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Cancers after HLA-matched related Bone Marrow Transplantation for Aplastic Anemia

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Abstract

We analyzed subsequent cancers in 329 patients with aplastic anemia given HLA-matched related marrow grafts. Median follow-up: 26 (range 1-47) years. Conditioning: cyclophosphamide ± antithymocyte globulin; graft-vs.-host disease (GVHD) prevention: methotrexate ± cyclosporine. The long follow-up and homogeneous treatment allowed definitive analyses of incidence, nature, time of onset, and potential causes of cancers. Fifty-three cancers occurred in 46 patients, 42 had solid tumors and 4 blood cancers. Of the 42, 22 had non-melanoma skin and 7 oropharyngeal cancers. The remainder had a spectrum of other cancers including 2 liver cancers from pre-transplant hepatitis C. The 26-year cumulative incidence (CI) of cancer was 11% and mortality 5%. Excluding non-melanoma skin cancers, the 26-year CI of cancer was 7%. Cancers were 2.03-fold more than expected from SEER data; that number was 1.89-fold after excluding liver cancers. Nearly all cancers developed between 14 and 34 years. Skin and oropharyngeal cancers showed significant association with chronic GVHD, whereby GVHD had resolved in most patients within 7 years of transplantation. Thus, tumors evolved after a lag time of 7 to 27 years. Other cancers showed no clear associations with chronic GVHD or drugs used for transplantation. Results reemphasize the importance of preventing chronic GVHD.

INTRODUCTION

Based on studies in mice [1], dogs [2] and monkeys [3], we introduced cyclophosphamide (CY) as a conditioning regimen for allogeneic marrow transplantation in patients with aplastic anemia in 1970. The studies in monkeys had shown that a regimen of CY, 50 mg/kg/day on each of 4 successive days was well tolerated, non-myeloablative and profoundly immunosuppressive. Since patients with aplastic anemia have an empty marrow, these properties made CY the ideal drug to condition patients with this disease for marrow

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grafts from HLA-identical siblings [4, 5]. The CY regimen has remained standard practice at our center for the past 50 years with the only change in the mid-1980s, based on canine studies [6, 7], being the addition of anti-thymocyte globulin (ATG) to CY in order to reduce the risk of graft rejection due to transfusion-induced sensitization to non-HLA antigen disparities between marrow donors and recipients [8, 9]. Graft-versus-host disease (GVHD) prevention included 102 days of intermittent methotrexate until the early 1980s and, since then, a combination of a short course of methotrexate and 180 days of a calcineurin inhibitor, most commonly cyclosporine [10].

The long-time frame of nearly half a century of CY-based transplantation for aplastic anemia provided a unique opportunity to definitively assess long-term sequelae of this transplant approach. Data from 329 marrow graft recipients have been captured in a comprehensive and continually updated database. The current report analyzed the incidence and nature of one of the long-term side effects, subsequent cancers, among patients with aplastic anemia not associated with genetic disorders transplanted between 1970 and 2017. Previous studies have addressed growth, development, fertility, immunologic recovery, polyclonal hematopoiesis and cancer; the latter, however, with a far shorter follow up and usually analyzed together with cancers among patients given a variety of other conditioning regimens. Cancer risk in current transplant recipients was compared to that among a matched U.S. population captured in the Surveillance, Epidemiology, and End Results (SEER) database.

PATIENTS AND METHODS

Patients

Between October 1970 and October 2017, 342 patients with severe aplastic anemia were conditioned with CY +/− ATG for HLA-matched related marrow grafts. All were transplanted on prospective trials which, since its inception, have been registered on ClinicalTrials.Gov. All patients signed consent forms including permission for long-term follow-up. For the purposes of this study we excluded from analysis 11 patients with Fanconi anemia and 2 with dyskeratosis congenita. After these exclusions, 329 patients were available for this study. Of these, 323 had HLA-identical sibling donors, while in 6 patients, donors were phenotypically HLA-matched parents. In early patients, HLA-identity among donor-recipient pairs was determined by serological matching for HLA-A and -B and non-reactivity of patient and donor lymphocytes in mixed leukocyte culture. Over time, HLA typing advanced, and current matching is based on identity for up to 14 HLA-alleles.

