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GITMO REGISTRY STUDY ON ALLOGENEIC TRANSPLANTATION IN PATIENTS AGED OVER 60 FROM 2000 TO 2017. IMPROVEMENTS AND CRITICISMS

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ABSTRACT

Background: Nowadays, allogeneic stem cell transplantation (Allo-SCT) can be offered to patients up to the age of 70-72 years and represents one of the most effective curative treatments for many hematological malignancies.

Objectives: The primary objective of the study is to collect data from the allo-SCTs performed in Italy from 2000 to 2017 in patients over 60 years of age to evaluate the changes in safety and efficacy outcomes as well as their distribution and characteristics over time.

Study design: The GITMO AlloEld study (ClinicalTrials.gov: NCT04469985) is a retrospective, analysis of the allo-SCTs performed 30 Italian transplant Centers on older patients (≥ 60 years) from 2000 to 2017 (n=1,996).

Results: For the purpose of analysis, patients were grouped into three time periods: time A: 2000-2005, n=256 (12%); time B: 2006-2011, n=584 (29%); and time C: 2012-2017, n=1156 (59%). After a median follow-up of 5.6 years, the 5-year Non Relapse Mortality (NRM) remained stable (time A: 32.8%; time B: 36.2%; and time C: 35.0%, $p = 0.5$); the Overall Survival (OS) improved (time A: 28.4%; time B: 31.8%; and time C: 37.3%, $p = 0.012$); and the Cumulative Incidence of Relapse (CIR) reduced (time A: 45.3%; time B: 38.2%; time C: 30.0%, $p < 0.0001$). The 2-year incidence of extensive cGVHD reduced significantly (time A: 17.2%; time B: 15.8%; and time C: 12.2%, $p = 0.004$). Considering times A and B together (2000-2011), the 2-year NRM was positively correlated to the HCT-CI score; patients with HCT-CI of 0, 1 or 2, or ≥3 had rates of NRM of 25.2%, 33.9%, and 36.1%, respectively, ($p < 0.001$). Meanwhile, after 2012, the HCT-CI score was not significantlly predictive of NRM.

Conclusions: The study shows that the transplant procedure in elderly patients became more effective over time. Relapse incidence remains the major problem and strategies to prevent it are under investigation (e.g. post-transplant maintenance). Today, the selection of patients aged over 60 could be improved by combining HCT-CI and frailty assessments to better predict NRM.

Key words

Elderly, Allogeneic stem cell transplantation, Co-morbidities, Frailty

INTRODUCTION

In the era of target therapies, the first-line treatment strategy for many haematological malignancies still includes allogeneic stem cell transplantation (allo-SCT)[1], even in patients aged over 60[2, 3].

GITMO *(Italian Group for Bone Marrow Transplantation, Haematopoietic Stem Cells and Cell Therapy)* has reported that the number of patients aged over 60 who underwent a transplantation between 2010 and 2020 increased from 9% to 26%, respectively, and a progressive growth is expected in the coming years, due to the ageing of the population[4, 5]. Moreover, thanks to the introduction of reduced-intensity and reduced-toxicity conditioning regimens, allo-SCT can currently be offered to patients up to 75 years old and the clinical and biological tools used to select patients have significantly improved.

Considering older patients, many barriers against their referral to a transplant procedure have been discussed in the literature. Most of them regard the age *per se*, the non-white race, the socioeconomic status, and the insurance costs[6]. Overall, patient comorbidity and frailty are considered to be one of the major obstacles to transplantation success in advanced age. In order to improve the selection of patients, several scores have been generated over the last two decades and are currently applied in this field, but none of them can be considered completely satisfactory[7-9]. The HCT-CI score[7], based on patient comorbidity, and the EBMT[8] or Shouval[9] scores, based on the characteristics of the patients and the disease, donor type, conditioning intensity and transplant center activity, are useful to stratify patients with different risks of non-relapse mortality (NRM), cumulative incidence of relapse (CIR), and overall survival (OS). However, they need to be integrated on a case-by-case basis, considering patient fitness or frailty, conditioning regimen intensity, graft versus host disease (GVHD), and infectious prophylaxis and therapy.

In this manuscript, we report the results of a registry-based retrospective study on behalf of GITMO (GITMO AlloEld). The primary goal of the study was to evaluate the changes in safety and efficacy outcomes and the distribution and characteristics over time of allo-SCTs performed in Italy from 2000 to 2017 in patients aged over 60 years.

PATIENTS AND METHODS

The GITMO AlloEld study (ClinicalTrials.gov: NCT04469985) is a retrospective, nationwide analysis of the allo-SCTs performed on patients aged over 60 from 2000 to 2017. Among all the 50 Italian transplant Centers accredited to GITMO for adult allo-SCT, 30 (60%) gave their adhesion to participate to the protocol. Following the approval of all ethics committees of the participating centers, data from all transplants registered in the European PROMISE database were extracted (n=2,061), and additional queries were then submitted to each center in order to minimise missing data. Finally, a total of 1,996 allo-SCTs were included for analysis, referring to the first transplant for each patient. All patients included in the registry provided informed consent for data registration in the PROMISE database. The study was conducted in compliance with current national and European legislation on clinical trials, in accordance with the Declaration of Helsinki and the principles of good clinical practice.

Statistical analysis

Dichotomous variables were summarised as numbers and percentages and compared using the Chi-Squared or Fisher's Exact test; continuous variables were summarised as median and range and compared using the Wilcoxon Rank-sum test. Median follow up was assessed with the method of reverse Kaplan-Meier[10].

