includes information about discharged patients' hospital, surgical procedures, discharge diagnoses, and day of discharge. Discharge diagnoses in the DNHDR are classified according to the ICD-8 for 1977 to 1993 and the ICD-10 for 1994 to the present.

The personal identification codes of the cancer registries were combined with the FNHDR and DNHDR data. The data from the NHDRs were used to determine the number of discharges according to the ICDs and procedures coding. Patients' orthopedic diagnoses and procedures performed before the age of 40 during 1980–2008 were extracted. This age limit was chosen because the incidence of TJA increases significantly after the age of 40.²⁸ From the extracted data, this study reports the cases in which patients underwent primary hip or knee TJA. We also obtained data concerning the diagnoses of ON and rheumatoid diseases, fractures, and allogeneic stem cell transplantation. Data on allo-SCT were retrieved for analysis as a potential risk factor. Patients with rheumatoid diseases or fractures as the indication for TJA were excluded from the analysis.

Finnish Arthroplasty Registry. The Finnish Arthroplasty Registry has been collecting information on total hip and knee

TABLE 1. PATIENTS WITH TOTAL JOINT ARTHROPLASTY BY LEUKEMIA OR LYMPHOMA TYPE (N=6358)

Diagnosis	Patients with TJA, n (hip/knee)	Total number of patients	Proportion of patients with TJA (95% CI)	Mean age in years (range) at cancer diagnosis among patients with TJA	Mean age in years (range) at time of TJA	Mean time in years (range) from cancer diagnosis to TJA
CML	8 (8/0)	201	4.0 (1.7–7.7)	20.5 (11.0–27.4)	26.9 (20.1–36.0)	6.4 (2.8–10.1)
AML	8 (7/1)	449	1.8 (0.8–3.4)	24.3 (19.1–28.2)	29.1 (23.6–34.3)	4.8 (0.7–9.6)
HL	17 (16/1)	2319	0.7 (0.4–1.2)	22.3 (14.0–29.0)	29.9 (17.3–40.0)	7.6 (0.1–17.1)
NHL	6 (6/0)	1191	0.5 (0.2–1.1)	21.0 (16.5–30.8)	25.5 (18.5–39.1)	4.5 (0.8–8.4)
ALL	9 (8/1)	2198	0.4 (0.2–0.8)	19.9 (7.5–30.2)	26.7 (17.3–37.1)	6.7 (1.7–23.7)
All cancers	48 (45/3)	6358	0.8 (0.6–1.0)	21.7 (7.5–30.8)	28.1 (17.3–40.0)	6.4 (0.1–23.7)

ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; CI, confidence interval; CML, chronic myeloid leukemia; HL, Hodgkin lymphoma; NHL, non-Hodgkin lymphoma; TJA, total joint arthroplasty.

FIG. 1. Cumulative incidence of total joint arthroplasty due to osteonecrosis following cancer diagnosis. ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; CML, chronic myeloid leukemia; HL, Hodgkin lymphoma; NHL, non-Hodgkin lymphoma; TJA, total joint arthroplasty.

replacements since 1980.²⁹ All hospitals that perform TJA procedures, including private and community hospitals, are required to provide the National Agency for Medicines information essential for maintaining the registry. The Finnish Cancer Registry personal identification codes were combined with the Finnish Arthroplasty Registry data to ensure that all patients with TJA were included. For Finland, we used the Arthroplasty Registry and the Hospital Discharge Register to identify all the arthroplasties performed. For Denmark, we used only the Hospital Discharge Register because the Danish Arthroplasty Registry was not initiated until 1995.

Treatment protocols

The Nordic protocols have been used to treat pediatric patients with ALL since July 1981 and patients with acute myeloid leukemia (AML) since July 1984.^{30,31} All other patients were treated using various international protocols.

