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Impact of the Donor KIR Genotype on the Clinical Outcome of Hematopoietic Stem Cell Unrelated Transplants: A Single Center Experience

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Abstract

In recent years, the anti-leukemic potential of Natural Killer (NK) cells and their role in hematologic malignancies and in Hematopoietic Stem Cell Transplants (HSCT) has attracted greater interest and a recent study by Cooley S. et al. showed a better clinical outcome when patients with Acute Myeloid Leukemia received a transplant from unrelated Group B KIR haplotypes donors. As a consequence of these results, an algorithm called “KIR B-content score” was formulated. The aim of our research is a retrospective analysis of HSC unrelated transplants performed in our center to analyze the effect of the donor KIR B status on the clinical-outcome. Our results showed a better overall survival-rate in the AML recipients, HLA mismatched with the donor, when the donor KIR B content status is Best/Better (37% vs 18% at three years $P=0,028$). Moreover, we observed that AML recipients, whose Donors KIR B status was Best/Better, had more incidence of aGvHD grade I and II than patients whose Donors KIR B status was Neutral (70% vs 26%) and also a lower rate of relapse (36% vs 58%) and a better Disease Free Survival-rate (58% vs 38% at three years $P=0,1$) because of a better GvL effect.

Keywords: UDHSCT, NK cells, donor KIR B status, AML, GvL effect

1. Introduction

1.1. Hematopoietic stem cell transplantation (HSCT)

Hematopoietic stem cell transplantation (HSCT) has emerged as one of the most useful therapeutic strategies in the treatment of hematologic malignancies (acute or chronic myeloid or lymphoid leukemia) or hereditary (Thalassemia major) for which conventional therapies offer little or no chance of cure. HSCT consists of the replacement of the diseased or non-functional bone marrow with healthy stem cells capable of regenerating all blood cells and restoring the normal hematologic and immunologic functions. The source of hematopoietic stem cells (HSC) can be bone marrow (BMT), peripheral blood after appropriate stimulation (PBHSCT) or cord blood (CBHSCT). The transplant can be autologous (the patient's own HSC transplant after suitable treatment) or allogeneic (HSC transplant from a healthy donor). In the latter case, it is essential to find a donor with genetic characteristics similar to those of the receiver because one of the most important variables that influence the success of HSCT is the compatibility of the genes of the HLA system. The Class I and II HLA matching between donor and recipient is crucial to prevent alloreactivity and, consequently, rejection, graft failure and, above all, the graft versus host disease (GVHD), because the transplanted cells from the donor are immunologically competent and can attack cells and tissues of the recipient [1–3].

A very important aspect of the HSC transplant is the graft versus leukemia effect (GvL), which is a GvHD directed toward the leukemic cells: donors' T lymphocytes attack the cells of the tissues causing GvHD but they can also attack and eliminate residual leukemic cells [4]. If the donor-recipient HLA compatibility is high, the GvL effect is low, consequently, the possibility of relapse is high; on the contrary, when the HLA compatibility is low, the GvHD reaction will be great. A major challenge in improving the success of allogeneic hematopoietic stem cells in the treatment of leukemia is to minimize GvH reactions and simultaneously preserve and optimize GvL reactions. It has also been demonstrated that the GvL effect may be mediated by NK cells [5].

It has been shown that only 25% of patients who need a HSC transplant find an HLA-identical sibling donor; the remaining 75% do not have an HLA-identical donor in their own family; in this case, the alternative is to look for a HLA-matched, unrelated volunteer donor (matched unrelated donor (MUD)) in the worldwide register of bone marrow donors. If there is no compatible donor, the choice of the haploidentical donor is a viable alternative, because there might often be half-identical donors such as parents or siblings [6]. Recently, the number of so-called alternative donor transplants, MUD and haploidentical transplants with one or more HLA mismatches has significantly increased. This is due to the rise in the average age of the patients and therefore the impossibility of finding a compatible donor in their own family. For this reason research has steered toward the study of factors other than HLA matching, which could have a positive influence on the outcome of the transplants, including the role of natural killer (NK) cells in hematopoietic stem cell transplants and, consequently, the study of killer-cell immunoglobulin-like receptors (KIRs) genes.

1.2. Natural killer cells and KIRs

The human NK cells are a part of the immune system with an important role in the host's defense against infections from pathogens and in "immune surveillance" against cancer cells. Their function depends on several families of activating and inhibitory receptors including KIR (killer-cell immunoglobulin-like receptors). The "missing-self" concept [7, 8], put forward by Karré and colleagues in the 1980s, formed the basis for understanding the mechanisms of the action of NK cells (**Figure 1**). According to this hypothesis, the function of NK cells is to recognize and kill autologous cells which are deficient in MHC Class I expression, a frequent event in tumor or virus-infected cells.

