Hematopoietic stem cell transplantation for acute lymphoblastic leukemia: why do adolescents and young adults outcomes differ from those of children? A retrospective study on behalf of the Francophone Society of Stem Cell Transplantation and Cellular Therapy (SFGM-TC).

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Hematopoietic stem cell transplantation for acute lymphoblastic leukemia: why do adolescents and young adults outcomes differ from those of children? A retrospective study on behalf of the Francophone Society of Stem Cell Transplantation and Cellular Therapy (SFGM-TC).

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Abstract:

Purpose: In the Acute Lymphoblastic Leukemia (ALL) landscape, Adolescents and Young Adults (AYA) often present high-risk diseases and increased chemotherapy-related toxicity. Studies analyzing outcomes of AYA after Hematopoietic Stem Cell Transplant (HSCT) are scarce. Our study aimed to compare the outcomes of children and AYA with ALL after HSCT and to determine factors influencing potential differences.

Method: 891 patients, from the SFGM-TC registry, aged between 1 and 25 years who received HSCT between 2005 and 2012 were included. Outcomes of AYA were compared to the ones of their younger counterparts.

Results: Five-year OS and GRFS were lower in AYA: 53.1% *versus* 64% and 36% *versus* 47% (p = 0.0012 and p=0.007 respectively). While CIR were similar in both groups, 5 year-Treatment Related Mortality was higher in AYA: 19% versus 13% (p=0.04). The lower GRFS in AYA was mainly explained by a higher chronic Graft versus Host Disease (cGvHD) incidence: 32% *versus* 19% (p<0.001). Use of Peripheral Blood Stem Cells and use of anti-thymoglobulin appeared to be the main factors impacting cGvHD occurrence in AYA.

Conclusion: AYA have worse outcomes than children after HSCT for ALL because of a greater risk of TRM due to cGvHD. HSCT practices should be questioned in this population.

Main text

Introduction:

The prognosis of childhood acute lymphoblastic leukemia (ALL) has improved continuously during the last thirty years. Currently reported overall 5-year survival (OS) is about 90% in privileged countries (Curran and Stock, 2015). The prognosis of AYA ALL is poorer than the ones of their younger counterparts, as 5-years survival decreases from 85.8% in children (ages between 0 to 14 years), to 62.2% in adolescents (15 – 19 years); and 52.8% in young adults (20 – 39 years) (Curran and Stock, 2015; Trama et al., 2016) . The biology of ALL differs between children and AYA. Indeed high-risk cytogenetic abnormalities are more frequent in this population (Boissel and Baruchel, 2018; Boissel et al., 2003; Burke and Douer, 2014). Moreover, AYA show higher incidence of acute toxicities after intensive treatments (Boissel and Baruchel, 2018; Boissel and Sender, 2015; Burke and Douer, 2014; Stock et al., 2011). Nevertheless, despite this increased toxicity, the prognosis of AYAs ALL is better following pediatric protocols than after adults protocol as shown in the first French comparative study (Boissel et al., 2003), subsequently confirmed by other studies led by pediatric and adult cooperative groups (Boissel and Baruchel, 2018; de Bont et al., 2004; Ibrahim et al., 2014; Pui et al., 2011; Stock et al., 2008).

Either in pediatric or in adult protocols Hematopoietic Stem Cell Transplantation (HSCT) indications have been progressively restricted to patients with early poor response to chemotherapy (e.g.persistence of MRD after consolidation therapy). This has led to a decrease of HSCT indications in AYA, which are still more frequent than in the pediatric patients as in the NOPHO 2008 trial (5.5% in 1 to 17 years, and 15.8% in 18 to 45 years) (Boissel and Baruchel, 2018; Toft et al., 2018). Outcomes of AYAs after HSCT, seemed to be worse than the ones of children in three previous studies published in 2013, 2014 and 2019 (Burke et al., 2013; Hangai et al., 2019; Wood et al., 2014). In two of these studies the lower overall survival in AYA was attributed to an excess of Treatment Related mortality (TRM) (Burke et al., 2013; Hangai et al., 2019).

Our study aimed to compare outcomes of HSCT for ALL between pediatric and AYA patients in a large cohort, with sufficient follow-up, in order to determine factors influencing OS and TRM.

