Graft Failure

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41.1 Introduction

Engraftment is defined as the first of 3 consecutive days with an absolute neutrophil count higher than 0.5×10^9/L (sustained $>20 \times 10^9$/L platelets and hemoglobin >80 g/L, free of transfusion requirements).

In the setting of RIC protocols, it is also recommended to confirm the donor origin through chimerism studies.

The incidence of GF is <3–5% in the auto- and matched allo-HSCT setting, but it increases up to 10% in the cases of haploidentical or CBT.

The prognosis of graft failure (GF) is poor, and most patients die because of causes related to infections or bleeding, with an OS at 3–5 years after the diagnosis of GF less than 20%.

41.2 Definitions

Primary graft failure (GF)	ANC $<0.5 \times 10^9$/L by day +28 Hemoglobin <80 g/L and platelets $<20 \times 10^9$/L *RIC*: Confirmation of donor cell origin is required *CBT*: Up to day +42
Secondary GF	ANC $<0.5 \times 10^9$/L *after initial engraftment* not related to relapse, infection, or drug toxicity *RIC*: Loss of donor hematopoiesis to <5%
Poor graft function	Two or three cytopenias >2 weeks, after day +28 in the presence of donor chimerism >95%
Graft rejection	GF caused by *immune rejection* of donor cells mediated by host cells

41.3 Causes and Risk Factors

The etiology of GF is multifactorial in most of the cases (Fig. 41.1, Table 41.1).

41.3.1 Donor Type, HLA Matching, and Graft Source

Classical studies showed a close relationship between the degree of HLA mismatch and the incidence of GF, but it is difficult to draw conclusions because most of them used a limited HLA matching including only low-resolution A, B, and DR locus (Anasetti et al. 1989; Petersdorf

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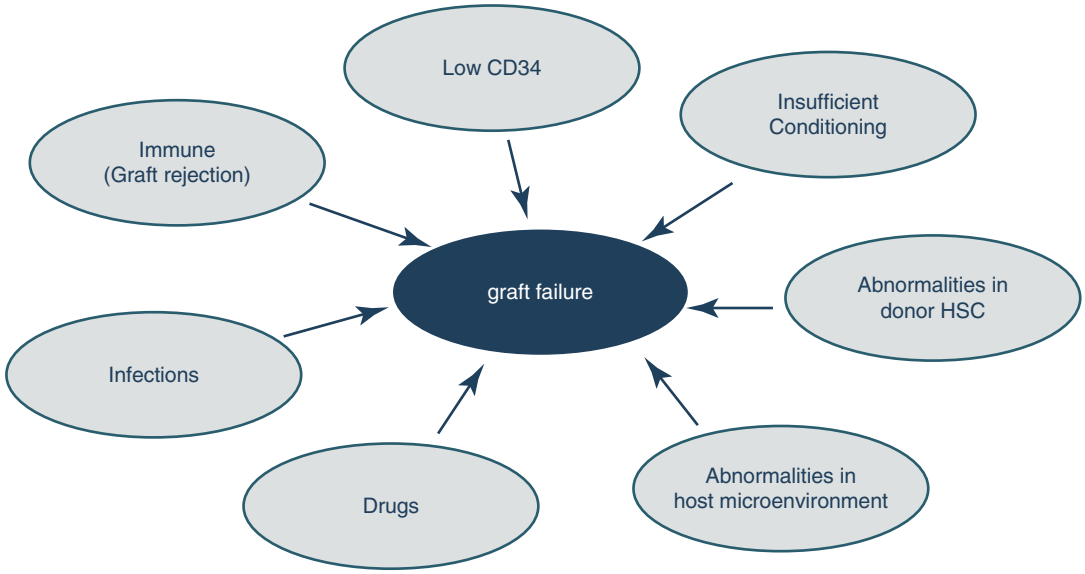

Fig. 41.1 Causes associated with the development of GF

Table 41.1 Risk factors for GF

Pre-transplant difficult to modify	Pre-transplant easy to modify	Peri-post transplant
HLA mismatches Nonmalignant disease Advanced disease Extensive marrow fibrosis extensive prior treatment Donor age Splenomegaly	Graft source Conditioning T-cell depletion	CD34+ cell count Viral infections GVHD Drug toxicity
Iron overload HLA antibodies Transfusion history		

et al. 2001). More recent studies, using high-resolution techniques for HLA typing and including 10–12 loci (A, B, C, DR, DQ, and DP), did not find differences in GF rates between no HLA antigen mismatch and a single HLA mismatch in both conventional MAC (Lee et al. 2007) or RIC (Passweg et al. 2011).