Statistical analysis

Incidence rates of ON requiring TJA and 95% confidence intervals (CI) were calculated for the various cancer diag-

noses. The differences in incidence rates per 1000 person-years between patients with and without allo-SCT were tested using Fisher's exact test. The associations between patient characteristics and TJA were analyzed by univariate and multivariate Cox regression analyses. The results of the analyses are presented as hazard ratios (HRs) and the 95% CIs. The timing of TJA from the date of cancer diagnosis to event was estimated according to Kaplan-Meier analysis. The follow-up time for patients without TJA ended when the patient reached 40 years of age or the date of data extraction if the patient was younger at that time. Patients who died or had not undergone TJA before 40 years of age were censored at that time. The log-rank test was used to assess the differences in cumulative survival between the different types of cancers. Two-tailed *p*-values of <0.05 were considered significant. All analyses were performed using SPSS Statistics version 20.0.0 (IBM, Chicago, IL) and StatsDirect 2.7.2 (StatsDirect Ltd., England).

This study was approved by the Ethics Committee of Oulu University Hospital in Finland and the Danish Data Protection Agency. The Ministry of Social Affairs and Health and Statistics in Finland gave permission for the use of data from the registers.

Results

Patients requiring total joint arthroplasty

The total number of patients in this cohort was 6358 (Table 1). TJA was performed on 48 (0.8%) patients, of whom 33 were male. The mean age at primary cancer diagnosis was 21.7 years (range: 7.5–30.8) for patients requiring TJA. The mean time from cancer diagnosis to the first TJA was 6.4 years (range: 0.1–23.7; Fig. 1). The estimated cumulative incidence of TJA was 4.5% at 20 years from diagnosis for patients treated for chronic myeloid leukemia (CML), followed by 2.1% for patients treated for AML (Fig. 1). In comparison, the rate was considerably lower for patients with ALL at only 0.4%. The hip was the most commonly involved joint (*n* = 45); knee TJA was performed in only three patients. Allo-SCT was performed in 574 of the 6358 (9.0%) patients; TJA was primarily detected in this group (Table 2). Included in this cohort is one patient with Hodgkin lymphoma (HL) who had TJA only 1 month after his primary cancer was diagnosed, which is unusual, but he was included, as he did not have any excluding diagnoses of fracture or rheumatoid arthritis.

TABLE 2. COMPARISON OF INCIDENCE RATE OF TOTAL JOINT ARTHROPLASTY PER 1000 PERSON-YEARS BETWEEN PATIENTS WITH AND WITHOUT ALLO-SCT (*N* = 6538)

Diagnosis	Patients with allo-SCT, <i>n</i> = 574 (TJA/person-years)	IR	Patients without allo-SCT, <i>n</i> = 5784 (TJA/person-years)	IR	Rate ratio	95% CI	<i>p</i> -value
CML	7/935	7.5	1/2791	0.3	20.9	2.7–942	<0.001
AML	8/1485	5.4	0/5214	0	∞	6.0–∞	<0.001
HL	0/633	0	17/39,921	0.4	0	0–15	0.999
NHL	2/510	3.9	4/19,148	0.2	18.8	1.7–131	0.009
ALL	3/3526	0.9	6/33,477	0.2	4.7	1.0–19	0.053
All cancers	20/7089	2.8	28/100,551	0.3	10.1	5.4–19	<0.001

Note. *p*-values <0.05 are indicated in bold.

allo-SCT, allogeneic stem cell transplant; ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; CI, confidence interval; CML, chronic myeloid leukemia; HL, Hodgkin lymphoma; IR, incidence rate; NHL, non-Hodgkin lymphoma; TJA, total joint arthroplasty.

FIG. 2. Age at cancer diagnosis for patients with total joint arthroplasty. ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; CML, chronic myeloid leukemia; HL, Hodgkin lymphoma; NHL, non-Hodgkin lymphoma; TJA, total joint arthroplasty.

Age at cancer diagnosis in patients with total joint arthroplasty

The probability of ON requiring TJA was very low in children diagnosed before the age of 10. The single case was a patient diagnosed with ALL before the age of 10 who underwent TJA 23 years after the cancer diagnosis. The incidence increased among those diagnosed at age 10 years or greater and continued to increase steadily thereafter (Fig. 2).

Among patients with CML who were diagnosed between 10 and 30.9 years of age, the percentage of patients who underwent TJA remained constant as compared to the incidence of CML. In contrast, the incidence of AML peaked in early childhood, but TJA was performed mainly in patients who were diagnosed when they were older than 20 years of age. TJA was performed more often in patients with ALL diagnosed at an older age, particularly in patients whose age at diagnosis was 15 or older. The incidence of HL and non-Hodgkin lymphoma (NHL) increased with age, similar to that of subsequent TJA (Fig. 3).

