The Rome Transplant Network model compared to the Italian Bone Marrow Donor Registry activity for unrelated donor search process and transplant efficiency for hematologic malignancy

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BACKGROUND: From 2011 to 2014, a total of 71% of the 3834 patients with hematologic malignancies successfully identified a matched unrelated donor (MUD) through the Italian Bone Marrow Donor Registry (IBMDR), corresponding to a transplant efficiency of 62%.

STUDY DESIGN AND METHODS: From 2006, the Rome Transplant Network (RTN) followed a hierarchical selection strategy for the alternative donor search: first MUD, second cord blood, and third haploidentical donor. Using a low-resolution HLA, a preliminary query (PQ) was performed in all cases with assignment of good or poor score if more or less than 10 MUDs were identified in Bone Marrow Donors Worldwide. Herein we assessed the utility of PQ and of high-resolution (HR) HLA from the start of the search. Moreover, we compared the donor identification and the transplant efficiency between IBMDR and RTN.

RESULTS: At RTN 79% of 417 patients met a good PQ with a 50% MUD identification versus 12.5% with poor PQ. Our policy led to 78 and 74% of alternative donor identification and transplant efficiency, respectively, higher than IBMDR data equal to 71% ($p = 0.007$) and 62% ($p < 0.0001$). The timing for donor identification was significantly reduced using HR HLA at the start of the search from 88 to 66 days at IBMDR ($p < 0.001$) and from 61 to 41 days at RTN ($p < 0.001$).

CONCLUSIONS: Both PQ and HR HLA at the start of the process represents a useful tool to address the search towards the best and timely donor choice. Moreover, establishing a specific donor policy significantly improves the transplant efficiency.

ABBREVIATIONS: BMDW = Bone Marrow Donors Worldwide; CB = cord blood; CBT = cord blood transplant; CBU(s) = cord blood unit(s); HR = high resolution; HSC(s) = hematopoietic stem cell(s); IBMDR = Italian Bone Marrow Donor Registry; MUD(s) = matched unrelated donor(s); PQ = preliminary query; RTN = Rome Transplant Network.

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Allogeneic stem cell transplantation represents a potentially curative treatment for several hematologic disorders,[1-8] but its application depends on the availability of a suitable donor. It is well known that approximately 30% of patients might find an HLA-identical sibling donor; however, due to the small average of family size, in some countries, such as the United States, this percentage progressively decreased to 20%.[9] For patients who lack a suitable related HLA-matched donor, unrelated donor registries of adult volunteers and banked umbilical CBUs provide potential alternative allogeneic stem cell sources. Over the past 25 years, the international donor registries and cord blood (CB) banks have progressively expanded so that more than 28 million potential volunteer matched unrelated donors (MUDs) and more than 700,000 cord blood units (CBUs) are available worldwide. Despite the impressive number of MUDs enrolled worldwide, not more than 60% of the northwest European patients are able to identify a 10/10-allele MUD, mostly due to the extensive polymorphism of the HLA system. This percentage greatly decreases if the patients belong to an ethnic minority or express an unusual HLA allelic linkage or uncommon haplotype.[10-12] Moreover, recent data have shown that donor identification increases only up to 1% each year for patients who do not rapidly identify a MUD.[13] On the other hand it is worth noting that after the first 2 months from the beginning of the search process only less than 5% of the patients further successfully identify a MUD.[14]

The Bone Marrow Donors Worldwide (BMDW) database provides a comprehensive listing of almost all potential donors and CBUs existing in the world.[15] Since many of the recruited donors in BMDW (http://www.bmdw.org/) are not typed for all the HLA loci,[15] and only few at high resolution (HR), a confirmatory typing of the selected donors always requires comprehensive DNA-based typing methods to determine the overall compatibility. Histocompatibility testing for the identification of MUD is therefore a costly and time-consuming procedure. The duration and success rate of an unrelated donor search greatly depends on patients' HLA typing. The frequency of the patient HLA alleles and haplotypes in the different various ethnic populations can be determined through websites listing the frequencies of alleles and haplotypes.[16,17] Waiting for a potential donor may delay nontransplant strategies or transplant from hematopoietic stem cell (HSC) alternative sources such as haploidentical donors.[18-25] A more precise estimation of the probability of identifying a MUD at the preliminary phase of the search, allowing a prompt classification of patients in low or high category, may improve the general therapeutic strategy. BMDW provides this important information through a specific "matching program."[15-17]

