ORIGINAL ARTICLE

The incidence, risk factors, and outcomes of primary poor graft function after unmanipulated haploidentical stem cell transplantation

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Abstract Primary poor graft function (PGF) is a severe complication after allogeneic stem cell transplantation (SCT). The incidence, risk factors, and outcomes of PGF have not been well described, especially in the haploidentical SCT setting. We retrospectively reviewed patients who received haploidentical SCT at Peking University Institute of Hematology between January 1, 2011, and December 31, 2012. PGF was defined as persistent neutropenia ($\leq 0.5 \times 10^9$ L^{-1}), thrombocytopenia (platelets $\leq 20 \times 10^9$ L^{-1}), and/or hemoglobin ≤ 70 g L^{-1} after engraftment with hypocellular bone marrow and full donor chimerism, without concurrent graft-versus-host disease or disease relapse. Incidence was calculated from all patients. Of the 464 total patients, 26 (5.6 %) developed primary PGF. The risk factors were analyzed and compared with control patients with good graft function who were selected using the case-pair method. Finally, 104 patients were selected as a control group according to the matching conditions: (1) the type (acute leukemia, myelodysplastic syndrome (MDS), chronic myelogenous leukemia (CML)) and status (standard risk, high risk) of underlying disease, (2) sex, (3) year in which the transplantation was received, and (4) a 1:4 ratio of case-control. No factors were found to be associated with primary PGF. Compared to cases with good graft

function, patients with primary PGF experienced poor overall survival (34.6 vs. 82.7 %, $p < 0.001$). Of the 26 primary PGF patients, only nine achieved hematopoietic recovery and survived. In conclusion, primary PGF is a rare but life-threatening complication after haploidentical SCT, and effective therapies need to be explored.

Keywords Graft function · Haploidentical · Stem cell transplantation · Human leukocyte antigen

Introduction

Hematopoietic reconstitution has been a cornerstone of successful allogeneic stem cell transplantation (allo-SCT). Recovery of hematopoiesis included the following: (1) rapid and persistent recovery of trilineage cell counts in peripheral blood and (2) the hematopoiesis originating from donor stem cells. Primary graft failure is a severe complication in which reconstitution of initial hematopoiesis after allo-SCT fails [1]. Its criteria are predominantly operational and based on peripheral blood cell counts. One of the known causes of primary graft failure is graft rejection. Graft rejection is the immune-mediated rejection of the donor allograft by residual host effector cells that occurs because of the genetic disparity between the recipient and the donor. However, another type of primary graft failure involves failure to achieve adequate blood counts following allo-SCT despite the presence of complete donor hematopoietic cell chimerism [2]; this group of patients is defined as poor graft function (PGF). Rejection is related to the recipient's residual immune system, and a second transplantation is the only salvage treatment; however, the mechanism and characteristics of PGF remain unknown.

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PGF can be divided into two groups, primary and secondary PGF. The former did not achieve initial reconstitution, while the latter specifies the loss of initial reconstitution. Patients with primary PGF have significantly poorer prognosis. In PGF patients treated with a boost of CD 34+ selected peripheral blood cells, the rate of trilineage recovery was 69 % in secondary PGF compared to 36 % in patients with primary PGF [3]. We had similar results in a previous study [4, 2], in which the recovery rates in primary and secondary PGF were 25 and 66.7 %, respectively; however, we used a different treatment, unselected peripheral blood cells. This suggests that primary PGF and secondary PGF may be different entities with different underlying pathogeneses; therefore, these two kinds of PGF should be investigated separately.

In the present study, we focused specifically on primary PGF since it indicates a clinically critical situation. A few prior studies have described the characteristics of PGF [5, 6, 3]; however, none of these studies distinguished primary PGF from secondary PGF. In addition, studies about PGF are mainly in the human leukocyte antigen (HLA)-identical SCT setting. Until recently, there have been no data about PGF in haploidentical SCT. In fact, there are more and more haploidentical transplantations for patients without an HLA-matched sibling (MSD) and unrelated donor (URD) in current era [7, 8]. Peking University Institute of Hematology (PUIH) is one of the most important centers in this field; we have adopted a protocol of unmanipulated haploidentical SCT, and patients have achieved comparable outcomes to those of MSD and URD [9, 10]. Here, we report the incidence, risk factors, and outcomes of primary PGF after haploidentical SCT in a large cohort.