Transplant regimen (Table 1)

All 329 patients were conditioned with CY, 50 mg/kg body weight, on each of 4 successive days (days -5, -4, -3 and -2) (Table 1). A total of 105 patients received, in addition, horse ATG (ATGAM) that was administered intravenously (IV) in 3 doses of 30 mg/kg recipient body weight each 10 hours after each of the first 3 doses of CY (days -4, -3 and -2). Donor bone marrow was infused IV 36 hours after the last dose of CY. Between 1978 and 1988, 143 multiply transfused patients were administered unirradiated buffy coat cells from their respective marrow donors beginning one day after the marrow graft for a period of 4-6 days.

We observed that adding buffy coat cells significantly increased the rate of sustained marrow engraftment and improved overall survival; however, this was accompanied by an increased incidence of chronic GVHD [11]. Therefore, buffy coat cell infusions were abandoned in 1988 when we introduced a then novel, more immunosuppressive conditioning regimen consisting of CY combined with ATG [9]. GVHD prevention consisted of a long course of methotrexate (MTX) alone in early patients (n=155). Among later patients, 15 were given cyclosporine (CSP) alone, while all but two subsequent patients were given a short course of MTX combined with 180 days of CSP [10, 12].

Acute GVHD was diagnosed based on Seattle criteria [13]. Treatment of acute GVHD varied over time depending on the active protocols; primary therapy included single-agent or combination therapy with corticosteroids, ATG, or CSP [14-17]. During the early years chronic GVHD was diagnosed based on Seattle criteria [18] and, from 2005 on based on NIH criteria [19, 20]. Therapy for chronic GVHD also varied with time and included corticosteroids, azathioprine, and CSP, alone or in combination [21, 22], and later, tacrolimus, sirolimus, mycophenolate mofetil, extracorporeal photopheresis, ibrutinib and others have been used [23].

Patient follow-up and data collection

Patients have been followed for life by the Fred Hutch Long-term Follow-up Program under a standardized protocol approved by the Institutional Review Board. In addition to patient characteristics, details of conditioning regimens and the early post-transplant course, which were collected prior to discharge from the active service, information on late events, including the development of subsequent malignancies, has been collected in the hematopoietic cell transplant database. Patients are invited to return to Seattle for a comprehensive medical evaluation at one-year after transplant and again thereafter, if clinically indicated. In addition, on an annual basis, health status questionnaires are sent both to patients and referring physicians to obtain details on late effects, which are verified by the physicians' reports and, whenever possible, by pathology as well as surgical and other reports for confirmation.

Statistical methods

Patient characteristics, including treatment regimens and diagnoses, were summarized using standard descriptive measures. Overall survival was calculated using the Kaplan-Meier method. Cumulative cancer incidences were calculated using competing-risk methods, treating death without malignancy as a competing risk. The Greenwood method was used to calculate the confidence intervals of the rates. Cox regression was used to estimate risk of cancer by chronic GVHD. Standardized incidence ratios were calculated as ratios of observed numbers of cancers to the numbers expected in an age-, sex-, calendar year-matched US population tallied by the SEER program (SEER Cancer Statistics Review [CSR], 1975-2012 [http://seer.cancer.gov/csr/1975_2012/]). All p-values reported are 2-sided and no adjustments were made for multiple comparisons.

RESULTS

Patient characteristics

Patient and donor characteristics are shown in Table 1. The median age of patients was 21.1 (range 1.8–68.4) years. A total of 272 patients (82.7%) was diagnosed with idiopathic aplastic anemia; 18 (5.5%) had preceding hepatitis, in 34 (10.3%) aplastic anemia was thought to be drug or chemical induced; and in 5 (1.5%) it was secondary to PNH. A total of 28 patients (8.5%) had received immunosuppressive therapy before the transplant. Early results on 4 subsequent cancers among 257 of the 329 patients transplanted before 1993 were reported previously [24] although with a 27-year shorter follow-up.