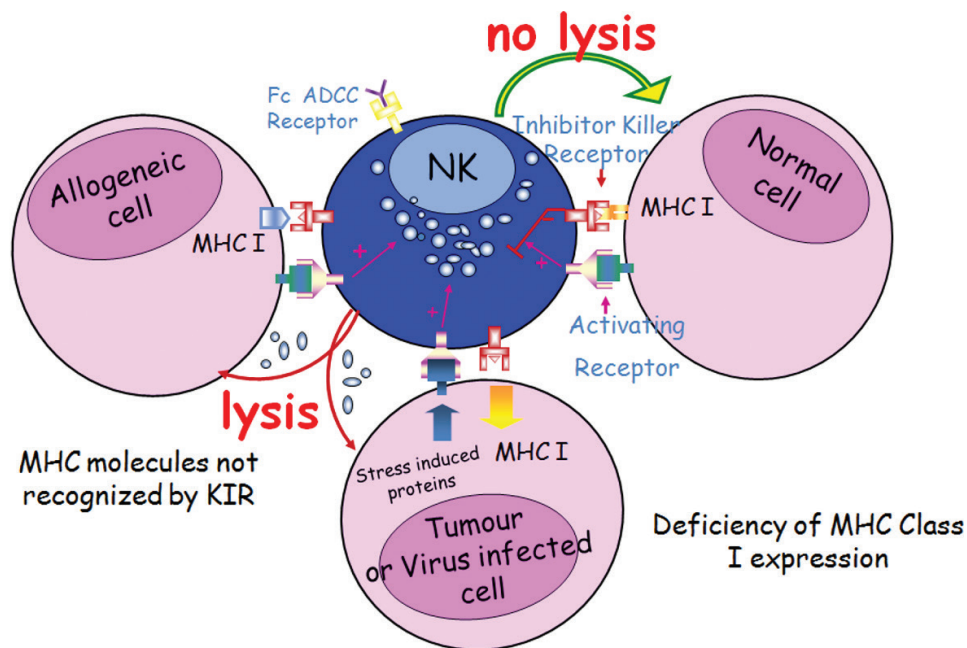


Figure 1. "Missing-self hypothesis" explains the mechanism of action of NK cells.

KIRs belong to the immunoglobulin superfamily and are structurally characterized by two or three extracellular immunoglobulin-like domains. KIRs recognize the MHC Class I molecules such as HLA-A, HLA-B and HLA-C. There are two distinct groups of KIRs: inhibitors and activators. The family of KIR genes, located on chromosome 19q13.4, includes 15 different loci [9]. Receptors are monomeric (single chain) with two (KIR2D) or three (KIR3D) immunoglobulin domains, which can be further divided into those with a long (Long) cytoplasmic tail (KIR2DL and KIR3DL) and those with a short (Short) one (KIR2DS and KIR3DS). The short tail generates an activation signal, while the long one generates an inhibition signal. Each group has the same extracellular domain, and consequently each group binds the same ligands. However, due to differences in their transmembrane and intracellular domains, a group of KIRs determines an inhibitory response, while the other group determines an activating response [10]. KIRs and their ligands are summarized in **Table 1**.

| KIRs | KIR ligands |
|---------|--|
| KIR2DL1 | Group 2 HLA-C Asn77 Lys80 (w2, w4, w5, w6) |
| KIR2DS1 | |
| KIR2DL2 | Group 1 HLA-C Ser77 Asn80 (w1, w3, w7, w8) |
| KIR2DL3 | |
| KIR2DS2 | |
| KIR3DL1 | HLA-Bw4 |
| KIR3DL2 | HLA-A3,-A11 |
| KIR2DL4 | HLA-G |
| KIR2DL5 | Unknown |
| KIR3DL7 | |
| KIR2DS4 | |
| KIR2DS5 | |
| KIR3DS1 | |

Table 1. KIRs and their ligands.

In normal cells the expression of Major Histocompatibility Complex (MHC) Class I molecules and their binding to NK inhibitory receptors inhibits the lysis, while in the virus-infected or cancer cells the lack of expression of self MHC molecules determines their susceptibility to lysis mediated by NK cells. In tumor or virus-infected cells, stress-induced molecules are expressed on the cell surface and are recognized by the activating receptors that enhance the lysis. NK cells can also lyse allogeneic cells expressing HLA Class I antigens that are not recognized by their inhibitory NK receptors.

The KIR genes are polymorphic in humans and there are different allelic variants; each individual possesses his own KIRs repertoire depending on the allelic variants possessed. Different haplotypes contain a different number of KIR genes; some have only one or a few activating receptors, others have more activating receptors. In humans, two groups of KIR haplotypes have been identified, A and B, based on the content of different KIR genes. Haplotypes of group A are present in the entire population and consist of six KIR inhibitory genes KIR3DL3, KIR2DL3, KIR2DL1, KIR2DL4, KIR3DL1 and KIR3DL2 and one activator KIR2DS4 that is often present in a null allele variant that is not expressed on the cell surface. Group B comprises haplotypes with a different genetic content including genes KIR2DS2, KIR2DL2, KIR2DL5, KIR2DS3, KIR2DS1, KIR2DS5 and KIR3DS1 that are not part of the haplotypes of Group A. As a consequence, many haplotypes in Group B encode for a greater number of activating receptors compared to haplotypes in Group A.

All individuals can be classified on the basis of the two KIR genotypes possessed: A/A, which is homozygous for the haplotypes of Group A, B/x, which contains one (heterozygous A/B) or two haplotypes of Group B (homozygous B/B). Individuals B/x possessing a larger number of activating receptors theoretically should have a better response against cancer or virus-infected cells.

1.3. Role of NK Cells in HSCT

In recent years, the antileukemic potential of natural killer (NK) cells and their role in hematologic malignancies and in HSCT has been attracting ever greater interest; however, it has not yet been clearly established whether the typing of KIR genes may be a useful tool in the selection of an HSC donor to promote a better outcome of the transplant [11].

