25.16, 95 % CI 1.76–369.10, $P = 0.018$) showed higher relapse, while uBMT (RR 0.33, 95 % CI 0.12–0.95, $P = 0.041$) was lower relapse compared with those in rBMT (Table 3).

Engraftment

The cumulative neutrophil recovery rate on day 90 was 97.5 % (95 % CI, 96.1–98.9 %) in CP1, 93.2 % (95 % CI, 90.5–95.9 %) in CP2-AP, and 82.3 % (95 % CI, 76.8–87.8 %) in BC. On day 180, the cumulative platelet recovery rate, as indicated by more than 2×10^{10}/L of platelets in blood, was 91.9 % (95 % CI, 89.5–94.3 %) in CP1, 85.1 % (95 % CI, 81.2–89.0 %) in CP2-AP, and 67.2 % (95 % CI, 60.3–74.1 %) in BC. Note that the neutrophil recovery and platelet recovery rates were lower after CBT, especially in patients in the advanced phase; i.e., neutrophil recovery in CBT: 90 % in CP1, 79.4 % in CP2-AP, and 64.0 % in BC; platelet recovery after CBT: 90.0 % in CP1, 72.5 % in CP2-AP, and 52.0 % in BC (Fig. 3a–f). Multivariate analysis showed that rPBSCT (RR 1.31, 95 % CI 1.02–1.69, $P = 0.0396$ was a significant factor for early neutrophil recovery in CP1. While, CBT (RR 0.53, 95 % CI 0.42–0.67, $P < 0.001$) was a significant factor for delayed neutrophil recovery in CP2-AP (Table 3). The factor statistically associated with delayed platelet recovery was CBT in CP2-AP (RR 0.78, 95 % CI 0.62–0.99, $P = 0.0049$) and in BC (RR 0.44, 95 % CI 0.26–0.74, $P = 0.0018$). Unrelated BMT (RR 0.21, 95 % CI 0.07–0.61, $P = 0.0039$) was also a significant factor for delayed platelet recovery in BC (Table 3).

Acute and chronic GVHD

The cumulative incidence of acute GVHD at all grades before day 100 was 62.8 % (95 % CI, 58.6–67.0 %) in CP1, 63.5 % (95 % CI, 58.2–58.8 %) in CP2-AP, and 68.6 % (95 % CI, 61.3–74.9 %) in BC. Patients who underwent uBMT showed a higher incidence of acute GVHD (all grades) in CP1 and CP2-AP (Fig. 4a, b). This association was confirmed by multivariate analysis; uBMT (RR 3.35, 95 % CI 1.50–6.22, $P < 0.001$) was a significant factor in CP1 (Table 3). Pre-transplant IM (HR 0.75, 95 % CI 0.57–0.99, $P = 0.04$) was a significant risk factor for acute GVHD (all grades) in CP1 (Table 2). Focusing exclusively on grade II or higher acute GVHD, uBMT (RR 4.28, 95 % CI 1.92–9.53, $P < 0.001$) (Table 3) was a significant risk factor in CP1 (Table 2). For patients in CP2-AP, body weight (>60 kg) was a factor significantly associated with increased risk of aGVHD (all grade; RR 1.35, 95 % CI, 1.01–1.82, $P = 0.045$, grade II or higher grade; RR 1.53, 95 % CI, 1.05–2.24, $P = 0.028$) (Table 2).

The cumulative incidence of chronic GVHD among evaluable patients who survived at least 100 days after allo-HSCT was 49.4 % (95 % CI, 44.7–54.1 %) in CP1, 42.2 % (95 % CI, 36.4–48.0 %) in CP2-AP, and 37.8 % (95 %CI, 30.0–45.6 %) in BC. For patients in CP1, rPBSCT showed a higher incidence of chronic GVHD (71.4 %), which was compared to other GS (Fig. 4d); however, this significant association was not confirmed in multivariate analysis (rPBSCT: RR 1.37 95 % CI 0.97–1.92, $P = 0.075$). For patients in CP2-AP and BC, chronic GVHD after CBT occurred at rates of 23.1 and 23.8 %, respectively, which were apparently lower than that of other GS (Fig. 4e, f), but these statistical associations were not also confirmed by multivariate analysis in CP2-AP or BC (Table 3). Concerning extensive chronic GVHD, multivariate analysis showed the significant association between body weight (>60 kg; RR 1.75, 95 % CI, 1.06–2.73, $P = 0.028$) and chronic GVHD in CP2-AP (Table 2).

Discussion

Our study reviewed 1,062 Japanese adult patients who underwent allo-HSCT during the past decade (2000–2009); thus, our cohort reflects the current use and results of allo-HSCT for CML in Japan. Moreover, the TRUMP database offers the advantage of a large number of patients with extensive data, which permits multivariate analysis. The 3-year OS was 70.6 % for patients in CP1, and the probability of 3-year LFS for patients in CP1 was 64.6 %. These survival data for patients in CP1 were comparable to those reported by others [12]. Based on the report from the EBMT, which included 13,416 CML patients and was apparently the largest CML transplant database including the 3 times cohorts (i.e., 1980–1990, 1991–1999, 2000–2003), the probability of OS at 2 years for patients transplanted in CP1 from an HLA-identical sibling was 74 %, with a cumulative incidence of TRM at 2 years of 22 % and of relapse of 18 % among the most recent cohort transplanted between 2000 and 2003 ($n = 3,018$) [13]. The Center for International Blood and Marrow Transplant Research (CIBMTR) recently reported the transplant outcomes of 449 patients with advanced phase CML; the disease-free survival rates remained as low as 35–40 % for CP2, 26–7 % for AP, and 8–11 % for BC [14]. Our series including 432 cases of CP2-AP and 189 cases of BC showed similar survival rates, as the probabilities of 3-year LFS in CP2-AP and BC were 46.1 and 19.2 %, respectively.

