OUTCOME OF PATIENTS ACTIVATING AN UNRELATED DONOR SEARCH IN ARGENTINA: A SINGLE-CENTRE EXPERIENCE

Ana L. Basquiera [1], Patricia L. Abichain [2], Pablo A. García [1], Gabriela Sturich [1], Juan C. Damonte[2], Adriana R. Berretta [1], Juan J. García [1]

[1]Hematology and Oncology Service, Hospital Privado Centro Médico de Córdoba, Córdoba, Argentina

[2] Hemotherapy Service, Hospital Privado Centro Médico de Córdoba, Córdoba, Argentina

[3]Instituto Universitario de Ciencias Biomédicas de Córdoba (IUCBC)

Corresponding author: Ana Lisa Basquiera, MD

Hospital Privado Centro Médico de Córdoba

Naciones Unidas 346 (5016)

Córdoba, Argentina

TE: +54-351-4688243. FAX: +54-351-4688263

abasquiera@hospitalprivadosa.com.ar

Short Title: Unrelated donor search in Argentinean patients

Abstract

For patients lacking a HLA-identical sibling donor, an international search for an unrelated donor (UD) must be initiated. An international UD search was activated from our center through the Instituto Nacional Central Único Coordinador de Ablación e Implante (INCUCAI) for 138 consecutive patients between January 2008 and June 2013 with hematological malignancies (n=122) and non-malignant diseases (n=16). The probability of finding a donor (cumulative incidence) was 47.5% at six months and 52.7% at 12 months; 63/138 patients underwent HSCT in a median time of 5.4 months (range 2.8-12.2) after search initiation. Searches initiated three months or less from diagnosis had more chances to find a donor (CI 64.8% vs. 48.6%; p=0.034). CI of relapse/progression after search activation was 35.5% at 6 months and this was the main cause for search discontinuation. In the multivariate analysis, absence of disease progression during the search was associated with better survival after HSCT (HR 0.40; p=0.024). In this series of Argentinean patients, an appropriate UD was found in half of the patients that activated an international search. More than one third of the patients progressed during the search, which highlights the importance of initiating it promptly after diagnosis.

Introduction

Allogeneic hematopoietic stem cell transplantation (HSCT) is a curative procedure for a wide variety of malignant and non-malignant diseases[1]. However, approximately one-third of the patients have a HLA-identical sibling donor. For the rest of the patients, an international unrelated donor (UD) search must be initiated, for both volunteer donors and cord blood (CB) units. An international centralized UD search system has allowed an increasing number of HSCT from UD donors along with a reduction in transplant-related mortality and the an increasing number of indications[2,3]. Also, high-resolution DNA matching for HLA-A, -B, -C, and -DRB1 alleles has clearly contributed to improve survival for transplants using UDs[4,5].

In spite of the increased donor pool, a proportion of patients worldwide with an HSCT indication do not receive a graft[6]. Obstacles to provision of UD include: delays in referral to a transplant centre, lack of matched donors (particularly for those from ethnic minorities and/or with rare HLA phenotypes), low- or intermediate-resolution donor HLA typing, donor attrition from the registries, donor ineligibility on grounds of health and difficulties encountered transporting hematopoietic cells cross international borders[3]. Also, the impact of UD search duration has been recognized as a factor affecting the outcome of HSCT[7].

Our transplant center started international UD searches in 1999. Since 2005, the Instituto Nacional Central Único Coordinador de Ablación e Implante (INCUCAI) is the central search coordinating unit in charge of national and international donor searches in Argentina. We aimed to assess the probability of finding a suitable UD, the search time

span, and the factors associated with failure or success for undergoing transplantation in our country based on searches activated at our centre.

Materials and Methods

Patients

An international UD search was activated at our center for patients who lacked related HLA-compatible donor and were considered eligible for an allogeneic HSCT. Searches were opened at INCUCAI, which addressed the search through the Bone Marrow Donors Worlwide (BMDW) network. For the purposes of this study, we included 138 consecutive patients with malignant and non-malignant diseases activating a search between January 2008 and June 2013 at our institution. This period was chosen because the time spans of every part of the search and the clinical outcome of the patients were registered in detail. Total searches for this period were 142 because four patients activated a search twice (two patients underwent a second transplant for relapse disease). We excluded three additional patients who underwent UD transplantation in this period because their search was started at other institution and no details were available. We included patients diagnosed at our hospital and also patients referred from other centers for UD searching and transplant, which covers a geographical area including the center and the north of the country. As a result, patients were from the following states of the country: Córdoba (n=95), La Rioja (n=9), Santa Fe (n=7), Mendoza (n=5), Tucumán (n=5), Chaco (n=3), Salta (n=3), San Juan (n=3), Santiago del Estero (n=3), Catamarca (n=2), Entre Ríos (n=2), San Luis (n=1). All patients included in this period were born in Argentina.

