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Probability of allogeneic hematopoietic stem cell transplant failure depending on the recipient's killer immunoglobulin-like receptor genotype

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Abstract

Background. *Natural killers are the "first line" of antitumor and antiviral protection in the early stages after allogeneic hematopoietic stem cell transplantation. Quantitative characteristics reach normal values already in the first month after the infusion of blood stem cells to the recipient. Self-tolerance of natural killers is achieved due to many receptors on their surface, but killer immunoglobulin-like receptors play a key role. Their role is to recognize "self" cells and block signals aimed at destroying their own cells. Knowledge of the functional activity of natural killers urged to studying the impact of mismatches between the inhibitory receptor gene and the ligand on the development of allogeneic hematopoietic stem cell transplant failure.*

The aim *of research was to study the probability of the graft failure development in allogeneic hematopoietic stem cell transplantation*

depending on the recipient's killer immunoglobulin-like receptor genotype.

***Material and methods**. Genotyping of killer-cell immunoglobulin-like receptors in 66 recipients of blood stem cells by the polymerase chain reaction method was performed in the study. Using an online calculator, receptors were classified as "best", "better" and "neutral" depending on the genotype. The end point of the assessment was the development of graft failure in the presence of different genotypes of immunoglobulin-like receptors in the recipient.*

***Results.** According to the data obtained, the presence of the "best" and "better" killer-cell immunoglobulin-like receptor genotype in the recipient significantly increased the risks of developing various forms of graft failure.*

***Conclusion.** The presence of the KIR2DL3 genotype in a recipient of hematopoietic stem cells significantly (by 3 times) reduces the likelihood of primary graft failure. This result is of great prognostic significance, although at present no ways of influencing it have been developed. The presence of the "best" killer immunoglobulin-like receptors genotype in the recipient increases the likelihood of developing graft failure by more than 3 times compared to the better and neutral genotype (44.4% vs. 13.4%).*

Keywords: killer-cell immunoglobulin-like receptors, natural killer, stem cell transplantation, graft failure

Conflict of interests Authors declare no conflict of interest

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ALL, acute lymphoblastic leukemia
allo-HSCT, allogeneic hematopoietic stem cell transplantation
AML, acute myeloblastic leukemia
BM, bone marrow
CML, chronic myeloid leukemia
GF, graft failure
HVG, "host versus graft"
KIR, killer-cell immunoglobulin-like receptor
MAC, myeloablative conditioning
MDS, myelodysplastic syndrome
MHC-I, major histocompatibility complex class 1 molecules
NK, natural killers
PCR-SSP, polymerase chain reaction with sequence-specific primers
PGF, primary graft failure
PMF, primary myelofibrosis
RIC, reduced intensity conditioning
SCID, severe combined immunodeficiency

Introduction

Natural killers (NKs) are the cells of the innate immune system that protect the body from infectious agents and tumor cells. In response to the penetration of a pathogen, NK cells are able to secrete cytokines for several minutes or hours, thus forming the "first line" of defense of the body. The maturation and training of NK cells fundamentally differ from those of other subpopulations of lymphocytes. NK cells recognize foreign cells without priming and prior activation, instead interacting with receptors other than the host's ones [1, 2]. Cytotoxic activity appears in

NK cells after passing through "licensing" (training). Self-tolerance of NK cells is achieved through the appearance of self-inhibitory receptors during maturation of NK cells [3].

NK cells are the first subpopulation of donor lymphocytes that recover after allogeneic hematopoietic stem cell transplantation (allo-HSCT) [4–8]. During the first month after transplantation, the number of NK cells returns to normal, but they acquire the immunophenotypic and functional characteristics of mature cells for several more months. The mechanism of action of most modern immunosuppressive drugs is associated with the effect on the cells of the adaptive immune system. That is why, in the early stages after allo-HSCT, innate immunity is an important factor in antitumor and anti-infection protection. Based on the surface expression of CD56, NK cells can be divided into two main subtypes: $CD56^{bright}$ CD16+/- and $CD56^{dim}$ CD16+ NK cells. On the 30th day after allo-HSCT, the total number of NK cells reaches normal values, but about half of them are represented by cells with an immature phenotype $CD56^{bright}$; normally, they account for about 10% of all NK cells in peripheral blood [8]. For further maturation, they need from 3 to 6 months. The immature phenotype NK cells have unique characteristics: they lack the killer cell immunoglobulin-like receptor (KIR), while a large number of other inhibitory receptors, CD94/NKG2A, are present. CB56bright NK cells preferentially secrete cytokines such as interferon-gamma and/or tumor necrosis factor and exhibit a high proliferative capacity. The second subtype of NK cells are $CD56^{dim}$, which secrete a large number of perforins and granzymes, thereby exhibiting a powerful cytotoxic ability. NK cell function is determined by the net effect of passing the signal to the target cell through multiple activating and inhibitory receptors.