Survival and chronic GVHD

Figure 1 shows survival curves of three consecutive cohorts of patients. The solid line represents survival of the earliest cohort 1 (n=81): CY conditioning, marrow graft, and MTX (n=40), CSP (n=31), CSP (n=9) for GVHD prophylaxis; the dotted line shows survival of patients in cohort 2 (n=143): CY conditioning, marrow plus donor buffy coat infusions, MTX (n=111), CSP (n=6) or MTX/CSP (n=25); the broken line shows survival among patients in cohort 3 (n=105): CY/ATG conditioning, marrow, MTX/CSP (n=101) or MTX (n=4). The curves illustrate the gradual improvements in survival. In fact, survival among the most recent subgroup of cohort 3, in which patients were given a dose of nucleated marrow cells limited to no more than 2.5×10^8 nucleated marrow cells/kg (median of 2, range 1.1–2.5x10^8 nucleated marrow cells/kg), has been 100% (n=34; update from [25]).

The cumulative incidences of chronic GVHD at 3 years were 26% in cohort 1, 41% in cohort 2 and 21% in cohort 3. Among patients in cohort 3 who received no more than 2.5×10^8 nucleated marrow cells/kg, the cumulative incidence of chronic GVHD was 16%.

Subsequent cancers

Overall incidence.—With a median follow-up of 26 (range, 1–47) years, a total of 53 cancers was seen among 46 patients (Table 2). Of the 46 patients, 42 had solid tumors and 4 had hematological malignancies. Among the 42 patients with solid tumors, 22 had non-melanoma skin cancers (squamous or basal cell). Six of the 22 had, in addition, another solid tumor. Twenty-six patients had one of a variety of solid tumors, most frequently breast cancer (n=7). Two patients had liver cancer and died 32 and 30 years after transplantation, respectively. The two were transplanted for hepatitis-associated aplastic anemia. They gradually developed liver cirrhosis after transplantation and eventually were diagnosed with cancer. In both patients, retrospective studies revealed that the cirrhosis was caused by hepatitis C virus, which had not yet been discovered when the patients were transplanted.

Four patients developed hematological malignancies. The first died from donor-derived Epstein-Barr (EBV)- associated lymphoproliferative syndrome on day 113. This patient had been treated for steroid resistant acute GVHD with an anti-CD3 monoclonal antibody and rabbit ATG. The second and third patients developed a myelodysplastic syndrome (MDS) in donor cells 23 and 27 years after marrow grafting, respectively. At the time of transplantation, they were 26 and 14 years old and their sibling donors were 19 and 22 years

old, respectively. Both were conditioned with CY alone, both received only methotrexate for GVHD prevention, and neither experienced chronic GVHD. The second patient was treated with a second marrow transplant at another institution and died of transplant-related complications. Cytogenetic studies in the third patient showed 5q- in the MDS cells. He had a successful second graft but died a year later from a shotgun accident. The fourth patient died of acute lymphoblastic leukemia of host origin one year after marrow transplantation.

The overall cumulative 26-year incidence of cancer was 11% (95% CI 8–16%) (Figure 2). If those 16 patients who only had non-melanoma skin cancer were excluded from the analysis, the 26-year incidence was 7% (95% CI 4–10%). Most cancers occurred during a 20-year time span between 14 and 34 years after transplantation. The cumulative incidences were at a very low level with flat curves during the first 14 years. Thereafter the curves rose but also began separating through year 23. That separation reflected an increasing incidence of non-melanoma skin cancers compared to other cancers. The separation of the two curves continued at a faster pace after a brief plateau between 23 and 26 years.

