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SECOND MALIGNANCIES AFTER AUTOLOGOUS HEMATOPOIETIC CELL TRANSPLANTATION IN CHILDREN

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SUPPLEMENTAL INFORMATION

Supplementary information related to this study is available at BMT's website.

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Abstract

Childhood autologous hematopoietic cell transplant (AHCT) survivors can be at risk for secondary malignant neoplasms (SMNs). We assembled a cohort of 1,487 pediatric AHCT recipients to investigate the incidence and risk factors for SMNs. Primary diagnoses included neuroblastoma (39%), lymphoma (26%), sarcoma (18%), CNS tumors (14%), and Wilms tumor (2%). Median follow-up was 8 years (range, <1–21 years). SMNs were reported in 35 patients (AML/MDS=13, solid cancers=20, subtype missing=2). The overall cumulative incidence of SMNs at 10 years from AHCT was 2.60% (AML/MDS=1.06%, solid tumors=1.30%). We found no association between SMNs risk and age, gender, diagnosis, disease status, time since diagnosis, or use of total body irradiation or etoposide as part of conditioning. Overall survival at 5-years from diagnosis of SMNs was 33% (95% CI, 16–52%). When compared to age- and gender-matched general population, AHCT recipients had 24 times higher risks of developing SMNs (95% CI, 16.0–33.0). Notable SMN sites included bone (N=5 SMNs, observed (O)/expected (E)=81), thyroid (N=5, O/E=53), breast (n=2, O/E=93), soft tissue (N=2, O/E=34), AML (N=6, O/E=266), and MDS (N=7, O/E=6603). Risks of SMNs increased with longer follow-up from AHCT. Pediatric AHCT recipients are at considerably increased risk for SMNs and need life-long surveillance for SMNs.

Keywords

Hematopoietic cell transplantation; Autologous; Pediatric; Second Cancers; Risk factors

INTRODUCTION

Autologous hematopoietic-cell transplantation (AHCT) is a well-established treatment option for some pediatric patients with aggressive malignancies, including neuroblastoma(1–3), brain tumors(4), Hodgkin's disease(5), and certain sarcomas.(6) The long-term toxicities, especially the incidence and risk factors for second malignant neoplasms (SMNs), have not been well characterized in this population.

The risk of developing SMNs is higher in childhood cancer survivors than in the general population.(7, 8) A recent study of the Childhood Cancer Survivor Study (CCSS) cohort (n=14,358 childhood cancer survivors) showed increased risk of SMNs among all primary childhood cancer diagnoses.(8) When compared to the general population, the overall standardized incidence ratio of developing SMNs was 6.4 with an estimated 30-year cumulative incidence of 9.3%. The use of high dose chemotherapy to eradicate disease in these aggressive pediatric malignancies, specifically alkylating agents, anthracyclines, and epipodophyllotoxins increased the risk of SMNs. Radiation has also been shown to increase the risk of SMNs. Revelations of the long-term effects of radiation therapy began to emerge in the 1970–1980's with development of SMNs in known radiation fields.(9) It has been shown that there is a close relationship between the risk of SMNs and radiation dose in childhood cancer survivors.(8) Central nervous system (CNS) SMNs, specifically

subsequent gliomas and meningiomas, have been associated with prior radiation therapy.(10, 11)

Allogeneic hematopoietic stem cell transplantation also increases the risk for SMNs in children.(12–15) In one of the largest studies to date, the Center for International Blood and Marrow Transplant Research (CIBMTR) assembled a large multi-institutional cohort of allogeneic transplant recipients with a median age of 27 years (58% of the cohort was <30 years of age). New solid malignancies occurred at twice the rate of expected general population rates, with risk increasing over time.(15) Furthermore, exposure to radiation was specifically associated with risks of SMNs in pediatric transplant recipients.

In comparison to childhood cancer survivors in general and pediatric recipients of allogeneic HCT, the incidence, characteristics, and risks of SMNs after AHCT in children have not been well described. We present a study of the incidence and risk factors for SMNs among pediatric AHCT survivors using a large cohort from the CIBMTR with extended followup.