Overall survival (OS) was calculated according to the Kaplan-Meier method, from the date of the transplant to the date of death or last follow-up; the log-rank test was used to detect significant differences among subgroups. NRM, CIR, and cumulative incidence of aGVHD and cGVHD were calculated based on competing risk models, and the Gray test was used to assess statistical differences among subgroups. Death without the event of interest was considered as competitive risk.
Cox and Fine-Gray proportional hazard regressions were utilised for univariate and multivariate analysis for OS and NRM, respectively.

The following variables were included in the regression models: age of donor (5-year interval); use of total body irradiation (TBI); *in-vivo* T-cell depletion; intensity of conditioning regimen; CD34+ and CD3+ /Kg dose (as continuous variables); disease status at transplant (responsive vs. non-responsive disease); source of hematopoietic stem cells [umbilical cord blood (UCB) vs. peripheral blood stem cell (PBSC) plus bone marrow (BM); PBSC vs. BM plus UCB]; donor type/stem cell source [sibling donor vs. UCB, sibling vs. haploidentical (Haplo) donor and sibling vs. unrelated donor (UD)]; diagnosis (acute leukaemia vs. other diseases); HCT-CI score (low vs. intermediate-high risk); Karnofsky performance status (KPS) (≥90 vs. <90); CMV serostatus (nega-

tive donor for positive recipient vs. other combinations); donor gender (female donor for male recipient vs. all other combinations); age of patients (5-year interval); and transplant era (2012-2017 vs. earlier period). All resulting variables associated with OS and NRM with $p<0.05$ in univariate analysis underwent multivariate analysis. In vivo T-cell depletion was found to be correlated with donor type (chi-square $p<0.0001$), therefore the latter was excluded from the multivariate analysis.

All p values <0.05 were considered statistically significant. Statistical analysis was performed with EZR software (v 1.54)[11].

RESULTS

Clinical and transplant characteristics of the study population

For analysis purposes, the patients were grouped into three time-periods: time A: 2000-2005, n=256 (12%); time B: 2006-2011, n=584 (29%); and time C: 2012-2017, n=1156 (58%). The median follow up of the three time periods in years was: 15 (95% CI 14,0-15,8), 9,7 (95% CI 9,2-10,2), 4 (95% CI 3,8-4,2). The total number of transplants performed by the 30 adult Centers independently on patients age is 3376 in time A, 4681 in time B and 5546 in time C. Of note the proportion of elderly patients increased over time: 256/3376 (8%) in time A vs. 584/4681 (12,5%) in time B vs. 1156/5546 (21%) in time C (p<0,0001). Figure 1 reports the distribution of transplants in the three time-periods across the 30 GITMO Centers. In 5 out of 30 Centers (17%) transplants were only performed in times B and C, and all 30 Centers performed more than 50% of their transplants in times B and C. Moreover, in 22 out of 30 Centers (73%), more than 50% of the transplants were performed in time C.

Patient characteristics are reported in Table 1. By comparing times A, B, and C, we observed several significant differences. Over time, the median patient age increased (62.6, 63.02, and 63.94, respectively, $p < 0.001$); more acute leukaemia were transplanted (27%, 48%, 61%, respectively, p <0,001); the percentage of CR at allo-SCT increased (29%, 47%, and 54%, respectively, $p < 0.001$); the proportion of patients with a HCT-CI at transplant of over 3 increased from 10% to 26% to 29%, respectively (p<0.001); and the percentage of patients with KPS 100 increased from 10% (time A) to 30% (time C) (p<0.001).

Table 2 reports the transplant characteristics of the 1,996 patients. The most important differences across the three time periods were a progressive increase in the use of bone marrow as a graft source (from 13% to 18% to 29%; p<0.001); a reduction in TBI-based regimens (from 43% to 18% to 7%; p<0.001); and an increase in MAC regimens (from 14% to 21% to 42%; p< 0.001). The distribution of the different alkylators was comparable between the three time periods, and none of them was associated with a different transplant outcome, both according to conditioning intensity (MAC vs. RIC) and disease phase at transplant (CR vs. no CR) (data not shown). Moreover, an increased use of *in vivo* T-cell depletion (from 16.5% to 42% to 43%; p<0.001), post-transplant cyclophosphamide (from 0% to 2% to 24%; p<0.0001), and UD and Haplo transplants (from 6% to 39% to 43% for UD and from 7% to 13% to 28% for Haplo; p<0.0001) was observed. Lastly, there was a significant reduction in the median age of donors (from 59.5 to 51.5 to 38.5 years old; p<0.001). In the whole cohort of the 419 Haplo transplants, GVHD prophylaxis was: post-

transplant cyclophosphamide in 269 (64%) cases (0 in time A, 6 in time B and 263 in time C), ATG/campath based in 112 (27%) cases (8 in time A, 50 in time B and 54 in time C) and cyclosporine/tacrolimus +/- methotrexate or mycophenolate in 38 (9%) cases (3 in time A, 6 in time B and 29 in time C). Interestingly, the use of UD declined at increasing age: 538 transplant in patients <65 years (40%), vs. 196 (34%) in 65-70 years category and only 4 (5%) in patients older than 70 years ($p<0.001$).