Methods:

Patients:

All patients aged between 0 and 25 years, who received a first HSCT in treatment for ALL between 2005 and 2012, from the Francophone Society of bone marrow transplantation and cellular therapy (SFGM-TC) registry were included in this retrospective and multicentric study.

The AYA group was defined by age range between 15 and 25 years old, according to European studies and the SFGM-TC group (Bleyer, 2002; Burke and Douer, 2014; Burke et al., 2013, 2014; Coccia et al., 2012; Curran and Stock, 2015; Majhail et al., 2012; Tewari et al., 2014; Wood et al., 2011, 2014).

Data about diagnosis and transplantation procedure were collected. Cytogenetic risk groups were defined following international criteria (Ma et al., 1999; Shago, 2017). Hyperdiploidy and translocation (12;21)/ETV6-RUNX1 were classified as low risk cytogenetic abnormalities. Other abnormalities including hypodiploidy (less than 46 chromosomes), t(9;22) / BCR-ABL, KMT2A rearrangements, translocations t(1;19)/TCF3-PBX1 and t(17;19)/TCF3-HLF, and amplification of chromosome 21 (iAMP21) were considered as high risk cytogenetic abnormalities. Patients with t (1; 19) ALL were indeed considered as HR because of poor prognosis of this entity in relapse. Performance status was evaluated using the age-related scoring system (Lansky and Karnofsky). A Lansky/Karnofsky score strictly below 80 defined a low performance status.

Cells provided by a matched sibling donor (MSD) defined geno-identical setting. A transplant from an HLA-matched unrelated donor (MUD) (9/10 or 10/10) defined a phenoidentical setting. All cord blood sources were pooled regardless of HLA-matching since HLA compatibility was not fully captured in the registry for this stem cell source.

Outcomes and statistical methods:

Outcomes

Outcomes were OS (time from HSCT to death), DFS (time from HSCT to relapse or death), TRM, GvHD, Cumulative Incidence of Relapse (CIR) and GvHD and Relapse Free Survival (GRFS). GRFS was defined as time from HSCT to grade 3 to 4 acute GVHD (aGvHD) or relapse or chronic GvHD (cGvHD) or death, whichever comes first. Chronic GvHD was described as limited or extensive GvHD as the NIH consensus was not available at the studied period (Martin et al., 2006). Data cut off was June 2015.

Statistical analysis

Diseases and HSCT procedures were compared between pediatric patients and AYA by Student or Wilcoxon test for quantitative variables and by Chi-2 or Fischer test for qualitative ones.

5-years OS, 5-years DFS and 5-years GRFS were determined by Kaplan-Meier method. Risks factors analyses were done using Cox models. The cumulative incidence of relapse (CIR) was estimated taking

into account death as competing event. The cumulative incidence of cGvHD was estimated taking into account death and relapse as competing events. A leukemia-related death was considering as competing event for the TRM estimation. Risk factors were analyzed using Fine and Gray models.

A p-value of ≤ 0,05 was considered as significant in all statistical tests.

Statistical analysis was performed using R version 4.0.2

Ethical aspects:

Patients or their parents/guardians receive information about the SFGM-TC registry before HSCT and provide a signed consent to be included.

Results:

Patients, disease, conditioning regimens

891 patients, 494 children and 397 AYAs were included. Median age at transplant in each group was 7.8 years [0.7-15] and 20 years [15-25] respectively. Median time of follow up was 45.6 months (0 to 114). A large part of AYAs (70.3%) was treated in an adult center (*versus* 8.5% of children).

There was a trend for a higher T-cell ALL incidence in the AYA population (29.8% *versus* 25.1%, p=0.1275). High-risk cytogenetic abnormalities were found in 25.9% of children and 29.5% of AYA (p=0.273).

HSCT was performed in first CR for 56.8% of the AYAs, whereas 57.5% of children received HSCT in second or higher CR (p<0.001). Note that 7.5% of AYAs and 3.7% of children presented a refractory disease at time of transplant (p=0.015).

HSCT procedures mainly included a Myelo-Ablative Conditioning regimen (MAC) based on Total Body Irradiation (TBI) or chemotherapy. See detailed MAC administered in supplementary data. TBI was used more frequently in AYA than in children (90.1% *versus* 83.1%, p=0.003). Performance status at transplant were similar in both groups. Nevertheless, AYA more often received a Reduced Intensity Conditioning (RIC) than children (5.8% *versus* 2.4%, p = 0.01).