Our primary object in this study was to assess the clinical impact of GS according to each disease status. Our study results revealed that the patients in CP1 who were

Fig. 3 The cumulative incidence of absolute neutrophil count (ANC) recovery for patients in CP1 (**a**), CP2-AP (**b**) and BC (**c**); and platelet (PLT) recovery for patients in CP1 (**d**), CP2-AP (**e**) and BC (**f**)
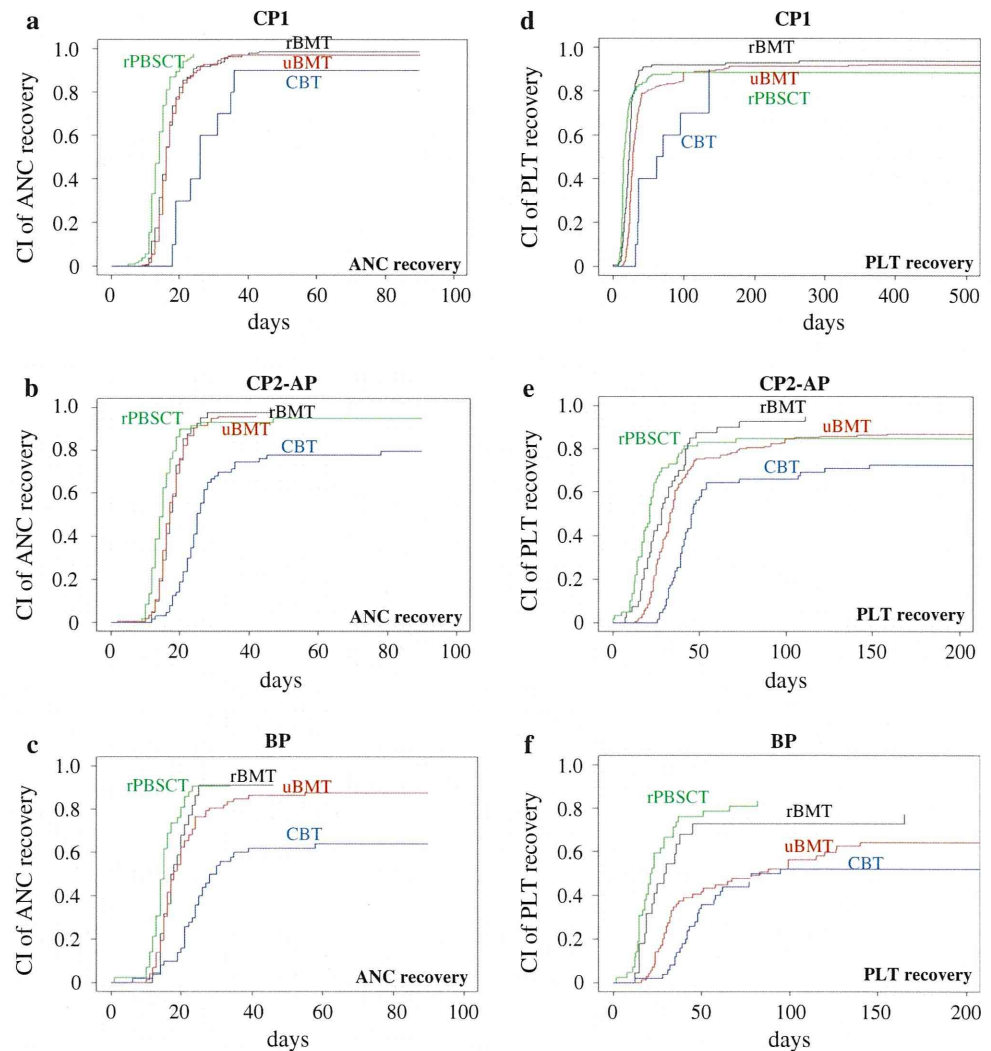

treated by rBMT showed a better 3-year OS (84.4 %) with a lower 1-year cumulative incidence of TRM, but the 3-year LFS and relapse rates were similar between patients receiving rBMT and patients receiving rPBSCT. These data were essentially in line with previous reports in which the CIBMTR reported the data of CML patients undergoing rPBSCT or rBMT in CP1; the 1-year LFS and relapse rates were similar for patients receiving rBMT or rPBSCT [14]. We also assessed the clinical impact of GS in CP2-AP; our results showed that there were no significant differences in OS or LFS between GS, despite lower probabilities of relapse after uBMT and lower probabilities of TRM after CBT. These results differ from the IBMTR reports in that for patients in CP2 or AP, rPBSCT was associated with a lower incidence of treatment failure and a higher probability of LFS at 1 year [15]. Regarding GVHD, a recent prospective randomized trial showed a trend toward a higher incidence of chronic GVHD after rPBSCT (59 % after rPBSCT vs. 40 % after rBMT,

$P = 0.11$) for patients in CP1 [16]. Our results may confirm this report; although multivariate analysis in our study showed that rPBSCT (RR 1.37 95 % CI 0.97–1.92, $P = 0.075$) was not a significant risk factor for developing chronic GVHD (Table 3), rPBSCT showed a higher incidence of chronic GVHD (71.4 %), which was compared to other GS in CP1 (Fig. 4d).