Data were collected from the donor search database and from the medical health records of patients. The diagnoses were categorized according to the Center for International Blood and Marrow Transplant Research (CIBMTR) considering the phase of disease at the beginning of the search as follow: Early-stage disease was defined as acute myeloid leukemia (AML) and acute lymphoblastic leukemia (ALL) in first complete remission, chronic myeloid leukemia (CML) in first chronic phase, and myelodysplastic syndrome (MDS) subtype refractory anemia; Intermediate-stage disease was AML or ALL in second or subsequent complete remission or in first relapse, and CML in accelerated phase or second chronic phase; and Advanced-stage disease was AML in second or higher relapse or primary induction failure, CML in blast phase, MDS subtype refractory anemia with excess blasts or in transformation, or MDS, not otherwise classified.[4]

Search Process

In our country, an UD search starts with the submission of a formal order to INCUCAI along with the attachment of the intermediate-resolution HLA typing result of the patient and siblings. After that, we must wait for the search authorization. Upon authorization, patient's blood is sent for high-resolution HLA typing. High-resolution HLA typing, both HLA class I and HLA class II, is performed at Ann & Robert Lurie Children´s Hospital of Chicago-HLA & Molecular Diagnostics Laboratory (USA), the reference laboratory chosen for both Argentinean patients and potential donors. With the high-resolution HLA test result, according to our local policies, we can select up to three potential available donors for confirmatory HLA typing. After this first application, if not suitable donor is found and the patient remains fit for transplant, we can request a new authorization for another three donors. Based on the result of confirmatory typing and other

donor characteristics, the transplant center decides which donor will be selected and sets the date for transplant. A volunteer UD was considered suitable for transplant if the compatibility with the patient was well-matched or partially-matched according to the CIBMTR definitions[8]. A cord blood (CB) unit was considered suitable for transplant when ≤2 HLA (A and B in intermediate-resolution and DRB1 in high-resolution) differences with the recipient were found and the number of nucleated cells was at least 3 x 10^7/kg of the recipient body weight[9]. At first, we looked for a volunteer UD for adults and pediatric patients. If a volunteer UD was not found, we looked for CB units for younger and pediatric patients.

Statistical Analysis

Patients' characteristics were described using numbers and frequencies for qualitative data, and median and range for quantitative data. Then, data were compared using χ^2 or Mann Whitney test as appropriated. Probability of finding a donor was estimated using cumulative incidence analysis and considering death as a competing event. Cumulative incidence of relapse/progression during search was estimated using death in complete remission, absence of acceptable donor and patient decision for discontinuation as competing risks. The difference between cumulative incidence curves in the presence of a competing risk was tested using the Gray method[10]. Overall survival (OS) during search was defined as the time from search start to death or last follow-up. Overall survival (OS) after HSCT was defined as the time from transplant to death or last follow-up. OS were calculated using the Kaplan–Meier estimator. The log-rank test was used for comparisons

of Kaplan-Meier curves. A Cox proportional hazard model was used to determine multiple comparisons. All P-values are two sided.

Results

Patients and donors identification

Patients' characteristics are shown in Table 1. An acceptable UD was identified for 69 patients in a median time of 3.7 months (range: 1.6–10.2 months). Cumulative incidence of finding a donor was 52.7% (95% CI 44.9 to 61.9), and it was at 3 months 12.3% (95% CI 7.9 to 19.1), at 4.5 months 39.2% (95% CI 31.8 to 48.2), at 6 months 47.5 % (95% CI 39.8 to 56.6), at 9 months 50.8% (95% CI 43 to 59.9) and at 12 months 52.7% (95% CI 44.9 to 61.9) (Figure 1).

A volunteer UD was identified for 61 patients and CB units were used for the rest of the patients. Median time to donor identification was not different between volunteer UD and CB units (3.7 months vs. 3.5 months, respectively; p=0.51). Countries being the main source of donors were Germany (47.8%), USA (23.2%) and Argentina (7.2%). Donors were full-matched in 26 (38%) cases and mismatched in 43 (62%) cases.

