Myeloablative Unrelated Cord Blood Transplantation in Adolescents and Young Adults with Acute Leukemia

Hiromi Hayashi, Fernanda Volt, Jaime Sanz, Eefke Petersen, Nathalie Dhédin, Rachael Hough, Noel Milpied, Emanuele Angelucci, Ibrahim Yakoub-Agha, Mauricette Michallet, et al.

Version of Record: https://www.sciencedirect.com/science/article/pii/S1083879119305038
Manuscript_931ddae824221de420538c8150467472

Myeloablative unrelated cord blood transplantation in adolescents and young adults with acute leukemia

Hiromi Hayashi[1,2,3], Fernanda Volt[1,2], Jaime Sanz[4],Eefke Petersen [5], Nathalie Dhedin[6], Rachael Hough[7], Noel Milpied[8], Emanuele Angelucci[9], Ibrahim Yakoub-Agha[10], Mauricette Michallet[11], Gerard Michel[12], Mahmoud Aljurf[13], Chantal Kenzey[1,2], Vanderson Rocha[1,2], Jean-Hugues Dalle[14, 15], Peter Bader[15, 16], Annalisa Ruggeri[1,2,17,18] Eliane Gluckman[1,2]: on behalf of Eurocord, Cellular Therapy & Immunobiology Working Party (CTIWP) and Paediatric Diseases Working Party (PDWP) of the European Society for Blood and Marrow Transplantation EBMT

1 Eurocord, Hôpital Saint Louis, APHP, IUH, Paris, France.
2 Monacord, Centre Scientifique de Monaco, Principauté de Monaco, Monaco
3 Department of Hematology and Oncology, Graduate School of Medicine, Kyoto University, Kyoto, Japan
4 Hospital Universitario La Fe, Valencia, Spain
5 University Medical Centre, Utrecht, the Netherlands
6 Hematology for Adolescents and Young Adults Unit. Hôpital Saint-Louis, Paris, France
7 University College London, United Kingdom
8 Hospital Haut-Lévêque, Bordeaux, France
9 Hematology and Transplant Center. IRCCS Ospedale Policlinico San Martino, Genova, Italy
10 CHU de Lille, LIRIC, INSERM U995, Université de Lille, Lille, France
11 Service d'Hematologie, Centre Léon Bérard, Lyon, France
12 Hôpital de la Timone Enfant, Marseille, France
13 King Faisal Specialist Hospital & Research Centre, Riyadh, Saudi Arabia
14 Hôpital Universitaire Robert-Debré
15 Peadiatric Disease Working Party of EBMT
16 Goethe-Universität Frankfurt am Main, Frankfurt, Germany
17 Ospedale Pediatrico Bambino Gesù, Rome, Italy
18 Cellular Therapy & Immunobiology Working Party of EBMT

Running title: UCBT in adolescents and young adults with leukemia

Corresponding author :

Eliane Gluckman, MD, Eurocord, Hôpital Saint Louis, APHP, IUH, Paris, France

1 Avenue Claude Vellefaux, 75474 Paris 10, France

Tel: +33 6 09 48 97 15, Fax: +33 1 42 38 53 90

E-mail address: eliane.gluckman@aphp.fr

Text: 3 530 words

Abstract: 250 words

Figures: 1

Tables: 4

Supplemental material: 1 (figure)

References: 33

Key points:

- This study describes UCBT outcomes in AYA and improves knowledge in a group that is underrepresented in clinical research.
- UCBT outcomes in AYAs improved in more recent years becoming comparable to results observed in children.

ABSTRACT

Outcomes for adolescents and young adults (AYA) with leukemia differ from other age groups but are still underrepresented in clinical research. The aim of this study was to analyze outcomes of umbilical cord blood transplant (UCBT) in AYA with acute leukemia reported to Eurocord/EBMT. Patients (n=504) had acute lymphoblastic (59%) or myeloid leukemia (41%), were aged 15-25 years, and received UCBT after myeloablative conditioning regimens between 2004 and 2016. Primary endpoint was 3-year overall survival (OS). Median follow-up was 3.9 years. Transplant was single in 58% and double UCBT in 42%.

Three-year OS was 45% and leukemia free survival (LFS) was 41%. Cumulative incidence functions (CIF) of non-relapse mortality (NRM) and relapse were 31% and 28%, respectively. CIF of acute GVHD grade II-IV at day-100 was 28%. Three-year CIF of chronic GVHD was 25%.

In adjusted analysis, better disease status at UCBT (HR 2.74, p <0.001) and more recent UCBT (HR 1.43, p=0.01) were associated with increased OS and a similar effect of these factors was observed on LFS. Contrastingly, the use of ATG had a negative effect in LFS.

The risk of acute GVHD grade II-IV increased with the use of double UCBT (HR 1.65, p =0.02) and decreased with more recent transplantation period (HR 0.65, p=0.02) and ATG use (HR 0.55, p =0.01).

Outcomes of AYA UCBT improved in more recent years becoming comparable to pediatric results.

Demonstrating the feasibility of UCBT in AYA facilitates stem cell source selection and provides the basis for future prospective studies.

INTRODUCTION

Adolescents and young adults (AYAs) form a unique group of patients with biological, clinical, social and psychological features that differ from other age groups. These differences may have an important effect on treatment outcomes; therefore, research focused on this specific population is warranted. However, the participation rate of AYA patients in clinical trials is lower than the rates of children and older adults [1-3].

Another difficulty surrounding research on AYA population is the lack of an exact definition for the age range considered for this group [4,5]. Depending on the aim of the study or reporting organizations, the defined age range varies considerably, making the interpretation of the limited available data a difficult task[4].

EUROCARE-5 reported poorer survival in AYA compared to children for several prevalent cancers including acute leukemia [6]. For patients with acute lymphoblastic leukemia (ALL), there is clear evidence that clinical outcomes after chemotherapy are markedly better in children than older patients, including AYAs[7]. The difference may be related to tumor biology [6], but it may also reflect increased toxicity, the lack of specific research on AYA and poor adherence to clinical protocols [1,7].

Acute leukemia represents about 6% of the neoplastic disease in AYAs with similar incidence of acute myeloid leukemia (AML) and ALL[8]. Hematopoietic stem cell transplantation (HSCT) is a potentially curative treatment for acute leukemia and other hematological diseases. However, HSCT involves intensive treatment protocols with a non-negligible risk of possible life-threatening complications and life-long side effects [7,9]. Most studies on AYA with hematological malignancies are focused on new medications or chemotherapy protocols, but not on HSCT results [7,10-12]. In fact, AYAs are often included as a subset of pediatric or adult patients on HSCT research, but they are usually not considered as a main group of interest [7,13-15].