Several investigators have addressed the clinical impact of pre-transplant IM on post-transplant outcomes for CML [14, 17–20]. The CIBMTR data demonstrated that pre-transplant IM was associated with better survival, but revealed no statistically significant differences in TRM, relapse, and LFS for patients in CP1 [17]. Among patients transplanted in the more advanced phases beyond CP1, pre-transplant IM was not associated with TRM, relapse, LFS, OS, or acute GVHD [17]. In contrast to these studies, our analysis showed that pre-transplant IM was significantly associated with better OS for patients in BC. In addition, multivariate analysis found pre-transplant IM was a

Fig. 4 The cumulative incidence of acute GVHD at all grades for patients in CP1 (**a**), CP2-AP (**b**) and BC (**c**); and chronic GVHD at all grades for patients in CP1 (**d**), CP2-AP (**e**) and BC (**f**)
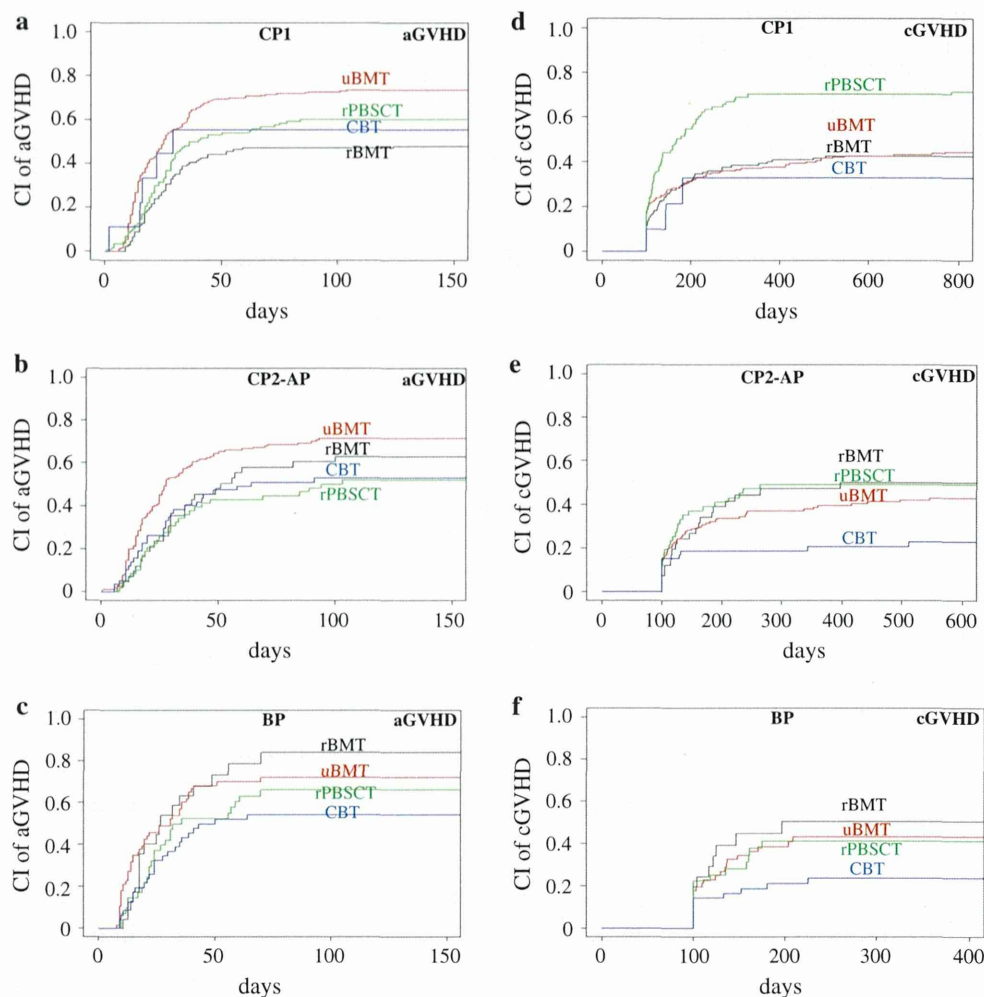
significant factor associated with acute GVHD (>grade II) in CP1 (data not shown). Despite the study in the era of TKI, half of patients were in CP1, and 61 % of patients underwent allo-HSCT without use of pre-transplant TKI in this study. We should interpret these findings with utmost caution. We assume that most patients had already initiated the conventional treatment but could not reach a new, but expensive IM treatment before allo-HSCT, as a reason for these findings. Moreover, the findings that the number of patients in CP1 underwent allo-HSCT was 447 in the early period of IM from 2000 to 2004 and only 84 from 2005 to 2009 might support our assumption. Deininger et al. reported an effect of pre-transplant IM in their study that included 70 cases of CML and 21 cases of Ph (+) acute lymphoid leukemia. These investigators compared the outcomes with historical controls identified in the EBMT database [21], and observed a trend towards higher relapse mortality and significantly less chronic GVHD in patients with pre-transplant IM (OR = 0.44, P = 0.027). Thus, the clinical impact of pre-transplant IM is still a contentious issue; additional studies evaluating the long-term use of IM with a larger number of patients might permit a more refined analysis of the effect of pre-transplant IM.

Although data on clinical outcomes after CBT are conflicting, CBT has apparent advantages over uBMT, including no risk to the donor and ease of availability. Previous reports, mostly from pediatric studies, have shown that, despite higher HLA mismatch, CBT carries a lower risk of acute GVHD and chronic GVHD in comparison with uBMT [22–24]. A recent Japanese retrospective analysis assessing 86 patients, including pediatric patients, disclosed the transplant outcomes of CBT: 2-year OS was 53 %; for patients in CP, AP and BC, the OS rates were 71, 59 and 32 %, respectively [25]. Although our small population with only 10 cases of CBT in CP1 may prohibit drawing meaningful conclusions, a trend of higher relapse and lower TRM, OS and LFS in CP1 was similar to results obtained by previous study groups. Nevertheless, in CP2-AP and BC, transplant outcomes after CBT were comparable to those of other GS,

suggesting CBT as an acceptable alternative option in advanced phases of CML.

As with all retrospective studies, this study had several limitations. Reported data from transplant centers were often incomplete: data on pre-transplant IM, duration from diagnosis to transplantation, and conditioning regimen could not be fully retrieved. The reasons for which patients in CP1 with IM proceeded with transplantation (planned, or IM resistance) or the reasons for delay in proceeding with transplantation in BC were unknown. Information on post-transplant use of TKIs as maintenance therapy or data on the presence of *BCR/ABL1* mutations was also unavailable in our cohort. Moreover, the selection of GS would often be governed by several unmeasured factors, but our data nonetheless provide a clinical basis for current selection of GS for the treatment of CML in the era of TKIs.