PATIENTS AND METHODS

Data Sources

The CIBMTR, is a research affiliation of the International Bone Marrow Transplant Registry (IBMTR), Autologous Blood and Marrow Transplant Registry (ABMTR), and the National Marrow Donor Program (NMDP). The CIBMTR comprises a voluntary working group of more than 450 transplantation centers worldwide that contribute detailed data on consecutive allogeneic and autologous hematopoietic cell transplantation to a Statistical Center at the Medical College of Wisconsin in Milwaukee and the NMDP Coordinating Center in Minneapolis. Participating centers are required to report all transplants consecutively. Patients are followed longitudinally. Computerized checks for discrepancies, physicians' review of submitted data, and on-site audits of participating centers ensure data quality. Observational studies conducted by the CIBMTR are performed in compliance with all applicable federal regulations pertaining to the protection of human research participants. Protected Health Information used in such research is collected and maintained in CIBMTR's capacity as a Public Health Authority under the HIPAA Privacy Rule.

Patients

Our study analyzed a cohort of patients who underwent AHCT from 1987 to 2003 in transplant centers located in the United States or Canada and for whom CRF-level data were reported to the CIBMTR. Patients were included in this study if they were younger than 21 years of age at time of AHCT. The cohort was restricted to survivors of first AHCT for lymphoma or solid tumors (neuroblastoma, CNS tumors, rhabdoid tumors, Ewing's sarcoma, primitive neuro-ectodermal tumors, Wilms tumor, or other sarcomas).

Overall, 1,626 patients met the study eligibility criteria. Since follow-up information regarding long-term survival and secondary malignancies was required, patients from centers with a follow-up completeness index (ratio of total observed to potential person-time of follow-up) of <80% at 5 years after transplantation were excluded (139 patients from 21 centers).(16) The final study population consisted of 1,487 patients from 111 centers.

Pathology and physician reports of second cancers were reviewed centrally, and if necessary, tumors were reclassified.

Statistical Analysis

The objectives of this study were to determine the incidence of SMNs in pediatric AHCT survivors, to evaluate risk-factors for SMNs in this population and to compare the risks of SMNs with an age- and gender-matched general population. The cumulative probability of a new cancer was estimated by the cumulative incidence function that accounted for the competing risk of death among patients who did not develop a second malignancy.(17) Univariate probabilities of overall survival were calculated by the Kaplan-Meier estimator.(18) Among patients who had received more than one AHCT, follow-up and time to event were considered from the first transplant. Thirty-nine patients received an allogeneic transplant after their first AHCT; follow-up time for these patients was censored at the time of their allogeneic transplant.

Potential risk factors for second cancers were analyzed with the use of Cox regression models.(19) Variables considered included age at AHCT, gender, diagnosis (lymphoma, sarcoma, CNS tumor, Wilms tumor and neuroblastoma), remission status at AHCT (complete remission and not in complete remission), time from diagnosis to AHCT (<6 months, 6–12 months and >12 months), use of TBI, use of etoposide as part of conditioning, use of any irradiation pre- or post-transplantation, number of transplants (1 and >1), and year of transplantation. Factors were tested for their association with development of SMNs by means of backward selection of variables. Multivariate analyses were also conducted using Poisson regression to compare risks of solid cancers for various subgroups of HCT recipients.(20, 21) Both Cox and Poisson regression analyses yielded similar results. Analyses for cumulative incidence and risk factors were conducted for the whole cohort as well as separately for secondary acute myeloid leukemia/myelodysplastic syndromes (AML/MDS) and secondary solid tumors (including new lymphomas).

We also evaluated the excess risk of SMNs compared to the general population using methods described previously.(13–15) Briefly, for each transplant recipient, the number of person-years at risk was calculated from the date of transplantation until the date of last contact, death, or diagnosis of a new cancer, whichever occurred first. Age-, sex-, and country-specific incidence rates for all SMNs combined and for cancers at specific anatomical sites were applied to the appropriate person-years at risk to compute the expected numbers of cancers. Incidence rates for all cancers were obtained from national registries.(22, 23) Observed-to-expected (O/E) ratios, also called standardized incidence ratios (SIRs), were calculated, and Poisson distribution was used to calculate 95% confidence intervals (CI).(20)

All *P*-values are two-sided. All analyses were carried out using SAS statistical software (SAS Institute Inc., Cary, NC, USA).