Methods

Patients

Incidence cohort All consecutive patients who received haploidentical SCT at PUIH from January 1, 2011, to December 31, 2012, were retrospectively reviewed. Patients who were diagnosed with acute myeloid leukemia (AML), acute lymphoblastic leukemia (ALL), myelodysplastic syndrome (MDS), and chronic myelogenous leukemia (CML), and patients who received the first time of allo-SCT were included in the incidence cohort.

Risk factor cohort In the incidence cohort, patients were divided into five groups according to the status on day 28 after allo-SCT: (1) good graft function (GGF), defined as achievement of both neutrophil and platelet engraftment on day 28 and independent of transfusion; (2) PGF, defined as persistent neutropenia ($\leq 0.5 \times 10^9$ L^{-1}), thrombocytopenia (platelets $\leq 20 \times 10^9$ L^{-1}), and/or hemoglobin ≤ 70 g L^{-1} for at least three consecutive days by day 28 post-transplantation, transfusion-dependence, associated with hypoplastic-aplastic bone marrow (BM), and complete donor chimerism without concurrent graft-versus-host disease (GVHD) or disease relapse, primary PGF was defined as the failure to achieve initial engraftment by day 28 after transplantation and secondary PGF was defined as the fulfillment of the criteria after initial engraftment HSCT; (3) graft rejection, defined as never having achieved engraftment with mixed chimerism or complete recipient chimerism; (4) isolated cytopenia, defined as presence of one cytopenic count; or (5) early death before day 28. To analyze the risk factors, the control group was selected from the GGF patients using the case-pair method. Matching conditions included the following: (1) the type (acute leukemia, MDS, CML) and status (standard risk, high risk) of underlying disease, (2) sex, (3) year in which the transplantation was received, and (4) a 1:4 ratio of case-control. Finally, 104 patients were selected as a control group.

Transplantation regimen

Donor selection, HLA typing, and stem cell harvesting have been previously described [10, 9]. In brief, the conditioning therapy consisted of cytarabine (4 g m^{-2} day^{-1} on days −10 to −9), busulfan (3.2 mg kg^{-1} day^{-1} intravenously on days −8 to −6), cyclophosphamide (1.8 g m^{-2} day^{-1} on days −5 to −4), semustine (250 mg m^{-2} orally on day −3), and anti-thymocyte globulin (2.5 mg kg^{-1} day^{-1}, rabbit [Sang Stat, Lyon, France] on days −5 to −2). Transplant recipients received cyclosporine A, mycophenolate mofetil, and short-term methotrexate for prevention of GVHD.

Definitions

Engraftment of neutrophils was defined as the first of three consecutive days when the absolute neutrophil count achieved 0.5×10^9 L^{-1} without granulocyte colony-stimulating factor stimulation (G-CSF). Engraftment of platelets was defined as the first of seven consecutive days when the platelet count was $\geq 20 \times 10^9$ L^{-1}, independent from platelet substitution. Underlying disease was classified as high-risk or standard-risk. High-risk disease included acute leukemia either in non-remission or in the third or greater complete remission, and chronic myeloid leukemia in the blast phase; standard-risk disease included all other diagnoses. Hematological recovery was defined as neutrophils $>0.5 \times 10^9$ L^{-1}, platelets $>20 \times 10^9$ L^{-1}, and hemoglobin >70 g L^{-1} and without transfusion or G-CSF.

Statistical

All clinical data were analyzed retrospectively using SPSS package software (SPSS, Chicago, IL, USA). The incidence

of PGF was calculated by the proportion of PGF in the total cohort. Univariate analysis in comparing crude incidence rates used χ^2 test or Fisher's exact test. Risk factors with $p<0.2$ in univariate analysis were chosen for further evaluation by multivariate logistic regression. Significant risk factors were added to the final model using a stepwise forward method with significance margins for entry of 0.10 and removal of 0.15.