In conclusion, this retrospective study evaluated the results of allo-HSCT for CML patients according to disease status and GS. For patients in CP1, rBMT may be the preferred option for better survival, whereas rPBSCT carries a higher risk for chronic GVHD, which could be a major drawback for patients in CP1. In advanced phases, GS had no significant impact on survival, suggesting that CBT is a reasonable alternative therapy when there is no related or unrelated donor available, or when a transplant is needed urgently. In the era of the new-generation TKIs, indications for allo-HSCT and selection of GS for advanced CML need further evaluation.

Conflict of interest The authors declare no conflict of interest.

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Continuing increased risk of oral/esophageal cancer after allogeneic hematopoietic stem cell transplantation in adults in association with chronic graft-versus-host disease

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Background: The number of long-term survivors after hematopoietic stem cell transplantation (HSCT) showed steady increase in the past two decades. Second malignancies after HSCT are a devastating late complication. We analyzed the incidence of, risk compared with that in the general population, and risk factors for secondary solid cancers.

Patients and methods: Patients were 17 545 adult recipients of a first allogeneic stem cell transplantation between 1990 and 2007 in Japan. Risks of developing secondary solid tumors were compared with general population by using standard incidence ratios (SIRs).

Results: Two-hundred sixty-nine secondary solid cancers were identified. The cumulative incidence was 0.7% [95% confidence interval (CI), 0.6%–0.9%] at 5 years and 1.7% (95% CI, 1.4%–1.9%) at 10 years after transplant. The risk was significantly higher than that in the general population (SIR = 1.8, 95% CI, 1.5–2.0). Risk was higher for oral cancer (SIR = 15.7, 95% CI, 12.1–20.1), esophageal cancer (SIR = 8.5, 95% CI, 6.1–11.5), colon cancer (SIR = 1.9, 95% CI, 1.2–2.7), skin cancer (SIR = 7.2, 95% CI, 3.9–12.4), and brain/nervous system cancer (SIR = 4.1, 95% CI, 1.6–8.4). The risk of developing oral, esophageal, or skin cancer was higher at all times after 1-year post-transplant. Extensive-type chronic graft-versus-host disease (GVHD) was a significant risk factor for the development of all solid tumors (RR = 1.8, $P < 0.001$), as well as for oral (RR = 2.9, $P < 0.001$) and esophageal (RR = 5.3, $P < 0.001$) cancers. Limited-type chronic GVHD was an independent risk factor for skin cancers (RR = 5.8, $P = 0.016$).

Conclusion: Recipients of allogeneic HSCT had a significantly higher ~2-fold risk of developing secondary solid cancers than the general population. Lifelong screening for high-risk organ sites, especially oral or esophageal cancers, is important for recipients with active, or a history of, chronic GVHD.

Key words: secondary solid cancers, late effect, hematopoietic stem cell transplantation

introduction

Hematopoietic stem cell transplantation (HSCT) is a curative treatment of choice for malignant and non-malignant hematological disorders [1]. The annual number of allogeneic HSCT has increased steadily over the past three decades worldwide [2–6]. Progress in transplant procedures in addition to this steady increase in the number of HSCT procedures worldwide has contributed to an increase in the number of long-term survivors.

Secondary malignancies, including new solid cancers, are an important cause of late mortality. Several studies have reported that survivors of HSCT have a 2–3-fold increased risk of

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developing new solid cancers compared with an age-, sex-, region-, and calendar-year-adjusted population and the risk among long-term survivors ranges from 1% to 6% at 10 years after transplantation [7–14]. Identified risk factors include exposure to radiation as a part of the conditioning regimen and chronic graft-versus-host disease (GVHD), and the latter has been shown to be strongly correlated with the development of squamous cell carcinoma [8, 10, 12, 15–17]. However, a recent long-term follow-up analysis of patients who were transplanted after myeloablative doses of busulfan and cyclophosphamide without total body irradiation (TBI) found a similar increased incidence of 0.6% at 5 years and 1.2% at 10 years after transplantation [13]. We conducted a nationwide, retrospective cohort study with a large and different cohort from those used in previous reports from North America and Europe, to determine the incidence and risks of developing secondary solid cancers.

methods

data source and collection of data

The recipient clinical data were collected by the Japan Society for Hematopoietic Cell Transplantation (JSHCT) using the Transplant Registry Unified Management Program, as described previously [18]. The JSHCT collect recipients' baseline, disease, transplant, and transplant outcome information who received HSCT in the previous year. Patient information regarding survival, disease status, and long-term complications including chronic GVHD and second malignancies are renewed annually. This study was approved by the data management committee of the JSHCT, as well as the institutional review board of Nagoya University Graduate School of Medicine.

patients

Adult patients (at least 16 years of age) who received a first HSCT between 1990 and 2007 were considered as subjects for the present study. Those who were inherently susceptible to developing cancer [Fanconi anemia ($N = 3$) and congenital immunodeficiency ($N = 12$)] were excluded. Three-hundred five recipients (1.7%) were excluded because of insufficient follow-up data. The study included 17 545 recipients; 5358 recipients of related bone marrow, 3587 recipients of related peripheral blood stem cells (including 134 bone marrow and peripheral blood stem cells combined), 6508 recipients of unrelated bone marrow, and 2092 recipients of unrelated cord blood.