The putative mechanism of action of NK cells was first described in the 1980s by Lungren and Karré. Their hypothesis was called "missing self" and stated that in order not to harm the body's own cells, NK cells must distinguish healthy cells from infected ones. In their study, they noted that NK cells killed mutant cells that did not carry the major histocompatibility complex class I molecules (MHC-I) on their surface, while they did not affect their own MHC-I+ cells [9]. Thus, tumor or virus-infected cells rearrange MHC-I to escape the influence of the T-cell immune response, but fall under the influence of NK cells. Recognition of the “missing self” occurs in people due to the killer immunoglobulin-like receptor (KIR), which is present on 90–95% of $CD56^{dim}$ NKs [10–11].

KIRs are the transmembrane receptors expressed on NK cells. They were originally identified as inhibitory receptors and named "killer cell inhibitory receptors". KIR genes are located on chromosome 19q13.4 and are inherited independently of MCH. Thus, only 1/4 of HLA-identical related transplants will be KIR-compatible, and in case of unrelated transplants, KIR identity is practically not found.

Based on the structural features of the receptor structure, the KIR genes were classified and divided into four groups: KIR2DL1-5, KIR3DL1-3, KIR2DS1-5 and KIR3DS1 (D is the number of immunoglobulin-like domains in the molecule, L is long, S is short. These letters in the name indicate a long or short cytoplasmic "tail", the last digit indicates the number of the gene encoding the protein with this structure). Two pseudogenes are also distinguished: KIR2DP1 and KIR3DP1 (P denote pseudogenes). Genes with a long cytoplasmic “tail” are inhibitory, and those with a short one are activating receptor genes. These groups are combined into two haplotypes: a wider haplotype B,

which is characterized by the presence of one or more of the genes: KIR2DL5, KIR2DS1, KIR2DS2, KIR2DS3, KIR2DS5, and KIR3DS1, in various combinations, while haplotype A has practically no variations and is characterized by the absence these genes, including only one activating receptor, KIR2DS4 [12].

Interaction of KIR with his ligand (HLA-I: HLA-A, HLA-B, HLA-C) leads to different functional activity of NK cells. HLA-C is the main KIR ligand and, in turn, is divided into two epitopes, C1 and C2, based on dimorphism at position 80 of the α1 domain. The main epitope of the KIR system is C 1, which interacts with KIR2DL2 and KIR2DL3. It is the interaction with this epitope that prevents NK cells from attacking healthy body cells by regulating their cytotoxicity. It encodes two haplotypes: KIR2DL2 belongs to haplotype B, and KIR2DL3 belongs to haplotype A. A substitution in the amino acid sequence of KIR results in the disruption of the interaction between the receptor and ligand, leading to the exclusion of the corresponding ligand recognition [13].

By contacting the relevant ligand, KIR activates or inhibits the NK cell. KIRs with a short cytoplasmic "tail" (KIR3DS1 and KIR2DS1) are referred to as activating ones, while a long cytoplasmic "tail" characterizes the inhibitory potential (KIR3DL1, KIR2DL1 and KIR2DL5A/B).

Ligands for activating KIRs are unknown. The lack of a specific ligand expression by allogeneic donor cells allows KIR to recognize foreign cells, thereby mediating of NK cell alloreactivity.

When performing transplantations from HLA-incompatible donors, the inappropriate ligand can lead to the activation of NK cell alloreactivity, thereby providing a "graft against leukemia" effect by destroying residual tumor cells. This effect was noted among recipients

suffering from acute myeloid leukemia, which is due to physiological interactions between myeloid NK cells [14]. With lymphoblastic leukemia, this effect was not observed. The described phenomenon occurs when the donor has a certain HLA-C epitope that the recipient does not have, thus the donor's NK cells cannot be inhibited and die under the influence of the recipient's natural killer cells.