The beneficial GvL effect, promoted by alloreactive NK cells derived from the donor, was demonstrated for the first time in the HSC haploidentical transplants in patients with acute myeloid leukemia (AML); the best donor is NK mismatched with the recipient and therefore the donor's KIRs do not recognize HLA class I molecules expressed by the host. In this way, the donor's NK cells are responsive to the direction GvH and this results in a better antileukemic effect with a better overall survival rate and a lower rate of relapse of leukemia [12].

More recently, Cooley et al. [13] have demonstrated that AML patients who received HSC transplants from unrelated Group B KIR haplotype donors had a better outcome after transplant, whereas recipient KIR genotype had no effect. The clinical outcome was better when the donors had one or two KIR B haplotypes (KIR B/x donors) rather than donors who had two KIR A haplotypes (KIR A/A donors); with a KIR B/x donor, relapse was reduced and the leukemia-free survival rate (LFS) was increased. This is because the haplotypes of Group B have a larger number of activating receptors, and this translates into better antileukemic activity. A subsequent study [14] sought to determine whether the protective effect of KIR B could be mapped to either the centromeric or the telomeric region of the KIR locus. The centromeric region contains genes encoding the inhibitory receptors for the C1 and C2 epitopes of HLA-C, whereas the telomeric region contains genes encoding the inhibitory receptors for the Bw4 and A3/11 epitopes and the activating C2 receptor. It was found that both the centromeric and telomeric regions of KIR B correlated with protective effect, but the much stronger association was with the centromeric region. As a consequence of these results, an algorithm was formulated, called "KIR B-content score", based on the number of centromeric and telomeric Group B KIR haplotypes gene-content motifs. The KIR B-content score defines three categories of donors: neutral donors have none or one KIR B motifs, better donors have two or more B motifs without KIR Cen B/B and best donors have two or more B motifs with KIR Cen B/B. A calculator for classification of the donor KIR B status (best, better and neutral) may be found at <http://www.ebi.ac.uk/ipd/kir/>.

Recently, these results have been confirmed in HSCT from HLA-identical sibling donor [15]. Together, these results highlight the need for further studies of KIR polymorphisms, possibly at allelic level, to determine whether the typing of the donor KIR genes may be useful in donor selection for HSCT.

2. Research aims

The aim of our research is a retrospective analysis of HSC transplants performed at the Bone Marrow Transplant Unit (UTMO) of the "V. Cervello" Hospital in Palermo. The category of HSC transplants to be studied is the one from MUD.

The objectives of this study are the following:

1. Typing of the donors' KIR genes of the transplants performed.
2. Donors classification in accordance with the KIR B Content Score in three categories: neutral, better and best.
3. Correlation of the donor KIR B status with the clinical outcome of the transplants considering overall survival, the degrees of graft versus host disease (GvHD) graft versus leukemia (GvL), relapse and disease-free survival (DFS).

3. Materials and methods

3.1. Patient cohort

We analyzed 89 patients, who received a URD HSCT between 1996 and 2013. The median age of the 89 patients was 43 years (14–65). The transplanted patients had different hematological malignancies: 33 acute myeloid leukemia (AML), 19 acute lymphoblastic leukemia (ALL), 9 myelodysplastic syndromes (MDS), 6 non-Hodgkin lymphoma (NHL), 6 multiple myeloma (MM), 5 Hodgkin lymphoma (HL), 4 chronic myeloid leukemia (CML), 3 chronic lymphocytic leukemia (CLL), 1 aplastic anemia syndrome (AAS), 1 Fanconi syndrome, 1 ematodermic neoplasia and 1 biphenotypic acute leukemia (BAL). The HSC source was: bone marrow no. 19, peripheral blood no. 70. Complete high-resolution, allele-level HLA-A, B, C, DRB1 and DQB1 typing of the 89 pairs of recipients and donors was previously performed: 32 pairs were 10/10 matched, 33 pairs were 9/10 and 24 were $\leq 8/10$. Patient and transplant characteristics are summarized in **Tables 2** and **3**.

| Median age (range) | 43 (14–65) |
|-----------------------|------------|
| Diagnosis | |
| AML | 33 |
| ALL | 19 |
| MDS | 9 |
| NHL | 6 |
| MM | 6 |
| LH | 5 |
| CML | 4 |
| CLL | 3 |
| AAS | 1 |
| Fanconi syndrome | 1 |
| Ematodermic neoplasia | 1 |
| BAL | 1 |

Table 2. Patient characteristics.

| | |
|--|----|
| Graft type | |
| Bone marrow | 19 |
| Peripheral blood progenitor cells | 70 |
| Conditioning | |
| Busilvex-ciclofosfamide | 15 |
| Busilvex-fludarabine | 15 |
| Fludarabine-melphalan | 4 |
| Thiotepa + others | 7 |
| Ciclofosfamide + others | 14 |
| Endoxan | 4 |
| Unknown | 32 |
| TBI | 6 |
| ATG | 12 |
| Donor/recipient HLA-allele matching at A, B, C, DRB1 and DQB1 | |
| 10/10 | 32 |
| 9/10 | 33 |
| ≤8/10 | 24 |

Table 3. Transplants characteristics.

3.2. KIR genotyping

The donors' DNA that has already been typed for HLA has been preserved in our biobank; about 80% of the samples is still available. The DNA was extracted from buffy coat or whole blood by the automatic extractor Maxwell 16 (Promega) or by the salting out method.