Bone Marrow (BM) or CB were often used in children (60.2% and 29.4% respectively) *versus* 55.6% and 16.4% in AYA respectively, whereas Peripheral Blood Stem Cells (PBSC) were used for 28% of AYA and 10.3% of children (p < 0.0001). Moreover, when being transplanted in an adult center, PBSC were more commonly used for AYA (30% of AYA's HSCT in adult centers *versus* 21.2% of AYA's HSCT in pediatric centers, p=0.051). No difference of choice of stem cell source depending on center of transplant was

observed for children. BM and PBSC cells were provided by a MSD in 40.2% of children and 43.4% of AYA and from a MUD in 57.2% and 55.1% of cases respectively (p = 0.474) (other patients received CB, for which HLA compatibility was not fully captured in the registry). GvHD prophylaxis mainly included ciclosporin (n= 835), methotrexate (n = 461), mycophenolate mofetil (n = 141), corticosteroids (n = 91). Anti-thymoglobulins (ATG) were used for 48% of children and 26% of AYA (p<0.001). When AYA received HSCT in a pediatric center, they more often received ATG as GvHD prophylaxis than in adult centers 47.5% *versus* 16.8 % (p < 0,001), as well as observed for children: 49.8% of children received ATG in pediatric center, *versus* 31% in adult center (p = 0.02). See patient's characteristics in Table 1.

Poorer results of HSCT in Adolescents and Young Adults

2-years OS and 5-year OS were significantly lower in the AYA group (60% *versus* 71% and 53% *versus* 64% respectively, p=0.0012) with in multivariate analysis a Hazard Ratio (HR) of 1.40 [1-1.95], (p=0.05), see Figure 1. In multivariate analysis, an altered performance status, a refractory disease at transplant, or use of PBSC or CB were associated with lower OS. In sub-group analysis the 5 year-OS difference remained significant in patients who received HSCT in CR2 or higher (42% in AYA, versus 59% in children, p= 0.0003).

Interestingly, analysis of different sub-groups of age at transplant, excluding patients with refractory diseases at transplant, showed a gradual significant decrease of OS (see Figure 2 and Table 2).

2-years and 5-years GRFS were lower in our AYAs group (40.6 *versus* 49.2% and 36.4% *versus* 47.2% respectively) (p=0.0078), (HR 1.23 [0.94-1.61], p=0.13).

ALL subtype and relapse do not explain the worst outcomes of HSCT in AYAs

2-years and 5-years DFS were lower in AYA than in younger patients (54.5% *versus* 62.3% and 49.2% *versus* 59.5% respectively, p=0.0071), but CIR were similar in both groups (32% and 27% at 5 years, p=0.19) (Figure 1). There was no significant difference of DFS probability or CIR in each age subgroup (Table 2). In multivariate analysis, a refractory disease at transplant, a low performance status and a transplant from CB were associated with a lower DFS probability. In patients treated for a T-ALL, 5-years DFS and CIR were not significantly different between AYA and children (see in supplementary data).

In multivariate analysis, having received a TBI-based conditioning regimen was associated with a higher DFS probability (HR 0.7 [0.49-0.01], p=0.06). When comparing outcomes of children and AYA who received a TBI-based conditioning, CIR were similar in both groups (25% *versus* 31%, p=0.081).

Moreover, even for TBI-conditioned patients, 5-years OS, 5-years DFS and 5-years GRFS were still lower in older patients, see in supplementary data.

Excess of mortality after transplant in AYAs is linked to increased toxicity

The 1-year, 2-years and 5-year TRM incidences were significantly higher in AYAs: 14%, 16% and 19% *versus* 11%, 12% and 13% in their younger counterparts respectively (p=0.041) (Figure 1). These results were confirmed in multivariate analysis (HR: 1.76 [1.03-3], p=0.037) (Figure 3). Main causes of HSCT-related deaths in AYA were GvHD (implicated in 47.6% of deaths), infections (28.6%) and organs toxicity (23.8%). Causes of HSCT-related deaths in children were infections, organs toxicity and GvHD for 43.1%, 36.2% and 25.9% respectively. Regarding ages-subgroup analysis, the TRM incidence markedly rose from 9% before 10 years old to 20% between 10 and 15 years, and 17% after 15 years (Figure 2 and Table 2). Having received a PBSC or a CB transplant are the two other factors associated with higher risk of TRM (HR 2.73 [1.66-4.48], p<0.001 and HR 2.38 [1.45-3.91], p=0.001 respectively).

