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Letter

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Second Solid Cancers After Hematopoietic Stem Cell Transplantation: Active Surveillance During Long-term Follow-up

Maria Teresa Lupo-Stanghellini[1], Simona Piemontese[1], Andrea Assanelli[1], Fabio Serpenti[1,§], Sara Mastaglio[1], Daniela Clerici[1], Fabio Giglio[1], Raffaella Greco[1], Francesca Lorentino[1], Francesca Pavesi[1], Francesca Farina[1], Sarah Marktel[1], Consuelo Corti[1], Jacopo Peccatori[1], Fabio Ciceri[1,2]

Correspondence: Maria Teresa Lupo-Stanghellini (lupostanghellini.mariateresa@hsr.it).

Allogeneic hematopoietic stem cell transplantation (HSCT) is increasingly used as a curative option in the treatment of malignant and nonmalignant diseases.

Eighty percent of those who survive the first 2 years are expected to become long-term survivors. However, the prevalence of chronic-health conditions approaches 75% among HSCT survivors. Second solid cancers (SSCs) are the most clinically relevant late effects: cumulative incidence increases steadily between 2% and 6% at 20 years and is substantially higher when compared to general population.[1–3] Among risk factors radiation, graft versus host disease (GvHD), immunosuppression related to GvHD and association with viral infection (such as hepatitis C virus and human papillomavirus) increased risk for SSCs after HSCT.[4]

Recently, an EBMT cohort study evaluated the outcome of patients with a SSC after HSCT. Among 1443 patients with 18 different SSCs, 5-year overall survival (OS) was only 47%.[5]

Our study seeks to evaluate the utility of an intensive screening and counseling planned follow-up for SSCs after HSCT to pursue early detection and intervention.

An all-comprehensive standardized life-time follow-up of HSCT survivors is applied at our Center, according to Jacie Standards and international guidelines.[6,7] Health promotion, SSCs counseling and screening are part of this follow-up. In addition to blood tests, SSCs screening included yearly abdominal ultrasound, ophthalmologist, ENT, dermatological, and dental consultation, in addition to gynecological consultation, mammography and PAP test for female patients (Supplemental Digital Table 1; http://links.lww.com/HS/A203).

Table 1

Characteristics of Patients

		All Patients	SSCs Patients
N		**442**	**81**
Sex (M/F)		276/166	32/16
Age (at HSCT/at SCCs/at last FU)		49/n.a./56	58/61/64
Primary disease			
Acute leukemia		246	45
Hodgkin disease		34	2
Non-Hodgkin disease		51	13
Myeloma		25	4
Myelodysplasia		55	11
Others		31	6
Donor type			
MRD		129	22
MUD		141	28
CB		8	1
MMRD		164	30
Acute GvHD history		171	29
Chronic GvHD history		214	36
SSCs diagnosis			
Favorable[a]	Thyroid		1
	Cervix		10
	Prostate		4
	Breast		3
	Melanoma		2
	NMSC		43
Intermediate[a]	Kidney		3
	Oropharyngeal		1
	Bladder		2
	Ovarian		0
	Sarcomas		0
	Colorectal		1
	Endometrial		1
Poor[a]	Gastric		1
	Brain		0
	Esophageal		0
	Hepatobiliary		0
	Lung		9
	Pancreas		2
	Donor leukemia		2

[a]Classification adapted from Tichelli et al.[5]

CB = cord blood; FU = follow-up; GvHD = graft versus host disease; HSCT = hematopoietic stem cell transplantation; MMRD = mismatch-related donor; MRD = match-related donor; MUD = match-unrelated donor; NMSC = nonmelanoma skin cancer; SSCs = second solid cancers.

[1]Hematology and Bone Marrow Transplantation Unit, IRCCS San Raffaele Scientific Institute, Milano, Italy
[2]Vita-Salute San Raffaele University, Milano, Italy
[§]Current address for Dr Serpenti: Department of Hematology, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Università degli Studi di Milano, Italy.

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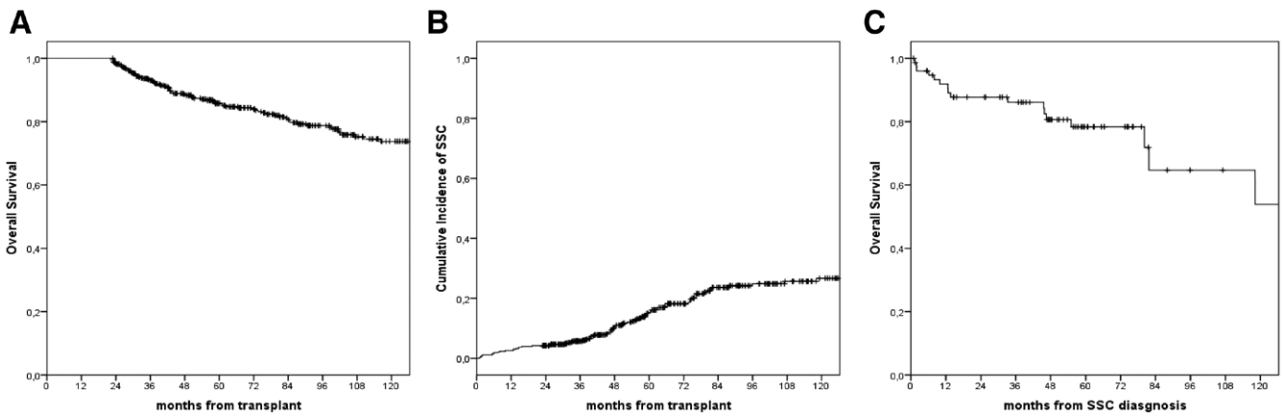