Typing of KIR genes was performed with PCR-SSO Luminex, the same method already used in our laboratory to type the HLA genes. The kit used for KIR genes typing was the SSO KIR Genotyping Test (One Lambda Inc., Canoga Park, CA) and the method was performed in accordance with the manufacturer's instructions. Luminex technology is based on the ability to soundly measure multiple analytes simultaneously in a single reaction and this is done through the use of plastic microbeads (microspheres), which are color-coded with two fluorescent dyes so as to emit two different wave lengths in red and infrared. In this way a set of over 100 different microspheres can be created. The microspheres represent the solid support of oligonucleotide probes which can bind amplified DNA that is labeled with a fluorescent labeled reporter. Subsequently, the microbeads are acquired by the Luminex machine through a precision sheath fluid system, based on classical flow cytometry, which aligns them in single file, where they pass through two lasers: the red laser excites the colors inside the microbeads to identify which microbead is currently being read, while the green laser excites the color on the microbead surface, that is, the labeled reporter tag. Finally, the color signals are detected by an advanced optical system, and the signals are processed into data for each reaction [16].

The PCR using specific primers for the KIR genes is first conducted with a specific amplification program via the GeneAmp PCR System 9700 (Applied Biosystems, Forster City, CA). The amplification products are tested by electrophoresis on 2% agarose gel and then observed and photographed under a UV transilluminator. The PCR product is biotinylated, which allows it to be detected by streptavidin-conjugated with PE (SAPE). Subsequently, the PCR products are denatured facilitating rehybridization to complementary DNA probes bound to the microbeads with a specific sequence (SSO) to recognize the polymorphic sites within KIR genes. The amplified products which have undergone a hybridization reaction are labeled with streptavidin conjugated with R-Phycoerythrin and then acquired with the flow cytometry system LABScan™ 100 (Luminex), which measures the fluorescence intensity of phycoerythrin on each microsphere. The data are then analyzed with the software HLA Fusion.

4. Results

4.1. Donor classification

We typed KIR genes of the 89 selected donors of the transplanted patients and we classified them on the basis of the KIR haplotypes possessed. KIR gene frequency among the donor population was similar to that of published data [17, 18]: no. 30 (33.7%) donors were A/A and no. 59 (66.3 %) were B/x.

Then we classified them using the donor KIR B Content Score Calculator at <http://www.ebi.ac.uk/ipd/kir/>: no. 63 (70.8%) donors were neutral, no. 18 (20.2%) better and no. 8 (9%) best. In our analysis we combined the better and best groups to form the KIR better/best donor group (with two or more B motifs). The classification of the donors in accordance with the KIR B content score is summarized in **Table 4**.

| Donor/ recipient HLA- allele matching at A, B, C, DRB1 and DQB1 | Total n = 89 | AML recipients n = 33 | | | | ALL recipients n = 19 | | | | Other hematological malignancies n = 37 | | |
|---|-----------------|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|---|--------------------------|--------------------------|
| | | Donor KIR B status | Donor KIR B status | Donor KIR B status | Donor KIR B status | Donor KIR B status | Donor KIR B status | Donor KIR B status | Donor KIR B status | Donor KIR B status | Donor KIR B status | Donor KIR B status |
| | Total (89) | Neutral (63) | Best/ better (26) | Tot (33) | Neutral (21) | Best/ better (12) | Tot (19) | Neutral (14) | Best/ better (5) | Tot (37) | Neutral (28) | Best/better (9) |
| 10/10 | 32 | 24 | 8 | 10 | 9 | 1 | 7 | 4 | 3 | 15 | 11 | 4 |
| 9/10 | 33 | 22 | 11 | 14 | 7 | 7 | 8 | 7 | 1 | 11 | 8 | 3 |
| ≤8/10 | 24 | 17 | 7 | 9 | 5 | 4 | 4 | 3 | 1 | 11 | 9 | 2 |

Table 4. Donor classification in accordance with the KIR B content score.

4.2. Clinical outcome analysis

4.2.1. Overall survival, relapse and disease-free survival

The overall survival rate was analyzed generating the Kaplan-Meier curves, using the GraphPad6 Demo software; the data were compared using the log-rank test 95%CI.

We observed no significant difference in the overall survival rate of those patients transplanted from A/A donor and those from B/x donor, while we found a better overall survival rate in the AML recipients, HLA mismatched with the donor, when the donor KIR B content status is best/better (37 vs. 18% at three years log-rank test $P = 0.028$) (Figure 2), whereas there is no beneficial effect in recipients with other hematological malignancies (Figure 3).

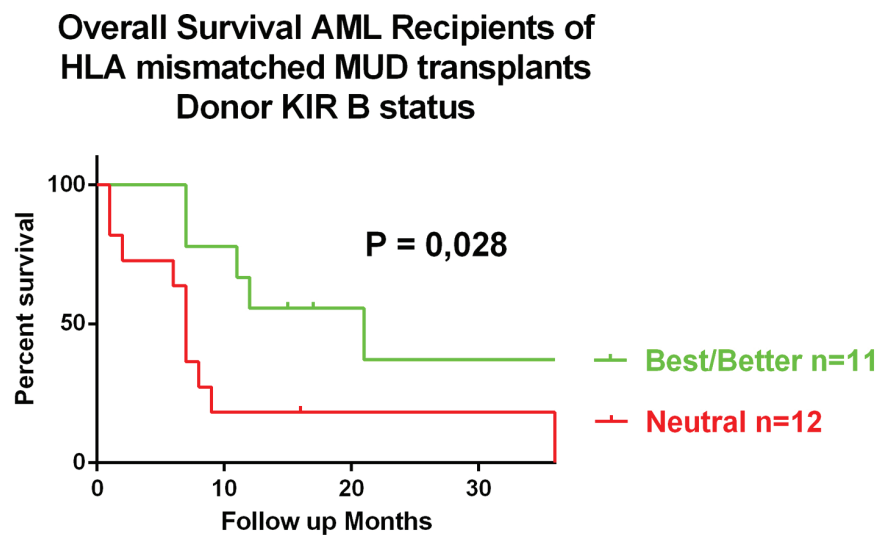


Figure 2. Overall survival rate of AML recipients of HLA mismatched MUD transplants.