Moreover, in the subgroup of patients who received a MAC followed by a BM transplant, TRM incidences were similar in both groups (9% in children and 12% in AYA, p=0.3), while OS probability remains significantly lower in AYA (59.5% *versus* 69.6%, p= 0.014).

Chronic GvHD strongly impacts AYA outcomes after HSCT for ALL

aGvHD cumulative incidences were similar in both groups (61% in AYAs and 59% in children, p=0.62). On the contrary, cGvHD occurred more frequently in AYA than in children (32% *versus* 19%, p< 0.001), among which 44% and 31% were extensive respectively (Figure 1). Having received ATG (HR 0.63 [0.43-0.92], p=0.016) or presenting a good performance status were both associated with a lower risk of cGvHD in multivariate analysis, while having received PBSC was associated with a higher risk of cGvHD (HR: 1.46 [0.99-2.14], p=0.05) (Figure 3).

In patients who received bone marrow stem cells after a MAC, cGvHD incidence was still significantly higher in AYA (30% *versus* 17%, p < 0.001).

Discussion:

Our study confirmed the lower prognosis after HSCT for ALL of AYA compared to children. Decrease of OS after HSCT started after 10 years of age. Moreover, excess of mortality in the AYA group was linked to a higher TRM due to excess of cGvHD. Indeed, GRFS probability was significantly lower in AYA than in children, while CIR and aGvHD incidences were similar in both groups and cGvHD incidence was

higher in AYA than in children. The main factors involved in TRM and cGvHD excess in AYA were the use of PBSC, and the absence of use of ATG. These results pointed to the importance of transplantation practices in AYA.

Our study included patients who received a first HSCT for ALL in the pre-FORUM study era. We showed a significant decrease of 5-years OS in AYA compared to younger patients consistent with previous studies (Burke et al., 2013; Wood et al., 2014). Of note, outcomes of HSCT in our pediatric group (5-years OS of 63.9% and 5-years DFS of 59.5%) were consistent with previous published studies. The BFM study showed a 4-years DFS of 67% and 71% in children who received HSCT in the same era of procedure (Peters et al., 2015). The international FORUM study found higher 2-year-OS and DFS than in our study (91% (IC95 86-95%) and 86% (IC95 79-90%) respectively) in children transplanted after a TBI-based conditioning between 2013 and 2019 for ALL (Peters et al., 2020). These differences could be related to improvement of supportive therapy notably through improved early detection of infection as well as prophylactic and preemptive antimicrobial drug (Singh and McGuirk, 2016).

Leukemia relapse does not contribute to the excess of mortality in AYA after HSCT. AYA often present high risk-ALL (Iacobucci and Mullighan, 2017; Soulier et al., 2003), and have a worse prognosis than younger children even after pediatric-inspired first-line therapeutic protocols (Toft et al., 2018). Nevertheless, as in our study, following HSCT, relapse rates are similar in both children and AYA in several studies (Burke et al., 2013; Goldstone et al., 2008; Wood et al., 2014). In our study, despite a higher incidence of high-risk cytogenetic abnormalities in AYA (not statistically significant), CIR were similar in both groups overall (27% in children, and 32% in AYA, p= 0.19) and when stratifying according to immunophenotype. Knowing the impact of TBI on relapse incidence (Peters et al., 2020) we compared AYA and children receiving TBI based conditioning regimens. Again relapse rates were similar (25% in children *versus* 31% in AYA, p=0.08).

Treatment-related toxicity was the main cause of higher mortality in AYA in our study. Of note, 2-year and 5-year TRM incidences in our pediatric group (12% and 13% respectively) were consistent with previous studies (Peters et al., 2015). In our study, AYA had a higher 2-year and 5-years TRM than children (16% *versus* 12%, and 19% *versus* 13%, p = 0.04). In other studies, higher treatment-related toxicity in AYA was previously observed, either following chemotherapy first line treatment, or HSCT (Boissel and Sender, 2015; Burke et al., 2013; Hangai et al., 2019; Rank and Schmiegelow, 2020; Toft et al., 2018; Wood et al., 2014). The Minneapolis comparative study showed a higher TRM at one year after HSCT in AYA than in children (28% *versus* 14% respectively, p=0.04). May be due to small numbers, except use of matched CB (RR= 0.31 [0.13-0.78], p = 0.01), no factor significantly impact TRM in their multivariate analysis (Burke et al., 2013). In the Japanese study, AYA presented excess of TRM (19%, 17% and 11% in patients aged between [20-29 years], [10-19 years] and [1-9 years] respectively, p<0.001). In this study infections related-deaths tended to be more frequent in older AYA. No multivariate analysis on TRM was performed (Hangai