RESULTS

Patient Characteristics

Among the 1,487 patients included in our study, the median age at AHCT was 8 years (range, <1–21 years). Primary diagnoses were neuroblastoma (39%), lymphoma (26%), sarcoma (18%), CNS tumors (14%), and Wilms tumor (2%). TBI was part of the conditioning regimen in 19% of patients, 3% received other irradiation (e.g., total lymphoid irradiation or thoraco-abdominal irradiation) as part of conditioning, and 68% received etoposide. Fifteen percent of patients (N=227) had received more than one transplant; among these, 39 had received a subsequent allogeneic transplant. Median follow-up of survivors was 8 years (range, <1–21 years) from transplantation. Overall, 80% of patients had received chemotherapy prior to AHCT. Overall survival was 43% (95% CI, 40–45) at 5 years and 36% (33–39) at 10 years after AHCT.

As expected, there were differences in patient demographics based on the underlying disease (Table 1). Patients with lymphoma and sarcoma were more likely to be older at AHCT (median age 17 and 15 years, respectively) compared to patients with CNS tumors, Wilms tumor, and neuroblastoma (median age 7, 8, and 4 years, respectively). Similarly, the pre-AHCT exposures (e.g., pre-transplant chemotherapy, number of chemotherapy regimens, and pre-transplant radiation therapy) varied for each disease. Patients with lymphoma, sarcoma, and neuroblastoma were more likely to have received TBI as part of conditioning regimen.

Incidence and Risk-factors for SMNs

SMNs were reported in 35 patients. Confirmatory pathology reports were available for 33 patients; for 2 patients, the transplant center confirmed that a SMN had occurred, but the pathology report was not provided for review. The two patients were included in the descriptive analyses but excluded from the multivariate analyses.

Thirteen patients had secondary AML/MDS (AML=6, MDS=7), and 20 had a secondary solid tumor. Secondary solid cancers included cancers of the bone (N=5), thyroid (N=5), breast (N=2), soft tissue (N=2), brain (N=1), head and neck (N=1), testis (N=1), and uterine cervix (N=1); 1 patient had Kaposi’s sarcoma, and 1 patient had 2 separate SMNs (soft tissue sarcoma and hepatocellular carcinoma). The median time from AHCT to occurrence of SMNs was 6.3 years (range, 4.5 months–20.4 years). The median time from AHCT to occurrence of AML/MDS was 2 years (range, 5 months–10 years) and for solid tumors was 7 years (range, 4.5 months–20.4 years).

The 5-year and 10-year cumulative incidence of all SMNs was 1.04% (95% CI, 0.58–1.63%) and 2.60% (95% CI, 1.69–3.70%). The corresponding cumulative incidence of AML/MDS was 0.56% (95% CI, 0.24–1.01%) and 1.06% (95% CI, 0.52–1.77%) and for solid tumors was 0.41% (95% CI, 0.15–0.81%) and 1.30% (95% CI, 0.69–2.10%), respectively (Figure 1).

In multivariate risk-factor analysis, we did not find any association between risks of SMNs and age, gender, diagnosis, remission status at AHCT, time from diagnosis to AHCT, use of

TBI, use of etoposide as part of conditioning, use of any irradiation, number of transplants, and year of transplantation. Although the number of specific SMNs was small, we also investigated whether these risk factors were associated with risks of cancer of the bone, thyroid, or AML/MDS. None of these factors significantly increased risks of secondary cancers at these specific sites.

Exposures among Patients with SMNs

Tables 2 and Supplemental Table 1 describe characteristics of patients with and without SMNs.

Although the numbers were small, we also looked at treatment exposures among patients with specific SMNs. Among the 5 patients with secondary cancers of the bone, indications for AHCT were neuroblastoma (N=2), Hodgkin lymphoma (N=1), sarcoma (N=1), and CNS tumor (N=1). SMN of the bone occurred at a median of 5.5 years (range, 1.3–8.4 years) after AHCT. Out of these 5 patients, 2 had pre-transplant radiation exposure: 1 patient with secondary osteosarcoma of the fibula received radiation to the tumor bed after resection of neuroblastoma followed by TBI as part of AHCT conditioning, and 1 patient with secondary osteosarcoma of the femur received mantle field irradiation for the treatment of Hodgkin lymphoma. Secondary thyroid cancer was reported in 5 patients at a median of 6.8 years (range, 1.9–12.5 years) after AHCT; among these, indications for AHCT were neuroblastoma (N=2), Hodgkin lymphoma (N=1), sarcoma (N=1) and Wilms tumor (N=1). Radiation exposure to the thyroid region was documented in 3 patients (1 prior to AHCT, 1 received TBI and 1 received TBI plus post HCT irradiation at primary tumor bed). Of the 2 patients with breast cancer, 1 patient had non-Hodgkin lymphoma and had received pre-transplant irradiation and TBI as part of conditioning, and 1 patient had Hodgkin lymphoma and received mantle field irradiation pre-transplantation. Of the 2 patients with secondary cancer of the soft tissue, 1 patient received TBI as part of AHCT conditioning, and 1 patient had no radiation exposures.