Umbilical cord blood (UCB) is one alternative donor source for HSCT for AYA patients whose leukemia often presents high risk biological features and who could benefit of an immediate

transplant. UCB is readily available for use in contrast to other unrelated grafts in which search and recruitment of adult donors with an acceptable HLA compatibility with recipient may delay transplantation [16]. Other alternative graft sources, such as haplo-identical donors, must also be considered; however for patients with comorbidities such as cardiomyopathy or renal failure, haploidentical protocols with post-HSCT cyclophosphamide that require intense hydration, might be problematic [9,17], making UCB, a desirable choice in these situations.

There is a lack of research studies on AYA, especially on umbilical cord blood transplantation (UCBT). The aim of the current study is to fill this gap by providing comprehensive information on unrelated UCBT outcomes after myeloablative conditioning regimens in a homogeneous cohort of AYA patients, aged 15 to 25, with acute leukemia (AL).

METHODS

Data collection

This is a registry based retrospective study using Eurocord, the Paediatric Disease Working Party (PDWP) and the Cellular Therapy & Immunobiology Working Party (CTIWP) of the European Society for Blood and Marrow Transplantation (EBMT). All patients or legal guardians provided informed consent for research. This study was conducted according to the Declaration of Helsinki and approved by the PDWP and CTIWP of EBMT and the institutional review board of Eurocord.

Inclusion and exclusion criteria

Inclusion criteria for the study were: age between 15 to 25 years; diagnosis of acute lymphoblastic leukemia (ALL) or acute myeloid leukemia (AML); single or double UCBT as first allogeneic transplantations between 2004 and 2016 in an EBMT center; and myeloablative conditioning (MAC) regimen.

Patients who received a related umbilical cord blood (UCB), a manipulated graft, or an UCB co-infused with other stem cell source were excluded.

Definitions

Overall survival (OS) was defined as time from transplant to last follow-up or death. Leukemia free survival (LFS) was defined as time from transplant to relapse, death or date of last follow-up. Refined graft-versus-host disease (GVHD) free-/relapse free- survival (rGRFS) was defined as being alive with neither grade III-IV acute GVHD nor extensive chronic GVHD, relapse or death [18]. Non relapse mortality (NRM) was defined as the time to death without relapse. Relapse was defined as morphologic or clinical evidence of disease after a period of complete remission. Neutrophil engraftment was defined as the first day of 3 consecutive days with a neutrophil count ≥ 0.5×10^9/L without autologous reconstitution or graft rejection within the first 100 days of UCBT. Acute and chronic GVHD were diagnosed and defined according to standard criteria [19,20]. Myeloablative conditioning (MAC) was defined as regimens containing total body irradiation (TBI) ≥ 6Gy fractionated or ≥ 8Gy in total dose, thiotepa ≥ 10mg/Kg, intravenous busulfan (BU)> 6.4mg/Kg or equivalent dose in oral BU (>8.0mg/Kg), melphalan >140mg/m2. HLA compatibility between donor and recipient was defined considering low resolution for HLA-A and HLA-B and high resolution typing for HLA-DRB1. Donor-recipient HLA match assignment for dUCBT was based on the unit with the higher number of mismatches with the recipient. TNC doses reported for double UCBT grafts represent the combined information of the two UCB units.

Endpoints

Primary endpoint of the study was OS at 3 years. Secondary endpoints were probability of LFS, rGRFS, and cumulative incidence of relapse, NRM, neutrophil engraftment, and acute and chronic GVHD.

Statistical methods

Kaplan-Meier estimator was used to calculate the probabilities of OS, LFS, and rGRFS. Cumulative incidence functions (CIF) were used to calculate the cumulative incidences (CI) of relapse, NRM, neutrophil/platelet engraftment, and acute/chronic GVHD. Competitive events were considered as following: for engraftment, death without engraftment; for relapse, death without disease recurrence or progression; for NRM, relapse after UCBT; for GvHD, relapse or death without GvHD (acute or chronic as applicable). All tests performed were two-sided. Type I error was fixed at a p-value of 0.05. Covariates reaching a significance level of 0.1 in the univariate analyses (UVA) were included in the multivariate (MVA) models. Age at UCBT was modeled as a continuous variable. Variables frequently associated with transplant outcomes were also included in the final models regardless of the statistical significance in UVAs. Cox and Fine-Gray proportional hazards models were used for the MVA [21].

Statistical analyses were performed with IBM® SPSS® statistics for Windows, version 25(IBM Corp., Armonk, N.Y., USA) and R for Windows 3.5.1 (R development Core Team, Vienna, Austria).

RESULTS

Patient and transplant characteristics

A total of 504 patients from the Eurocord/EBMT database met the criteria for the study. Patient and transplant characteristics are shown in table 1 and 2, respectively. Median age at diagnosis was 17.5 [(range: 4.5-25.4, 1st -3rd interquartile range (IQR):15.2-20.7] years. Median age at UCBT was 19.4 (range: 15-25.9, IQR: 16.7-22.2) years. Male patients comprised 63.9% of the patients. Median time from diagnosis to transplant was 11 months (range: 1 month-16.7 years, IQR: 5-29 months). More than half of the patients received UCBT within a year from the diagnosis of acute leukemia (52.0%). ALL (n=297, 58.9%) was more frequently observed than AML (n=207, 41.1%). Twenty patients were reported as having a secondary

acute leukemia (4.0%), mostly due to other type of hematological malignancy and/or history of chemotherapy and/or radiotherapy.

Positive CMV serology was observed in 57.1% of patients (n=270). Median total nucleated cell (TNC) dose was 3.6 $\times 10^7$ for single (range: 0.9-9.0, IQR: 3.0-4.4) and 5.3 $\times 10^7$ for double UCBT (range: 2.3-10.6, IQR: 4.4-6.2). A conditioning regimen containing TBI was used in 57.9% (n=288) patients. The most frequently used conditioning regimens were cyclophosphamide + fludarabine + TBI (n=139, 27.6%) and thiotepa + busulfan + fludarabine (n=110, 21.8%). For GVHD prophylaxis, cyclosporine A (CsA) + mycophenolate mofetil (MMF) was used for 46.8 % of patients (n=223).