et al., 2019). In the HSCT for myeloid acute leukemia setting, a recent retrospective study also showed a lower 2-years OS, and a higher TRM in AYA than in children (61.1% versus 71.4%, p = 0.0009, and 10.6% versus 7%; p < 0.0001 respectively) (Pochon et al., 2021).

In our study, 5-years GRFS probability was lower in AYA than in younger patients (36% versus 47%, p = 0.0078), while aGvHD incidence (61% and 59%, p = 0.6) and CIR (32% versus 27%, p = 0.19) were similar in both groups. Thus, post-HSCT morbi-mortality in AYA was mainly impacted by cGvHD occurrence, which was higher in AYA (32% *versus* 19% in children, p<0.001). This could be consistent with TRM estimation curve, which showed a gap between AYA and children, starting from 3 months after HSCT. Of note, the incidence of cGvHD observed in our pediatric group was consistent with previous pediatric studies (Peters et al., 2015; Zheng et al., 2015). A higher cGvHD incidence in AYA was previously described in other studies. In the Minneapolis comparative study cGvHD incidence was higher in AYA (15% *versus* 7% in pediatric patients, p=0.06) (Burke et al., 2013). In the BFM trial, patients upon than 12 years old, receiving a genoidentical stem cell transplant, had higher incidence of extensive cGvHD than younger patients (Peters et al., 2015).

In our multivariate analysis, two factors were associated with a higher risk of cGvHD: use of PBSC (HR 1.46 [0.0.99-2.14], p = 0.05), and absence of ATG use (HR of use of ATG 0.63 [0.43-0.92], p = 0.016).

Impact of PBSC is not surprising since it is now well known that using PBSC increases cGvHD incidence (Campregher et al., 2015; Eapen et al., 2004). In our study, AYA more frequently received PBSC (28% of cases) than children (10.3% of cases) (p< 0.001), particularly when they were transplanted in adult centers (30.8% of cases, versus 21.2% of cases in pediatric centers, p= 0.05). This difference of stem cell source is not described in the Minneapolis study, but the small number of patient may explain this discrepancy with our data (Burke et al., 2013). Moreover, preference of PBSC in adults HSCT programs was previously described (Mehta et al., 2018), and could be supported by the fact that stem cell source (PBSC *versus* BM) does not impact neither OS, nor TRM of adult patients (Giebel et al., 2017) . Of interest is the fact that our subgroup analysis in patients who received bone marrow as stem cell source, after a MAC, showed no difference of TRM or CIR between AYA and children, but a remaining higher incidence of cGvHD in AYA (30% *versus* 17% in children, p < 0.001).

In our study, AYA received ATG less frequently than children (26% versus 48.1%, p< 0.001), and they also less frequently received ATG when treated in adult centres (16.8%) than in paediatric centres (47.5%) (p < 0.001). We of course checked that there was no difference of donor type between AYA and children who received a BM and a PBSC transplant. Interestingly, an Italian retrospective study showed no difference of TRM or GvHD incidence between adolescents and children transplanted for ALL in second CR. In this study, use of PBSC was rare (6% in children, and 10% in AYA) without significant difference, and ATG prophylaxis was used with the same frequency in both groups (Dini et al., 2011). Moreover, in

the AML setting, use of PBSC and ATG prophylaxis both impact higher cGvHD incidence observed in AYA (Pochon et al., 2021).

Finally, our study could not capture data regarding GvHD-oriented treatment adherence of AYA. Indeed poor adherence to GvHD treatment has been described in AYA which could obviously lead to increase incidence of cGvHD (McGrady et al., 2014; Mehta et al., 2018; Pulewka et al., 2020).

Conclusion

AYA or patients aged more than 10 years, compared to children aged less than 10 years have worse outcome after HSCT for ALL. Excess of death in this specific population is mainly due cGvHD. Choice of stem cells source and use of ATG in those patients should be discussed.

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Conflict of Interest

All authors declare no competing financial interest.