Risk factors in Cox regression analysis

Univariate analyses for allo-SCT, age at diagnosis, and gender revealed allo-SCT was an important risk factor for ON requiring TJA in patients with CML, AML, and NHL. Older

FIG. 3. Total number of cancer patients (graph) and cancer patients with total joint arthroplasty (black boxes) according to age at primary cancer diagnosis. Note: Different scales are used for each cancer type. ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; CML, chronic myeloid leukemia; HL, Hodgkin lymphoma; NHL, non-Hodgkin lymphoma; TJA, total joint arthroplasty.

TABLE 3. UNIVARIATE ANALYSIS OF RISK FACTORS IN LEUKEMIA AND LYMPHOMA PATIENTS USING TOTAL JOINT ARTHROPLASTY AS A DEPENDENT VARIABLE (N=6538)

Diagnosis	Characteristic	TJA – (n)	TJA + (n)	HR	95% CI	p-value
CML	allo-SCT					
	No	126	1	1		
	Yes	67	7	13.2	1.6–109.3	0.017
AML	allo-SCT					
	No	315	0	1		
	Yes	126	8	42.4	2.4–740.1	<0.001
	Gender					
	Female	236	1	1		
	Male	205	7	8.1	0.98–66.7	0.052
NHL	allo-SCT					
	No	1143	4	1		
	Yes	42	2	13.6	2.4–76.4	0.003
ALL	Age ^a					
	<10 years	1588	1	1		
	10–19 years	447	4	14.2	1.6–127.5	0.018
	≥20 years	154	4	41.2	4.6–71.3	0.001
All cancers	Gender					
	Female	2768	15	1		
	Male	3542	33	1.7	0.9–3.2	0.083
	Age ^a					
	<10 years	2058	1	1		
	10–19 years	1628	18	22.8	3.0–170.6	0.002
	20–30 years	2624	29	22.8	3.1–67.1	0.002
	allo-SCT					
	No	5766	28	1		
	Yes	554	20	7.4	4.2–13.3	<0.001

Note. p-values <0.05 are indicated in bold.

^aAge at diagnosis.

allo-SCT, allogeneic stem cell transplant; ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; CI, confidence interval; CML, chronic myeloid leukemia; HR, hazard ratio; NHL, non-Hodgkin lymphoma; TJA, total joint arthroplasty.

age at diagnosis of ALL was found to increase the risk of undergoing TJA significantly (Table 3). None of the tested variables was statistically significant in patients with HL.

The results of the multivariate analysis with allo-SCT, age, and gender entered into the model revealed that allo-SCT and age at diagnosis were the significant risk factors for undergoing TJA. SCT increased the risk of TJA (HR=9.4; 95% CI: 5.3–16.9; $p<0.001$). Older age at diagnosis increased the risk of undergoing TJA for patients aged 10–19 years old (HR=26; 95% CI: 3.2–192; $p=0.002$) and for those 20 years or older at diagnosis (HR=27; 95% CI: 3.6–196; $p=0.001$) compared to those younger than 10 years of age at diagnosis. Gender was not significantly associated with TJA (HR=1.6; 95% CI: 0.84–2.9; $p=0.160$).

Discussion

Based on our review of the medical literature, this is the first population-based study of the incidence of ON requiring TJA. We report the incidence of ON requiring TJA in patients diagnosed with leukemia or lymphoma in childhood, adolescence, and young adulthood. The highest estimated cumulative incidence at 20 years from diagnosis was in patients treated for CML (4.5%); the lowest was in patients treated for ALL (0.4%). Allo-SCT was the most important risk factor. Older age at diagnosis increased the risk of undergoing

TJA: patients who were 10–19 and 20–30 years old at diagnosis were at higher risk of TJA than those <10 years old at diagnosis. The incidence of severe ON requiring TJA may be even higher because the follow-up ended at 40 years of age. We found no impact for gender on TJA.