Neutrophil and platelet engraftment

The CIF of neutrophil engraftment at day 60 was 87.7% [95% confidence interval (CI): 95%CI 84.5-90.3%] with a median time to engraftment of 24 days. In UVA, patient negative CMV serology, non-TBI regimen, better disease status, and recent transplantation were associated with improved neutrophil engraftment. In the adjusted analysis (MVA), better disease status [advanced diseases vs. 1st complete remission (CR1): hazard ratio (HR) 1.67, 95%CI 1.25-2.27, p<0.001] and recent year of UCBT (HR 1.41, 95%CI 1.15-1.72, p<0.001) were confirmed to be independently associated with a higher neutrophil engraftment, while the association with the use of non-TBI regimen was no longer observed. The CIF of platelet engraftment at day 100 was 59.6% (95%CI 0.55-0.64). Platelet engraftment occurred in a median time of 61 days. Recent year of UCBT and better disease status were similarly identified as significant factors associated with platelet engraftment in MVA. AML diagnosis compared to ALL showed significant impact on platelet engraftment in UVA (ALL 55.6% [95%CI 49.7-61.0] vs. 65.5 [58.5-71.6], *p*=0.04), however it was not significant after adjustment (Table 4).

Survival

The UVA of OS, LFS, and rGRFS are provided in Table 3. Three-year OS was 44.9% (±2.4) and median follow-up for survivor was 3.9 years. In UVA, better disease status at UCBT and recent year of transplantation were associated with a higher OS. Negative CMV serology and the absence of ATG in the protocols were also significantly associated with higher probability of OS, whereas the type of acute leukemia (ALL vs. AML) and graft (single vs. double UCBT) had no significant impact. In MVA, recent year of transplantation and better disease status remained significantly associated with a favorable OS, and the use of ATG showed a borderline negative effect on OS (HR1.36 [95% CI 1.00-1.85], *p*=0.05) (Table 4).

Three-year LFS was 40.9±2.3% and LFS according to disease status is shown in Figure 1. The MVA showed that advanced disease status compared to CR1 (HR 2.51, p<0.001) and the use of ATG HR 1.43, p=0.02) had a detrimental effect on LFS, while being transplanted in more recent years (HR 0.74, p=0.02) had a favorable effect.

Three-year rGRFS was 31.5±2%. In UVA, rGRFS was lower in males, in those with ALL (29.0% in ALL vs. 35.1% in AML, p=0.045), and in patients with positive CMV serology (28.0% vs. 37.7%, p<0.01). In MVA for rGRFS, negative CMV serology and better disease status (CR1 vs. advanced disease) were observed to have a significant favorable impact on rGRFS, whereas the impact of gender was no longer significant in the adjusted model. There was a tendency for higher rGRFS in patients undergoing transplant in more recent years, but the results were not statistically significant (Table 4).

During the follow-up period, 265 patients died. The reported causes of death were relapse (n=109, 41.0%), infection (n=75, 28.2%), GVHD (n=34, 12.8%), other transplanted related causes (n=44, 16.6%) or unknown (n=2, 0.8%).

Acute and chronic GVHD

One hundred fifty-five patients developed grade II-IV aGVHD (73/155 had grade III-IV) during the observation period. The CIF of aGVHD at day 100 was 27.8% (95%CI: 23.8-31.9%). Use of double UCBT, non-ATG protocols, and TBI including regimens were associated with a higher

incidence of grade II-IV aGVHD in UVA (Table 3). In MVA, recent year of transplantation, use of ATG, and use of single UCB decreased the risk of grade II-IV aGVHD (Table 4).

One hundred twenty four patients developed chronic GVHD during the follow up period, with the extensive form being reported in 52 of them. The 3-year CIF of cGVHD was 25.3% (95%CI: 21.4-29.3). Onset of cGVHD occurred, mostly, within 1 year of UCBT (1-year incidence of cGVHD was 22.0%). Higher risk of cGVHD was observed in patients with advanced disease (Table 4).

Non relapse mortality and relapse incidence

The 3-year non-relapse mortality (NRM) was 31.1% and the results of the UVA are provided in Table 3. In the MVA, recent transplant, better disease status remained strong factors for lower NRM, whereas CMV serology had a borderline effect on it (Table 4). CIF of relapse at 3 years was 27.9% (95%CI 23.9-32.1). Disease status was the only factor identified as having a significant impact in relapse in the adjusted analysis.

DISCUSSION

The unique characteristics of AYA patients and the lack of specific studies on this group limit knowledge on treatment outcomes and, consequently, hinder improvement in survival for this population. Our study reporting outcomes of AYA patients undergoing myeloablative UCBT for acute leukemia provides important novel data and, to our knowledge represents the largest series in this setting.

AYAs have specific needs and complications and should be studied separately from children and older adults. Some patients are treated in pediatric units with high intensity protocols while others are treated in adult transplant units [3,14,22]. The transition from pediatric to adult transplant units involves changes in chemotherapy, conditioning, supportive care and psycho-social support [3].

The classification of AYA is very controversial [3-5]. In the available definitions, the lower age limit varies from 10 to 21 years old, while the upper limit can fluctuate from 25 to 39, and even beyond in some rarer occasions [3,5]. This absence of consensus of the age definition of AYA makes the available results difficult to compare and interpret.

In the present study, AYA was defined as patients aged between 15 and 25 years because there is some consensus that this narrower group is truly representative of this developmental stage of life [5]. Moreover, according to a population-based study in the USA, after the age of 25, patients are seldom treated by pediatricians, consequently, only a fraction of AYA with ALL receive a pediatric protocol[22] despite evidence of improved results with intensified chemotherapies of pediatric or pediatric-inspired regimens[10]. Keeping the upper age limit in our studies at 25 years potentially increases the proportion of patients treated with intensified protocols and makes the cohort more homogeneous for studying.

In our analyses, disease status and UCBT period were constantly observed to have an effect in outcomes, especially in OS and LFS as observed in previous studies [13,14]. In the adjusted analysis the risk of death of patients with advanced disease was almost three folds the risk in of patients in CR1, and an improvement of over 40% in OS was observed for UCBT performed in more recent years. On the other hand, relapse incidence barely changed across transplant periods, and this was also reflected in a stable rGRFS.