Cord blood transplant (CBT) is currently considered a valid alternative in both pediatric and adult patients[26-31] with a matching requirement criteria less stringent than MUD. Although the CBU selection is mainly done according to prefreezing cell dose and HLA donor-recipient compatibility,[32] its overall quality assessment represents an important drive before the final selection.[33] Eurocord recommendations consist of selecting CBUs with at at least 4/6 HLA loci matched with the recipient, considering antigen level for A and B loci and HR for DRB1. However, further analyses are improving the knowledge concerning the HLA matching on CBT outcome suggesting that the combination between HR HLA matching and cell dose is crucial in terms of TRM.[34] The NMDP Registry has recently shown that, adopting a simultaneous search strategy for MUD (8/8 HR HLA matching) and CBUs (at least 4/6 HLA and total nucleated cell count of 2.5×10^7/kg), the identification of the unrelated donor increases from 75% to 96% for white Europeans and from 18% to 81% for minor ethnic groups such as African or African American in the US adult population. Moreover, CB identification allows for coping with the potential volunteer donor's unavailability or unsuitability mainly due to emigrations or medical reasons.[13] In light of all these studies, the transplant physicians should define a search strategy with a well-established policy for an alternative donor selection. Herein, according to a unique prospective policy, we report the results of the unrelated donor search process of the Rome Transplant Network (RTN), a JACIE-accredited metropolitan transplant program. To understand the potential advantages of an established transplant center policy for donor identification, including the preliminary query (PQ) and the haploidentical relative stem cell source, data from the RTN strategy and the Italian Bone Marrow Donor Registry (IBMDR) were compared in terms of unrelated donor rate identification and transplant efficiency. The fact that the IBMDR limits its search to unrelated donors and CBUs does not mean that other individual Italian transplant centers do not use haploidentical donors for those patients without a good unrelated donor. On the other hand not many Italian transplant centers use haploidentical procedures, whose donor selection is not available in the database of IBMDR. Moreover, we tried to assess the impact of the use of HR HLA typing from the start of the donor search on the timing for the unrelated donor identification.

MATERIALS AND METHODS

IBMDR is the Italian registry that supports donor identification and coordinates the procurement of HSCs for all Italian transplant centers that are accredited to perform unrelated allogeneic transplantation. Although the IBMDR suggests the donor search strategy, the outcome of this process depends on the transplant centers' decisions. Haploidentical donor identification is not part of IBMDR procedures, whereas the PQ is a developed tool by the

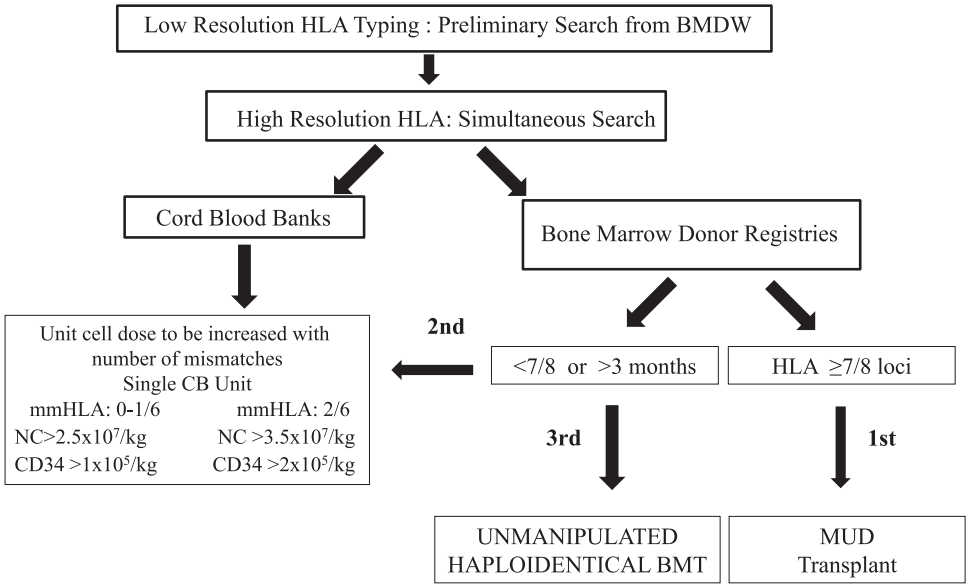

Fig. 1. RTN strategy for the alternative stem cell donor search. BMT = bone marrow transplant.