Among the 13 patients with secondary AML/MDS, indications for AHCT were Hodgkin lymphoma (N=5), sarcoma (N=4), neuroblastoma (N=2), non-Hodgkin lymphoma (N=1), and CNS tumor (N=1). Only 3/13 (23%) patients had received TBI, while 11/13 (65%) had received etoposide as part of AHCT conditioning regimen. As noted above, the median time to occurrence of AML/MDS after AHCT was 2 years (range, 5 months-10 years).

Five patients with SMNs received more than one AHCT. Among these, 3 patients developed secondary AML/MDS, and 2 patients had solid cancers (bone and testis each).

Outcomes of Patients with SMNs

Overall survival at 2 years and 5 years from the time of diagnosis of all SMNs (N=35) was 65% (95% CI, 48–91%) and 33% (95% CI, 46–52%), respectively. Among patients with secondary solid tumors, 2-year and 5-year survival from time of diagnosis of SMNs was 69% (44–89) and 41% (16–70), respectively. Survival at 2 years and 5 years after diagnosis of AML/MDS was 54% (28–79) and 18% (2–45), respectively. Among patients with secondary AML/MDS, 4 received a subsequent transplant (myeloablative allogeneic=3, reduced-intensity allogeneic=1). Of these 4 patients, 2 died at 1 and 32 months after second

transplant, and 2 are still alive with follow-up of 2 and 9 years after second transplant, respectively (both patients received myeloablative allogeneic transplants).

SMN Risk Compared to General Population

When compared to an age- and gender-matched population, AHCT recipients had 24 times higher risk of developing SMNs (SIR 24.0 [95% CI, 16.0–33.0]) (Table III). Specifically, AHCT recipients had significantly higher risks of cancers of the bone (N=5, SIR 81), thyroid (N=5, SIR 53), breast (N=2, SIR 93), soft tissue (N=2, SIR 34), AML (N=6, SIR 266), and MDS (N=7, SIR 6603). Higher risks were also observed for cancers of the pharynx and for Kaposi's sarcoma; however, only 1 patient each had SMNs at these sites. Risks of SMNs increased over time since AHCT; SIR were 17, 18, 29, and 39 for patients followed for <1 year, 1–4 years, 5–9 years, and ≥10 years after transplantation (Table 3). The 2 patients with unknown SMN type were excluded from these analyses.

DISCUSSION

AHCT is a curative treatment modality for selected hematologic and solid tumors in children. The conditioning regimens in AHCT use intensive, high dose chemotherapy with or without radiation to achieve tumor kill and consolidate therapy. The aggressive nature of these conditioning regimens raises concern for the development of SMNs. Our large, multi-institution study with extended followup adds important information to the emerging knowledge of secondary cancer risks among childhood AHCT survivors. Although the overall incidence of SMNs among pediatric recipients of AHCT is low, they are at increased risk for SMNs compared to the general population. The risk of SMNs increases with longer survival since transplantation and does not plateau after 10 years of follow-up. Our findings reinforce the importance of long-term follow-up of pediatric AHCT survivors and continued vigilance and surveillance for SMNs in this population.

These increased risks for SMNs have also been noted in other pediatric cancer studies. In the CCSS study, SIR for SMNs remained elevated over time, despite aging in both the case and control group.(7) Although the two studies cannot be compared directly, the SIR's for SMNs overall and for specific cancers were notably higher in our study than the CCSS study. Due to lack of sufficient data, our study could not address whether AHCT imparts any incremental risks for SMNs over pre-transplant chemotherapy and radiation exposures. We found no association between SMNs risk and age, gender, diagnosis, disease status, time since diagnosis, or use of total body irradiation or etoposide as part of conditioning. In comparison, the CCSS study observed a modest association between SMNs and female gender (RR=1.5), older age at cancer diagnosis (RR=1.3), radiation exposure (RR=2.7) and primary diagnosis of Hodgkin lymphoma (RR=1.5).(7) More studies are still needed to understand the role of inherited and acquired genetic factors in modulating risks for SMNs. Also, since AHCT continues to be an integral part of therapy in selected children with high-risk malignancies, more studies are still needed to better understand the risks associated with chemotherapy and radiation versus AHCT for SMNs in this population.