URD transplant was associated with a higher risk of GF (HR 1.38, $p < 0.001$ compared to HLA identical sibling) that was even higher when there were two or more mismatches (HR 1.79, $p < 0.001$) (Olsson et al. 2015).

In the haploidentical setting, the incidence of GF is around 10% which seems higher than the 3–5% currently reported MSD or URD HSCT although there are not well-designed comparative studies.

41.3.2 Graft Source and Cellular Content

BM is consistently associated with delayed neutrophil and platelet engraftment across all types of transplant; the impact on GF depends on donor type. GF incidence is not different for HLA MRD (Bensinger, 2012), but it is higher in the setting of URD (9% vs 3%, for BM and PB, respectively, $p < 0.001$) (Anasetti et al. 2012). There are no prospective randomized data either looking at MAC or RIC, but retrospective results from EBMT and CIBMTR suggest there were no differences in GF between BM and PB (less than 5% in all cases). In contrast, in a study evaluating donor characteristics, the use of BM was the only factor associated with GF after RIC (HR 2.3; $p = 0.02$) (Passweg et al. 2011).

The minimum cellular content required is still a matter of debate. Table 41.2 depicts a conservative proposal based on the literature review.

Table 41.2 Minimum cell content recommended

Progenitors	Type of transplant	Amount of cells
BM progenitors	Autologous	TNC: 2×10^8/kg
	Allogeneic	TNC: 3×10^8/kg
PB progenitors	Autologous	Minimum: CD34 $>1 \times 10^6$/kg Optimum: CD34 $>2 \times 10^6$/kg
	Allogeneic MAC	Minimum: CD34 $>2 \times 10^6$/kg Optimum: CD34 $>4 \times 10^6$/kg
	Allogeneic RIC	Minimum: CD34 $>2 \times 10^6$/kg Optimum: CD34 $4–8 \times 10^6$/kg
Cord blood	HLA 4–6/6	TNC $>2.5–3 \times 10^7$/kg CD 34 $>1 \times 10^5$/kg

TNC total nucleated cells, *MAC* myeloablative conditioning, *RIC* reduced intensity conditioning regimen

41.3.3 Anti-HLA Antibodies

The presence of donor-specific anti-HLA antibodies (DSA) is associated with higher risk of GF in the context of haploidentical CBT and URD transplants, and it may in fact translate into a reduced OS (Spellman et al. 2010; Ciurea et al. 2009; Ciurea et al. 2015). The high prevalence of anti-HLA antibodies (10–40%) (Morin-Zorman et al. 2016) and the increasing use of mismatched donors prompted the EBMT to write a set of advices and recommendations on this issue (Table 41.3) (Ciurea et al. 2018).

41.3.4 Conditioning Regimen

Increasing the intensity of MAC conditioning protocols does not reduce the incidence of GF. In contrast, RIC may be associated with a higher risk.

Although it is well accepted that TBI reduces the risk of GF, there are no comparative studies that confirm this latter point. In combination with CY, the use of full-dose TBI does not seem to reduce GF in comparison with BU. The use of ATG in the preparative regimen in combination