Figure 1. Overall survival analysis. (A) Overall survival for entire cohort of patients; (B) cumulative incidence of second solid cancer; (C) overall survival from diagnosis of second solid cancer.

This is a prospective cohort analysis of data collected at our long-term follow-up clinic between 2011 and 2019 including 442 adult patients—with at least 24 months follow-up—transplanted between 1996 and 2017.

A written consent was given by patients allowing the use of medical records for research in accordance with the Declaration of Helsinki.

Primary endpoints were incidence of SSC, incidence of death from SSC, and OS following a diagnosis of SSC.

Cumulative incidence functions were used to estimate the incidence of both SSCs and death from SSCs. Death without SSCs and any death not due to SSCs, such as death from primary disease and transplant-related death, were competing events for incidence of SSCs and death from SSCs, respectively.[8]

OS from transplant was calculated from the day of HSCT until death or the last follow-up. Survival following SSC diagnosis was calculated from the time of SSC diagnosis to death from any causes. The probability of OS and of survival after SSC was estimated using the Kaplan–Meier method. All tests were two-sided. Statistical analyses were performed with SPSS 20 (SPSS Inc./IBM, Armonk, NY).

Patients features including patients underlying disease and donor type are reported in Table 1. Median follow-up was 78 months (range 24–326 mo). At last evaluation, 360 patients were alive and the 5-year OS was 85% ± 2% (Fig. 1A) in the entire population.

Eighty-five SSCs occurred in 81 patients during time of observation (Table 1).

Five- and 10-year SSCs cumulative incidence was 15% ± 2% and 27% ± 3% (Fig. 1B), median time to diagnosis was 39 months (range 2–243 mo).

When considering outcomes after cancer events, median follow-up after diagnosis of SSCs was 56 months (range 1–190 mo). Five- and 10-year OS following occurrence of SSCs was 78% ± 5% and 54% ± 1% (Fig. 1C).

Table 2

Multivariate Analysis of the Association Between Patients/ Transplant Characteristics and SCC

	Second Solid Cancer	
	HR (95% CI)	***P***
Patient age		
>60 vs <60 y	3.1 (1.467–6.884)	0.003
TBI	1.6 (0.731–3.510)	0.239
Moderate/severe chGvHD	1 (1–1)	0.236

CI = confidence interval; HR = hazard ratio GvHD = graft versus host disease; SSCs = second solid cancers.

In multivariate analysis, the only risk factor for a higher incidence of SSCs was age at transplant >60 years (Table 2). The other covariates used in the cox model were as follows: patient sex, TBI, presence of metabolic syndrome, type of donor, and previous occurrence of chronic GvHD moderate/severe as a T-dependent covariate. SSCs were referred to the appropriate oncology specialists and treated according to standard practice. The cumulative incidence of mortality for SSCs was 1% at 5 years and 4% ± 2% at 10 years.

HSCT survivors are at a defined risk of developing SSCs. The pathogenesis of SSCs is multifactorial: interaction between cytotoxic treatment, genetic predisposition, environmental factors, viral infections, GVHD, and its immunosuppression may play a role.[7] Compared with general population, HSCT recipients are 3.6 times more likely to die of SSCs.[2,3]

Our 5-year cumulative incidence of SSCs was 15%: this is higher than the previously reported registry studies.[1–6] Possible explanations for this difference are the changes occurred in the field of HSCT such as the use of more oncogenic drugs (ie, voriconazole as antifungal prophylaxis), the older patient population, or the higher sensitivity offered by a dedicated intensive follow-up program including proactive oncologic screening.

In this regard, a recent CIBMTR/EBMT working group's guidelines for SSCs outlined how incidence of SSCs based on registry data may underestimate the true incidence.[7] Notably, the observed cancer cases in our cohort outnumber the expected in the general population matched for age and sex (Supplemental Digital Figure 1 and Supplemental Digital Table 2; http://links.lww.com/HS/A203)[9]—confirming the results summarized from existing literatures by Inamoto et al.[7]

Our prospective experience of intensive oncology screening suggests that the real-life incidence of SSCs is high, especially in patients transplanted after their 60s. Earlier detection of SSCs may result in better survival (Fig. 1C), unveiling the importance of dedicated surveillance program to enhance diagnosis, treatment, and overall outcome.

Disclosures

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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