Depending on the genes of haplotype B, three groups of donors are distinguished: “best”, “better” and “neutral”. For distribution in groups, the calculator https://www.ebi.ac.uk/ipd/kir/ is used. The “best” is a donor whose haplotype contains two B-motifs of genes of the centromeric part (*CenB/B).* The “better” donor is the one, whose haplotype has one or more B-motifs present, but without homozygosity in the centromeric part (not *CenB/B*). The “Neutral” one is a donor whose haplotype completely lacks B-motifs or has only one present, no matter in which part (*TelB* or *CenB).* According to D. Weisdorf et al., the prevalence of the best, better, and neutral donor genotypes was 11%, 20%, and 69%, respectively [15].

The reverse effect of NK cell alloreactivity may be the effect of recipient's remaining NK cells, which interact with the graft, potentially being a risk factor for the development of graft failure (GF). GF is a syndrome characterized by cytopenia in combination with hypo/aplasia of the bone marrow. The concept of graft failure, according to the European Society for Bone Marrow Transplantation (EBMT) 2019 classification, includes primary and secondary graft failure, namely the lack of acceptance (primary GF) or loss of donor hematopoiesis due to various reasons (secondary GF). Primary and secondary graft hypofunction are two or three lineage cytopenia in combination with 100% donor hematopoiesis, provided there is no disease relapse.

In connection with the above, we decided to study the effect of various KIR haplotypes on the development of GF in a small group of patients who underwent allo-HSCT under the conditions of the National Research Center for Hematology of the Russian Federation Ministry of Health.

The aim was to study the probability of graft failure in recipients of allogeneic hematopoietic stem cells depending on different killer cell immunoglobulin-like receptor genotypes in diseases of the blood system.

Material and methods

The study included 66 recipients of hematopoietic stem cells, including 31 women (47%) and 35 men (53%), who underwent allo-HSCT in the period from 2018 to 2020. In all cases, the patients were in clinical and hematological remission, and blood stem cells served as a transplant source. Patients having second and subsequent transplantations were excluded from the study. Low-intensity conditioning was predominantly performed (n=57, 86%), the remaining 9 patients (14%) underwent myeloablative conditioning.

KIR genotyping was performed by polymerase chain reaction with sequence-specific primers (PCR-SSP) using KIR Genotyping SSP Kit (IBAG Healthcare, Germany). The material for the study was patient's peripheral blood. The presence of all known KIR domains (*KIR3DL3*, *KIR2DS2*, *KIR2DL2*, *KIR2DL3*, *KIR2DL5A/B*, *KIR2DS3/2DS5*, *KIR2DP1*, *KIR2DL1*, *KIR3DP1*, *KIR2DL4*, *KIR3DL1*, *KIR3DS1*, *KIR2DS1*, *KIR2DS4*, and *KIR3DL2*) was determined.

KIR genotypes were designated as A/A if they did not contain the B genotype (Cen A/A, Tel A/A). In the presence of at least one B haplotype, they were designated as B/x. KIR was classified as “best”,

“better” and “neutral” using the online calculator https://www.ebi.ac.uk/ipd/kir/matching/ligand/.

The end point was the assessment of the graft failure development depending on the KIR genotype. The effect of the presence or absence of KIRD2DL3, the best genotype compared to the better and neutral were separately assessed; the best and better genotypes compared to other KIR genotypes comprised the third comparison group.

Statistical data analysis was carried out using the R 4.1 programming language. The cumulative incidence of graft failure was assessed taking into account competing risks. The Gray test was used to assess the significance of differences between groups. P-values <0.05 corrected for false discovery rate (FDR, the mean proportion of hypothesis false rejections (among all rejections)) were considered statistically significant.

Results

Demographic data, patient characteristics, diseases, information about allo-HSCT performed are shown in Table. 1. Successful acceptance was achieved in 29 patients (44%). Primary graft failure developed in 15 patients (23%). Secondary graft failure was twice as rare, only in 10% of cases (n=7). The incidence of primary and secondary graft hypofunction was 14% and 10%, respectively (n=7/n=9). Haploidentical transplantations were predominantly performed (37 patients or 56%); 38% were unrelated HLA-identical donors allo-HSCT, in 4 cases, transplantation was performed from unrelated partially compatible donors (n=4), and 1 transplantation was also performed from a related partially compatible and completely HLA-identical donors.