IBMDR and available for all transplant centers. The PQ allows the probability of a matched donor identification to be assessed, through the BMDW database, using a low-resolution HLA typing (A, B, and DRB1 loci). However, its clinical impact is not yet known. During the study period, minimal HLA matching requirements for unrelated volunteer donor identification consisted of antigenic matching for A and B loci and allelic matching for DRB1 loci regardless the matching level for C loci, according to the IBMDR standards. On the other hand, minimal HLA matching requirements for unrelated CB consisted of antigenic matching for at least three antigens of A and B loci in presence of DRB1 allelic mismatching or double DRB1 allelic compatibility in presence of two antigenic mismatches for HLA-A and -B loci.

From April 2006 to December 2014, for patients lacking an HLA-identical sibling, the RTN has established a hierarchical algorithm to be followed for donor selection: first MUD, second CB, and third haploidentical (Fig. 1). Since 2006, the PQ is systematically included in the searching donor process of RTN in combination with the aforementioned hierarchical donor selection and the unrelated donor identification was carried out according to the minimal HLA requirements of IBMDR standards. Criteria for the alternative donor selection are described in Figs. 2 through 4. A simultaneous search for MUD or CBUs has been performed for 417 adult neoplastic patients. IBMDR has supported the overall RTN activity throughout the whole period. Patient characteristics at the RTN and IBMDR are detailed in Table 1.

RTN and IBMDR provided donor identification and transplant efficiency data from 2006 and from 2011, respectively, because the RTN unique policy started in April 2006. Concerning the timing of donor identification, the analysis compares results before and after 2011, when IBMDR standardized the use of patients' HR HLA typing from the beginning of the search activation. This observational clinical protocol was approved by the Policlinico Tor Vergata Institutional Review Board and data collection and research participation was in accordance with the Declaration of Helsinki.

Definitions

The efficiency of the search is determined by the likelihood to identify a "matched" donor (confirmed by transplant centers through confirmatory typing) by testing a "reasonable" number of donors and by the time required for the process. The gold standard for neoplastic diseases is the identification of two young male donors, 8/8 or 7/8 matched within 3 months. Transplant efficiency was defined as the percentage of transplanted patients out of the patients for whom an alternative donor has been identified.

According to RTN policy, the result of the PQ was considered good or poor if more or less than 10 low-resolution HLA-A, -B, and -DRB1 matched donors were identified in the BMDW database. The timing for donor identification was considered the period needed by the IBMDR transplant centers and RTN for identifying a suitable unrelated donor from the beginning of the search process.

HLA typing of patient and family

According to the RTN strategy, the HLA typing must be carried out on all available members of the immediate family, to study the haplotype inheritance. In the case of absence of a HLA-identical or 5/6-matched donor among the siblings, it is necessary to immediately perform a HR