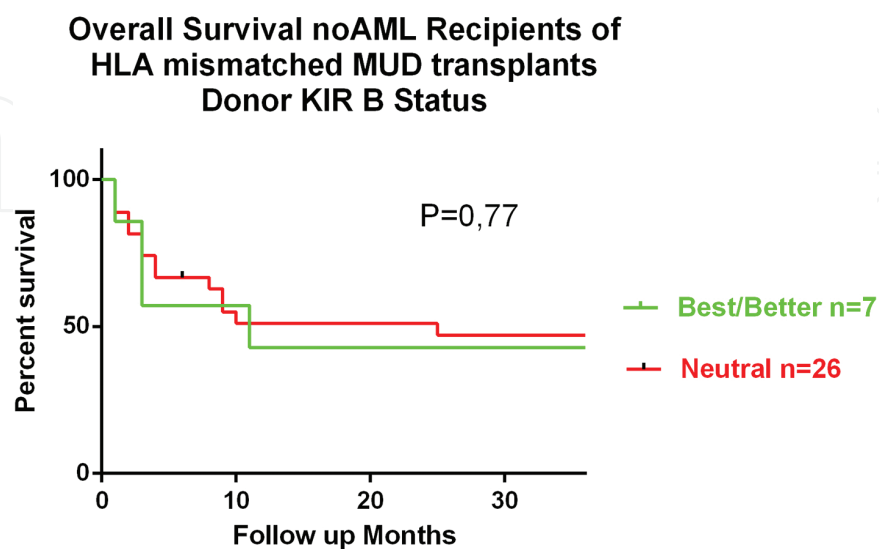


Figure 3. Overall survival rate of recipients with other hematologic malignancies of HLA mismatched MUD transplants.

Moreover, we observed that AML recipients, whose donor KIR B status was best/better, had a lower incidence of relapse than patients whose donor KIR B status was neutral (36 vs. 58%) (Figures 4 and 5) and a better disease-free survival rate (58 vs. 38% at three years $P = 0.1$) (Figure 6).

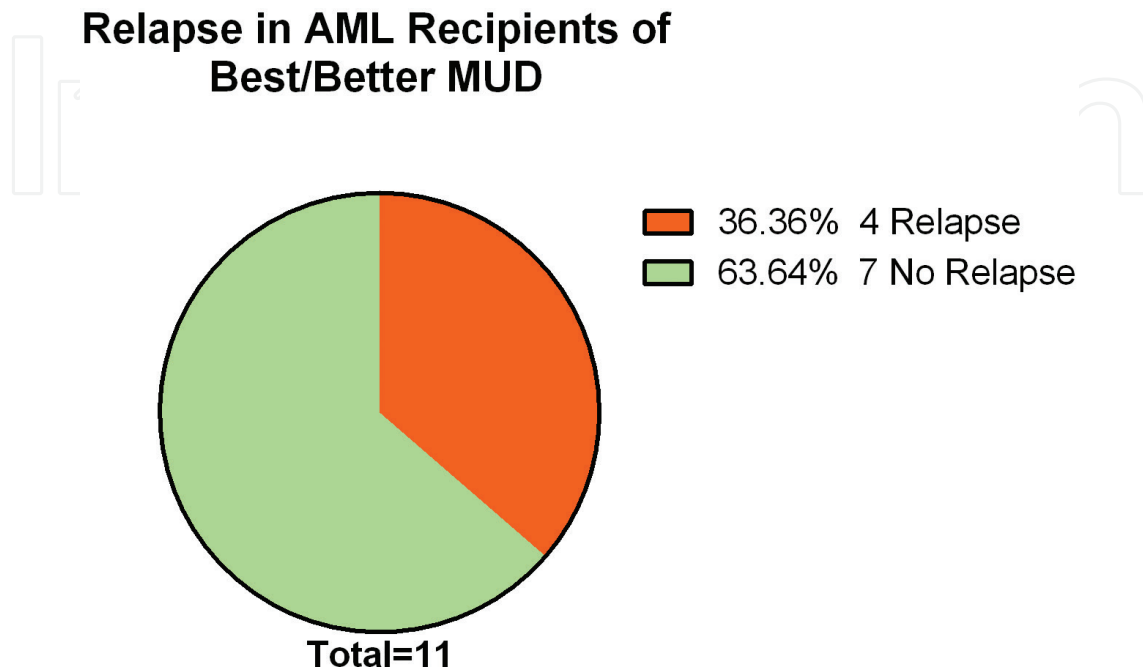


Figure 4. Incidence of relapse in AML recipients of best/better MUD.