Authorship statement:

AG and FR conceived and designed the study. AG, FR and AB wrote the manuscript. AG collected and assembled data. LP realized all the statistical analysis. All other co-authors included patients and critically reviewed the manuscript.

All co-author consented to publish this manuscript.

References:

Bleyer, W.A. (2002). Cancer in older adolescents and young adults: Epidemiology, diagnosis, treatment, survival, and importance of clinical trials. Med. Pediatr. Oncol. *38*, 1–10.

Boissel, N., and Baruchel, A. (2018). Acute lymphoblastic leukemia in adolescent and young adults: treat as adults or as children? Blood *132*, 351–361.

Boissel, N., and Sender, L.S. (2015). Best Practices in Adolescent and Young Adult Patients with Acute Lymphoblastic Leukemia: A Focus on Asparaginase. J. Adolesc. Young Adult Oncol. *4*, 118–128.

Boissel, N., Auclerc, M.-F., Lhéritier, V., Perel, Y., Thomas, X., Leblanc, T., Rousselot, P., Cayuela, J.-M., Gabert, J., Fegueux, N., et al. (2003). Should adolescents with acute lymphoblastic leukemia be treated as old children or young adults? Comparison of the French FRALLE-93 and LALA-94 trials. J. Clin. Oncol. Off. J. Am. Soc. Clin. Oncol. *21*, 774–780.

de Bont, J.M., Holt, B. van der, Dekker, A.W., van der Does-van den Berg, A., Sonneveld, P., and Pieters, R. (2004). Significant difference in outcome for adolescents with acute lymphoblastic leukemia treated on pediatric vs adult protocols in the Netherlands. Leukemia *18*, 2032–2035.

Burke, P.W., and Douer, D. (2014). Acute lymphoblastic leukemia in adolescents and young adults. Acta Haematol. *132*, 264–273.

Burke, M.J., Gossai, N., Wagner, J.E., Smith, A.R., Bachanova, V., Cao, Q., MacMillan, M.L., Stefanski, H.S., Weisdorf, D.J., and Verneris, M.R. (2013). Survival differences between adolescents/young adults and children with B precursor acute lymphoblastic leukemia after allogeneic hematopoietic cell transplantation. Biol. Blood Marrow Transplant. J. Am. Soc. Blood Marrow Transplant. *19*, 138–142.

Burke, M.J., Gossai, N., Cao, Q., Macmillan, M.L., Warlick, E., and Verneris, M.R. (2014). Similar outcomes between adolescent/young adults and children with AML following allogeneic hematopoietic cell transplantation. Bone Marrow Transplant. *49*, 174–178.

Campregher, P.V., Hamerschlak, N., Colturato, V.A.R., Mauad, M.A., de Souza, M.P., Bouzas, L.F. da S., Tavares, R. de C.B., Barros, J.C., Chiattone, R., Paz, A., et al. (2015). Survival and graft-versus-host disease in patients receiving peripheral stem cell compared to bone marrow transplantation from HLA-matched related donor: retrospective analysis of 334 consecutive patients. Eur. J. Haematol. *95*, 421–425.

Coccia, P.F., Altman, J., Bhatia, S., Borinstein, S.C., Flynn, J., George, S., Goldsby, R., Hayashi, R., Huang, M.S., Johnson, R.H., et al. (2012). Adolescent and young adult oncology. Clinical practice guidelines in oncology. J. Natl. Compr. Cancer Netw. JNCCN *10*, 1112–1150.

Curran, E., and Stock, W. (2015). How I treat acute lymphoblastic leukemia in older adolescents and young adults. Blood *125*, 3702–3710.

Dini, G., Zecca, M., Balduzzi, A., Messina, C., Masetti, R., Fagioli, F., Favre, C., Rabusin, M., Porta, F., Biral, E., et al. (2011). No difference in outcome between children and adolescents transplanted for acute lymphoblastic leukemia in second remission. Blood *118*, 6683–6690.

Eapen, M., Horowitz, M.M., Klein, J.P., Champlin, R.E., Loberiza, F.R., Ringdén, O., and Wagner, J.E. (2004). Higher mortality after allogeneic peripheral-blood transplantation compared with bone marrow in children and adolescents: the Histocompatibility and Alternate Stem Cell Source Working Committee of the International Bone Marrow Transplant Registry. J. Clin. Oncol. Off. J. Am. Soc. Clin. Oncol. *22*, 4872–4880.