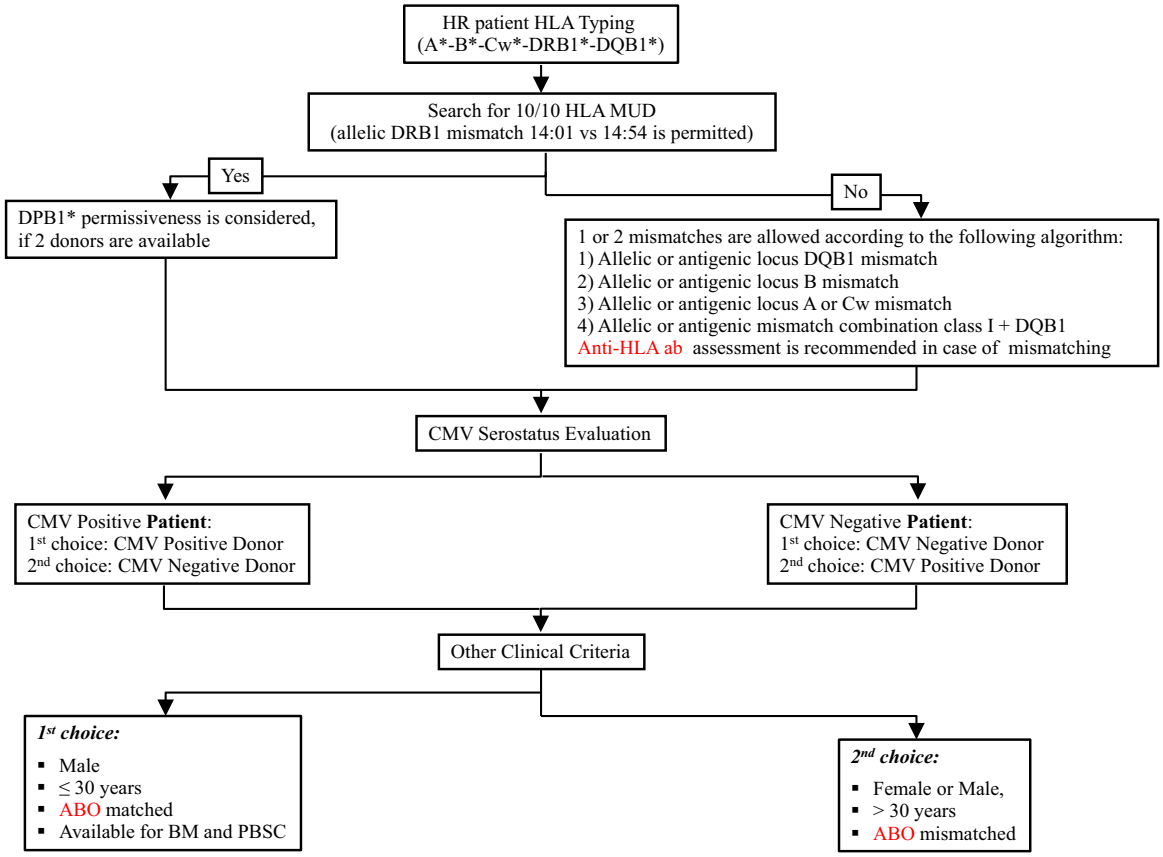

Fig. 2. RTN selection criteria for MUD. Ab = antibody; CMV = cytomegalovirus; PBSC = peripheral blood stem cell. [Color figure can be viewed at wileyonlinelibrary.com]

TABLE 1. Patient characteristics

Characteristics	RTN	IBMDR	p value
Number	417	3834	
Age (years)	47 (16-69)	45 (16-70)	NS
Sex			NS
Male	229 (55)	2121 (55)	
Female	188 (45)	1713 (45)	
Diagnosis			<0.0001
AML	164 (39)	1709 (45)	
ALL	70 (17)	626 (16)	
NHL	67 (16)	713 (18)	
MDS/MPN	41 (10)	407 (11)	
HL	34 (8)	340 (9)	
MM/PCD	26 (6)	29 (0.7)	
Other	15 (4)	10 (0.3)	

Data are reported as median (range) or number (%).
ALL = acute lymphoblastic leukemia; AML = acute myeloid leukemia; MDS = myelodysplastic syndrome; MPN = myeloproliferative disorders; HL = Hodgkin's lymphoma; MM = multiple myeloma; NHL = non-Hodgkin's lymphoma; NS = not significant; PCD = plasma cell disorders.

HLA typing of the patient (HLA-A, -B, -Cw, -DRB1/3/4/5, -DQB1, and -DPB1) acquiring simultaneously the informed consent for an unrelated donor search. Moreover, presuming that the parents are haploidentical with the offspring, based on our strategy, we perform the HLA typing for adult children, in case of patients with a poor PQ. To start the search for an alternative donor quickly, the time to perform the HLA typing represents another crucial variable so that monthly meetings are held to ensure close cooperation between hematologists, the HLA laboratory, and the transplant team within the RTN.

Statistical analysis

Patient characteristics and data of the alternative donor search process are summarized using descriptive techniques, including absolute and relative frequencies for categorical variables, while continuous variables are expressed as median and range. The interdependence between groups is evaluated using both the Wilcoxon and the chi-square tests. A p value of less than 0.05 was considered as significant. All the analyses were conducted using computer software (SAS 9.3.1, SAS Institute).