Non-Relapse Mortality, Cumulative Incidence of Relapse, and Overall Survival

After a median follow-up of 5.6 years (95% CI 5.2-6.0) for the whole patient cohort, the cumulative incidence of NRM at 1, 2, and 5 years was 26.3%, 30.6%, and 35.2%, respectively (; the CIR was 24.4%, 30.0%, and 34.9%, respectively ; and the probability of OS was 57.4%, 46.1%, and 34.5%, respectively . Over the course of the time period studied, there was a significant improvement in the 5-year OS (time A: 28.4%, time B: 31.8%, and time C: 37.3%, $p = 0.012$; Figure 2A), and a significant reduction in 5-year CIR (45.3%, 38.2%, and 30.0%, respectively, $p < 0.0001$; Figure 2B) was also observed. No significant changes in 5-year NRM (32.8%, 36.2%, and 35.0%, respectively, $p = 0.5$; Figure 2C) were found. Table 3 reports the distribution of NRM causes over time. Notably, there was a reduction in 5-year NRM due to GVHD (47%, 45%, and 32%, respectively, $p = 0.006$), and in parallel, an increase in 5-years NRM due to infections (32%, 40%, 45%, respectively, $p = 0.003$).

Data and onset time of aGVHD and cGVHD were available in 1779 (89%) and in 1993 (99%) patients, respectively. The cumulative incidence of aGVHD (any grade) at 30 and 100 days was 15.8% and 29.2%, respectively, whereas the incidence of aGVHD (grades II-IV) were 11.1% and 20.1%, respectively. At 100 days, the overall incidence of aGVHD did not change significantly from time A to time B to time C (any grades: 25.6%, 31.4%, and 29.2%, respectively, $p = 0.106$; grades II-IV: 16.8%, 21.3%, and 20.1%, $p = 0.289$; Supplementary Figure 1A and 1B). Focusing on cGVHD, the cumulative incidence at 2 years was 27.6% (any grade) and 13.9% (extensive cGVHD). The incidence of cGVHD (any grade) at 2 years was 31.6% for time A, 29.9% for time B, and 25.6% for time C, $p = 0.0181$ (Supplementary Figure 2A). Similarly, the incidence of extensive cGVHD for times A, B, and C was 17.2%, 15.8%, and 12.2%, respectively, $p = 0.004$ (Supplementary Figure 2B).

Considering the whole cohort of patients, the 1-year NRM was positively correlated to the HCT-CI score; patients with HCT-CI of 0, 1 or 2, or ≥3 had NRM rates of 21.8%, 28.4%, and 31.9%, respectively $p < 0.001$ (Figure 3A). When times A and B were grouped together, due to the

relatively small number of patients, NRM was significantly correlated to the HCT-CI (Figure 3A; p<0.02). However, this phenomenon had borderline significance among patients transplanted after 2011 (time C; Figure 3A; p=0.052). Moreover, the NRM for each HCT-CI category (0, 1 – 2, and ≥3) remained stable when comparing 2000-2011 (times A and B) and 2012-2017 (time C) (data not shown). Furthermore, HCT-CI was significantly correlated to OS (Figure 3B); for the whole cohort at 5-year follow-up, patients with HCT-CI scores of 0, 1 – 2, and ≥3 had an OS rate of 40.2%, 33.6%, 31.4%, respectively, $p < 0.001$. When the patients in times A and B were grouped together, the predictive value of HCT-CI was present (OS at 5 years: 40.7%, 29.8%, and 20.4%, respectively, $p < 0.001$), whereas it lost its impact in time C group (OS at 5 years: 39.5%, 36.3%, and 35.7%, respectively, $p = 0.074$).

Figures 4A, 4B and 4C represent the long term outcome according to patients age (60-65 years, 66-70 years and > 70 years) in time A + B (n=627, 197 and 16, respectively) vs. time C (n=714, 384 and 58, respectively). The three age groups have significantly different OS in time A + B only (at 5 years: 33,7% vs. 22,7% vs. 18,8%; $p = 0{,}003$; Figure 4A). On the other hand, NRM and CIR according to age were not significantly different in the two time-periods (Figure 4B and 4C).

We performed univariate and multivariate analysis on NRM and OS .

Considering the multivariate analysis on NRM (Figure 5A), UCB (HR4.19; 95%CI 1.74-10.1; $p = 0.001$), Haplo (HR2.00; 95%CI 1.37-2.90; $p < 0.001$), and UD (HR1.77, 95%CI 1.20-2.62; $p = 0.004$) significantly increased NRM, whereas an acute leukaemia diagnosis (HR 0.64; 95%CI 0.53-0.79; $p < 0.001$), low-risk HCT-CI (<1) (HR 0.74, 95%CI 0.60-0.90; $p = 0.003$), and KPS 90-100 (HR0.68, 95%CI 0.55-0.84; $p < 0.001$) significantly reduced NRM.

According to the multivariate analysis (Figure 5B), the factors that significantly impaired OS were UCB (HR 2.07; 95%CI 1.33-3.23; $p = 0.001$), Haplo (HR 1,22; 95% CI 1,02-1,47; p=0,031), non-response (meaning non-remission) at the time of SCT (HR 1.68; 95%CI 1.46-1.94; $p < 0.001$), and male recipient (HR 1.15; 95%CI 1.01-1.32, $p = 0.04$). On the other hand, HCT-CI <1 (HR 0.81; 95%CI 0.71-0.93; $p = 0.002$), KPS 90-100 (HR0.65; 95%CI 0.57-0.75; $p <$ 0-001) and transplant between 2011-2017 (HR0.86, 95%CI 0.74-0.99; $p = 0.03$) significantly improved OS.