In this study of patients treated for leukemia or lymphoma, total hip arthroplasty ($n=45$) was far more common than total knee arthroplasty ($n=3$). The rate of total hip arthroplasties performed was 0.7% (45/6358). A Finnish population-based study of the same study period found that the respective rate of hip arthroplasties was estimated at 0.08% (80/100,000) among patients between 30 and 39 years of age,²⁸ indicating that TJA is an extremely rare procedure in young patients, even among those slightly older than our study population.

The high risk of severe ON in patients treated for myeloid leukemia could be due to the higher frequency of allo-SCT in this group: 37% of patients with CML and 30% of patients with AML had undergone allo-SCT. For CML in particular, the disease itself and the high leukocyte count could explain the high risk of severe ON and TJA. Some case reports have described patients who developed ON at the time of diagnosis when laboratory investigations revealed hyperleukocytosis and leukostasis,^{32–34} which may be associated with microcirculatory obstruction of the femoral head.

Allo-SCT was a significant independent risk factor for ON requiring TJA among patients with AML, NHL, and CML, but not in patients with HL or ALL. Patients treated for HL were the largest group with ON requiring TJA but who had not had allo-SCT, which may be explained by the intensive use of glucocorticoids in HL protocols. Previous studies among patients treated with allo-SCT have revealed that both acute and chronic graft-versus-host disease and its treatment with glucocorticoids are risk factors for ON.^{12–14} Patients with ALL were at the lowest risk for severe ON requiring TJA. Only 0.4% of the patients with ALL required TJA, which is consistent with the results of a recent Dutch study¹⁵ in which only 2 of 694 (0.3%) patients with pediatric ALL received total hip arthroplasties. Despite the high reported incidence of ON in patients with ALL,¹⁵ the incidence of the most severe form of ON necessitating TJA due to joint destruction with severe pain appears to be rare.

While it is well established that patients diagnosed between 10 and 20 years of age are at increased risk of ON,^{9,10} there is a paucity of studies about ON in young adults. In a study conducted in the United Kingdom, adolescents younger than 20 years of age at the time of diagnosis with ALL were at higher risk of ON than were ALL patients older than 20 years of age at the time of diagnosis.¹¹ In our study, the risk of ON requiring TJA increased with age at diagnosis, even for patients diagnosed between 20 and 30 years of age.

Our study has many advantages, including the nationwide coverage of cancer patients in cancer registries and systematic follow-up using the national hospital discharge registers of two countries. Arthroplasty and hospital discharge registers are used worldwide as a source for orthopedic research. The registers used in this study have been shown to be very reliable.^{25,26} The cohort size of 6358 survivors with hematological malignancies enabled us to investigate less prevalent late effects, such as ON requiring TJA. Even large ON on an MRI scan can be asymptomatic and not cause problems to the patient in the future. By using TJA as an endpoint, the most severe symptomatic cases of ON can be identified.

The weakness of our study is that the register-based data do not include detailed data on medical treatment, such as glucocorticoids, radiological staging of ON, or precise indication for TJA. In the orthopedic literature, there are no standardized clinical or radiological indications for TJA. The generally accepted indication for TJA is symptomatic destruction of the joint caused by arthritis, ON, or trauma that is not treatable with conservative protocols, such as pain medication, physiotherapy, or other surgical means. Therefore, even the availability of all medical records would not have changed the study in terms of determining indication for TJA. Indications for TJA are always relative, but symptoms and radiological findings have to be severe enough to justify a major operation. This is always a patient-dependent consideration.

Conclusion

Severe ON requiring TJA is rare among survivors of leukemia and lymphoma in childhood, adolescence, or young adulthood. ON requiring TJA is most prevalent among those treated for myeloid leukemia between 10 and 30 years of age, particularly following allogeneic stem cell transplantation. Although ON detected by MRI is a common complication in ALL, in the current study, the frequency of TJA was lowest in patients with ALL.

Based on our results, prospective MRI monitoring of patients with leukemia and lymphoma after stem cell transplantation should be considered. Prospective intervention studies on medical treatment, such as bisphosphonates or surgical procedures other than TJA, are needed to evaluate whether early detection and treatment of ON could prevent the need for TJA.

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Author Disclosure Statement

No competing financial interests exist.

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