Patient´s chances for finding a donor were not different between adults and pediatric patients (cumulative incidence 51.4% vs. 56.5%; p=0.327), neither from year to year of the search activation (2008= 45.4%; 2009= 55.5%; 2010= 45.6%; 2011= 54.2%; 2012= 53.5%; 2013= 56.9%; p=0.831). However, searches initiated 3 months or less from diagnosis had more chances to find a donor (cumulative incidence 64.8% vs. 48.6%; p=0.034) (Figure 2). For disease categories according to the CIBMTR stratification (n=111), no difference was found between early, intermediate and advanced category (cumulative incidence for category: advanced= 47%; intermediate= 52.2%; and early= 46.2%; p=0.901).

Events during the search

A total of 63 patients underwent transplantation.(Figure 3) The median time spam between UD search initiation and HSCT was 5.4 months (range 2.8-12.2), leading to a median interval between diagnosis and HSCT of 11.1 months (range 4.3-110.9). Transplants were not performed in six patients for whom a donor was identified because the patients became medically unfit (4 cases) or patients refused to undergo transplantation (two cases). Globally, searches were discontinued due to the absence of a suitable donor in 19 patients, disease-related events (relapse/progression/death) in 54 patients, patient's decision in six patients and physician's decision in two patients. Two patients without an identified donor underwent mismatched familiar transplant.

Among all patients, median time to relapse/progression after search activation was 4 months (range 0.2 to 21 months), with a cumulative incidence (CI) of relapse/progression after search activation and before any type of transplant of 19.1% at 3 months and 35.2% at 6 months. For acute leukemias in complete remission at search activation (n=59), the CI of a further relapse was 20.7% at 3 months and 37.3% at 6 months. For CIMBTR categories (n=109), the CI of relapse/progression at 6 months was 28.3% for early disease, 40.5% for intermediate risk disease, and 52.8% for advanced disease (p=0.090). However, when we grouped intermediate and advanced disease versus early disease, the difference was statistically significant (at 6 months: 47.1% vs. 28.3%, respectively; p=0.036).

Overall Survival

OS for the whole population was 23.1% (95% CI 1.5 to 19.3%) at five years from the search activation, with a median time of 10.3 months. We evaluated factors associated with survival including age, sex, diagnosis, time between diagnosis and search initiation, change of disease status during search (relapse/progression) and transplantation. In the

multivariate analysis, one-year OS after search initiation was significantly better in patients who underwent HSCT (62% vs. 29%; HR 0.41; CI 0.27-0.64; p <0.0001) and in patients without relapse/progression after search initiation (58% vs. 15%; HR 0.45; CI 0.29-0.69; p=0.0003). Factors associated with better overall survival after transplantation were absence of relapse/progression during the search (HR 0.40; 95% CI 0.18 to 0.88; p=0.024) and full-matched donor (HR 0.44; 95% CI 0.20 to 0.97; p=0.041).

Essential Parts of the Search Process

In order to identify factors other than the clinical characteristics of the patients that influence the efficiency of the search process, and to compare with the literature, we evaluated the time span of the different parts of the search in our country. (Figure 4) The median time between the start of the search (since formal order is submitted to INCUCAI) and the shipment of the patient's blood for high-resolution HLA typing was 36 days (range: 2–154 days). An authorization from the health insurance (public or private) of the patient is required for activating this phase. The median time span to receive the patient´s HLA test result was 15 days (range: 8–100 days). With the result of patient's high-resolution HLA test, donor search is strictly speaking initiated. The median time span between requesting and selecting a donor for transplantation (after receiving the result of the last requested donor) was 53 days (range: 23–138 days). And finally, the transplantation was carried out in a median time of 52 days (range: 22 -114 days) after selecting the donor. A second authorization is needed for this last phase.

Discussion

We described the outcome of patients activating an UD search based on a single centre in Argentina. To our knowledge, the probability of finding an UD and the factors affecting the search process in our country have not been specifically addressed.

We found that the cumulative incidence of finding a donor was 12.3% at 3 months, 39.2% at 4.5 months, 47.5 % at 6 months and 52.7% at 12 months with no further increase beyond this point. This means that the majority of donors were found after six months of search initiation, with a median time to transplant of 5.4 months. Global percentage of identified donors was a little inferior to more recent studies reporting between 75 to 90% of successful rate[11,12,13]. A low representativity of HLA-argentinean patients in international registries may account for this difference. Only 7% of donors from our series were from Argentina; similarly, a shortage of UDs in patients with different origin within Europe has been described as a cause for lower search successful rates[6]. In line with this, some registries have adopted a policy to identify the probability of a successful search based on allele and haplotype frequencies[14]. Patients with a low probability estimate to find a donor could benefit from a transplant with an alternative donor (haploidentical, autologous)[14]. A delay in referral to a transplant centre is another factor affecting the possibility of finding a donor and accessing to transplant[2,13]. We found that searches initiated three months or less from diagnosis had more chances to find a donor, achieving a successful rate of 64.8% in this group of patients.