Table 41.3 Considerations regarding the presence of anti-HLA antibodies

Anti-HLA and DSA prevalence	Anti HLA: 10–40% DSA: 10–20%. Higher in female (increase with each pregnancy)
Detection methods	• Cell based (direct test): Donor viable lymphocytes and patient serum are needed. Complex and time-consuming technique. Low specificity and variable sensitivity (higher with flow cytometry assays than complement-based assays) • Solid phase immunoassays (virtual test): Only requires patient serum, and the technique is easy and fast. Sensitivity and specificity are intermediate/high depending on the type of assay. Modified techniques such as C4d or Cq1 assays allow to detect complement-fixing antibodies, which are at higher risk of inducing GF. These are the test most commonly used nowadays; initial DSA testing and complement assay in case of positivity are recommended • Although not well validated, the threshold of positivity for DSA can be considered >1000 and specially >5000 MFI, which is probably associated with the presence of complement binding antibodies • DSA study should be done during donor identification to select a donor and also within the month prior to transplant
Management, desensitization treatment	• No standard scheme is widely accepted; different combinations have proven to be efficacious – Ab removal: Plasmapheresis 1–4 procedures days-10 to -17 and even after transplant – Inhibition of Ab production: Rituximab 375 mg/m^2 IV days – Ab neutralization: Infusion of 20–40 platelet units selected to share donor antigens or buffy coat from 1 unit of blood, on day-1. IVIg can also be used *Avoid complement activation*: IVIg, eculizumab

DSA donor-specific antibodies, *MFI* mean fluorescence intensity, *Ab* antibodies, *IVIg* intravenous immunoglobulins

with CY seems to reduce the incidence of GF in patients with aplastic anemia. Also, in aplastic anemia patients, the addition of two Gy TBI to FLU/CY did not reduce the incidence of this complication.

41.3.5 Other Factors Associated with the Development of GF

ABO mismatch: Major incompatibility was associated with primary GF (HR 1.24; $p = 0.012$).

Cryopreservation: Associated with primary GF (HR 1.43; $p = 0.013$).

Female donor to male recipient: Associated with primary GF (HR 1.28; $p = 0.001$).

Splenomegaly: Associated with primary GF in MPN (HR 3.92; $p = 0.001$) and MDS (HR 2.24; $p = 0.002$).

Use of G-CSF: Associated with reduced risk of primary GF (HR 0.36; $p < 0.001$) vs no growth factors.

Underlying disease: Nonmalignant diseases are associated with higher incidence.

Previous treatments: Impairment engraftment through the damage of marrow microenvironment. The absence of treatments may induce graft rejection.

Graft manipulation: Ex vivo TCD is associated with a higher risk of primary GF in most studies.

41.4 Management of GF

OS after GF is consistently low, even in those patients who receive a salvage transplant; thus, the most important measures should be directed to avoid graft failure GF and to identify it as soon as possible in order to adopt the measures to revert it.

41.4.1 Prevention and Early Diagnosis of GF

The identification of DSA is of utmost importance in the mismatch setting. Desensitization treatment in patients at higher risk seems reasonable. Although barely supported by well-designed studies, we would probably recommend the following measures to be adopted in patients at high risk of GF: the use of PB as stem cell source, include low dose TBI and/or ATG in the conditioning regimen, consider the use of G-CSF post transplant, and a close evaluation of engraftment including marrow chimerism studies shortly after transplant (day +14). In a single-CBT study, a level of donor chimerism in BM lower than 65% was associated with a higher risk of GF (Moscardó et al. 2009); these results cannot be directly extrapolated to other types of transplant.

Olson and colleagues developed a score to predict GF in patients at risk at day +21 post-HSCT (Olsson et al. 2015): age (<30, 1 point), Karnofsky status (<90%, 1 point), disease (MDS, 1; CLL or CML, 2; and MPN, 3 points), status (advanced, 1 point), HLA matching (mismatched, 2 points), graft (BM $<2.4 \times 10^8$/kg, 1 point; PB, 2 points), conditioning (no TBI, 2 points), and GVHD prophylaxis (no CNI + MTX, 2 points; TCD, 3 points). A score >6 at day +21 had a positive predictive value of 28–36%, while the negative predictive value of a score <7 was 81% for GF.

41.4.2 Initial Measures

It is important to apply them as soon as GF is suspected.