DISCUSSION

Since a significant increase in transplant age is reported in all transplant registries[4], and elderly patients are expected to exceed one third of the whole population in the coming years[5], we conducted this retrospective registry-based study to evaluate the safety, efficacy, and outcomes of alloSCTs performed in 1,996 patients aged over 60, who received their transplants from 30 GITMO Centers over the last two decades (2000 - 2017). Participating Centers represent 60% (30/50) of all the allogeneic adult transplant programs accredited in Italy. We are aware that this percentage dose not fully covers all the Italian activity, but these were the Centers that gave the consent to participate to the study.

One major strength of this analysis is represented by the number of transplants included (1,996 first transplants) and the long median follow-up (10.4 years) that makes the value and interpretation of the results quite reliable. Moreover, to the best of our knowledge, although some recently published studies cover the topic of outcome and toxicity of allo-SCT in the elderly with specific hematological malignancies [12-15], this is the first registry study that includes a comprehensive analysis of allo-SCT consecutively performed in Italy, thus reflecting the transplant trend in our country in the last 17 years. However, some limitations should be underlined, such as the retrospective nature of the study. In particular, the lack of missing value concerning HCT-CI (22%) as well as death cause (23%) limits the strength of the results and suggest that caution should be taken in drawing final conclusions. Moreover, roughly one quarter of the Centers performed nearly 50% of all the 1996 transplants. This Center effect should be considered, as a learning curve is inevitably present when transplanting elderly patients.

The significant increase in the number of transplants in patients aged over 60 during this time frame (Figure 1) was due not only to the ageing of the population and to the increased prevalence of haematological malignancies among the elderly, but also to clinicians' greater propensity to use allo-SCT to cure rather than to control these diseases, as confirmed by the progressive increase of the proportion of elderly patients transplanted over time. Notably, more than 50% of the registered transplants were performed between 2012 and 2017, by 73% of the participating Centers. This means that, although allo-SCT in the elderly has been performed in Italy since 2000, the transplant procedure has evolved so much over time that by 2017 the percentage of transplants in patients aged over 60 had nearly doubled in most of the Centers (Figure 1). In fact, there was a significant change in most allo-SCT procedures worldwide, starting from the HLA typing[16] and the selection of patients, through to the evolution of the conditioning platforms[17-19], moving from standard MAC to reduced-toxicity regimens. As a consequence, the characteristics of the patients receiving allo-SCT

significantly changed over time (Table 1). More acute leukaemia in CR have been transplanted in the most recent years. This reflects the improvement in the biological characterization of these diseases over time[20], in order to rapidly identify patients with a high risk of relapse who should be treated with allo-SCT in CR[21]. In parallel, transplant platforms have also significantly changed, with a modification of the conditioning regimens, an increasing use of MAC regimens, *in vivo* T-cell depletion, and post-transplant cyclophosphamide (Table 2). Focusing on the conditioning regimen, TBI was progressively abandoned in favour of alkylators, namely busulfan (switching from oral in the early 2000 to intravenous thereafter), thiotepa and, more recently, treosulfan, often included in reduced-toxicity conditioning regimens (total dose greater than 10 g/sqm). This is relevant, considering that the balance between the anti-leukemic activity and toxicity of these conditioning regimens has become progressively more favorable[19, 22, 23]. In other words, the extensive use of MAC in recent years reflects the idea that the chemotherapy dose of the conditioning does matter in determining the final cure of the disease.

The direct consequence of all these changes is that the NRM remained stable over time (Figure 2A) while the CIR significantly reduced (Figure 2B). Notably, we should remember that with the increasing of age, death is an expected event that may be not related to transplant or disease recurrence. Interestingly, the stability of NRM over time was caused by a balance between an increase in NRM due to infections (mainly bacterial) and a reduction in NRM due to GVHD (Table 3), even though caution in data interpretation is mandatory due to the high number of missing data. A possible explanation for the increase in infective NRM could be that, moving from 2000 to 2017, we transplanted older patients, more often selecting a matched unrelated or Haplo donor, adopting more intensive conditioning regimens. These two latter aspects could be at least partially explained by the idea that, particularly in acute leukemias, the timing of transplant is more important than the HLA matching and that chemotherapy dose matters in determining the cure of the disease. Moreover, an increased use of both *in vivo* T-cell depletion and post-transplant cyclophosphamide was observed (Table 1 and 2). Notably, these two latter platforms for GVHD prophylaxis are associated with a reduction of the GVHD incidence, [24-27] which explains the reduction in GVHD-related NRM. The consequence of NRM stability and CIR reduction over time is that OS significantly improved (Figure 2C).

One would expect that the improvement in OS should be related to a reduction in NRM, considering that NRM was identified, in the past, as the major limitation to allo-SCT success among the elderly[28]. Interestingly, focusing on the interval 2000-2011 (time A + time B), the NRM was significantly lower in patients with HCT-CI 0 vs. 1 or 2 vs. 3, while it remained stable in time C across all the HCT-CI groups (Figure 3A). This may be related to the changing over time in patients charac-