In a review by Metha et al [23] the authors compared OS of AYA with other age groups receiving either a matched sibling or an unrelated transplant for acute leukemia. They showed that overall results for patients with ALL and AML improved over time, however survival for AYA patients was inferior to children and superior to older adults [23]. In an exploratory analysis (results not shown) using the same selection criteria of the current study, but considering a different population of patients (in addition to the study population) from other age groups, Eurocord database shows a 3-year OS in children (0-14 years) of 52.1% and 30.2% in adults (26-55 years). In the same database, restricting the results to UCBT performed on year 2010 or later, the 3-year OS was 53.8% and 39.6% in children and adults, respectively (unpublished data from EUROCORD database). Interestingly, the results of the current study for AYA

patients shows a 3- year OS of 36.8% for UCBT performed before 2010 and 53.8% for transplants performed thereafter, suggesting that in more recent years outcomes in AYA have improved to comparable levels of results observed for pediatric patients (supplemental figures 1.1 and 1.2). The relatively stable incidence of relapse over the years may indicate that some of the improvement in outcomes observed in our study is the result of a reduction in NRM related to better UCB unit selection algorithms, lower toxicity of conditioning regimens, improved patient management and supportive care, and possibly a less frequent use of ATG in the recent era. Nevertheless, these recent changes were likely to have benefited patients for all generations confounded and a reduction of NRM alone may not explain the drastic advances observed in AYAs. In part, the improvement in outcomes demonstrated in this group is probably a reflection of the modification of pre-transplant chemotherapy towards more frequent use of high intensity pediatric protocols [7,12]. A meta-analysis evaluating the association of minimal residual disease (MRD) with clinical outcome in children and adults with ALL showed that achieving MRD negativity is important regardless of the age group[24]. The intensification of treatment protocols for AYAs in more recent years might have contributed for achievement of a deeper CR, with no MRD, in a larger number of patients, improving UCBT outcomes over the years as demonstrated in our AYA cohort. However, testing this hypothesis or performing a formal comparative analysis was out of the scope of this study. Moreover, to perform a comparative study, it is essential to have comprehensive data on pre-transplant chemotherapy, biological characteristics at diagnosis (cytogenetics, molecular, etc.) and minimal residual disease status at transplantation data[7,12,15,25], which is usually lacking from retrospective data registries. Nevertheless, the results presented in this report will help establishing recommendations for transplant for this particular population and serve as the basis for designing prospective protocols.

GVHD is a main concern for patients undergoing HSCT as it is associated with higher incidence of NRM and may have an impact in the quality of life [19,26,27]~~, which is particularly worrisome for AYA patients with educational and/or professional responsibilities~~. The specific incidence of GVHD in AYAs has been seldom addressed. One European analysis of patients (aged 5 to 35 years) with acute leukemia, undergoing HSCT with bone marrow or peripheral blood stem

cell grafts, showed a significantly higher risk of II-IV aGVHD for the patients aged between 15 and 24 years [26] in the comparison to other age groups.. In our study, the incidence of acute GVHD grade II-IV was 27.8 % and the incidence of chronic GVHD was 25.3%. Noteworthy, our study includes only UCB, which has been generally associated with a lower incidence of GVHD compared to other unrelated donor graft sources [16]. A prospective study in children and AYAs receiving UCBT reported higher incidence of grade II-IV aGVHD (41% in sUCBT and 45% in dUCBT, respectively) than our study [28]. The contrasting results observed might be related to differences in the age range of the cohort (0-34 years) and distribution of patients receiving ATG in each study (40% in the previous study compared to 60% in our cohort) Our adjusted results (MVA) showed that the use of single UCBT and ATG significantly reduced grade II-IV aGVHD. Neither of these factors had an impact on the incidence of cGVHD.

It is important to emphasize the potential benefits of the low rates of cGVHD, which is an inherent characteristic of UCB. CGVH is not only a major cause of NRM, but it also has been shown to have an important detrimental impact in patients' quality of life, psychological and functional status[29,30] which is particularly worrisome for AYAs. These patients are often not emotionally or socially established as adult patients, and have to manage their educational and/or professional responsibilities along with the burden of their disease and comorbidities[2,4].

Relapse rate was 27.9 % and the only factor having a significant effect in the relapse incidence was disease status at UCBT. Patients in CR1 and CR2 had a risk of relapse of 27.6% and 24.5%, respectively, while patients with advanced disease had a risk of relapse of 36.8%. There was no difference in relapse according to the type of leukemia (AML or ALL), the use of single or double UCBT nor the use of ATG. A previous study showed that the use of ATG decreased OS and increase NRM for UCBT compared to other stem cell sources in patients in CR1/CR2 [25]. Our adjusted findings revealed a 30% lower LFS with the use of ATG. In a subgroup analysis of a prospective study of children and young adults undergoing either single or double UCBT, the authors report a significant lower relapse risk for patients who received double UCBT with TBI based conditioning and no ATG [28]. In our cohort, patients who received ATG had a 21% increase in the risk of relapse, but the result was not statistically significant (HR 1.21, 95%CI

0.71- 2.08); p=0.49). Despite the positive effect of ATG in preventing GVHD, ATG had a detrimental effect on survival. Therefore, our results together with the plethora of previous reports indicating that ATG use in CBT has deleterious effect on TRM, survival, immune reconstitution, and infectious mortality[31,32], we suggest that ATG should be omitted in UCBT for AYA patients. However, alternative non-lymphodepleting strategies to abrogate severe aGVHD should be investigated."

A limitation of the current study was the unavailability of data on long-term complications which prevented us from studying the incidence of secondary neoplastic diseases, endocrine abnormalities and infertility among other complications. Reproductive concerns in AYA patients after cancer treatments have been shown to have a negative psychological and social repercussion in this group of patients [2,33]. However, because treatment timing is usually prioritized to future complications, preservation of infertility are sometimes not thoroughly discussed despite having major consequences in the life of AYA HSCT survivors.

Further studies focused on AYA are required, including prospective research considering pre-HSCT information and comparison with other stem cell sources. To facilitate research in AYAs, group effort among pediatrician and adult hematologists, as well as other health care providers is needed.

In conclusion, this study showing large comprehensive MAC-UCBT outcomes in AYAs contributes to a better understanding of HSCT for an age group that is not thoroughly described in most publications. Demonstrating the feasibility of UCBT in AYA patients is important to facilitate the decision of stem cell source selection.

Acknowledgments

We thank all the participating centers: Spain - Valencia - Hospital Universitario La Fe; The Netherlands - Utrecht - University Medical Centre; France - Paris -Hôpital Saint-Louis; United Kingdom - London - Royal Free and University College Medical School; France - Bordeaux -

Haut-Lévêque; Italy - Genova Ospedale San Martino Department of Haematology II; France - Lille - Claude Huriez; France - Lyon - Edouard Herriot (adults team) ; France - Marseille - La Timone (pediatric team); Spain - Barcelona - Hospital Santa Creu i Sant Pau; Saudi Arabia - Riyadh - King Faisal Specialist Hospital & Research Centre; Greece - Athens - Evangelismos Hospital; France - Besançon – Hospital Saint Jacques; Italy - Firenze - Azienda Ospedaliero Universitaria Meyer - Ospedale di Careggi ; Canada - Montréal - Ste-Justine Hospital ; France - Nice – Archet; Spain -Barcelona-Hospital Vall d`Hebron Unidad de Adultos; France - Montpellier - Lapeyronie- adult; Italy - Bergamo - Ospedali Riuniti di Bergamo; France - Rennes – Pontchaillou and 115 other centers

Authorship Contributions

A.R., E.G, and H.H. designed the study, H.H. and C.K. prepared the data, H.H. and F.V. analyzed the data, and H.H., F.V., and E.G. wrote the paper, J.S., E.P., N.D., R.H., N.M., E.A., I.Y.A., M.M., G.M., M.A., J.H.D., and P.D. provided cases for the study. All authors edited and approved the manuscript.