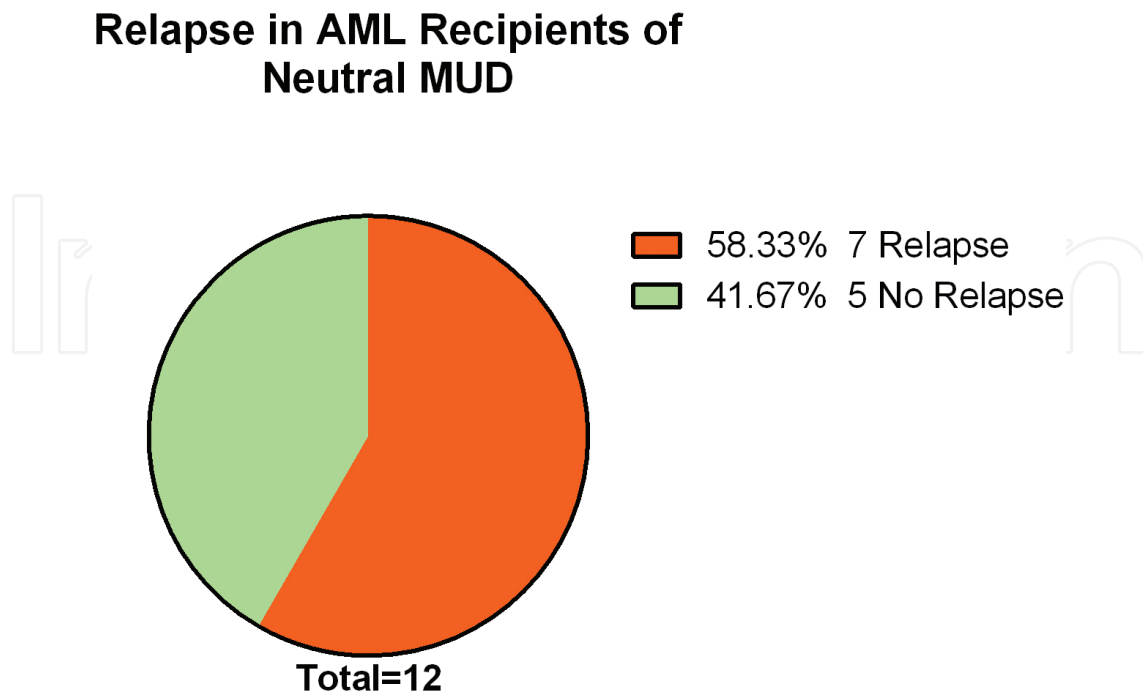


Figure 5. Incidence of relapse in AML recipients of neutral MUD.

Disease Free Survival AML Recipients of HLA mismatched MUD transplants Donor KIR B Status

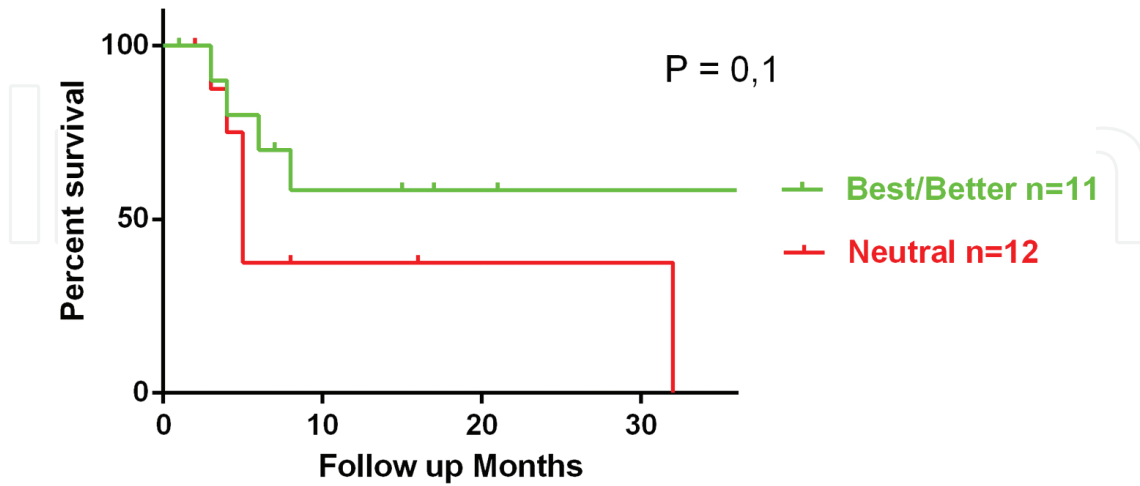


Figure 6. Disease-free survival rate of AML recipients of HLA mismatched MUD transplants.

We have not been able to make a comparison of the 10/10 HLA matched AML recipients because only one donor was best/better.

4.2.2. aGvHD

The incidence of aGvHD in AML patients was: 55.17% (no. 16/29) of no aGvHD, 41.38% (no. 12/29) of aGvHD grade I and II, 3.45% (no. 1/29) of aGvHD grade III and IV (Figure 7).