Results

Incidence and characteristics of primary PGF

A total of 464 patients were enrolled in the incidence cohort, and of these, 26 (5.6 %) patients experienced primary PGF, 2 (0.4 %) with secondary PGF, 65 (14.0 %) with isolated thrombocytopenia, 2 (0.4 %) with early death, and 1 (0.2 %) with graft rejection. The basic characteristics of patients with primary PGF are listed in Table 1. In the 26 patients with primary PGF, 14 were male and 12 were female. The median age of patients and donors were 30 years (4–55) and 34.5 years (17–60), respectively. Twenty-one patients were diagnosed with acute leukemia, three with MDS, and two with CML. Of the 26 patients, 2 developed cytomegalovirus (CMV) viremia before day 28; none developed Epstein-Barr virus (EBV) or adenovirus.

The crude incidence of primary PGF was 5.6 %; the incidence was 4.1 % among those aged ≤35 and 10.0 % in those aged >35, respectively. In patients with AML, ALL, MDS, and CML, the incidence was 5.1, 5.8, 7.7, and 5.1 %, respectively. The incidences of primary PGF in patients with standard-risk and high-risk disease were 5.8 and 3.3 %, respectively.

Risk factors of PGF

The control group consisted of 104 patients with GGF and was used to identify the risk factors for PGF, which are shown in Table 2. Patients with donors of five matched loci had lower incidence of PGF ($p=0.026$). Patients with older age, an older donor, and low CD4+ cells had p values <0.2 and were included in the multivariate model. However, none of these factors were found to be associated with the occurrence of primary PGF (Table 2).

Outcomes of primary PGF

In the 26 primary PGF, 9 recovered finally with a median time of 50 days (35–100) after transplantation. In the 26 patients, 14 received supportive therapy (G-CSF and transfusion) only and 7 recovered, 11 received second donor cell infusion and 2 recovered, 1 received second transplantation and did not

recover. Finally, the nine patients with hematological recovery survived. All the patients without response died, only 1 death was attributed to relapse, the other 16 was attributed to infection-caused treatment-related mortality (TRM).

Regarding the long-term prognosis, patients with primary PGF have significantly poorer survival than patients with GGF (34.6 vs. 82.7 %, $p<0.001$, Fig. 1). In the multivariate analysis, primary PGF was an independent factor associated with poor overall survival.

Discussion

PGF is an infrequent complication after allo-SCT that is not well understood, and little is known about the incidence and characteristics of PGF. Early reports found that the incidence of PGF ranged from 5 to 27 % [3, 11]; however, there were a number of flaws with these studies, including a lack of distinction between PGF and graft rejection, as well as a lack of separation between cases of primary and secondary PGF. It is important to distinguish between these two types of PGF because we now realize that primary and secondary PGF are distinct entities with significantly different prognoses [4] and the majority of cases are actually secondary PGF. Another limitation of previous studies was the heterogeneity of criteria used to define PGF [5, 3, 2]. We chose to define PGF in terms of its most insidious effects, infection, and hemorrhage attributed to severe neutropenia and thrombocytopenia [2]. The cutoff values that we selected for this study represent the minimal sufficient values that do not require blood or platelet transfusion and are associated with reduced risk of infectious complications.

A retrospective study by Xiao et al. [12] reported that the incidence of primary PGF was 12.1 %; this was significantly higher than that reported in our studies, possibly because the criteria of PGF in our study were stricter. In addition, most of the patients in the study by Xiao et al. were HLA-identical. Importantly, PGF may be more likely to occur in mismatched transplantation, and there are no data of PGF after haploidentical SCT. Our data provide the exact incidence of PGF after haploidentical transplantation for the first time since the wide adoption of this technique.

In previous reports, patient age, donor-recipient blood-type matching, and CMV infection were associated with PGF [12]. In our report, however, we did not find any of these associations. These differences may be due to the different patients group (both primary and secondary PGF), definition of PGF, types of transplantation, and so on. GVHD [13] and virus [14] are clearly associated with secondary PGF, and our previous study suggested that patients with secondary PGF have an impaired microenvironment [2]; however, this may not be applicable to primary PGF. In fact, these might be part of the different mechanisms through which primary and secondary PGF occur; primary PGF may be immune-related, while