Conflict of Interest Disclosures

None

REFERENCES

1. Butow P, Palmer S, Pai A, Goodenough B, Luckett T, King M. Review of Adherence-Related Issues in Adolescents and Young Adults With Cancer. *Journal of Clinical Oncology*. 2010;28(32):4800-4809.
2. Husson O, Huijgens PC, van der Graaf WTA. Psychosocial challenges and health-related quality of life of adolescents and young adults with hematologic malignancies. *Blood*. 2018;132(4):385-392.
3. Cortes J. Introduction to a review series on adolescent and young adult malignant hematology. *Blood*. 2018;132(4):345-346.
4. Bleyer WA. Cancer in older adolescents and young adults: Epidemiology, diagnosis, treatment, survival, and importance of clinical trials. *Medical and Pediatric Oncology*. 2002;38(1):1-10.
5. Pollock BH, Birch JM. Registration and classification of adolescent and young adult cancer cases. *Pediatric Blood & Cancer*. 2008;50(S5):1090-1093.
6. Ferrari A, Barr RD. International evolution in AYA oncology: Current status and future expectations. *Pediatric Blood & Cancer*. 2017;64(9):e26528.
7. Boissel N, Baruchel A. Acute lymphoblastic leukemia in adolescent and young adults: treat as adults or as children? *Blood*. 2018;132(4):351-361.
8. Mattano L NJ, Ross J, et al. . Chapter 4— Leukemias. In: Bleyer A, O'Leary M, Barr R, et al. (Eds). Cancer epidemiology in older adolescents and young adults 15 to 29 years of age, including SEER incidence and survival: 1975-2000. 2006.
9. Felicetti F, Fortunati N, Brignardello E. Cancer survivors: An expanding population with an increased cardiometabolic risk. *Diabetes Research and Clinical Practice*. 2018;143:432-442.
10. Stock W, Luger SM, Advani AS, et al. A pediatric regimen for older adolescents and young adults with acute lymphoblastic leukemia: results of CALGB 10403. *Blood*. 2019:blood-2018-2010-881961.
11. Siegel SE, Stock W, Johnson RH, et al. Pediatric-Inspired Treatment Regimens for Adolescents and Young Adults With Philadelphia Chromosome-Negative Acute Lymphoblastic Leukemia: A Review. *JAMA Oncol*. 2018;4(5):725-734.
12. O'Dwyer K, Freyer DR, Horan JT. Treatment strategies for adolescent and young adult patients with acute myeloid leukemia. *Blood*. 2018;132(4):362-368.
13. Majhail NS, Brazauskas R, Hassebroek A, et al. Outcomes of allogeneic hematopoietic cell transplantation for adolescent and young adults compared with children and older adults with acute myeloid leukemia. *Biol Blood Marrow Transplant*. 2012;18(6):861-873.
14. Wood WA, Lee SJ, Brazauskas R, et al. Survival Improvements in Adolescents and Young Adults after Myeloablative Allogeneic Transplantation for Acute Lymphoblastic Leukemia. *Biology of Blood and Marrow Transplantation*. 2014;20(6):829-836.
15. Tomizawa D, Yoshida M, Kondo T, et al. Allogeneic hematopoietic stem cell transplantation for children and adolescents with high-risk cytogenetic AML: distinctly poor outcomes of FUS-ERG-positive cases. *Bone Marrow Transplantation*. 2019;54(3):393-401.
16. Ballen KK, Gluckman E, Broxmeyer HE. Umbilical cord blood transplantation: the first 25 years and beyond. *Blood*. 2013;122(4):491-498.
17. Emadi A, Jones RJ, Brodsky RA. Cyclophosphamide and cancer: golden anniversary. *Nature Reviews Clinical Oncology*. 2009;6:638.

18. Ruggeri A, Labopin M, Ciceri F, Mohty M, Nagler A. Definition of GvHD-free, relapse-free survival for registry-based studies: an ALWP–EBMT analysis on patients with AML in remission. *Bone Marrow Transplantation*. 2015;51:610.
19. Glucksberg H, Storb R, Fefer A, et al. Clinical manifestations of graft-versus-host disease in human recipients of marrow from HL-A-matched sibling donors. *Transplantation*. 1974;18(4):295-304.
20. Shulman HM, Sullivan KM, Weiden PL, et al. Chronic graft-versus-host syndrome in man. A long-term clinicopathologic study of 20 Seattle patients. *Am J Med*. 1980;69(2):204-217.
21. Fine JP, Gray RJ. A Proportional Hazards Model for the Subdistribution of a Competing Risk. *Journal of the American Statistical Association*. 1999;94(446):496-509.
22. Muffly L, Lichtensztajn D, Shiraz P, et al. Adoption of pediatric-inspired acute lymphoblastic leukemia regimens by adult oncologists treating adolescents and young adults: A population-based study. *Cancer*. 2017;123(1):122-130.
23. Mehta PA, Rotz SJ, Majhail NS. Unique Challenges of Hematopoietic Cell Transplantation in Adolescent and Young Adults with Hematologic Malignancies. *Biology of Blood and Marrow Transplantation*. 2018;24(12):e11-e19.
24. Berry DA, Zhou S, Higley H, et al. Association of Minimal Residual Disease With Clinical Outcome in Pediatric and Adult Acute Lymphoblastic Leukemia: A Meta-analysis. *JAMA Oncol*. 2017;3(7):e170580.
25. Kuwatsuka Y, Tomizawa D, Kihara R, et al. Prognostic value of genetic mutations in adolescent and young adults with acute myeloid leukemia. *International Journal of Hematology*. 2018;107(2):201-210.
26. Vignon M, Andreoli A, Dhedin N, et al. Graft-Versus-Host Disease in Adolescents and Young Adults (15-24 Years Old) After Allogeneic Hematopoietic Stem Cell Transplantation for Acute Leukemia in First Complete Remission. *J Adolesc Young Adult Oncol*. 2017;6(2):299-306.
27. Flowers MED, Inamoto Y, Carpenter PA, et al. Comparative analysis of risk factors for acute graft-versus-host disease and for chronic graft-versus-host disease according to National Institutes of Health consensus criteria. *Blood*. 2011;117(11):3214-3219.
28. Michel G, Galambrun C, Sirvent A, et al. Single- vs double-unit cord blood transplantation for children and young adults with acute leukemia or myelodysplastic syndrome. *Blood*. 2016;127(26):3450-3457.
29. Pidala J, Kurland B, Chai X, et al. Patient-reported quality of life is associated with severity of chronic graft-versus-host disease as measured by NIH criteria: report on baseline data from the Chronic GVHD Consortium. *Blood*. 2011;117(17):4651-4657.
30. Lee SJ, Flowers ME. Recognizing and managing chronic graft-versus-host disease. *Hematology Am Soc Hematol Educ Program*. 2008:134-141.
31. Pascal L, Tucunduva L, Ruggeri A, et al. Impact of ATG-containing reduced-intensity conditioning after single- or double-unit allogeneic cord blood transplantation. *Blood*. 2015;126(8):1027-1032.
32. Wakamatsu M, Terakura S, Ohashi K, et al. Impacts of thymoglobulin in patients with acute leukemia in remission undergoing allogeneic HSCT from different donors. *Blood Adv*. 2019;3(2):105-115.
33. Benedict C, Shuk E, Ford JS. Fertility Issues in Adolescent and Young Adult Cancer Survivors. *Journal of adolescent and young adult oncology*. 2016;5(1):48-57.