statistical analysis

Standard incidence ratios (SIRs) were calculated to determine whether the number of recipients in the present cohort who developed secondary solid tumor after receiving a HSCT was different than that in the general population (supplementary method, available at *Annals of Oncology* online). Cumulative incidences of solid cancer or GVHD were estimated by taking into account the competing risk of death among patients who did not develop a second malignancy or GVHD [19]. The influence of potential risk factors was estimated by using the Cox proportional hazard model [20]. A stepwise multivariate approach was used to identify the most important predictor with respect to the development of secondary solid cancers. The variables considered were age at transplant, patient sex, donor-type (related versus unrelated), graft source, TBI as part of the conditioning regimen, reduced-intensity conditioning, grade 2–4 acute GVHD, and chronic GVHD. The model was stratified into four categories according to the primary disease; acute myeloid leukemia, acute lymphoblastic leukemia, chronic myeloid leukemia, and others. Acute and chronic GVHD were

considered as time-dependent covariates. TBI and chronic GVHD were frequent risk factors and were always kept in the model. Risk factors for high-risk cancer sites with adequate numbers of events for analyses were also analyzed: oral cavity/pharynx, esophagus, colon, and skin. The models for high-risk cancer sites were stratified according to the primary disease as described, and patient age at transplantation (<19, 20–29, 30–39, 40–49, 50–59, and >60), and also adjusted by patient age as a continuous variable. All *P*-values were two-sided.

results

patient and transplant characteristics

Table 1 shows the patient characteristics, their disease, and transplant regimens for 17 545 recipients of a first HSCT. The cumulative incidences of grade 2–4 acute GVHD at 150 days and chronic GVHD at 2 years post-transplant were 35% [95% confidence interval (CI), 35%–36%] and 41% (95% CI, 40%–41%), respectively. The observation period reached 69 465 person-years among the subjects for analyses. Of the 17 545 recipients, 5864 had survived for 5 or more years, and 2192 recipients had survived 10 or more years at the time of analysis (Table 2).

incidence and types of secondary solid cancers

The cumulative incidence of solid cancers was 0.7% (95% CI, 0.6–0.9) at 5 years, 1.7% (95% CI, 1.4–1.9) at 10 years, and 2.9% (95% CI, 2.5–3.4) at 15 years after transplantation (Figure 1). Two-hundred sixty-nine solid cancers were identified. Multiple solid cancers were observed in 11 patients. Nineteen recipients were diagnosed within 1-year post-transplantation (Table 2).

risk compared with the general population

HSCT recipients had a 1.8-fold higher risk of invasive solid cancers compared with the general population (95% CI, 1.5–2.0). SIR was significantly higher for cancers of the oral cavity/pharynx (SIR = 15.7), esophagus (SIR = 8.5), colon (SIR = 1.9), skin (SIR = 7.2), and brain/nervous system (SIR = 4.1; Table 2). The risks of developing secondary cancers of the oral cavity/pharynx, esophagus, and skin were significantly higher than those in the general population throughout all periods after 1 year (Figure 2). The risk for developing colon cancer was elevated during the period of 1–4 years (SIR = 2.7), whereas the risks for developing cancer of the pancreas (SIR = 4.5) were elevated during the period of 5–9 years. Recipients were at higher risk of developing cancers of the rectum (SIR = 3.6) and the brain/nervous system (SIR = 19.1) after 10 years post-transplantation. The risk of developing secondary solid cancers of all types compared with the general population increased with the time since transplantation. This trend was observed for oral/pharynx and esophageal cancer (Table 2; Figure 2).

recipients' age at transplantation and risks for developing secondary solid cancers

SIRs were also analyzed according to the recipient's age at transplantation (Table 3). Compared with the general population in Japan, the SIRs were significantly increased for all solid cancers, oral/pharynx, esophagus, liver, bronchus/lung, and brain/nervous system for recipients who were 16–19 years of age at transplant, all solid cancers, oral/pharynx, and esophagus for recipients who

Table 1. Patient, disease, and transplant characteristics

Characteristics	Number	Percent
Total number	17 545	
Year of transplant		
1990–1994	1630	9
1995–1999	3750	21
2000–2004	7078	40
2005–2007	5087	29
Patient sex		
Male	10 386	59
Female	7149	41
Missing	10	<1
Patient age		
Median (range)	40 (16–85)	
16–19	1399	8
20–29	3506	20
30–39	3787	22
40–49	4167	24
50–59	3549	20
≥60	1137	6
Diagnosis		
Acute myeloid leukemia	6096	35
Acute lymphoblastic leukemia	3334	19
Chronic myeloid leukemia	2514	14
Myelodysplastic syndromes	1716	10
Adult T-cell leukemia	591	3
Other leukemia	130	1
Myeloproliferative disorders	224	1
Non-Hodikin's lymphoma	1652	9
Hodikin's lymphoma	46	<1
Other lymphoma/type missing	54	<1
Multiple myeloma	210	1
Aplastic anemia	745	4
Pure red cell aplasia	4	<1
Paroxysmal nocturnal hemoglobinuria	20	<1
Solid tumor	109	1
Others	86	<1
Data missing	14	<1
Donor		
Related, siblings	7825	45
Related, other relatives	941	5
Related, data missing	179	1
Unrelated	8600	49
Stem cell source		
Bone marrow	11 866	68
Peripheral blood	3453	20
Bone marrow and peripheral blood	134	1
Cord blood	2092	12
Conditioning regimen		
Myeloablative		
Cyclophosphamide + TBI ± other	8298	47
Other TBI regimen	1321	8
Busulfan + cyclophosphamide ± other	2798	16
Other non-TBI regimen	778	4
Reduced intensity		
Fludarabine + busulfan ± other	1527	9
Fludarabine + cyclophosphamide ± other	503	3
Fludarabine + melphalan ± other	1480	8

Continued

Table 1. *Continued*

Characteristics	Number	Percent
Other RIST	631	4
Data missing	209	1
GVHD prophylaxis		
No	85	<1
Cyclosporine A + sMTX	10 091	58
Cyclosporine A ± other	1175	7
Tacrolimus + sMTX	4682	27
Tacrolimus ± other	876	5
Other	323	2
Data missing	312	2