Although the development of SMNs in this relatively large cohort was rare, the incidence doubled from 5 years post-transplant (1.04%) to 10 years post-transplant (2.60%), and it did

not plateau over time. Another important finding from our study was the progressive increase in SIR's of SMNs with increasing follow-up since AHCT. These increased risks in very long-term survivors have also been noted in other pediatric cancer survivor studies.(7–9, 24)

The major limitations of our study relate to the fact that these are registry data that did not capture the full details of pre-AHCT treatment regimens and exposures. Of the evaluable SMNs (N=33), the majority of both secondary solid tumors (15/20, 75%) and secondary AML/MDS (11/13, 85%) occurred in patients with underlying neuroblastoma, sarcoma, and Hodgkin lymphoma. These pediatric malignancies have known chemotherapeutic backbones, including high-dose alkylating agents, high-dose topoisomerase inhibitors, and radiation; these exposures have all been implicated in increasing risk for SMNs, and we could not tease out the contribution of AHCT versus these previous exposures and the risks of SMNs. Since these data were generated by reporting from the transplant centers and long-term survivors may no longer be in contact with the transplant center, it is possible that our study may have under-reported the incidence of SMNs in this population and that the actual incidence and risks of SMNs may even be higher. The absolute number of SMNs in our study was relatively small, and we could not evaluate the risks and risk factors for cancers at specific sites.

Our study has important implications for future research and clinical practice related to pediatric AHCT survivors. It emphasizes the need for ongoing life-long surveillance for SMNs in this population. It also highlights the need for more investigation on whether pediatric AHCT survivors have higher risks of SMNs than childhood cancer survivors in general and whether the former require specific recommendations for secondary cancer screening and prevention (e.g., more frequent screening, targeted screening for specific cancer sites based on risk factors). Studies with detailed information describing pre- and post-AHCT therapeutic exposures and genetic risk factors are critical to understand the risk of SMNs in these patients.(25)

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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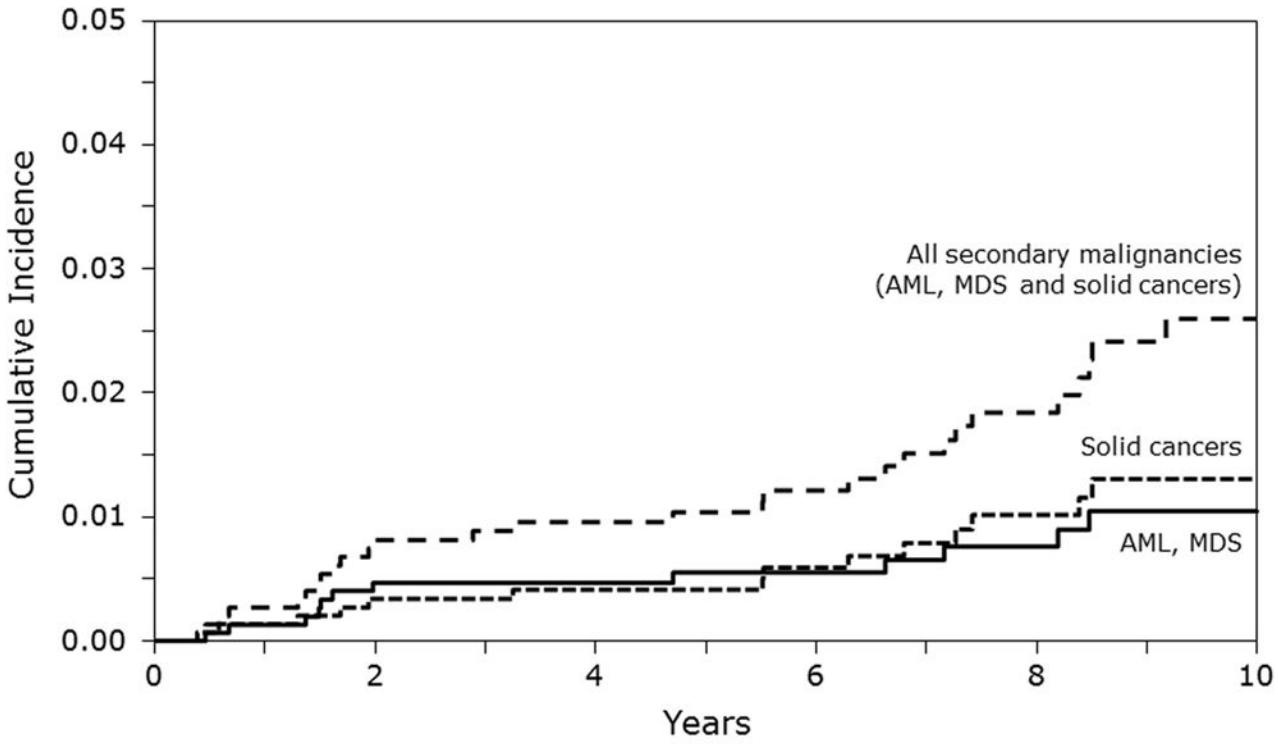