Table 1. Characteristics of patients (n=66) included in the study

Characteristic	KIR2DL3		"Best"/ "Better+Neutral"		"Best + Better"/"Neutral"	
	Yes n=48	No n=18	Yes n=48	No n=18	Yes n=19	No n=47
Diagnosis						
Lymphoma	4 (8.3%)	1 (5.6%)	1 (5.6%)	4 (8.3%)	1 (5.3%)	4 (8.5%)
MDS	3 (6.2%)	3 (17%)	3 (17%)	3 (6.2%)	3 (16%)	3 (6.4%)
ALL	16 (33%)	4 (28%)	5 (28%)	16 (33%)	6 (32%)	15 (32%)
AML	24 (50%)	5 (28%)	5 (28%)	24 (58%)	5 (26%)	24 (51%)
PMF	0 (0%)	3 (17%)	3 (17%)	0 (0%)	3 (16%)	0 (0%)
CML	1 (2.1%)	1 (5.6%)	1 (5.6%)	1 (2.1%)	1 (5.3%)	1 (2.1%)
Donor type (p-value)						
Partially matched unrelated	14 (29%)	9 (50%)	9 (50%)	14 (29%)	9 (47%)	14 (30%)
Fully matched unrelated	3 (6.2%)	1 (5.6%)	1 (5.6%)	3 (6.2%)	1 (5.3%)	3 (6.4%)
Partially matched related	1 (2.1%)	0 (0%)	0 (0%)	1 (2.1%)	0 (0%)	1 (2.1%)
Haploidentical	29 (60%)	8 (44%)	8 (44%)	29 (60%)	9 (47%)	28 (60%)
Fully matched related	1 (2.1%)	0 (0%)	0 (0%)	1 (2.1%)	0 (0%)	1 (2.1%)
Conditioning mode (p-value)						
MAC	7 (15%)	2 (11%)	2 (11%)	7 (15%)	2 (11%)	7 (15%)
RIC	41 (85%)	16 (89%)	16 (89%)	41 (85%)	17 (89%)	40 (85%)
Graft failure (GF) (p-value)						
No	22 (46%)	7 (39%)	7 (39%)	22 (46%)	8 (42%)	21 (45%)
Primary GF	7 (15%)	8 (44%)	8 (44%)	7 (15%)	8 (42%)	7 (15%)
Secondary GF	4 (8.3%)	1 (5.6%)	2 (11%)	4 (8.3%)	2 (11%)	4 (8.5%)
Primary graft hypofunction	8 (17%)	1 (5.6%)	1 (5.6%)	8 (17%)	1 (5.3%)	8 (17%)
Secondary graft hypofunction	7 (15%)	0 (0%)	0 (0%)	7 (15%)	0 (0%)	7 (15%)
Death	21 (44%)	6 (33%)	6 (33%)	21 (44%)	7 (37%)	20 (43%)

Notes: MDS, myelodysplastic syndrome; ALL, acute lymphoblastic leukemia; AML, acute myeloblastic leukemia; PMF, primary myelofibrosis; CML, chronic myeloid leukemia; MAC, myeloablative conditioning; RIC, reduced intensity conditioning

According to our data, the CRIR2DL3 absence was 3 times more common in recipients who subsequently developed graft failure (Table 2). The probability of graft failure in patients with/without KIR2DL3 expression was statistically significantly different, being 44.4% in the group of recipients without KIR2DL3, 13.4% in the group of recipients with KIR2DL3 (p=0.007) (Fig. 1). Similar results were obtained in assessing the graft failure incidence when comparing the treatment results between patients with the "best" KIR genotype and patients with "neutral"/"better" genotypes (Fig. 2): 44.4% vs. 13.4% (p=0.007). Accordingly, the probability of graft failure development in the group with the “best” and “better” KIR genotypes was statistically significantly

higher than that in patients with a neutral genotype, 42.1% versus 13.7% (Fig. 3) (p=0.013).