RESULTS

BMDW preliminary search

The BMDW downloaded files, provided by IBMDR to the physicians, represent a helpful tool concerning the

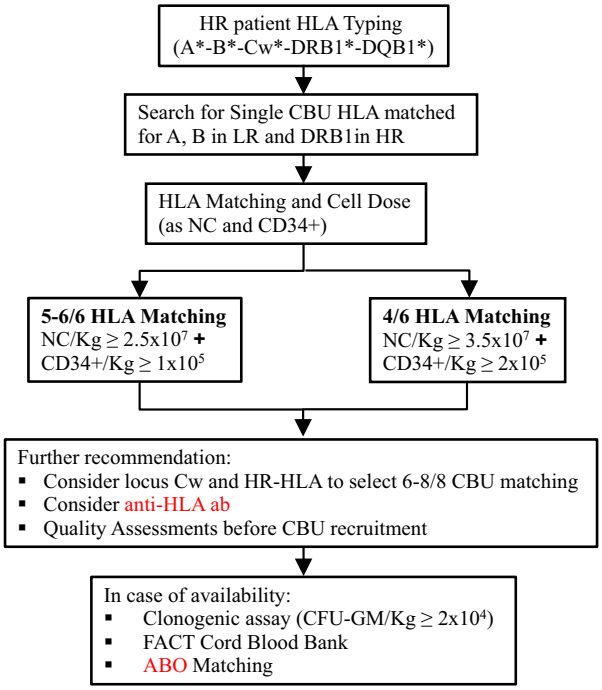

Fig. 3. RTN selection criteria for CBUs. Ab = antibodies; CFU-GM = colony-forming unit–granulocyte monocyte; FACT = Foundation for the Accreditation of Cellular Therapy; LR = low resolution; NC = nucleated cells. [Color figure can be viewed at wileyonlinelibrary.com]

likelihood of identifying a MUD. Although this initial search, called "preliminary search," is very easy to use in the clinical practice, a recent IBMDR survey has shown that it is restricted to only 33% of Italian transplant centers.[35] After the RTN strategy, adopted since 2006, the PQ is performed for each patient that has an indication to allogeneic transplant procedure, but lacking a HLA-identical sibling, based on the patient low-intermediate HLA typing (two digits). Up to 2014, a total of 417 preliminary queries were processed.

Our data showed that 79% of the searching patients had a positive PQ, but only 50% of them could subsequently find a 8/8 HR HLA-A, -B, -Cw, and -DRB1–matched MUD. On the other hand, among the 21% of patients with a poor PQ, the proportion of 8/8 HR-matched MUD found was equal to 12.5%. The analysis of these results led us to continue to take into consideration the opportunity to perform a formal search activation for patients characterized by a poor PQ, but also to extend the HLA typing to parents and/or offspring to eventually propose a haplo-transplant treatment. Meanwhile request of information relative to cell dose and further compatibility features of potentially available CBUs to the CB banks were performed. Among the immunogenetics characteristics, we took into consideration the presence in the patients' HLA typing of rare or infrequent alleles and of a

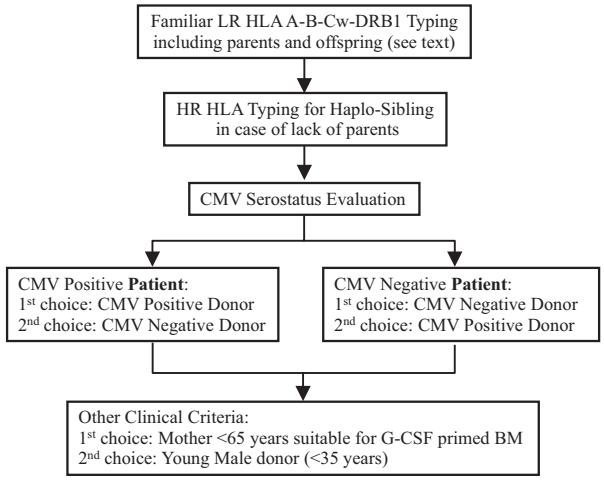

Fig. 4. RNT selection criteria for haploidentical donors. CMV = cytomegalovirus; G-CSF = granulocyte–colony-stimulating factor; LR = low resolution.

potential unfavorable HLA-B/C allelic combination. It is well known in fact that some B alleles are associated with many different C alleles. For example, among the most frequent B alleles, B*51:01 is linked to many different C alleles, as well as B*18:01 or B*44:03. Similarly, HLA Class II–specific DRB1 alleles are often associated with multiple DQB1 antigens.