Figure 1.

Table 1

Patient, disease, and transplant characteristics by diagnosis

Variable	Lymphoma	Sarcoma	CNS tumor	Wilms tumor	Neuroblastoma
Number of patients	394	271	207	31	584
Number of centers	84	57	43	18	59
Median age at transplant, years (range)	17 (3–21)	15 (1–21)	7 (1–20)	8 (2–21)	4 (<1–21)
Age at transplant, years					
<5 yrs	12 (3)	25 (9)	73 (35)	10 (32)	419 (72)
6–10 yrs	26 (7)	40 (15)	53 (26)	14 (45)	138 (24)
11–15 yrs	72 (18)	74 (27)	54 (26)	3 (10)	18 (3)
16–21 yrs	284 (72)	132 (49)	27 (13)	4 (13)	9 (2)
Recipient gender					
Male	232 (59)	173 (64)	135 (65)	9 (29)	346 (59)
Female	162 (41)	98 (36)	72 (35)	22 (71)	238 (41)
Disease status prior to transplant					
Lymphoma, CR	154 (42)	--	--	--	--
Lymphoma, relapsed/refractory	215 (58)	--	--	--	--
Solid tumor, CR/VGPR	--	153 (58)	123 (67)	18 (60)	373 (65)
Solid tumor, PR/SD/PD	--	111 (42)	60 (33)	12 (40)	200 (35)
Missing	25	7	24	1	11
Pre-transplant chemotherapy					
No	0	1 (<1)	18 (29)	0	6 (1)
Yes	353	232 (100)	44 (71)	0	511 (99)
Missing	41	38	145	31	67
Median number of chemotherapy cycles (range)	7 (1–21)	6 (1–44)	4 (1–8)	-	5 (1–34)
Pre-transplant radiation therapy					
No	79 (34)	94 (41)	42 (66)	0	287 (56)
Yes	153 (66)	135 (59)	22 (34)	0	229 (44)
Missing	162	42	143	31	68
Median time from diagnosis to transplant, months (range)	15 (2–157)	9 (3–226)	9 (<1–165)	15 (2–108)	7 (2–88)
Time from diagnosis to transplant, months					

Variable	Lymphoma	Sarcoma	CNS tumor	Wilms tumor	Neuroblastoma
<6	44 (11)	71 (26)	78 (38)	2 (6)	141 (24)
6–12	110 (28)	94 (35)	43 (21)	7 (23)	355 (61)
>12	240 (61)	106 (39)	86 (42)	22 (71)	88 (15)
Irradiation (TBI or other radiation) as part of conditioning regimen					
No	296 (75)	203 (75)	204 (99)	30 (97)	421 (72)
Yes	98 (25)	68 (25)	3 (1)	1 (3)	163 (28)
Median TBI dose, cGy (range)	1200 (500– 1440)	1200 (800– 1500)	--	--	1200 (982–2520)
TBI dose, cGy					
No TBI	303 (77)	206 (77)	206 (100)	31 (100)	454 (78)
<1200	14 (4)	2 (1)	0	0	61 (10)
≥ 1200	76 (19)	61 (23)	0	0	68 (12)
Missing	1	2	1	0	1
Etoposide as part of conditioning regimen					
No	79 (20)	96 (35)	131 (63)	9 (29)	156 (27)
Yes	315 (80)	175 (65)	76 (37)	22 (71)	428 (73)
Graft type					
Bone marrow	186 (47)	48 (18)	69 (33)	5 (16)	287 (49)
Peripheral blood	208 (53)	223 (82)	138 (67)	26 (84)	297 (51)
Planned post-transplant irradiation					
No	316 (83)	205 (85)	82 (95)	3	351 (66)
Yes	67 (17)	35 (15)	4 (5)	0	181 (34)
Missing	11	31	121	28	52
Year of transplant					
1987–1990	59 (15)	8 (3)	7 (3)	0	44 (8)
1991–1995	203 (52)	61 (23)	68 (33)	11 (35)	215 (37)
1996–2000	114 (29)	179 (66)	88 (43)	18 (58)	253 (43)
2001–2003	18 (5)	23 (8)	44 (21)	2 (6)	72 (12)
Number of transplants					
1	359 (91)	230 (85)	150 (72)	31	490 (84)
2	32 (8)	27 (10)	17 (8)	0	74 (13)
≥ 3	3 (1)	14 (5)	40 (19)	0	20 (3)