Our median time to identify an acceptable donor was 3.7 months, with a median time to transplant of 5.4 months. It is difficult to compare our results with the literature available since many studies report that search activation starts with the result of the high-resolution HLA

typing of the patient.[13]. In Argentina, it is required to start the search first and then the high-resolution HLA typing of the patient can be applied. This process has a median time span of 36 days; high-resolution HLA typing study was obtained in a median time of 15 days. As a result, almost two months are added in our country before starting the donor search process. For volunteer UD search only, Heemskerk et al reported that patients received a graft from an UD with a median time span of 4.4 months from the start of the search[6]. For GITMO registry, 121 out of 326 patients (37%) activating an UD search underwent transplantation in a median time of 5.6 months[15]. CB unit search could reduce search duration[16]. Taking this issue into account, Iori et al reported a cumulative incidence of finding a donor of 59.2% at 3 months with a simultaneous search of volunteer UD and CB unit, and patients underwent transplant at a median time from the start of the search of 4.1 months (range 1.9–37)[12]. In our series, no difference was found between volunteer UD search and CB units; however, CB units were priority for us only in pediatric population and the administrative processing time was the same for both volunteer and CB donors.

The main cause of search discontinuation in our experience was relapse/progression of disease, which accounted for 58% of all search cancellations. Median time to relapse/progression and cumulative incidence of relapse/progression after search activation was 4 months and 35.2% at 6 months, respectively. Our results are similar to the ones previously reported[7,12]. By using CIMBTR categories, we found that patients with intermediate or advanced risk disease had a higher cumulative incidence of relapse/progression during the search. In the series reported by Heemskerk et al, high-risk patients did have 2.3 higher odds to become medically unfit for transplantation[6]. Due to the high relapse rate in the first six months after search initiation and the low probability to find a donor beyond this time span, it could be reasonable to look for an alternative familiar

donor in high-risk patients who need an allogeneic HSCT[17]. HLA typification of parents at the moment of sibling's typification is a current practice in many centers[13,18].

Factors that significantly affected the OS for the whole population were relapse/progression of disease and to achieve of transplant. For patients who underwent transplant, the absence of relapse/progression during search and a full matched donor were associated with better survival. Optimal matching but also search duration have been identified as independent factors for survival[12,19]. Craddok et al found that a time to transplant from diagnosis less than four months was associated with better OS in patients with refractory AML[20]. We could not identify factors such as time from diagnosis to search activation or search duration as adverse variables; however, we include a heterogeneous group of patients regarding age, diagnosis, phase of disease and conditioning regimens used for transplant.

In this series of Argentinean patients, an acceptable unrelated donor was found in half of the patients that activated an international search based in one center. More than one third of the patients progressed during the search and for these high-risk patients a donor search needs to be initiated promptly. Reduction of time to authorizations and administrative paperwork could make the search process more efficient.

Acknowledgements

Conflict of interest statement: There are no conflicts of interest to disclose.

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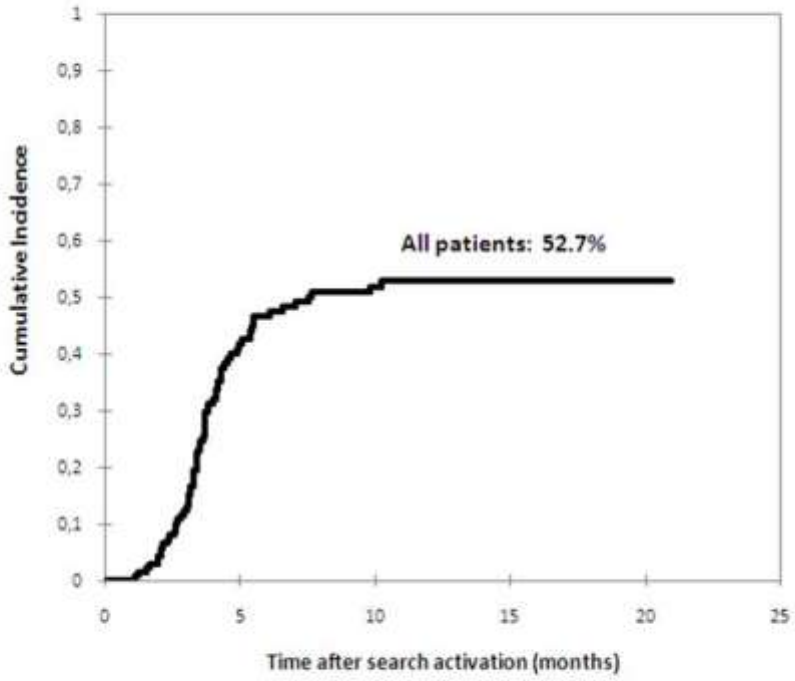
Table 1. Characteristics of patients at the beginning of the search (n=138)*