The overall 26-year cumulative mortality from any cancer was 5% (95% CI 2-8%). Of the 46 patients with cancer, 24 are surviving while 22 died, 19 from cancer and 3 from other causes (shotgun accident, stroke, unknown).

Association of subsequent cancer and chronic GVHD.—Table 3 shows the data. The overall 26-year incidence of cancer was 8.71% for patients without chronic GVHD compared to 16.65% among patients with chronic GVHD (p=0.13). When the two liver cancer cases were excluded from the analysis, the corresponding data remained 8.71% vs 16.65% between patients without chronic GVHD and with chronic GVHD (p=0.17). Non-melanoma skin cancer (3.44 % vs. 9.59 %; HR 2.48; p=0.04) and oropharyngeal cancer (0.59 % vs. 4.72 %; HR 11.5; p=0.007) showed significant associations with chronic GVHD. After removing these types of cancer from the analysis, other cancers showed no associations with chronic GVHD (5.35% vs. 4.75 %; HR 0.64 (0.24, 1.71); p= 0.35).

Association of subsequent cancer with drugs used for GVHD prevention.—The 26-year cumulative incidence of non-melanoma skin cancers was lower among patients who received MTX alone compared to those given CSP ± MTX for GVHD prevention, but this difference was not statistically significant (3.47% vs 8.16% (p=0.1; HR = 2.08 [95% CI, 0.86-5.05]).

The 26-year cumulative incidence of oropharyngeal cancers was not different among patients who received MTX alone compared to those given CSP ± MTX for GVHD prevention (2.04% vs 1.89% (p=0.76; HR = 1.28 [95% CI, 0.26-6.41]).

Association of subsequent cancer with preceding immunosuppressive therapy (IST) and ATG used in the conditioning regimen.—Twenty-eight patients (8.5%) received IST before the transplant and 321 patients (91.5%) did not. The overall 26-year incidence of cancer was 23.1% for patients given preceding IST compared to 9.96% among patients not given IST. This difference, while suggestive did not reach statistical significance (p=0.08).

One hundred and five patients (32%) were given ATG in the conditioning regimen while 224 (68%) patients did not. Of those given ATG, 18.39% developed subsequent cancers compared to 8.92% of patients without ATG in the conditioning regimen. The difference did not reach statistical significance (p=0.19).

Comparison with SEER data.—Standardized incidence ratios were calculated by comparing the number of cancers observed in the 329 transplanted patients to those expected to occur among a matched, non-transplanted US population. This comparison excluded non-melanoma skin cancers, for which information was not available in the SEER data base (Table 4). The overall number of cancers among current patients was 2.03-fold higher than expected (p=0.0007). Much of the increased cancer incidence was driven by tumors of the oropharyngeal cavity with 7 cases overall, with the observed number 13.63-fold higher than expected (95% CI 5.0-29.7, p <0.0001). Another higher than expected number of cancers was seen in the liver. The ratio was 8.91-fold higher than expected (p 0.04); however, in both, patients' hepatic carcinomas were associated with a history of hepatitis C, which we considered a pre-existing condition. If the two cases of hepatic carcinoma were removed from the analysis, the overall number of cancers among current patients was 1.89-fold higher than expected (p=0.003). The observed number of MDS cases was 11.5-fold higher than expected (95% CI 1.4-41.5, p 0.03) with 2 cases, both of which were donor derived. There was no statistically significant increase in risk of leukemia.

DISCUSSION

A strength of the current study is that all patients had a non-malignant disease, aplastic anemia; all received an HLA-matched, related marrow graft after a single conditioning regimen, CY, 50 mg/kg/day on each of 4 successive days with or without ATG; and all were given methotrexate either alone or in combination with a calcineurin inhibitor for GVHD prevention. A further strength is the long and comprehensive follow-up ranging from 1 to 47 years with a median of 26 years. At 26 years, the cumulative incidence of subsequent cancers was 11%. When non-melanoma skin cancers were removed from the analysis, the incidence was 7%, which was 2.03-fold higher than expected from SEER data (95% CI 1.4-29, p 0.0007). After we censored the two liver cancers since they evolved from pre-existing hepatitis C, that number declined to 1.89. (p 0.003). With few exceptions, subsequent cancers were late events which were predominantly diagnosed between 14 and 34 years after transplantation.