TBI, total body irradiation; sMTX, short-term methotrexate.

were 20–29 years of age at transplant, all solid cancers, oral/pharynx, esophagus, and gallbladder for recipients who were 30–39 years of age at transplant, all solid cancers, oral/pharynx, esophagus, and skin for recipients who were 40–49 years of age at transplant, all solid cancers, oral/pharynx, esophagus, colon, and skin for recipients who were 50–59 years of age at transplant (Table 3).

risk factors for the development of secondary solid cancers

Extensive-type chronic GVHD and age at transplantation were important risk factors for the development of secondary solid cancers (Table 4). The risk was not increased in recipients who received TBI for conditioning. The results were similar when subjects were limited to those who received myeloablative conditioning (RR = 1.5, $P = 0.069$ for limited-type chronic GVHD, RR = 1.9, $P < 0.001$ for extensive-type chronic GVHD, and RR = 0.9, $P = 0.751$ for TBI). Risk factor analyses for high-risk organs with more than 10 cancer cases revealed that extensive-type chronic GVHD was an independent risk factor for cancers in the oral cavity/pharynx and esophagus. Limited-type chronic GVHD was a risk factor for cancers of skin (Table 4). For secondary cancers which developed within 1-year post-transplant, the only risk factor identified was older age at transplant (age 60 years or older; supplementary Table, available at *Annals of Oncology* online).

discussion

Our main objective was to determine the incidence of, the risk compared with the general population, and risk factors for secondary solid tumors after allogeneic stem cell transplantation in a large cohort of adult recipients. Allogeneic HCT recipients were at higher risk of developing cancers of the oral cavity, esophagus, colon, and skin. The incidence and SIR of developing all solid cancers continued to increase with follow-up, which suggested a continuous increase as follow-up progressed. Our data are important since we included a large number of subjects and person-years of follow-up, in a transplant cohort that is different from those in previously reported large studies.

Table 2. Standard incidence ratio, ratio of observed versus expected number of secondary solid cancers according to duration post-transplant

| Secondary cancer sites | Time since transplantation (years) | | | | | | | | Total | | |
| | <1 | | 1–4 | | 5–9 | | 10 or longer | | | | |
	O	SIR	O	SIR	O	SIR	O	SIR	O/E	SIR	95% CI
Number of recipients	17 545		10 210		5864		2192		17 545		
Person-years at risk	12 803		30 599		18 845		7218		69 465		
All solid cancers	19	0.7	97	1.5*	90	2.0*	63	3.1*	269/153.6	1.8*	1.5–2.0
Oral/pharynx	0	0.0	16	9.5*	27	23.4*	21	38.5*	64/4.1	15.7*	12.1–20.1
Esophagus	0	0.0	13	6.5*	17	12.6*	11	16.8*	41/4.8	8.5*	6.1–11.5
Stomach	2	0.4	7	0.6	6	0.8	1	0.3	16/26.0	0.6	0.4–1.0
Colon	2	0.8	16	2.7*	5	1.2	4	2.2	27/14.3	1.9*	1.2–2.7
Rectum	0	0.0	1	0.2	0	0.0	5	3.6*	6/10.7	0.6	0.2–1.2
Liver	1	0.6	5	1.4	0	0.0	2	1.8	8/8.6	0.9	0.4–1.8
Gallbladder	2	5.1	2	2.1	2	3.0	0	0.0	6/2.3	2.6	1.0–5.7
Pancreas	0	0.0	2	1.0	6	4.5*	1	1.6	9/4.7	1.9	0.9–3.7
Broncus/lung	3	1.2	4	0.6	9	2.1	3	1.5	19/15.1	1.3	0.8–2.0
Skin	2	7.0	6	8.1*	3	5.7*	2	8.4*	13/1.8	7.2*	3.9–12.4
Female breast	0	0.0	3	0.3	1	0.1	3	0.9	7/24.5	0.3	0.1–0.6
Cervix uteri	1	1.3	4	2.0	1	0.7	1	1.6	7/4.8	1.5	0.6–3.0
Corpus uteri	2	3.7	1	0.7	2	1.8	0	0.0	5/3.6	1.4	0.4–3.2
Ovary	0	0.0	1	0.7	1	1.0	1	2.2	3/3.6	0.8	0.2–2.4
Prostate	1	1.2	0	0.0	1	0.6	1	1.4	3/5.4	0.6	0.1–1.6
Bladder	1	1.9	3	2.4	0	0.0	0	0.0	4/2.9	1.4	0.4–3.5
Kidney	0	0.0	1	0.6	1	0.9	0	0.0	2/4.1	0.5	0.1–1.8
Brain/nervous system	1	3.4	1	1.4	1	2.1	4	19.1*	7/1.7	4.1*	1.6–8.5
Thyroid	0	0.0	2	1.1	2	1.5	0	0.0	4/4.5	0.9	0.2–2.3
Other[a]	1		9		4		3		17		

[a]Other sites included two testicular cancers, four connective tissue cancers, four bone cancers, one larynx cancer, one malignant salivary gland tumor, one duodenum papilla cancer, one germ cell tumor, one carcinomatous pleurisy of origin unknown, and two squamous cell carcinomas of unknown origin.
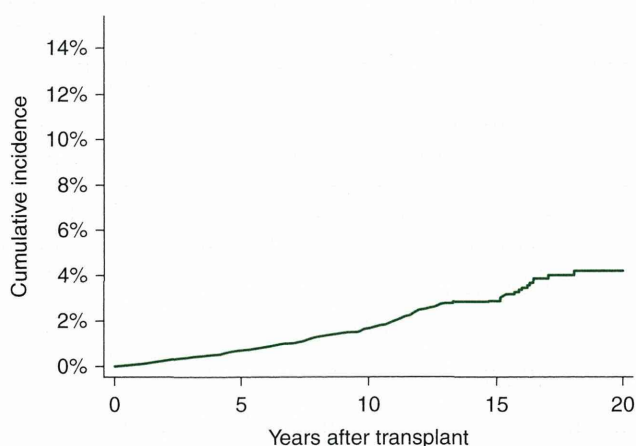*$P < 0.05$.