Table 2. The incidence of graft failure depending on the killer immunoglobulin-like receptor genotype

Characteristic	The presence of KIR2DL3, n=48	The presence of "Best"/"Better + Neutral" genotype , n=18	The presence of "Best + Better"/Neutral genotype, n=19
Graft failure (p- value)	0.06	0.059	0.07
Absent	22 (46%)	7 (39%)	8 (42%)
Primary GF	7 (15%)	8 (44%)	8 (42%)
Secondary GF	4 (8.3%)	2 (11%)	2 (11%)
Primary graft hypofunction	8 (17%)	1 (5.6%)	1 (5.3%)
Secondary graft hypofunction	7 (15%)	0 (0%)	0 (0%)

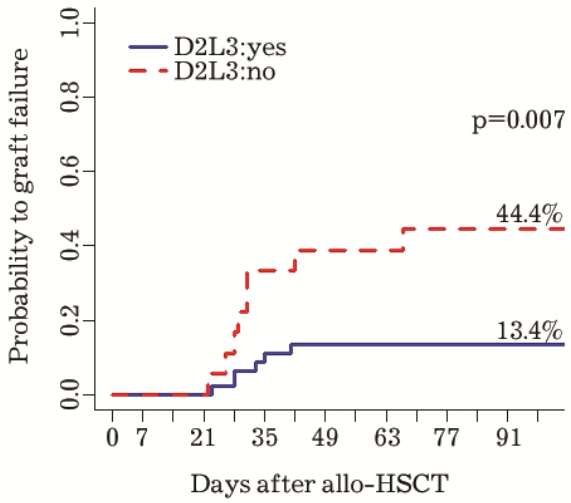

Fig. 1. The effect of the KIR2DL3 presence in a recipient on the graft failure development

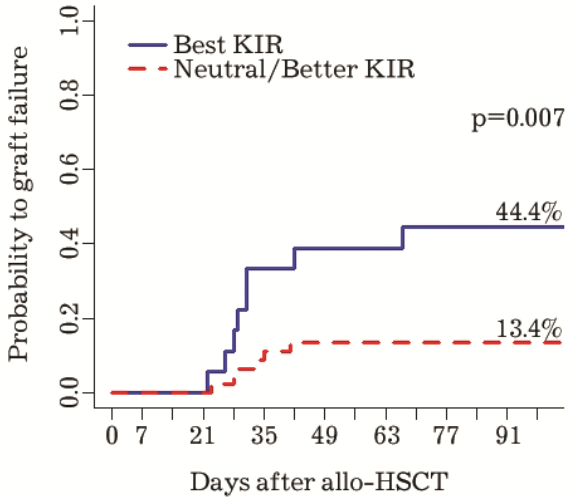

Fig. 2. The effect of the "best" killer immunoglobulin-like receptor genotype of the recipient on the graft failure development

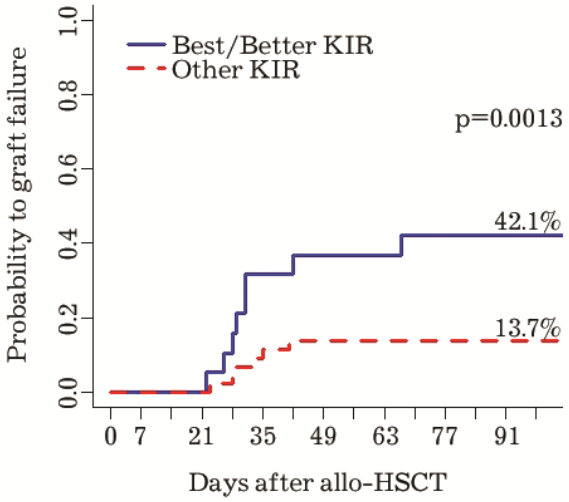

Fig. 3. The impact of the "best" and "better" killer immunoglobulin-like receptor genotype groups in a recipient on the graft failure development

The data obtained show significant differences in the incidence of primary GF, primary graft hypofunction, and secondary graft

hypofunction, depending on the KIR genotype (Table 1). The findings do not allow to draw any conclusions about the mechanism influencing the GF nature depending on the KIR genotype, but the best trends may become more indicative with an increase in the bulk of clinical data.

The mortality of recipients in comparison groups differed, however, the number of cases was still not enough to draw consistent conclusions, and more cases are required.