How do our data compare to those published by others? Most preceding analyses mixed patients transplanted for malignant and non-malignant blood disorders who received a multitude of conditioning regimens including busulfan and irradiation. Two papers focused on aplastic anemia patients although, again, a variety of conditioning regimens was included, and follow-up was comparatively short. The largest experience came from the European Bone Marrow Transplant (EBMT) Registry [26]. This analysis included 748 aplastic anemia patients, of whom 670 received HLA-identical sibling grafts, 406 had CY alone for conditioning, 322 had CY combined with one of several radiation regimens and 20 had other conditioning. The 10-year cumulative incidence of cancer, primarily solid tumors, was 3.1%. This translated into a 6.67-fold higher than expected risk compared to the general

European population (95% CI, 3.05–12.65; p<0.001). The other study included 621 patients [24] who either received grafts from HLA-identical sibling donors, HLA-mismatched related or HLA-matched unrelated donors. Conditioning regimens varied considerably and included CY alone, CY combined with busulfan, CY combined with 5 to 6 Gray thoraco-abdominal radiation or 9.2 Gray total body irradiation. With a follow-up ranging from 3 to 23 years, the 20-year Kaplan-Meier estimate of developing a tumor was 14% (95% CI, 4-24%). Taken together, the incidence of subsequent malignancies in our cohort of patients was lower than those previously reported.

What were the reasons for the overall increased risk of tumors in our patients? Could tumors be attributed to drugs used in the conditioning regimen or for GVHD prevention? CY has been reported to cause bladder cancer and leukemia [27-29]. No bladder cancer was seen among our patients, even though during the early years MESNA was not available to avert bladder toxicity. Perhaps the solitary case of host-derived acute lymphoblastic leukemia was the result of CY toxicity. Methotrexate and prednisone have not been described as carcinogenic. However, both cyclosporine and azathioprine (the latter used in early patients to treat chronic GVHD) can increase the risk of non-Hodgkin lymphoma and skin cancers [30-32]. The single case of non-Hodgkin lymphoma seen among our patients was EBV-related and in donor cells and likely triggered by using both ATG and an anti-CD3 monoclonal antibody to treat GVHD. Non-melanoma skin cancers were the most frequent tumors encountered. Their development, while significantly associated with chronic GVHD, was not entirely explained by that immunological complication. Slightly more skin cancers were seen among patients given methotrexate/cyclosporine compared to those given methotrexate alone, although this difference was only suggestive. While the skin cancer incidence was high, a comparison with that in the general population was not possible since skin cancers have not been tracked by cancer statistics.

Among the remaining tumors, oropharyngeal cancers were highly significantly increased compared to the general population, while other tumors showed no significant increases except for breast cancer with a barely significant 2.5-fold higher incidence. Oropharyngeal cancers were even more tightly associated with chronic GVHD than non-melanoma skin cancers. Moreover, as with skin cancers, oropharyngeal cancers often occurred at sites previously or, very infrequently, concurrently involved with chronic GVHD, consistent with previous reports [33, 34]. Whether the development of these cancers was due to GVHD-induced skin and mucosal epithelial inflammation and repair processes or to the immunosuppressive agents used to treat chronic GVHD, such as azathioprine or cyclosporine, has remained unclear. In our cumulative experience in patients transplanted for aplastic anemia, the great majority of surviving patients with chronic GVHD responded well to therapy and were taken off all immunosuppressive medication within 7 years after transplantation [35]. It is therefore biologically interesting that non-melanoma skin and oropharyngeal cancers developed after long lag times ranging from 7 to 27 years after clinical resolution of chronic GVHD.