Figure 1. Cumulative incidence of developing a secondary solid cancer. The cumulative incidence of solid cancers was 0.7% [95% confidence interval (CI), 0.6–0.9] at 5 years, 1.7% (95% CI, 1.4–1.9) at 10 years, and 2.9% (95% CI, 2.5–3.4) at 15 years after transplantation.

Extensive-type chronic GVHD has repeatedly been shown to be a significant risk factor for the development of secondary solid tumor and is highly correlated with squamous cell carcinoma [8, 9, 12, 15, 16]. Extensive-type chronic GVHD was also shown to be a significant risk factor for oral cancer in our study. Extensive-type chronic GVHD was shown to be a significant risk factor for esophageal cancer, which was found to be increased in recipients compared with the general population in our study as well as in two other smaller Japanese cohorts in previous studies [11, 14]. Subjects were shown to be at a higher risk for the development of cancers of the oral cavity or esophagus at all time periods after 1 year. Data were not obtained for affected organ sites of chronic GVHD in JSHCT data collection prior to transplants in 2006. Therefore, we could not investigate whether oral or esophageal cancers were related to the chronic GVHD of the same organ. However, results of risk factor analyses for cancer sites of oral, esophagus, colon, and skin which showed high associations of extensive-type chronic GVHD and oral or esophagus cancer, limited-type chronic GVHD, and skin cancer showed that development of secondary solid tumors were likely to be influenced by GVHD-affected sites. Lifelong screening for oral, pharynx, or esophageal cancers for recipients with active or resolved chronic GVHD is important after 1-year post-transplant. The prognosis of solid cancers is highly influenced by the stage of the cancers when they are first detected. Our findings support recently published recommended screening guidelines [21, 22].
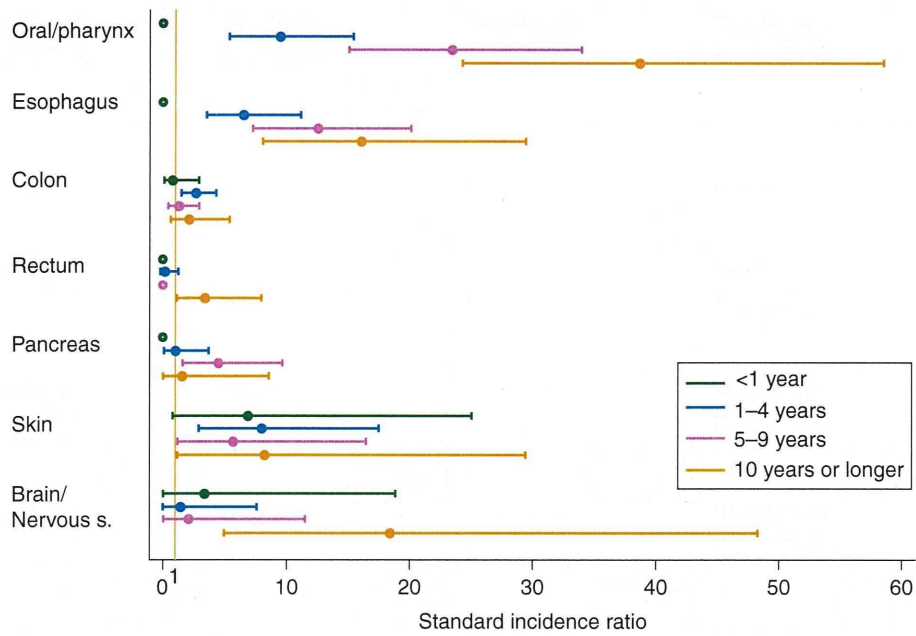
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Figure 2. Trends of standard incidence ratios (SIRs) and its 95% confidence intervals (CIs) of high-risk secondary solid cancer sites according to time since transplant. The SIR and 95% CIs for <1, 1–4, 5–9, and 10 years or longer post-transplant were 0.0, 9.5 (5.4–15.4), 23.4 (15.4–34.0), and 38.5 (23.8–58.9) for oral/pharynx cancer, 0.0, 6.5 (3.5–11.2), 12.6 (7.3–20.2), and 16.8 (8.4–30.1) for esophageal cancer, 0.8 (0.1–2.9), 2.7 (1.5–4.3), 1.2 (0.4–2.9), and 2.2 (0.6–5.7) for colon cancer, 0.0, 0.2 (0.0–1.3), 0.0, and 3.6 (1.2–8.4) for rectum cancer, 0.0, 1.0 (0.1–3.7), 4.5 (1.6–9.7), and 1.6 (0.0–8.9) for pancreatic cancer, 7.0 (0.8–25.1), 8.1 (3.0–17.5), 5.7 (1.2–16.7), and 8.4 (1.0–30.3) for skin cancer, and 3.4 (0.1–19.0), 1.4 (0.0–7.7), 2.1 (0.1–11.6), and 19.1 (5.2–49.0) for cancers of brain/nervous system, respectively.