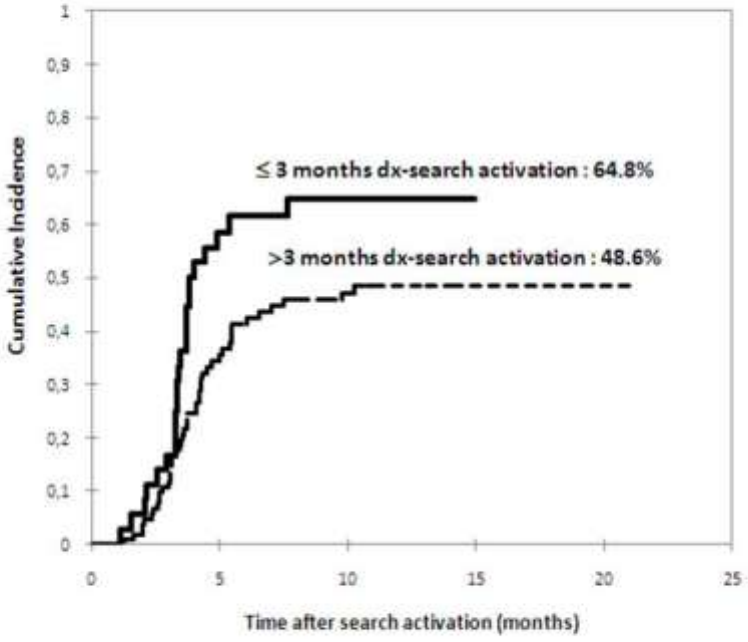
Variable	
Age, median years (range)	**25 (1-65)**
Pediatric (< 18 years old), n° (%)	**40 (29)**
Adults (≥ 18 years old), n° (%)	**98 (71)**
Gender, male/female	**84/54**
Diagnosis, n° (%)	
ALL	**42 (30.4)**
AML	**33 (23.9)**
Lymphoma	**11 (7.9)**
MDS	**23 (16.7)**
MPD	**10 (7.2)**
Other malignancies	**3 (2.3)**
SAA	**9 (6.5)**
Other nonmalignant diseases	**7 (5.1)**
Months from diagnosis to search activation, median	
All diagnosis	**5.9**
Malignancies	**5.6**
Non- malignant diseases	**7.4**
CIBMTR category, n° (%)†	
Early	**35 (32.1)**
Intermediate	**33 (30.3)**
Advanced	**41 (37.6)**

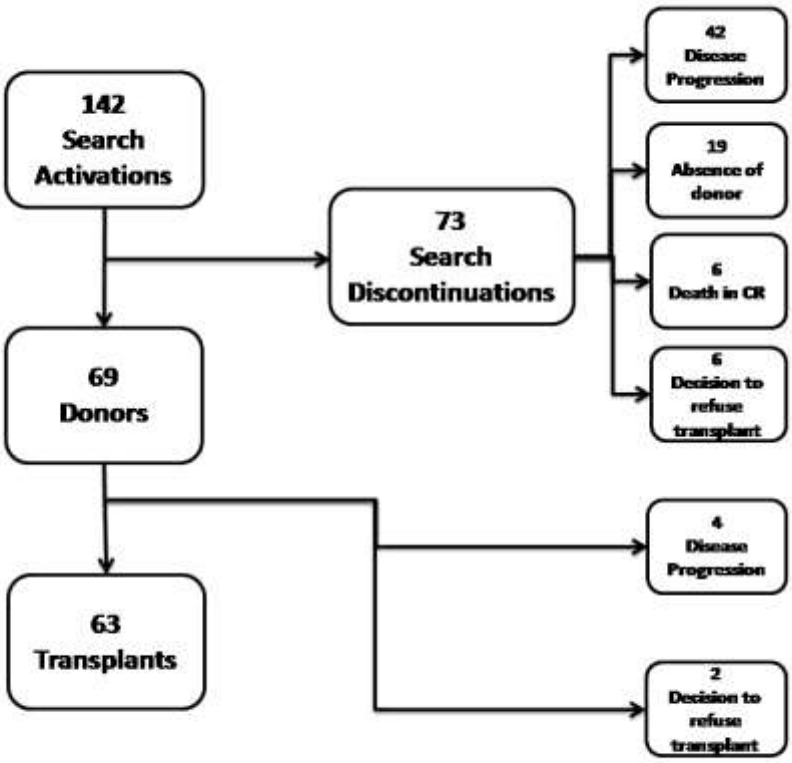
* ALL= acute lymphoblastic leukemia; AML= acute myeloblastic leukemia; MDS= myelodysplastic syndrome; MPD= myeloproliferative disorders; SAA= severe aplastic anemia.
† Only for ALL, AML, MDS and MPD