An unusual finding was two cases of donor cell derived MDS, which occurred in the third decade after transplantation. This was more than expected from the SEER database and from results of a 2011 review paper which estimated the risk of donor-derived malignancies

to be 124 in 100,000 allogeneic HCT, although with shorter observation times [36]. Long-lived hematopoietic cells are targets for mutational changes and may lose the capacity to adequately maintain tissue homeostasis after stress [37]. Perhaps the enormous stress placed on donor cells in rebuilding an entire hematopoietic system in the host places them at risk for developing clonal malignant disorders such as MDS. Others have postulated that donor-derived malignancies could be the result of poor immune surveillance by a dysfunctional donor immune system in the host [38] . This explanation seemed unlikely for our two patients since both had methotrexate GVHD prevention discontinued around day 100, neither developed chronic GVHD, both participated in extensive immunological studies which showed normal or near normal immune system recovery beginning around 6-12 months after transplantation [39, 40], and MDS did not evolve until 23 and 27 years, respectively, after transplantation. A recent study suggested that driver mutations for myeloproliferative neoplasms may already be acquired before birth or in childhood [41]. Consistent with this finding were observations of myeloid neoplasms developing in cells from unrelated cord blood donors [42, 43].

In summary, the incidence of subsequent cancers after BMT treatment in AA patients was increased compared with the general population. This increase was almost entirely due to a high incidence of non-melanoma skin cancers and oropharyngeal cancers. These, in turn, were significantly associated with chronic GVHD, re-emphasizing the importance of efforts to prevent this immunological complication of allogenic marrow transplantation. Overall, our findings emphasize the importance of long-term surveillance of SAA patients after HCT.

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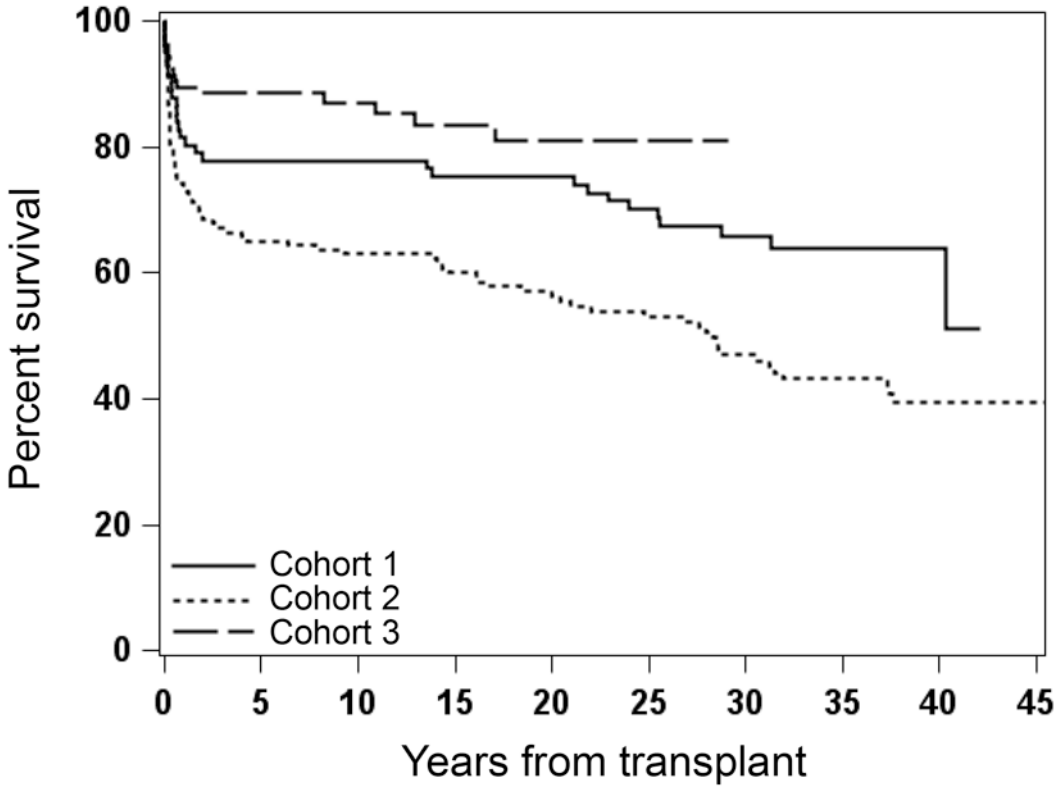

Figure 1. Overall survival.