Table 3. Standard incidence ratio according to recipient's age at transplant

	Recipient's age at transplantation											
	16–19		20–29		30–39		40–49		50–59		60 or older	
Number-of-recipients	1399		3506		3787		4167		3549		1137	
Person-years at risk	7083		17 912		17 303		16 198		9126		1843	
Secondary cancer sites	O	SIR	O	SIR	O	SIR	O	SIR	O	SIR	O	SIR
All solid cancers	18	17.0*	28	4.1*	51	2.4*	71	1.4*	79	1.5*	22	1.0
Oral/pharynx	7	140.0*	11	50.7*	19	36.5*	13	10.1*	12	8.1*	2	3.9
Esophagus	1	350.0*	3	131.0*	13	48.5*	10	7.0*	13	5.9*	1	1.1
Stomach	1	13.3	0	0.0	1	0.3	7	0.8	5	0.5	2	0.5
Colon	0	0.0	0	0.0	3	2.0	6	1.3	12	2.1*	6	2.6
Rectum	1	33.1	0	0.0	0	0.0	1	0.3	4	0.9	0	0.0
Liver	1	66.4*	1	8.1	0	0.0	2	0.8	3	0.8	1	0.6
Gallbladder	0	0.0	0	0.0	2	12.0*	1	1.5	2	2.1	1	2.0
Pancreas	0	0.0	0	0.0	2	5.5	1	0.7	4	2.0	2	2.3
Broncus/lung	1	44.3*	0	0.0	2	1.6	7	1.6	7	1.1	2	0.7
Skin	1	28.6	1	6.3	0	0.0	6	11.6*	4	7.4*	1	4.0
Female breast	0	0.0	1	0.7	1	0.2	1	0.1	3	0.5	1	0.9
Cervix uteri	0	0.0	1	1.2	3	1.9	2	1.4	1	1.4	0	0.0
Corpus uteri	0	0.0	1	5.2	0	0.0	2	1.4	2	1.6	0	0.0
Ovary	0	0.0	1	3.2	0	0.0	1	0.7	0	0.0	1	6.4
Prostate	0	0.0	0	0.0	0	0.0	2	2.4	0	0.0	1	0.5
Bladder	0	0.0	0	0.0	0	0.0	2	2.3	2	1.7	0	0.0
Kidney	0	0.0	0	0.0	0	0.0	2	1.4	0	0.0	0	0.0
Brain/nervous system	2	23.9*	1	3.8	1	2.7	1	2.0	1	2.6	1	9.1
Thyroid	0	0.0	2	3.9	0	0.0	1	0.7	1	0.9	0	0.0

*P < 0.05.

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Table 4. Risk factors for second solid cancers among >1 year survivors after hematopoietic stem cell transplantation

Solid cancer	Risk factor	Number of patients with second cancer	RR	95% CI	*P*-value
All second solid cancers[a]		249			
	Total body irradiation	151	0.9	0.7–1.1	0.294
	Chronic GVHD				
	Limited type	45	1.4	1.0–1.9	0.087
	Extensive type	93	1.8	1.4–2.4	<0.001
	Age at transplant (years)				
	16–29	45	1.0		
	30–39	46	1.6	1.0–2.4	0.042
	40–49	68	2.5	1.7–3.7	<0.001
	50–59	71	5.5	3.7–8.2	<0.001
	60 or older	19	7.9	4.4–14.1	<0.001
Oral cancer[b]		64			
	Total body irradiation	38	1.0	0.8–1.3	0.957
	Chronic GVHD				
	Limited type	10	1.4	0.6–2.9	0.440
	Extensive type	29	2.9	1.6–5.1	<0.001
Esophageal cancer[b]		41			
	Total body irradiation	22	0.6	0.3–1.1	0.108
	Chronic GVHD				
	Limited type	7	2.1	0.8–5.9	0.151
	Extensive type	25	5.3	2.4–11.8	<0.001
Colon cancer[b]		26			
	Total body irradiation	12	0.5	0.2–1.2	0.144
	Chronic GVHD				
	Limited type	6	1.7	0.6–4.9	0.353
	Extensive type	10	1.6	0.6–4.2	0.329
	Grade 2–4 acute GVHD	12	2.0	0.9–4.4	0.101
Skin cancer[b]		13			
	Total body irradiation	12	1.2	0.8–1.6	0.377
	Chronic GVHD				
	Limited type	6	5.8	1.4–23.9	0.016
	Extensive type	2	1.8	0.3–8.9	0.500

RR, relative risk; CI, confidence interval; TBI, total body irradiation; GVHD, graft-versus-host disease.

[a]Stratified for primary disease (acute myeloid leukemia, acute lymphoblastic leukemia, chronic myeloid leukemia, and other).

[b]Stratified for primary disease (acute myeloid leukemia, acute lymphoblastic leukemia, chronic myeloid leukemia, and other) and patient age groups (<19, 20–29, 30–39, 40–49, 50–59, and >60). Adjusted for patient age as a continuous variable.

The incidence of secondary solid tumors in our study was similar to those in previously reported large studies [8, 9, 12, 13]. Rizzo et al. [12] reported that the incidence of secondary solid cancers among 28 874 transplant recipients and 85 583 person-years at risk was 1% at 10 years and 2.2% at 15 years, which were very similar to our results using the same statistical method for cumulative incidence, while treating death before secondary solid tumor as a competing risk. Majhail et al. [13] reported that the incidence of secondary solid cancers after HSCT using non-TBI, busulfan-cyclophosphamide conditioning was also ~1.2% at 10 years. The oral cavity was the most prominent high-risk cancer site compared with the general population, as in previous reports [8, 9, 12, 13]. Despite regional and racial differences in cancer incidence and cancer sites in the general population, the impact of HSCT on secondary cancer was similar.

In previous studies, TBI was reported to be a significant risk factor for the development of secondary cancer, but significant differences were not found in our study [7, 8, 10, 12, 23]. The subjects in this study were adult recipients, which may explain the different findings. Conditioning with radiation was reported to be associated with the development of secondary solid cancer in recipients at a younger age at transplant [12]. Moreover, a recent long-term follow-up analysis of patients who were transplanted after myeloablative doses of busulfan and cyclophosphamide without TBI found a similar increased incidence of secondary solid cancers as previous reports [13].

An older recipient age at transplant was a significant risk factor for the development of secondary solid tumor, as in previous studies [9, 13]. This result was not surprising since it is also the case in the general population. However, it is important to note that older patients are at higher risk of developing

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