Table 1. Patient characteristics

Characteristics	Total (n=504)		ALL (n=297)		AML (n=207)	
	Median	**IQR**	**Median**	**IQR**	**Median**	**IQR**
Age at diagnosis	17.5	[15.2-20.7]	17.2	(14.9-20.0)	18.0	(15.8-21.5)
Age at UCBT	19.4	[16.7-22.2]	19.4	[16.8-21.9]	19.3	[16.6-23.0]
Time from diagnosis to UCBT in month	11.0	[5.0-29.0]	16.0	[6.0-39.0]	7.0	[4.0-19.0]
Weight at UCBT (Kg)	63.0	[55.0-73.0]	64.0	[55.0-73.5]	61.0	[55.0-72.5]
Gender	**N**	**%**	**N**	**%**	**N**	**%**
Male	322	(63.9)	203	(68.4)	119	(57.5)
Female	182	(36.1)	94	(31.6)	88	(42.5)
CMV serology						
Positive	270	(57.1)	162	(57.7)	108	(56.2)
Negative	203	(42.9)	119	(42.3)	84	(43.8)
Missing	31		16		15	
Disease status						
CR 1	207	(42.6)	113	(39.0)	94	(48.0)
CR 2	183	(37.7)	118	(40.7)	65	(33.2)
Advanced	96	(19.8)	59	(20.3)	37	(18.9)
Missing	18		7		11	
Year of UCBT						
2004-2009	246	(48.8)	147	(49.5)	99	(47.8)
2010-2016	258	(51.2)	150	(50.5)	108	(52.2)
Graft type						
Single UCBT	293	(58.1)	177	(59.6)	116	(56.0)
Double UCBT	211	(41.9)	120	(40.4)	91	(44.0)

Abbreviations: ALL, acute lymphocytic leukemia; AML, acute myeloid leukemia; IQR, 1^{st}-3^{rd} interquartiles; UCBT, umbilical cord blood transplant; Kg, kilogram; CMV, cytomegalovirus; CR, complete remission.

Table 2. Transplant characteristics

	Single UCBT (range) [IQR*]		Double UCBT (n=211) (range) [IQR]	
TNC dose	**3.6 × 10^7/Kg (0.9-9.0) [3.0-4.4]**		**5.3× 10^7/Kg (2.3-10.6) [4.4-6.2]**	
MAC regimens	**Single**		**Double**	
Non-TBI	167	(57.6)	42	(20.3)
TBI regimen	123	(42.4)	165	(79.7)
Missing	3		4	

Gender compatibility	**Total (n=504)**		**Single UCBT**		**Double UCBT**	
Male to Female	195	(40.3)	188	(66.0)	101	(50.8)
Other	289	(59.7)	97	(34.0)	98	(49.2)
Missing	20		8		12	
Number of HLA mismatches						
0-1 HLA mismatch	161	(38.1)	89	(35.9)	72	(41.1)
2 or >2 mismatches*	262	(61.9)	159	(64.1)	103	(58.9)
Missing	81		45		36	
GVHD prophylaxis						
CsA+MMF	223	(46.8)	102	(37.6)	121	(59.6)
CsA+Pred	122	(25.6)	98	(36.2)	24	(11.8)
CsA	46	(9.7)	22	(8.1)	24	(11.8)
Other(s)	85	(17.9)	49	(18.1)	36	(17.7)
Missing	28		22		6	
Use of ATG						
Yes	270	(57.9)	206	(75.7)	64	(33.0)
No	196	(42.1)	66	(24.3)	130	(67.0)
Missing	38		25		17	

Abbreviations: UCBT, umbilical cord blood transplant; IQR, 1^{st}-3^{rd} interquartiles; TNC, total nucleated cells; TBI, total body irradiation; HLA, human leukocyte antigen; GVHD, graft-versus-host-disease; CsA, cyclosporin; MMF, mycophenolate mofetil; Pred, corticosteroids; ATG, antithymocyte globulin.

*Only 25 patients with more than 2 HLA mismatches.

Table 3. Univariate analysis of UCBT

	OS	*p*-value	LFS	*p*-value	rGRFS	*p*-value
Patient gender						
Male	42.8 (±3.0)%	0.22	38.3(±2.9)%	0.13	28.0(±2.7)%	0.006
Female	48.5 (±3.9)%		45.2(±3.9)%		37.7(±3.8)%	
Body weight at UCBT*						
< 63.0 Kg	48.5(±3.5)%	0.51	45.0(±3.5)%	0.19	35.8(±3.4)%	0.25
>= 63.0 Kg	41.2(±3.5)%		38.4(±3.4)%		29.9(±3.2)%	
CMV serology						
Negative	51.9(±3.7%)	0.005	47.8(±3.7)%	0.005	37.9(±3.6)%	0.002
Positive	40.0(±3.3%)		35.6(±3.2)%		25.9(±2.9)%	
Type of acute leukemia						
ALL	44.8 (±3.1)%	0.69	38.5 (±3.0)%	0.15	29.0(±2.8)%	0.045
AML	45.2 (±3.7)%		44.4 (±3.7)%		35.1(±3.5)%	
Disease status						
CR 1	54.0(±3.7)%	< 0.001	48.5(±3.7)%	< 0.001	36.8(±3.6)%	< 0.001
CR 2	48.1(±4.0)%		48.1(±3.9)%		33.6(±3.7)%	
Advanced disease	20.4(±4.3)%		19.8(±4.3)%		16.3(±3.9)%	
Year of UCBT						
2004-2009	36.8(±3.2)%	0.001	33.4(±3.1)%	0.001	27.2(±2.9)%	0.03
2010-2016	53.8(±3.5)%		48.4(±3.5)%		35.4(±3.3)%	
Graft type						
Single UCBT	41.4(±3.2)%	0.21	37.1(±3.1)%	0.18	28.8(±2.9)%	0.63
Double UCBT	49.5(±3.6)%		46.2(±3.6)%		35.1(±3.4)%	
Number of HLA mismatches						
0-1 HLA mismatch	47.9(±4.2)%	0.25	46.6(±4.2)%	0.10	34.7(±4.0)%	0.27