teristics and transplant platform, in particular conditioning regimen and GVHD prophylaxis. Notably, the intensity of conditioning regimens became progressively higher (Table 2); in parallel, the proportion of patients with higher comorbidity increased, whereas their KPS significantly ameliorated (Table 1). Moreover, moving from 2000 to 2017, we observed a significant reduction in extensive cGVHD cumulative incidence, associated with the use of *in vivo* T-cell depletion, namely with ATG (Supplementary figure 2B). Interestingly, this did not increase the CIR, which is in line with prospective published data on the use of anti-tymocyte (ATG) or T-anti-lymphocyte globulin (ATLG) in allo-SCT [24, 29]. Overall, these data suggest that the selection of patients progressively improved over time, favouring fitter patients in CR, regardless of their comorbidity score, transplanted with intensive conditioning regimens and treated with a more active anti-GVHD prophylaxis. Nevertheless, efforts to improve the CIR are urgently needed and several pre-emptive strategies, such as the use of post-transplant maintenance with hypomethylating agents (e.g. azacitidine) or anti-apoptotic drugs (e.g. venetoclax) or molecular target drugs in case of targetable genetic lesions (e.g. Flt3 inhibitors)[30, 31] are currently under active clinical and experimental research.

Another interesting result is that increasing age was associated with worse outcome between 2000 and 2011 and not between 2012 and 2017 (Figure 4A), whereas CIR and NRM remained stable across all the time-periods. Once again, this suggests that age alone do not fully reflect the frailty and vulnerability of a patient aged over 60. In this regard, other frailty scores (such as the score by the Fondazione Italiana Linfomi - FIL) should be prospectively explored in the elderly, as they may predict the NRM and the OS better than the historical HCT-CI [7, 32-35]. The challenge for the future is might be finding a way to combine these clinical frailty scores with biomarkers of aging [3e6, 37] in order to improve the selection of elderly patients who are eligible for allo-SCT. Currently, at least in Italy, there are no standardized methods for multidimensional geriatric assessment, and each transplant Center performs its own evaluation, according to local guidelines. This lack of homogeneity in exploring this aspect of senescence should be a stimulus for designing prospective, multicentric trials, including a comprehensive assessment of frailty before allo-SCT.

Finally, focusing on the multivariate analysis, it is note-worthy that, in our study, the use of an alternative donor (in particular MUD or haplo) was associated with impaired outcome for increase in NRM (Figure 5A and 5B). Although some data from the literature suggest that the long-term outcome following allo-SCT is not influenced by the donor type, overall, this topic is still a matter of debate among Hematologists, especially in acute leukemias[38].

In summary, the use of allo-SCT in elderly patients progressively increased in Italy over the years in question. Moreover, the clinical and transplant characteristics of the patient population significantly changed over time, with the aim of increasing the curability of the underlying disease.

This explains why long-term OS progressively improved, thanks to a reduction in the CIR and cGHVD while NRM remained stable. In particular, the progressive use of intensive conditioning regimens over time, despite the increase in patient comorbidity, suggests that the selection of patients based on HCT-CI alone has been progressively abandoned in favor of paying closer attention to patient fitness, as reflected by the improvement in patient KPS.

Overall, these data strongly support the use of allo-SCT in elderly patients, in particular within clinical trials exploring different transplant platforms, in several disease groups. Moreover, age alone cannot be considered a factor limiting the access to allo-SCT, which remains the best post-induction therapy for several high-risk haematological malignancies. Patient selection remains crucial, and further investigation is needed in order to identify the best tool to predict NRM and OS. Future research in the field of allo-SCT especially in older patients should be addressed to the following objective: not one transplant for all the elderly, but different transplants basing on the heterogeneity of older patients.

Collaborators
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Authorship contributions

MM, MM, BB, FC, DR and FB designed the study. MM, NP, DR and FB analysed the data. MM, DR and FB wrote the manuscript. All the authors revised the manuscript and gave their final approval for submission.

Conflict of Interest Disclosures

All the authors declare that there are no potential conflicts of interest regarding the study.

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Figure 1. Distribution of allo-SCT according to time A (2000-2005), B (2006-2011) and C (2012-2017) in the 30 transplant Centers included in the study

Figure 1.

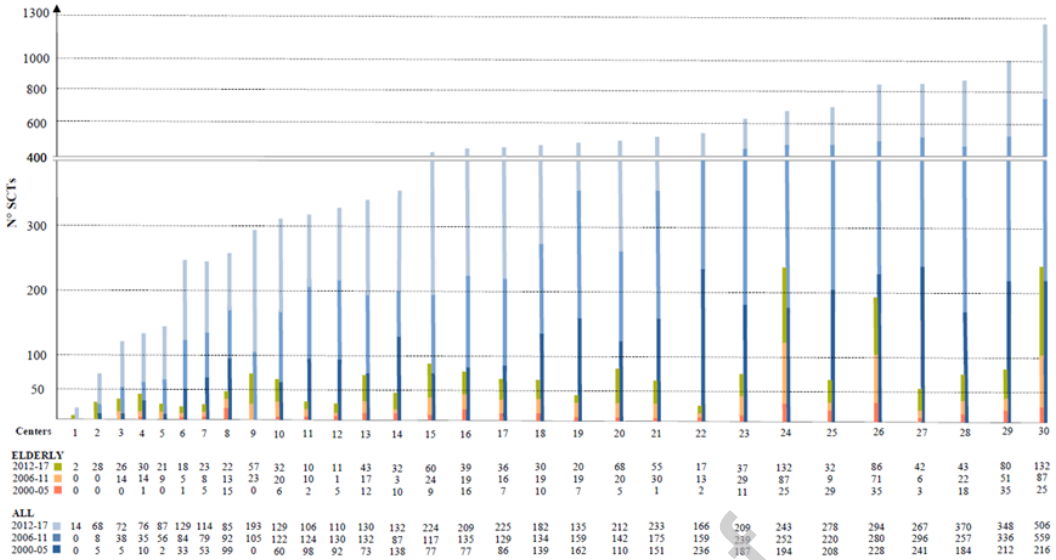


Figure 2. Overall survival (OS), cumulative incidence of relapse (CIR) and non-relapse mortality (NRM) according to time of allo-SCT. Probability of OS at 5 years: 28.4% time A vs. 31.8% time B vs. 37.3% time C; p=0.012 (**A**). CIR at 5 years: 45.3% time A vs. 38.2% time B vs. 30.0% time C; P<0.0001 (**B**). Cumulative incidence of NRM at 5 years: 32.8% time A vs. 36.2% time B vs. 35.0% time C; p=0.5 (**C**).