Timing and efficiency of the alternative donor search

In terms of donor identification efficiency, the IBMDR search activity restricted to adult patients with malignant diseases from 2011 to 2014 shows that a suitable MUD could be identified for 66% of 3834 patients in a median time of 39 days (range, 10-417 days). The compatibility degree was at least 7/8 HR HLA matched according to the IBMDR standards.[36] The efficiency of unrelated donor identification increases from 66% to 71% when 4/6 HLA-matched CBUs were considered. These results corresponded to a percentage of transplant procedures and transplant efficiency of 44 and 62%, respectively, for patients with suitable MUD or CBU in a median time of 131 days to be transplanted (range, 22-539 days). Moreover, the median duration of the search process for MUD identification has been significantly reduced by the use of HR HLA typing of the patient at the start of the formal search activation. In Italy, this rule, introduced in 2011 by IBMDR, significantly reduced the median number of days for volunteer donor identification either in IBMDR (66 days, range 8-905 days vs. 88 days, range 1-1016 days; $p < 0.001$) or in RTN (41, range 20-321 vs. 61 days, range 23-765 days; $p < 0.001$). The results are shown in Table S1 (available as supporting information in the online version of this paper).

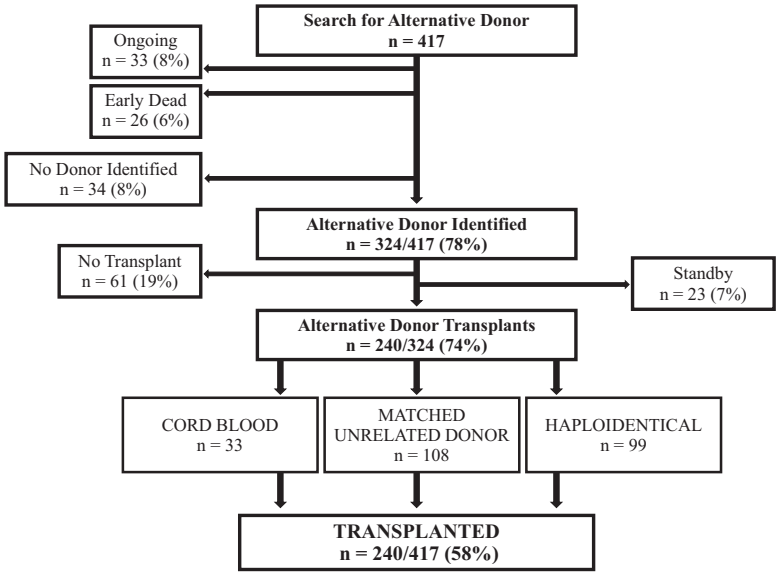

Fig. 5. RTN policy results (April 2006-December 2014). Ongoing = donor searches started too early (<1 week) at the time of analysis; standby = temporary suspended or transferred searches.

From April 2006 to December 2014, following the criteria adopted at RTN (Figs. 2–4), that hierarchically considered as first choice for the transplant a MUD, in second place a CBU, and as last a haploidentical donor, we were able to identify an overall proportion of 78% alternative donors, in a median time of 47.5 (range, 4-765) and 34 (range, 1-204) days for MUD and CBUs, respectively. The time to haplo-donor identification was not considered because even if a haploidentical relative donor was available, it then represented the third choice in the RTN algorithm.