Cohort 1 (n=81): CY conditioning, marrow, MTX (n=40), CSP (n=31), CSP (n=9) for GVHD prophylaxis; cohort 2 (n=143): CY conditioning, marrow plus donor buffy coat infusions, MTX (n=111), CSP (n=6) or MTX/CSP (n=25); cohort 3 (n=105): CY/ATG conditioning, marrow, MTX/CSP (n=101) or MTX (n=4).

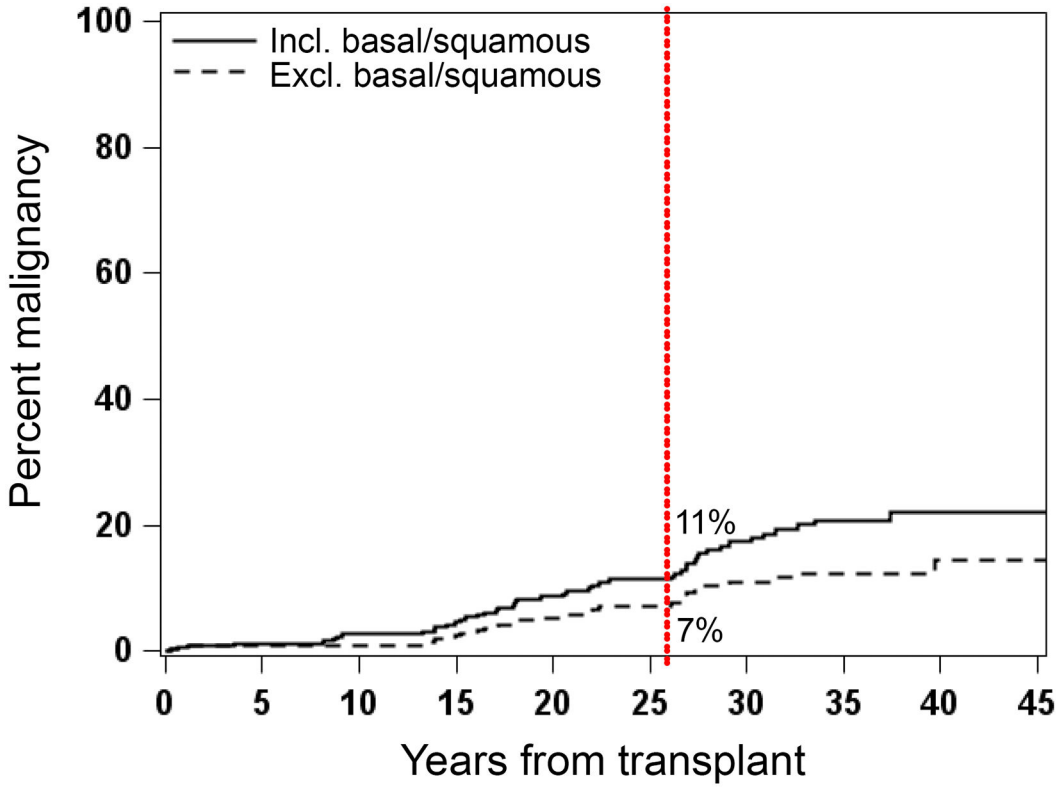

Figure 2.
The cumulative incidence of all observed subsequent cancers.

Table 1.