Figure 2A.

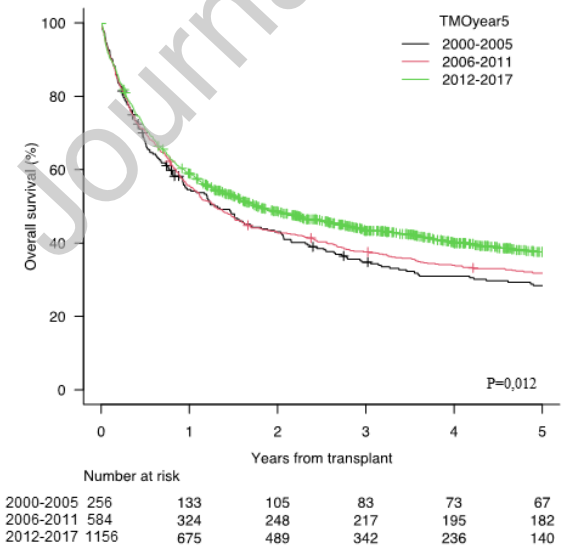


Figure 2B.

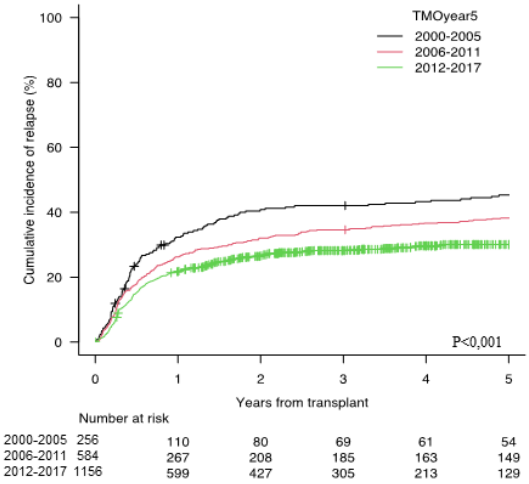


Figure 2C.

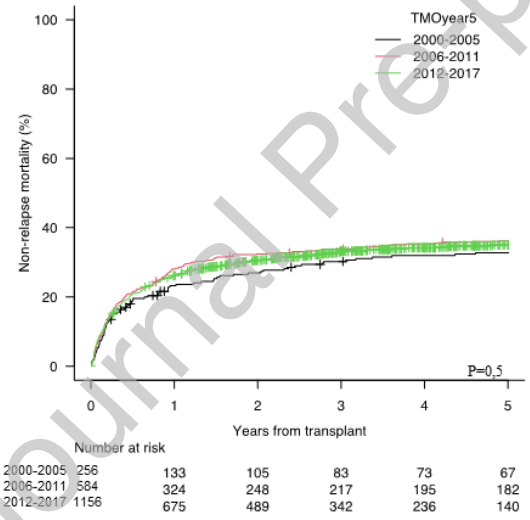


Figure 3. Non-relapse mortality (NRM) and overall survival (OS) according to HCT-CI. Cumulative incidence of NRM of score of 0, 1-2 and over 3: 21.8% vs. 28.4% vs. 31.9% (at 1 year); 25.2% vs. 33.9% vs. 36.1% (at 2 years); 30.2% vs. 38.3% vs. 40.2% (at 5 years); p<0.001 (significance in time A+B only) (**A**). Probability of OS for HCT-CI 0 vs. 1-2 vs. greater than 3 in times A + B: 65.5% vs. 54.7% vs. 46.7% (at 1 year); 53% vs. 41.7% vs. 31.1% (at 2 years); 40.7% vs. 29.8% vs. 20.4% (at 5 years) (p<0.001). Probability of OS for HCT-CI 0 vs. 1-2 vs. greater than 3 in time C: 65.1% vs. 53.8% vs. 56.4% (at 1 year); 53.5% vs. 44.9% vs. 47.3% (at 2 years); 39.5% vs. 36.3% vs. 35.7% (at 5 years) (p=0.074) (**B**).

Figure 3A.