As shown in Fig. 5, 6% of patients died early for clinical complications, while 8% started the alternative donor search too early (<1 week) at the time of analysis but were also included in the study for making an unbiased comparison with IBMDR data. Results obtained after the RTN strategy indicated that 324 of 417 patients (78%) identified an alternative donor corresponding to a transplant efficiency rate of 74% and to a percentage of transplant procedures of 58%, performed in a median time of 137 (range, 33-866) days from the beginning of the search. According to the type of donor, the patients received HSCs from MUDs, haploidentical donors, and CBUs in 45, 41, and 14% of cases, respectively. The low number of CBTs performed was due to the restrictive selection criteria of RTN, based on the combination of HLA compatibility with both variables of cell dose as nucleated and CD34+ cells/kg recipient body weight. Furthermore, in our experience, no significant difference was documented, in terms of median time to transplant among the different HSC sources used: 141 (range, 36-627), 125 (range, 56-232), and 145 (range, 33-866) days for MUD, CB, and haploidentical ($p = ns$), respectively, confirming that the haploidentical donor has been considered as a third choice, according to the RTN hierarchical policy. The reasons for adopting a standby choice or for a nontransplant procedure after the alternative donor identification at RTN and IBMDR are detailed in Table 2. Finally, comparisons between IBMDR and RTN experience are reported in Table 3 and provide significantly better results in terms of alternative donor identification, transplant efficiency, and percentage of transplant procedures in the RTN cohort of patients.

DISCUSSION

The annual survey of the European Blood and Marrow Transplantation Society reporting data over 20 years of activity has shown a continued and constant increase in the number of HSC transplants with allogeneic procedures, mostly relative to haploidentical family donors, which in 2015 exceeded the number of autologous donors.[37-39] However, the choice of the alternative donor type varies greatly throughout the European transplant centers. Although comparison studies have recently reported similar outcomes for patients transplanted from MUD, CB, or haploidentical donors,[25,40-42] no data are available concerning the impact of a defined transplant policy for the alternative donor selection on the transplant efficiency. To ensure to the patient a timely identification of an alternative donor for allogeneic stem cell transplantation, a huge cooperation between hematologists, HLA laboratory, and transplant team is mandatory, and a close and collaborative interaction among transplant centers and the donor registries is essential to reduce time wasting and to save financial resources in the donor identification

TABLE 2. Standby or nontransplant reasons after the alternative donor identification, at RTN and IBMDR*

RTN standby reasons (n = 23)	
Transferred search	4 (17)
Temporary search suspension (complete or partial remission)	19 (83)
RTN no transplant reasons (n = 61)	
Dead	36 (59)
Active disease or high Sorror index	20 (33)
Consent withdrawn	5 (8)
IBMDR standby reasons (n = 91)	
Transferred search	NA
Temporary search suspension (complete or partial remission)	87 (2.27)
IBMDR no transplant reasons (n = 800)	
Dead	558 (14.5)
Active disease or high Sorror index	206 (5.4)
Consent withdrawn	36 (0.9)

* Data are reported as number (%).
NA = not applicable because transferred searches between two Italian transplant centers are considered as IBMDR activity.

TABLE 3. RTN-IBMDR comparison*

Results	RTN	IBMDR	p value
Search for alternative donor (sample size)	417	3834	
Alternative donor identified	324/417 (78)	2740/3834 (71)	0.007
Transplant efficiency	240/324 (74)	1695/2740 (62)	<0.0001
Overall transplant rate	240/417 (58)	1695/3834 (44)	<0.0001

* Data are reported as number (%). Transplant efficiency was defined as the percentage of transplanted patients out of the patients for whom an alternative donor has been identified.