≥ 2 mismatches	45.3(±3.2)%		39.9(±3.2)%		31.2(±3.0)%	
TBI used regimen						
Non TBI regimen	39.5(±3.9) %	0.32	33.9(±3.7)%	0.19	27.1(±3.5)%	0.73
TBI regimen	47.2(±3.1) %		44.3(±3.0)%		33.4(±2.9)%	
Use of ATG						
No	52.2(±3.7)%	0.03	48.0(±3.7)%	0.01	34.9(±3.5)%	0.80
Yes	38.7(±3.2)%		34.3(±3.1)%		28.2(±3.0)%	

	II-IV acute GVHD at day 100		chronic GVHD at 3 years		NRM in 3 years		Relapse incidence	
	CIF (95% CI)	*p*-value	CIF (95% CI)	*p*-value	CIF (95% CI)	*p*-value	HR (95% CIF)	*p*-value
Patient gender								
Male	30 (25-35)%	0.20	28 (23-34)%	0.07	31 (25-36)%	0.90	31 (26-37)%	0.07
Female	24 (18-31)%		20 (15-27)%		32 (25-39)%		23 (17-29)%	
CMV serology								
Negative	28 (22-35)%	0.72	25 (19-32)%	0.97	25 (19-32)%	0.01	27 (21-34)%	0.72
Positive	30 (24-35)%		26 (21-32)%		36 (30-42)%		29 (23-34)%	
Number of HLA mismatches								
0-1 HLA mismatch	27 (20-34)%	0.07	25 (18-32)%	0.07	29 (22-37)%	0.51	24 (18-32)%	0.23
2 or >2 mismatches	31 (26-37)%		28 (23-34)%		32 (26-38)		28 (23-34)%	
Type of acute leukemia								
ALL	31 (26-37)%	0.06	27 (21-32)%	0.49	33 (28-39)%	0.16	28 (23-34)%	0.99
AML	23 (18-30)%		24 (18-30)%		28 (22-35)%		27 (21-34)%	
Disease status								
CR 1	29 (23-35)%	0.92	30 (19-33)%	0.04	24 (18-30)%	< 0.001	28 (21-34)%	0.05
CR 2	27 (21-34)%		26 (20-33)%		33 (26-40)%		24 (18-31)%	
Advanced disease	28 (19-37)%		25 (17-33)%		43 (33-53)%		37 (27-47)%	
Year of UCBT								
2004-2009	29 (24-35)%	0.47	25 (20-31)%	0.70	38 (19-29)%	0.001	29 (23-35)%	0.75
2010-2016	26 (21-32)%		26 (20-31)%		24 (19-30)%		27 (22-34)%	

Graft type								
Single UCBT	22 (17-27)%	< 0.001	23 (18-28)%	0.13	32 (27-38)%	0.74	24 (18-30)%	0.16
Double UCBT	36 (29-43)%		28 (22-35)%		30 (24-36)%		31 (25-37)%	
TBI used regimen								
Non TBI regimen	20 (14-25)%	0.001	23 (17-30)%	0.25	31 (25-38)%	0.95	35 (28-42)%	0.06
TBI regimen	34 (28-39)%		27 (22-33)%		31 (26-37)%		24 (19-30)%	
Use of ATG								
No	39 (31-46)%	< 0.001	28 (22-35)%	0.34	28 (22-35)%	0.29	24 (18-30)%	0.08
Yes	21 (16-26)%		24 (19-30)%		33 (28-39)%		32 (27-38)%	

Abbreviations: UCBT, umbilical cord blood transplant; OS, overall survival; LFS, leukemia free survival; rGRFS, refined graft-versus-host disease-free, relapse-free survival; Kg, kilogram; ALL, acute lymphocytic leukemia; AML, acute myeloid leukemia; CR, complete remission; HLA, human leukocyte antigen; TBI, total body irradiation; ATG, antithymocyte globulin; GVHD, graft-versus-host-disease; NRM, non-relapse-mortality; CIF, cumulative incidence function; CI, confidence interval; CMV, cytomegalovirus.

*Median body weight was 63.0 Kg

Table 4. Multivariate analysis

	OS		LFS		rGRFS*		NRM	
	HR (95% CI)	***p*-value**	**HR (95% CI)**	***p*-value**	**HR (95% CI)**	***p*-value**	**HR (95% CI)**	***p*-value**
Type of acute leukemia								
AML (vs ALL)	1.01(0.78-1.32)	0.92	0.89(0.69-1.16)	0.40	0.85(0.66-1.08)	0.18	0.89 (0.62-1.28)	0.54
Year of transplantation								
2010-2016 (vs 2004-2009)	0.70(0.53-0.92)	0.01	0.74(0.57-0.96)	0.02	0.79(0.62-1.01)	0.06	0.62 (0.43-0.91)	0.01
Graft type								
Double (vs Single)	1.16(0.85-1.58)	0.34	1.15(0.85-1.54)	0.36	1.07(0.81-1.40)	0.65	1.14 (0.76-1.72)	0.53
Disease status								
CR 2 (vs CR 1)	1.33(0.98-1.81)	0.07	1.31(0.98-1.76)	0.07	1.14(0.87-1.49)	0.35	1.53 (1.03-2.28)	0.04
Advanced (vs CR 1)	2.74(1.97-3.81)	< 0.001	2.51(1.82-3.46)	< 0.001	1.79(1.32-2.42)	0.00	2.13 (1.34-3.39)	0.001
Age at UCBT								
Continuous	0.98(0.94-1.02)	0.28	0.98(0.94-1.03)	0.45	0.99(0.96-1.03)	0.76	0.99 (0.94-1.05)	0.84
CMV serology								
Positive (vs negative)	1.28(0.97-1.69)	0.08	1.25(0.96-1.64)	0.10	1.3(1.01-1.66)	0.04	1.45 (0.99-2.12)	0.05
Use of ATG								
Yes (vs No)	1.36(1.00-1.85)	0.05	1.43(1.06-1.93)	0.02	0.99(0.75-1.30)	0.94	1.18 (0.79-1.76)	0.43