Table 1 Patients with primary poor graft function

UPN	Sex	Age	Disease	Status	Chemo[a]	D_{sex}	HLA	D_{Rbt}	D_{age}	Hematological recovery	Treatment	Time of recovery	Survival	Survival time[b]
4113963	F	35	ALL	SR	8	f	3	1	32	N	Support	–	D	78
4161611	m	30	ALL	SR	7	m	3	1	60	N	DCI	–	D	95
4169980	m	38	ALL	SR	5	m	3	0	34	N	DCI	–	D	208
4168079	F	13	ALL	SR	5	m	4	1	44	Y	Support	70	A	784
4137093	m	10	AML	SR	4	m	3	0	46	N	Support	–	D	310
4171691	F	11	AML	SR	4	f	4	0	40	Y	Support	100	A	787
4169751	F	14	AML	SR	8	f	4	0	25	Y	Support	60	A	737
4136263	m	21	AML	SR	3	f	3	0	44	N	DCI	–	D	285
4141645	m	43	AML	SR	3	m	3	2	17	N	DCI	–	D	155
4156860	m	35	AML	SR	6	f	4	0	47	N	Second transplantation	–	D	167
4168258	F	17	AML	SR	8	m	3	2	39	N	DCI	–	D	174
4169467	F	21	AML	SR	6	m	4	1	49	Y	Support	48	A	818
5017420	F	30	AML	SR	5	m	4	2	34	N	Support	–	D	142
4163073	F	54	AML	SR	4	m	4	0	42	Y	Support	50	A	700
4138406	F	4	ALL	SR	6	m	4	0	32	N	Support	–	D	198
4035149	F	20	ALL	SR	28	m	4	0	36	N	DCI	–	D	252
4156447	F	36	ALL	SR	6	m	3	0	33	Y	Support	35	A	301
5020051	m	26	ALL	SR	4	m	4	2	50	Y	Support	38	A	892
4167753	m	45	ALL	SR	5	m	3	0	22	N	DCI	–	D	229
4165074	m	21	ALL	SR	9	f	4	0	46	Y	DCI	50	A	833
4167012	F	7	ALL	SR	4	m	3	0	35	N	Support	–	D	67
4168505	m	48	CML	HR	6	m	3	0	29	N	DCI	–	D	214
4176947	m	41	CML	SR	0	f	3	1	17	Y	DCI	40	A	707
5023514	m	55	MDS	HR	0	m	3	0	28	N	Support	–	D	28
4175954	m	50	MDS	SR	0	f	3	0	26	N	DCI	–	D	191
4176340	m	48	MDS	SR	0	m	4	2	19	N	Support	–	D	74

UPN unique patient number; *m* male; *f* female; *AML* acute myeloid leukemia; *ALL* acute lymphoblastic leukemia; *CML* chronic myelogenous leukemia, *MDS* myelodysplastic syndrome; *SR* standard risk; *HR* high risk; D_{sex} donor sex; *HLA* matched HLA loci; D_{Rbt} donor-recipient blood type: *0*, matched, *1*, minor mismatch, *2*, major mismatch; D_{age} donor age; *N* no; *Y* yes; *DCI* donor cell infusion; *A* alive; *D* death; − not applicable

[a] Numbers of chemotherapy received before transplantation

[b] Days after transplantation

secondary PGF may be associated with impaired microenvironment due to GVHD and virus. We speculate that, to some extent, PGF after transplantation presents a similar situation to that of bone marrow failure. Immune-related impairment to the microenvironment and hematopoietic stem cells likely contribute to the pathogenesis of classical bone marrow failure syndrome (acquired aplastic anemia). The imbalance of T helper type 1 cells (Th1)/T helper type 2 cells (Th2), reduction of regulatory T cells, and activation of cytotoxic T lymphocytes (CTL) may involve in the pathogenesis [15, 16].

We notice that none of the patients with 1-locus mismatched donor developed PGF although the HLA disparity was not found to be associated with primary PGF in multivariate analysis. However, in previous studies, HLA-disparity has been shown to be related to increased incidence of PGF [3], though the underlying mechanism was not clear and this

phenomenon remains to be confirmed in prospective studies. The increased incidence of PGF in mismatched transplantation suggests that there may be immune-related mechanism in primary PGF. DSA was associated with graft failure after allogeneic SCT [17, 18]. Our recent unpublished data demonstrated that there is strong association between DSA and primary PGF (41st EBMT annual meeting, 2015, Istanbul, oral presentation O043). DSA-positive patients experienced higher incidence of primary PGF (31 vs. 3.2 %, $p=0.000$) than those of DSA-negative cases. However, these preliminary data needed to be confirmed, and the way how it associates with primary PGF needed to be explored in further study.