Discussion

Consistent studies of the impact of patient's NK cell alloreactivity on the development of graft failure can hardly be found in literature. There is a variety of data indicating a positive effect of donor NK cell alloreactivity, leading to the development of graft versus leukemia reaction with a more effective antitumor response, a decrease in the number of relapses, and an acute graft versus host reaction when allo-HSCT is performed from a donor, mainly with B haplotype. Ruggeri et al. (1999) assessed the risks of graft rejection when performing allo-HSCT from the donors who do not express recipient's KIR epitopes, that is, they are alloreactive with respect to the graft. The group included 17 patients, among whom 1 patient developed GF, and 5 patients developed a relapse of the underlying disease. Taking into account the small sample size for the analysis, it is difficult to judge the impact of the number of host-versus-graft HLA mismatches on the development of such a life-threatening complication as GF.

There are studies that show that NK cells are a barrier to the acceptance of bone marrow (BM) allografts and that they can cause the development of BM rejection in mice [15–19]. It is hypothesized that mature NK cells, whose KIRs cannot recognize HLA-I alleles on the allograft, mediate cytotoxicity and production of pro-inflammatory

cytokines as long as activating KIRs are recruited by ligands that are displayed on target cells. Mice with severe combined immunodeficiency (SCID), which lacked T and B lymphocytes but retained normal NK cell function, rejected BM (but not solid organ) grafts, even after lethal irradiation [16, 18].

Large studies of the KIR alloreactivity with regard to "host versus graft" (HVG) effect have not been conducted yet. In a single center study, L. Li et al. analyzed the data of 67 patients after umbilical cord blood transplantation and 26 patients after haplo-HSCT [1 8]. Sixty-four umbilical cord blood recipients underwent only one transplant, three patients required a second cord blood injection due to a primary graft failure (PGF), resulting in a total of 70 cord blood transplants. In 32 pairs, a mismatch in KIR was noted in the direction of HVG. GF developed in 23% (n=16) of patients, and the risk was higher in the presence of mismatches in the KIR HLA-C ligand in the direction of HVG. Among patients who achieved acceptance, the differences in KIR did not significantly affect the recovery time of the level of neutrophils and lymphocytes. Among patients with haplo-HSCT, there were 14 KIR mismatches in the direction of GVH, and 9 in the direction of HVG. Five transplants failed (19%), and in all those cases there was a difference in KIR in the direction of GVH. Thus, the PGF incidence in case of KIR mismatch in the direction of GVH in this cohort was 35.7% with a OR of 9.53; p=0.114. Due to the small sample size, it is not possible to conclude that this KIR finding is true.

Our data suggest that NK-mediated alloreactivity can take place not only in the “graft versus tumor” direction, but also have the opposite effect “recipient versus graft”, mediating the development of GF. The obtained results indicate that different KIR genotypes, as well as their

match in the donor-recipient pair, affect the risks of developing a group of complications associated with poor graft function, namely, primary and secondary graft failure and primary and secondary hypofunction. The use of the KIR genotype match classification (into “best”, “better”, and “neutral”) for the principal assessment of this effect is quite justified, although the name is paradoxical: the best donor KIR is associated with the highest risk of graft failure in the recipient.

As can be seen from the data presented, the KIR2DL3 genotype presence in a recipient of hematopoietic stem cells significantly (by 3 times) reduces the likelihood of primary graft failure. This result is of great prognostic significance, although at present no ways of influencing it have been developed. The presence of the “best” killer immunoglobulin-like receptor genotype in the recipient significantly increases the likelihood of graft failure compared to the "better" and "neutral" genotypes (44.4% vs 13.4%). Recipient genotypes belonging to the “best” and “better” groups significantly increase the possibility of graft failure development. This may determine the need to perform genotyping of the donor and recipient of hematopoietic stem cells before transplantation in order to develop predictive and decision-making tools. Potential factors to influence the revealed effect may be an increase in graft cellularity or intensification of conditioning regimens in order to minimize the number of circulating natural killer cells, i.e. the recipient's natural killer cells.

Thus, genotyping of killer immunoglobulin-like receptors in the recipient is a promising method for selecting the optimal donor for allogeneic hematopoietic stem cell transplantation.

Conclusion

The presence in the recipient of the "best" killer-cell immunoglobulin-like receptor genotype (expresses homozygous genes CenB/B and 2 or more genes of the KIR B haplotype) increases three-fold the risk of graft failure compared to "better" genotype (expresses 2 or more KIR gene loci of B haplotype, but not CenB/B) and the "neutral" one (does not express genes or expresses 1 gene of B haplotype).

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