Patient Characteristics

Patient characteristics	**N=329**
Median age (range) at transplant	21.1 (1.8-68.4)
Female	139 (42.2%)
Etiology of aplastic anemia	
Idiopathic	272 (82.7%)
Hepatitis	18 (5.5%)
Drugs/chemicals	34 (10.3%)
PNH	5 (1.5%)
Treatment with IST before marrow transplantation	28 (8.5%)
Conditioning regimen	
CY only	224 (68%)
CY+ ATG	105 (32%)
Donor	
Phenotypically HLA-matched parent	6 (2%)
HLA-identical sibling	323 (98%)
GVHD prevention	
MTX	155 (47.1%)
CSP	15 (4.6%)
MTX+ CSP	157 (47.7%)
None*	2 (0.6%)
Graft source	
Marrow	185 (56.2%)
Marrow+ Buffy coat cells	143 (43.5%)
PBSC	1 (0.2%)
Cord (from an HLA identical sibling)	(0.2%)

*1 patient died before starting on GVHD prophylaxis; 1 patient received syngeneic transplant.

Abbreviations: ATG: antithymocyte globulin; CSP: cyclosporine; CY: cyclophosphamide; GVHD: graft-vs.-host disease; MTX: methotrexate; PBSC: peripheral blood stem cells; PNH: paroxysmal nocturnal hemoglobinuria (determined by Ham's and sucrose water tests).

Table 2.

Type of Subsequent Cancers

Type of secondary malignancies	Number of events
Hematologic malignancies	
ALL (host origin)	1
MDS (donor origin)	2
EBV-associated lymphoma	1
Solid tumors	
Squamous and basal cell carcinoma	
Non-skin	7
Skin	22
Melanoma	1
Lung	1
Kidney	1
Pancreas	2
Liver (hepatitis C-associated)	2
Small intestine	1
Rectum	1
Breast	7
Cervical	1
Prostate	1
Neuro-endocrine	1
Thyroid	1

Abbreviations: ALL: acute lymphocytic leukemia; MDS: myelodysplastic syndrome; EBV: Epstein-Barr virus

Table 3.

Association Between Subsequent Cancers and Chronic GVHD

	26-year Cumulative incidence			
	Chronic GVHD			
Cancer	No	Yes	HR (95% CI)	P value
Overall	8.71%	16.65%	1.59 (0.88, 2.89)	0.13
Non-melanoma skin cancers	3.44%	9.59%	2.48 (1.07, 5.73)	0.04
Oropharyngeal cancers	0.59%	4.72%	11.5 (1.3, 98.1)	0.007
Overall after exclusion of both non-melanoma skin cancers and oropharyngeal cancers	5.35%	4.75%	0.64 (0.24, 1.71)	0.35

Table 4.

Standardized Incidence Ratio (SIR) for All Subsequent Cancers Excluding Non-Melanoma Skin Cancers

					Excluding 2 liver cancers (preexisting condition)			
	Number of cancers expected	**Number of cancers observed**	**SIR**	**P**	**Number of cancers expected**	**Number of cancers observed**	**SIR**	**P**
All cancers	14.788	30	2.03	0.0007	14.788	28	1.89	0.003
Tongue	0.129	2	15.52	0.02				
Gum & other mouth	0.048	4	82.76	<0.0001				
Esophagus	0.120	1	8.35	0.23				
Small intestine	0.070	1	14.24	0.14				
Rectum	0.309	1	3.23	0.53				
Pancreas	0.272	2	7.36	0.06				
Liver	0.225	2	8.91	0.04	0.225	0	0	1
Lung	0.576	1	1.74	0.88				
Melanoma	0.967	1	1.03	0.99				
Female breast	2.800	7	2.50	0.05				
Cervix	0.253	1	3.95	0.45				
Prostate	1.629	1	0.61	0.99				
Kidney	0.474	1	2.11	0.75				
Thyroid	0.645	1	1.55	0.95				
Large cell, immunoblastic	0.236	1	4.23	0.42				
Acute lymphocytic leukemia	0.050	1	20.12	0.10				
Myelodysplastic syndrome	0.174	2	11.50	0.03				

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