procedure.[43] Therefore, since prediction of donor search outcome could be of great value for the physicians to delineate the strategy of patient care, it becomes of crucial importance to know in advance if the immunogenetic characteristics of a patient are expected to result or not in a successful search.[44,45] The donor registry supports a successful search by working closely with transplant centers during the whole unrelated donor identification process, providing also easy tools for the clinical practice, such as the PQ, available through the BMDW database. Unfortunately, for many of the donor registries worldwide, typing data of the potential donors are generally available only at low-resolution typing for HLA-A, -B, and -DRB1, due to the attempt to control the cost effectiveness of the whole process. In other words, this means that if a patient has no worldwide HLA-A, -B, or -DRB1 low-resolution matched donors available during a PQ, it is very unlikely that he will be able to accomplish a subsequent successful donor-matched search in a reasonable time. The objective of this study was to evaluate the differences in the donor search process between RTN with a defined transplant policy and the IBMDR and analyze if cosharing a specific transplant policy for donor identification may improve the final transplant efficiency. Our comparison analysis has shown that among 3834 patients affected by hematologic malignancy, 66% were able to identify a 7 to 8/8 HLA MUD increasing up to 71%, when CBU 4/6 HLA matched was considered, based on IBMDR activity. However, according to the general policy of transplant centers, these results correspond to a percentage of unrelated transplant procedures of 44%, regardless of the identification time, mainly due to the loss of the patient's eligibility to allogeneic procedure and to the poor use of CBUs for adults. In contrast to the data obtained by the registry activity, the experience of the RTN sample of 417 eligible adult patients showed that a hierarchical policy for donor selection has led to a timely better alternative donor identification (78% vs. 71%, $p = 0.007$) and percentage of transplant procedures (58% vs. 44%, $p < 0.0001$), despite the fact that the IBMDR series includes a significantly larger sample of acute leukemias. The effect of including the haploidentical relative donor in the algorithm of the search process produced a significant improvement of donor identification and transplant efficiency and it is worth highlighting that this result has been achieved also considering the haploidentical source as third choice in the search donor process. This result is due to some factors that contribute to optimizing the unrelated donor search process such as the use of the patients' HR HLA typing at the start of the search process according to IBMDR standards of 2011 and the more close collaboration between hematologists, transplant physicians, and the HLA laboratory for a timely start to the unrelated donor search activation and confirmatory typing result. Moreover, a crucial role is played by the use of PQ through BMDW because a poor result represents an important criterion for the decision to switch from a well-matched to a less-compatible unrelated volunteer donor or to a CBU identification or to haplo-donor selection. Other search tools like OptiMatch or Haplogic might further speed the search process and IBMDR is actively working to define its own software to optimize search strategies. From a laboratory point of view, to identify a compatible donor, it is important to consider the presence of rare alleles, as classified by the international ImMunoGeneTics information system in the patients, but also to analyze the HLA disparities found at allelic level, knowing that some of these occur more frequently than others. Therefore, for a successful search it is important to consider the existence of a large number of different alleles belonging to the same serotype, such as, for example, A*02 or B*35. On the other hand it is relevant to consider that potential incompatibilities may be due to alleles with similar frequencies found inside the same allelic group, such as for B*44, in which the two main alleles, B*44:02 and B*44:03, are almost equally represented in the registries. On the other hand, it must be taken into account that the presence of some HLA-B alleles might be considered a possible negative predictive factor since they correlate with a broad distribution

in respect to their HLA-C association. As a matter of fact, in an Italian study recently published it has been reported that HLA-B*51:01 was linked to 12 different HLA-C alleles, while HLA-B*18:01 and HLA-B*44:03 were associated to nine and six C alleles, respectively.[46] Similarly, for HLA Class II discrepancies, it is noteworthy that DRB1*07:01 is related to 45.7% of all the DQB1 incompatibilities, due to the presence of different DQB1 alleles. In summary, to optimize the alternative donor search process and the transplant efficiency, the RTN strategy consists of: 1) examining PQ through BMDW while the HR HLA report is prepared for a formal search activation; 2) starting up the formal donor search regardless the PQ result as soon as the HR HLA report is available; 3) efficiently considering CBU and haploidentical related donor at the beginning of the search process in case of poor PQ; 4) assessment of unrelated donors with a single Class I HLA mismatch at the start of the search process, if the patient HLA typing carries a rare allele, alleles belong to the same serotype, or there are potential unfavorable HLA-B/C or HLA-DRB1/DQB1 allelic combinations.

In conclusion, a prospective RTN policy of timely and contemporary multiple transplant options ensures an allogeneic alternative transplant procedure to a majority of patients. Regardless the type of alternative donor selected, the RTN policy allows an allogeneic transplant to most candidates in adequate time. Finally, the knowledge of the transplant center's strategy in the donor search process could be a helpful tool for the national registry activity to address a tailored search donor identification according to the transplant center's criteria. The information on the alternative donor policy of transplant centers has become a necessity for correct patient counseling and health care planning.

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CONFLICT OF INTEREST

The authors have disclosed no conflicts of interest.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article at the publisher's website.

Table S1. Timing for unrelated matched donor identification according to patient's HLA typing