There are evidences demonstrating the correlation between natural killer cells with graft failure [19]. As one subgroup of primary PGF, NK cells may play role in its pathogenesis. However, we have to admit that we have no direct study of

Table 2 Risk factors associated with primary poor graft function

Variate		Primary PGF	GGF	Univariate (*p* value)	Multivariate (*p* value)
Sex	Male	14	60	0.826	
	Female	12	44		
Age	≤35	16	80	0.135	0.098
	>35	10	24		
Chemotherapy courses prior transplantation	<Median (4)	11	55	0.385	
	≥Median (4)	15	49		
Donor sex	Male	18	63	0.501	
	Female	8	41		
Donor age	<Median (40)	17	51	0.188	0.115
	≥Median	9	53		
Matched HLA loci	3	14	73	0.026	0.303
	4	12	23		
	5	0	8		
Blood type	Match	16	62	0.876	
	Major mismatch[a]	5	24		
	Minor mismatch	5	18		
MNC in graft	<Median (8.21×10^8 kg^{-1})	15	51	0.513	
	≥Median	11	53		
CD3+ cells in graft	<Median (1.56×10^8 kg^{-1})	15	50	0.511	
	≥Median	11	54		
CD4+ cells in graft	<Median (0.87×10^8 kg^{-1})	17	48	0.124	0.149
	≥Median	9	56		
CD8+ cells in graft	<Median (0.51×10^8 kg^{-1})	12	53	0.827	
	≥Median	14	51		
CD34+cells in graft	<Median (2.21×10^6 kg^{-1})	13	52	1	
	≥Median	13	52		

PGF poor graft function, *GGF* good graft function, *HLA* human leukocyte antigen, *MNC* mononuclear cell

[a] Major mismatch with concurrent minor mismatch was treated as major mismatch

NK cells in patients of homogenous primary PGF. This is a question needed to answer in our further study.

Some recent reports [20, 21] suggest that patients with idiopathic myelofibrosis might have higher incidence of PGF than patients with other underlying disease. However,
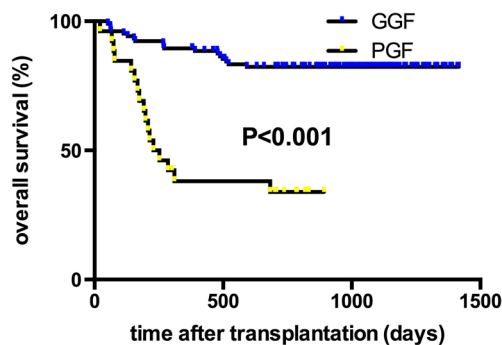

Fig. 1 The overall survival of patients with primary poor graft function (PGF) was significantly poorer than patients with good graft function (GGF) (*p*<0.001)

incidence and pathogenesis were not provided. In our study, no patient with idiopathic myelofibrosis received HSCT during this study period, so we do not have this data. This could be an interesting topic for further study. Our current study focuses on malignant hematological disease and suggests that primary PGF in malignant hematological disease is not very rare.

The prognosis of primary PGF is very poor, which can be easily understood. Most patients die of infection attributed to persistent leukocytopenia. Although some patients received a second infusion of donor cells or even second transplantation, the efficacy was very poor. Some recent studies have shown promising results from treating with a booster of CD34+ cells [20–22]; however, we should note that most patients who received the boosted cell infusion had secondary PGF, and we have already demonstrated that primary PGF has significantly worse prognosis than secondary PGF [4]. New therapeutic options are warranted to manage primary PGF on the basis of better understanding of primary PGF.

There were some limitations to our study. First, this was a retrospective study, and the event of primary PGF is still relatively rare. Second, no data regarding DSA or natural killer cell alloreactivity were available in the current study. Future prospective studies should be conducted to investigate the potential relationship between DSA or natural killer cells and primary PGF.

In conclusion, we demonstrated for the first time that primary PGF occurs in 5.6 % patients who received haploidentical transplantation, which was associated with poor survival. Our data suggest that further elucidation of the mechanisms underlying primary PGF is warranted so that effective therapies can be developed.

Conflict of interest　None.

Statement of human rights　All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. For this type of study, formal consent is not required.

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