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Abbreviations: CR – complete remission; VGPR – very good partial remission; PR – partial remission; SD – stable disease; PD – progressive disease; TBI – total body irradiation; CNS – central nervous system

Table 2

Selected characteristics of patients without secondary malignant neoplasm, with – secondary AML/MDS and with secondary solid cancers

Variable	No SMN	Secondary AML/MDS	Secondary solid cancers
N	1452	13	20
Age, years			
<10	791 (54)	6 (46)	13 (65)
11–21	661 (46)	7 (54)	7 (35)
Disease			
Non-Hodgkin lymphoma	177 (12)	1 (8)	2 (10)
Hodgkin lymphoma	204 (14)	5 (38)	3 (15)
Sarcoma	263 (18)	4 (31)	4 (20)
CNS tumor	204 (14)	1 (8)	2 (10)
Wilms tumor	30 (2)	0	1 (5)
Neuroblastoma	574 (40)	2 (15)	8 (40)
Irradiation as part of conditioning regimen			
No	1128 (78)	10 (77)	13 (65)
Yes	324 (22)	3 (23)	7 (35)
Pre-transplant radiation therapy			
No	486 (48)	5 (45)	9 (53)
Yes	525 (52)	6 (55)	8 (47)
Missing	441	2	3
Etoposide as part of conditioning regimen			
No	459 (32)	2 (15)	10 (50)
Yes	993 (68)	11 (85)	10 (50)
Planned post-transplant irradiation			
No	929 (77)	10 (83)	17 (94)
Yes	284 (23)	2 (16)	1 (6)
Missing	239	1	2

Abbreviations: SMN – secondary malignant neoplasm, AML/MDS – acute myeloid leukemia/myelodysplastic syndrome; CNS – central nervous system

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Table 3

Ratio of observed (O) to expected (E) cases of secondary cancers - overall and according to time since HCT

	Time since transplantation†								Overall		
	< 1 yr		1–4 yr		5–9 yr		≥ 10 yr				
Number of patients	**1485**		**1036**		**510**		**166**		**1485**		
Person-years at risk	**1240**		**2858**		**1614**		**449**		**6160**		
Secondary cancer site	**O**	**O/E**	**O**	**O/E**	**O**	**O/E**	**O**	**O/E**	**O**	**O/E**	**(95% CI)**
Pharynx	0	--	1	--	0	--	0	--	1	11803*	299–65762
Liver	0	--	0	--	0	--	1	--	1	89	2–498
Bone	0	--	2	73*	3	167*	0	--	5	81*	26–189
Kaposi's sarcoma	1	--	0	--	0	--	0	--	1	275*	7–1534
Connective, soft tissue	0	--	0	--	1	67	1	187	2	34*	4.06–121
Breast	0	--	0	--	0	--	2	226*	2	93*	11–336
Cervix uteri	1	--	0	--	0	--	0	--	1	48	1.2–270
Testis	0	--	0	--	1	--	0	--	1	7	0.2–38
Brain, nervous system	0	--	0	--	1	--	0	--	1	5	0.1–30
Thyroid	0	--	1	31	2	55*	2	116*	5	53*	17–123
Myeloid leukemia	0	--	3	309*	2	325*	1	481*	6	266*	98–580
MDS	2	9972*	3	5740*	2	8043*	0	--	7	6603*	2655–13604
All sites	4	17*	10	18*	12	29*	7	39*	33	24*	16–33

*P-value<0.01

†Observed/Expected (O/E) ratios for cancer sites with only ≤1 SMN are not show