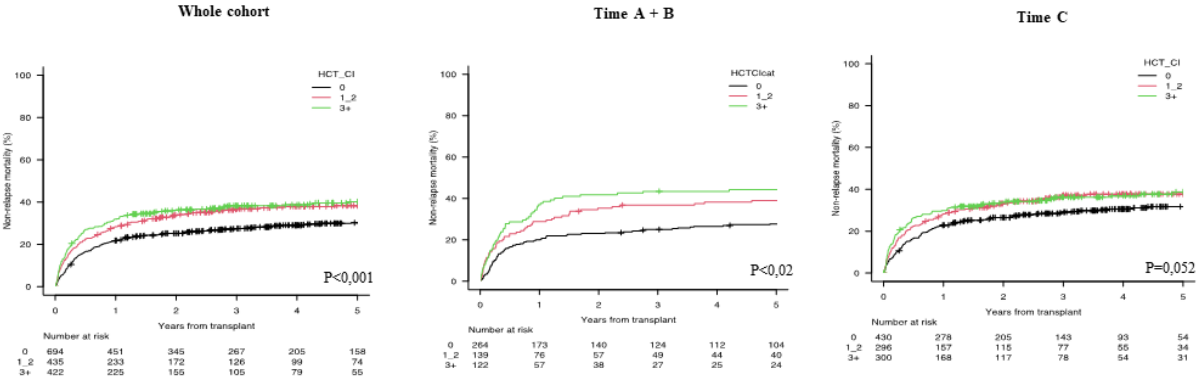


Figure 3B.

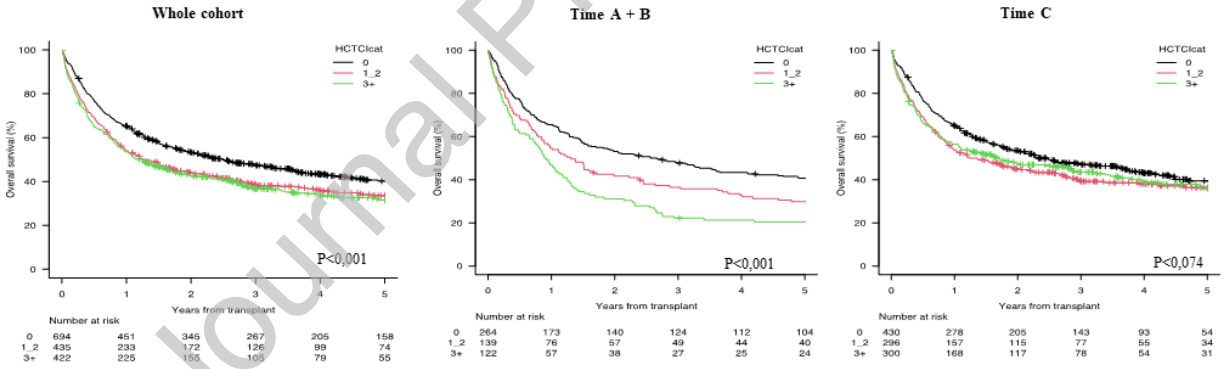


Figure 4. Overall survival (OS), cumulative incidence of relapse (CIR) and non-relapse mortality (NRM) according patients age. Probability of OS at 5 years according to patients age; time A + B: 33,7% vs. 22,7% vs. 18,8% (p=0,003); time C: 38,7% vs. 35,9% vs. 35,3% (p=0,476) (**A**). CIR at 5 years: time A + B: 39,2% vs. 49,7% vs. 49,3% (p=0,332); time C: 30,3% vs. 30,1% vs. 26,6% (p=0,826) (**B**). NRM at 5 years: time A + B: 34,6% vs. 36,7% vs. 37,5% (p=0,783); time C: 34,4% vs. 35,2% vs. 41,7% (p=0,500) (**C**).

Figure 4A.

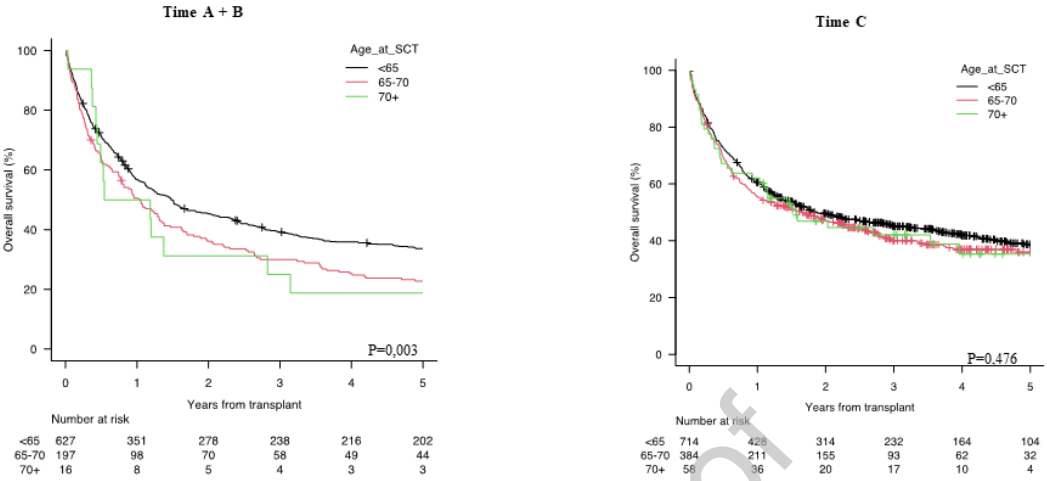


Figure 4B.