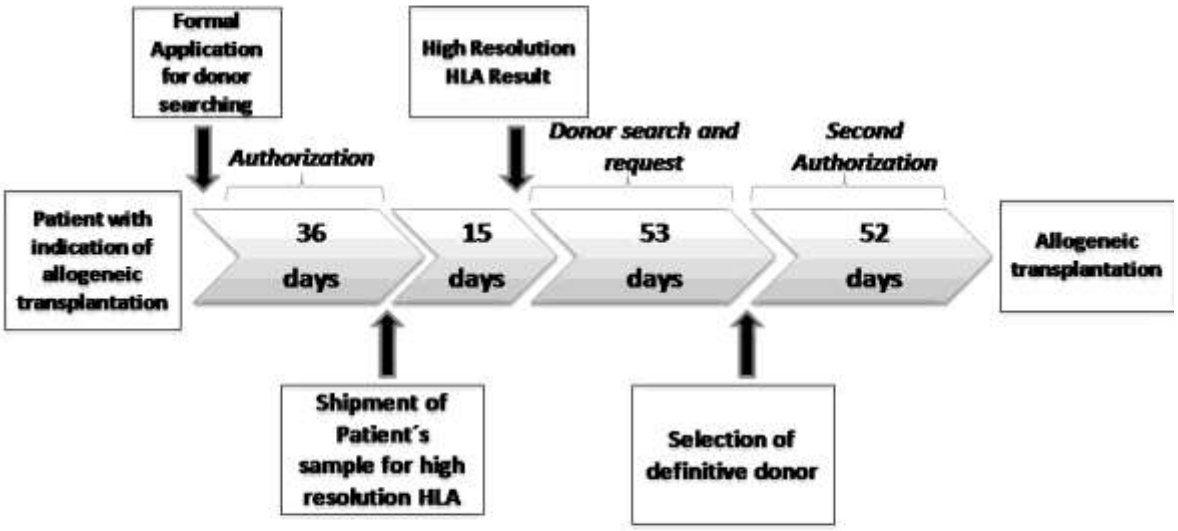
FIGURES LEGEND

Figure 1. Cumulative incidence of finding a donor for all population
Figure 2. Cumulative incidence of finding a donor according to the time between diagnosis and search activation.
Figure 3. Time span of the different parts of the search until transplantation (median).


Cumulative Incidence
1
0,9
0,8
0,7
0,6
0,5
0,4
0,3
0,2
0,1
0
All patients: 52.7%
0
5
10
15
20
25
Time after search activation (months)


Cumulative Incidence
1
0,9
0,8
0,7
0,6
0,5
0,4
0,3
0,2
0,1
0
0
5
10
15
20
25
Time after search activation (months)
≤ 3 months dx-search activation : 64.8%
>3 months dx-search activation : 48.6%


142
Search
Activations
73
Search
Discontinuations
42
Disease
Progression
19
Absence of
donor
6
Death in CR
6
Decision to
refuse
transplant
69
Donors
4
Disease
Progression
63
Transplants
2
Decision to
refuse
transplant


Formal Application for donor searching
High Resolution HLA Result
Authorization
Donor search and request
Second Authorization
Patient with indication of allogeneic transplantation
36 days
15 days
53 days
52 days
Allogeneic transplantation
Shipment of Patient´s sample for high resolution HLA
Selection of definitive donor