- Stop as many toxic drugs as possible; treat infections; although of limited utility, it would be reasonable a trial of G-CSF.
- Adjust post transplant IS. Maintain correct IS levels in the early post transplant period. Later on, after the third/sixth month and if mixed chimerism is present, especially after a RIC transplant, a faster tapering of IST could overcome mixed chimera (in patients with SAA, it is commonly recommended to increase IST).
- Data regarding the use of TPO analogues after transplant are scarce, but the results of eltrombopag in aplastic anemia and its favorable toxicity profile would support, in our view, a trial with this drug before considering more complex and risky options as DLI or second transplant.

Table 41.4 Second allogeneic stem cell transplant in patients with GF

Author (year)	*n* patients diagnosis	Donor (same/different) source	Engraftment (median *d*)	OS
Gaziev (1999)	32 (1°, 4; 2°, 28) Thalassemia	28/4 All BM	67.7% (+19)	3 year: 60%
Guardiola (2000)	82 (1°, 7; 2°, 54) Hem Neo, AA	56/26 72 BM; 10 PB	62% (+17)	3 year: 33%
Min (2000)	20 (1°, 7; 2°, 10) Hem Neo, AA	20/0 6 BM, 14 PB	75% (NR)	3 year: 70%
Chewning (2007)	16 (1°, 11; 2°, 5) Hem Neo, FA	6/16 13 PB (8 TCD), 2 BM, 1 CB	100% (+12)	3 year: 35%
Gyurkorcza (2009)	38 (1°, 18; 2°, 20) Hem Neo, AA	14/24 36 PB, 1 BM, 1 CB	87% (+15)	4 year: 42%
Schreiber (2010)	122 (1°, 122) Hem Neo, AA	98/24 60 PB, 62 CB	66% (NR)	1 year: 11%
Remberger (2010)	20 (1°, 6; 2°, 14) Hem Neo, Non-Mal	11/9 7 PB, 11 BM, 2 CB	90% (+20)	3 year: 60%
Fuji (2012)	220 (1°, 200; 2°, 19) Hem Neo, Non-Mal	0/220 24 PB, 16 BM, 180 CB	CB 30% (21) PB-BM 70–75% (18–14)	1 year PB:58% CB: 28%
Ferrá (2014)	89 (1°, 49; 2°, 40) Hem Neo, Non-Mal	38/37 61 PB, 6 BM, 8 CB	85% (+15)	5 year: 31%

Hem Neo hematological neoplasias, *AA* aplastic anemia, *FA* Fanconi anemia, *Non-Mal* nonmalignant disorders, *PB* peripheral blood, *BM* bone marrow, *CB* cord blood, *TCD* T-cell depletion

41.4.3 DLI and CD34 Boost

DLI could be recommended if decreasing levels of donor chimerism are observed. A careful risk/benefit evaluation is warranted as this is not a risk-free approach and a high risk of development of GVHD is anticipated.

In patients with poor graft function, the use of CD34 boost can be offered. Unfortunately, it is not clear when to perform it, but probably 2–3 months without improvement after the initial measures would be a reasonable cutoff.

41.4.4 Second Transplant

The limited utility and low success of cryopreserved autologous stem cells do not allow to formally recommend to perform auto-HSC harvest in any type of transplant procedure.

Results and recommendations for second allogeneic transplantation are detailed in Tables 41.4 and 41.5.

Table 41.5 Recommendations to perform a second allogeneic HSCT as treatment for GF

Type of donor	Similar results using the same/different donor. Consider different donor if it is not associated with significant delays. Consider haploidentical donors Always avoid donors if positive DSA
Conditioning regimen	It is always required. Better RIC
Post transplant IS	It is required; CNI-based schemes are the most commonly used
Stem cell source	PB or BM show similar results and should be preferred to CB
T-cell depletion	– Avoid ex vivo T-cell depletion, especially if with immune graft rejection – In cases of poor graft function, it can be a good option as it reduces the potential risk of GVHD – ATG or alemtuzumab has been used to foster IS and also to reduce GVHD risk

DSA donor-specific antigens, *BM* bone marrow, *PB* peripheral blood

Key Points

- Graft failure is an infrequent but often fatal complication of HSCT.
- Etiology is complex and very frequently multifactorial.
- Preventive measures and early identification of potential causes in order to try to revert them are the key aspects to treat it.

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