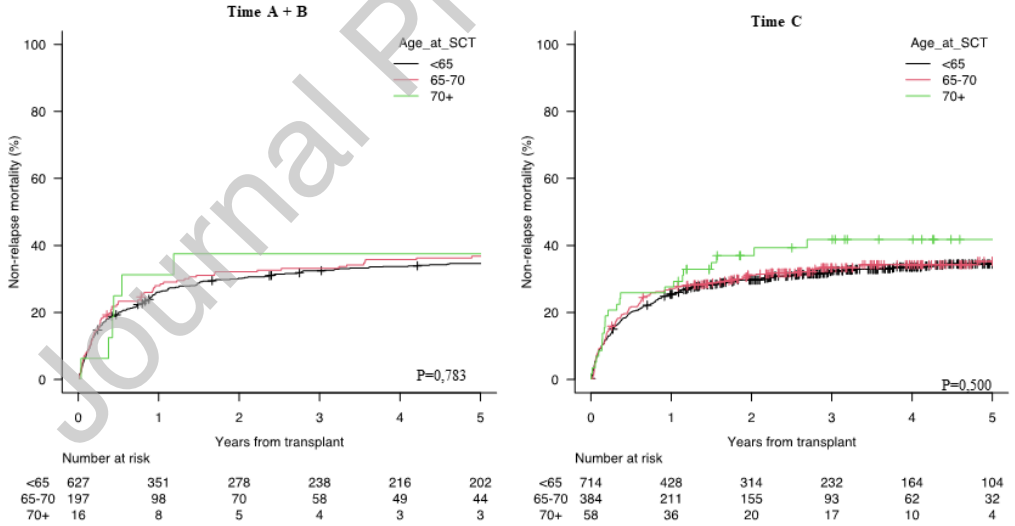


Figure 4C.

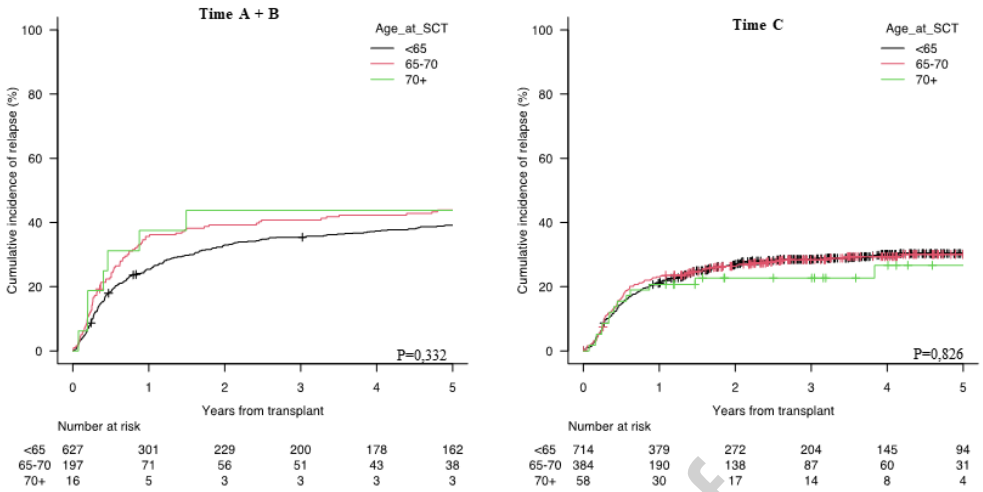
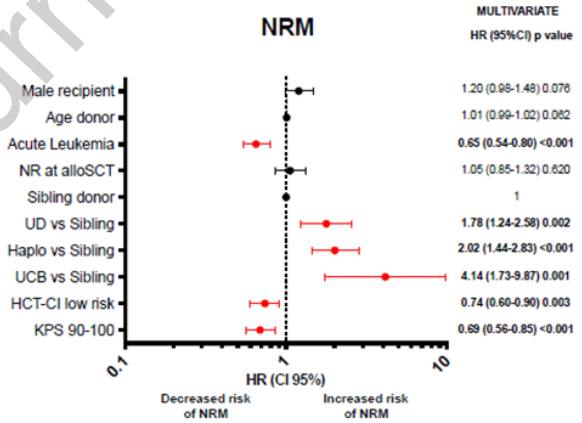


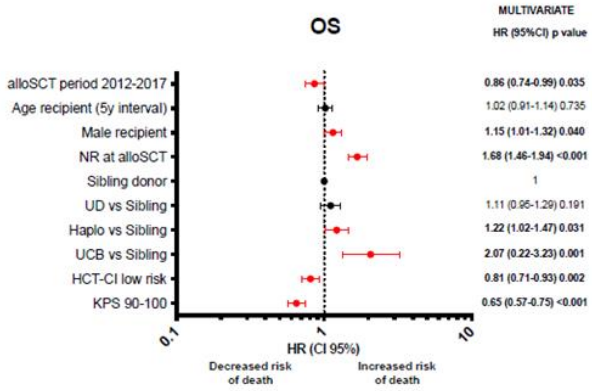
Figure 5. Multivariate analysis on NRM (A). UCB (p=0.001), Haplo (p<0.001) and MUD (p=0.004) significantly increased NRM, whereas an acute leukaemia diagnosis (p<0.001), low-risk HCT-CI (<1) (p=0.003) and KPS 90-100 (p<0.001) significantly reduced NRM. **Multivariate analysis on OS (B). A**lternative donor (p=0.001), non-response at the time of SCT (p<0.001) and male recipient (p=0.04) impaired the outcome, whereas HCT-CI <1 p=0.002), KPS 90-100 (p<0-001) and transplant between 2011-2017 (p=0.03) significantly improved OS.

Figure 5A.



List of abbreviations: allo-SCT=allogeneic stem cell transplantation; NR=non remission; UD= unrelated donor; Haplo=haploidentical; UCB=umbilical cord blood; HCT-CI= Hematopoietic Cell Transplantation Comorbidity Index; KPS=Karnofsky Performance Status

Figure 5B.



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