aGvHD in all AML recipients

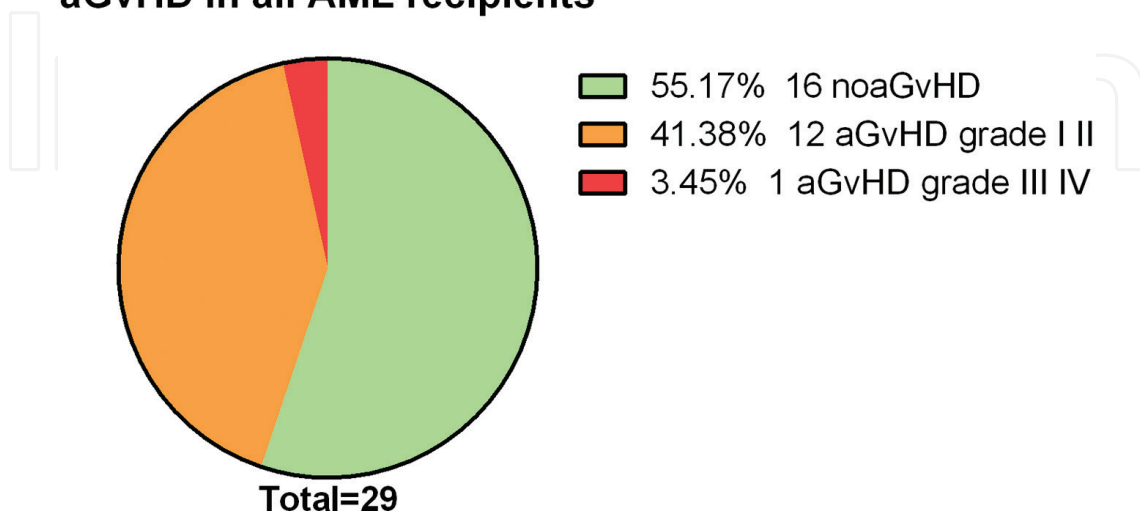


Figure 7. The incidence of aGvHD in AML patients.

We observed that AML recipients, whose donor KIR B status was best/better, had more incidence of aGvHD grade I and II than patients whose donor KIR B status was neutral: 70 vs. 26% (Figures 8 and 9).

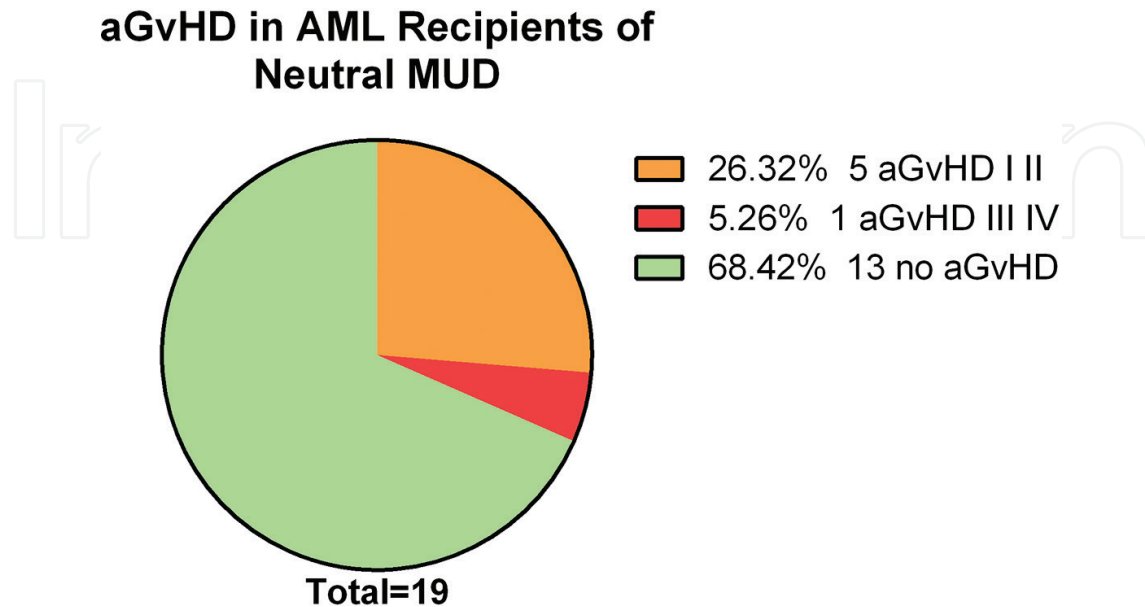


Figure 8. Incidence of aGvHD in AML recipients of neutral MUD.

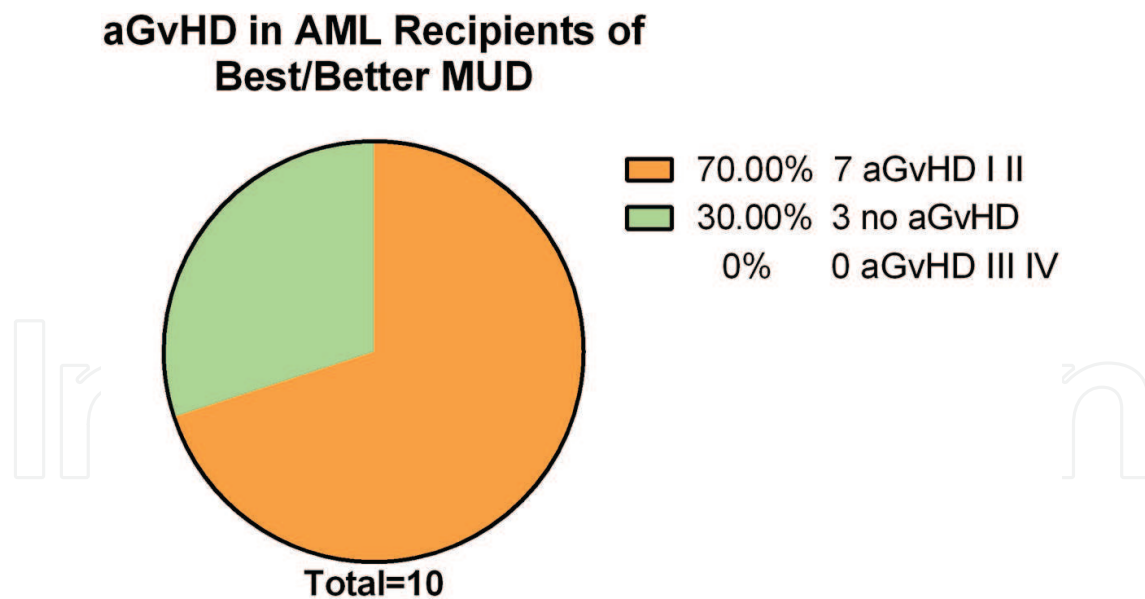


Figure 9. Incidence of aGvHD in AML recipients of best/better MUD.