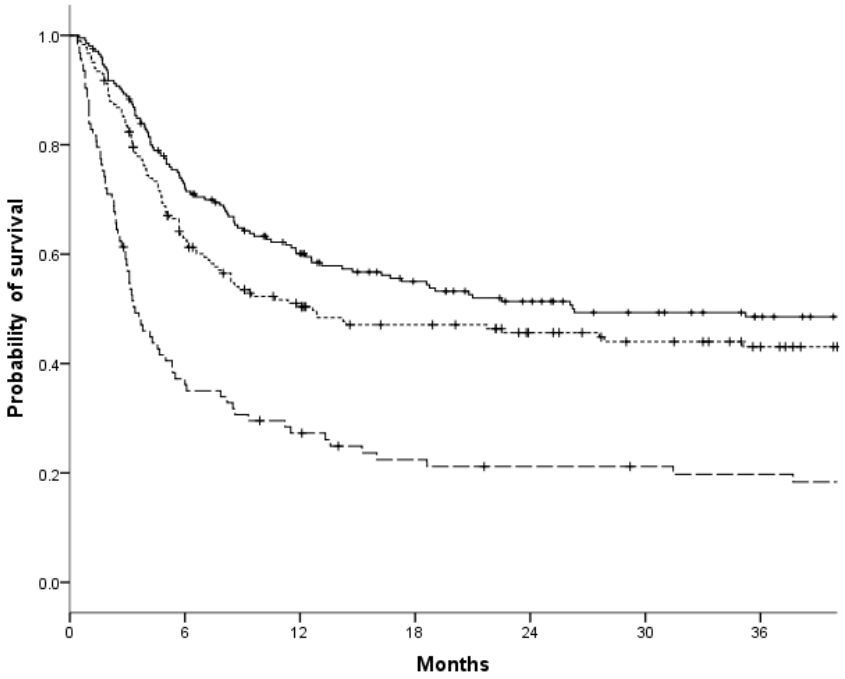
	Neutrophil engraftment		II-IV Acute GVHD		Chronic GVHD		Relapse**	
	HR (95% CI)	***p*-value**	**HR (95% CI)**	***p*-value**	**HR (95% CI)**	***p*-value**	**HR (95% CI)**	***p*-value**
Type of acute leukemia								
AML (vs ALL)	0.99 (0.81-1.22)	0.96	0.68 (0.46-1.01)	0.06	0.91 (0.62-1.34)	0.63	0.97 (0.65-1.44)	0.88
Year of transplantation								
2010-2016 (vs 2004-2009)	1.41 (1.15-1.72)	< 0.001	0.65 (0.45-0.94)	0.02	0.87 (0.59-1.27)	0.47	1.02 (0.7-1.49)	0.90
Graft type								
Double (vs Single)	0.90 (0.72-1.13)	0.35	1.65 (1.07-2.53)	0.02	1.26 (0.85-1.87)	0.25	1.03 (0.67- 1.6)	0.89
Disease status								
CR 2 (vs CR 1)	0.97 (0.78-1.19)	0.75	0.90 (0.60-1.35)	0.61	0.89 (0.6-1.32)	0.56	0.88 (0.57-1.36)	0.57
Advanced (vs CR 1)	0.60 (0.44- 0.80)	< 0.001	0.92 (0.56-1.53)	0.76	0.44 (0.24-0.81)	0.01	1.62 (1.02-2.56)	0.04

Age at UCBT								
Continuous	1.00 (0.97-1.03)	0.92	0.99 (0.93-1.06)	0.84	1.08 (1.02-1.14)	0.01	0.98 (0.92-1.03)	0.41
CMV serology								
Positive (vs negative)	0.83 (0.68-1.02)	0.071	1.28 (0.88-1.87)	0.20	N/A		0.89 (0.61-1.29)	0.54
Use of ATG								
Yes (vs No)	1.08 (0.84- 1.40)	0.55	0.55 (0.34-0.87)	0.01	0.86 (0.59-1.26)	0.44	1.21 (0.71-2.08)	0.49

Abbreviations: OS, overall survival; LFS, leukemia free survival; rGRFS, refined graft-versus-host disease-free, relapse-free survival; NRM, non-relapse-mortality; HR, hazard ratio; CI, confidence interval; ALL, acute lymphocytic leukemia; AML, acute myeloid leukemia; CR, complete remission; vs, versus; UCBT, umbilical cord blood transplant; CMV, cytomegalovirus; ATG, antithymocyte globulin; GVHD, graft-versu-host-disease.

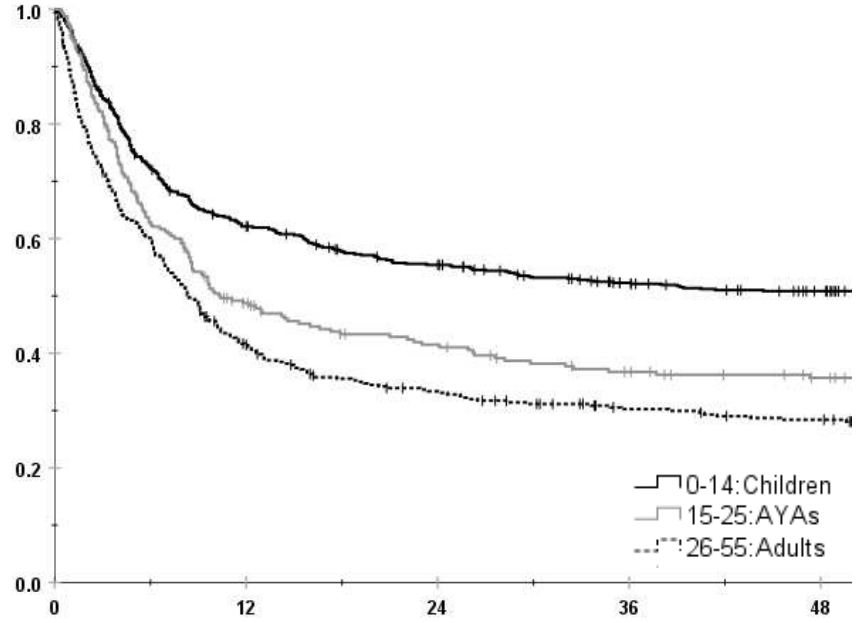
*rGRFS was also adjusted for gender

Figure 1. Three-year leukemia free survival according to disease status at UCBT



Legend: Solid line represents patients in CR1; dotted line represents patients in CR2; dashed line represents patients with advanced disease

Supplemental figure 1.1. Overall survival by age group in 2004-2009



Supplemental figure 1.2. Overall survival by age group in 2010-2016