Actually, as regards patients who have aGvHD grade I and II, this results in a beneficial effect on the overall survival rate. In fact, we observed that patients with aGvHD grade I and II had a significantly better overall survival rate than patients with noGvHD (51.6 vs. 38% at three years $P = 0.04$) (Figure 10). This agrees with those studies [4] showing that patients with aGvHD I and II have a better overall survival rate and a lower rate of relapse due to a GvL effect.

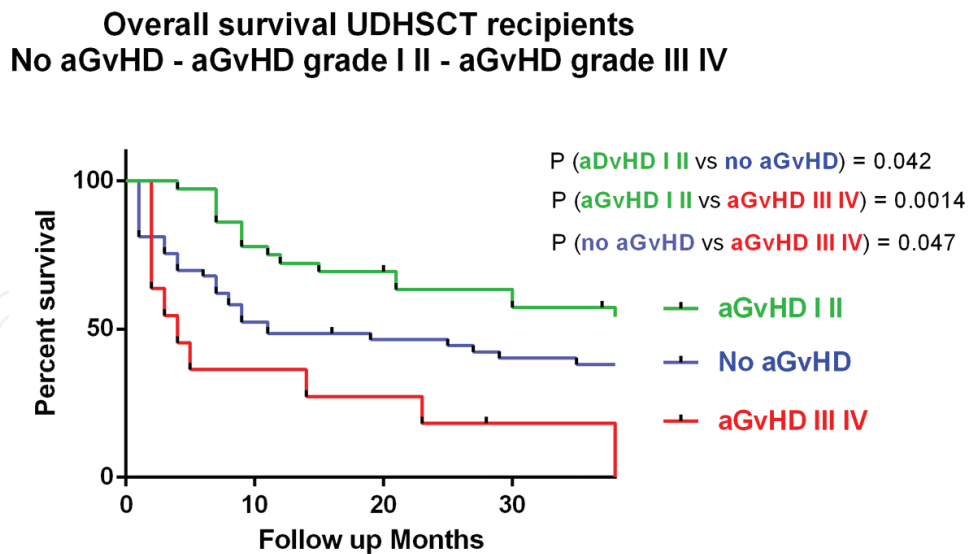


Figure 10. Patients with aGvHD grade I and II had a significantly better overall survival rate than patients with noGvHD (51.6 vs. 38% at three years $P = 0.04$).

5. Discussion

In recent years, various studies have shown that the beneficial GvL effect promoted by allo-reactive NK cells derived from the donor can improve the outcome of the HSCT from haplo-identical, unrelated and HLA identical sibling donors. In particular Cooley et al. [12] have demonstrated that AML patients who received HSC transplants from unrelated Group B KIR haplotypes donors, had a better outcome after transplant because the haplotypes of Group B have a larger number of activating receptors, and this translates into better anti-leukemic activity. In a subsequent study [13], they found that some particular KIRs had a stronger effect and they defined three categories of donors: neutral (none or one KIR B motifs), better (two or more B motifs without KIR Cen B/B) and best (two or more B motifs with KIR Cen B/B).

In our study we analyzed the impact of the donor KIR B status on the outcome of the unrelated HSC transplants performed in our center. We observed no significant difference in overall survival of those patients transplanted from A/A donor and those from B/x donor, probably because we do not have a large enough cohort of transplanted patients, and we were not able to make a meaningful comparison; on the other hand, despite this small cohort of patients, we have been able to observe the powerful effect of the best/better donor KIR B status in the AML recipients HLA mismatched with the donor. They had a significantly better overall survival rate if the donor KIR B content status was best/better and they also had a higher incidence of aGvHD grade I and II, and had a lower rate of relapse due to GvL effects.

Even though our cohort was small, our results confirmed that the presence of more activator KIR genes in donors can improve the outcome of UDHSCT HLA mismatched transplants in AML recipients whereas there is no benefit in recipients with other hematologic malignancies. Our next target is to increase the number of cases by adding the other transplants performed and to study the effect of GvL in relapse in the same patients.

In any case, our results confirm that NK cells derived from donors with two or more KIR B motifs have an improved ability to kill residual leukemic blasts in AML recipients of UDHSC. As a consequence of this, the KIR genotype of the donor is another important criterion to be taken into account for the choice of the best possible donor in unrelated, sibling and haploidentical HSC transplant settings, together with all the other important factors, such as HLA matching, CMV status, blood group, age and gender. Future studies should be aimed at finding the right alloreactive subsets among donor NK cell repertoires, opening up the possibility for successful NK cell-based immunotherapy. Antileukemic NK cells, either allogeneic or unlicensed autologous NK cells, emerge as a feasible therapy option and might improve the clinical outcome in myeloid leukemia.

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