Giebel, S., Labopin, M., Socié, G., Beelen, D., Browne, P., Volin, L., Kyrcz-Krzemien, S., Yakoub-Agha, I., Aljurf, M., Wu, D., et al. (2017). Improving results of allogeneic hematopoietic cell transplantation for adults with acute lymphoblastic leukemia in first complete remission: an analysis from the Acute Leukemia Working Party of the European Society for Blood and Marrow Transplantation. Haematologica *102*, 139–149.

Goldstone, A.H., Richards, S.M., Lazarus, H.M., Tallman, M.S., Buck, G., Fielding, A.K., Burnett, A.K., Chopra, R., Wiernik, P.H., Foroni, L., et al. (2008). In adults with standard-risk acute lymphoblastic leukemia, the greatest benefit is achieved from a matched sibling allogeneic transplantation in first complete remission, and an autologous transplantation is less effective than conventional consolidation/maintenance chemotherapy in all patients: final results of the International ALL Trial (MRC UKALL XII/ECOG E2993). Blood *111*, 1827–1833.

Hangai, M., Urayama, K.Y., Tanaka, J., Kato, K., Nishiwaki, S., Koh, K., Noguchi, M., Kato, K., Yoshida, N., Sato, M., et al. (2019). Allogeneic Stem Cell Transplantation for Acute Lymphoblastic Leukemia in Adolescents and Young Adults. Biol. Blood Marrow Transplant. *25*, 1597–1602.

Iacobucci, I., and Mullighan, C.G. (2017). Genetic Basis of Acute Lymphoblastic Leukemia. J. Clin. Oncol. Off. J. Am. Soc. Clin. Oncol. *35*, 975–983.

Ibrahim, A., Ali, A., and Mohammed, M.M. (2014). Outcome of Adolescents with Acute Lymphoblastic Leukemia Treated by Pediatrics versus Adults Protocols. Adv. Hematol. *2014*, 697675.

Ma, S.K., Wan, T.S., and Chan, L.C. (1999). Cytogenetics and molecular genetics of childhood leukemia. Hematol. Oncol. *17*, 91–105.

Majhail, N.S., Brazauskas, R., Hassebroek, A., Bredeson, C.N., Hahn, T., Hale, G.A., Horowitz, M.M., Lazarus, H.M., Maziarz, R.T., Wood, W.A., et al. (2012). 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. J. Am. Soc. Blood Marrow Transplant. *18*, 861–873.

Martin, P.J., Weisdorf, D., Przepiorka, D., Hirschfeld, S., Farrell, A., Rizzo, J.D., Foley, R., Socie, G., Carter, S., Couriel, D., et al. (2006). National Institutes of Health Consensus Development Project on Criteria for Clinical Trials in Chronic Graft-versus-Host Disease: VI. Design of Clinical Trials Working Group report. Biol. Blood Marrow Transplant. J. Am. Soc. Blood Marrow Transplant. *12*, 491–505.

McGrady, M.E., Williams, S.N., Davies, S.M., and Pai, A.L.H. (2014). Adherence to outpatient oral medication regimens in adolescent hematopoietic stem cell transplant recipients. Eur. J. Oncol. Nurs. Off. J. Eur. Oncol. Nurs. Soc. *18*, 140–144.

Mehta, P.A., Rotz, S.J., and Majhail, N.S. (2018). Unique Challenges of Hematopoietic Cell Transplantation in Adolescent and Young Adults with Hematologic Malignancies. Biol. Blood Marrow Transplant. J. Am. Soc. Blood Marrow Transplant. *24*, e11–e19.

Peters, C., Schrappe, M., Stackelberg, A. von, Schrauder, A., Bader, P., Ebell, W., Lang, P., Sykora, K.-W., Schrum, J., Kremens, B., et al. (2015). Stem-Cell Transplantation in Children With Acute Lymphoblastic Leukemia: A Prospective International Multicenter Trial Comparing Sibling Donors With Matched Unrelated Donors—The ALL-SCT-BFM-2003 Trial. J. Clin. Oncol. *33*, 1265–1274.

Peters, C., Dalle, J.-H., Locatelli, F., Poetschger, U., Sedlacek, P., Buechner, J., Shaw, P.J., Staciuk, R., Ifversen, M., Pichler, H., et al. (2020). Total Body Irradiation or Chemotherapy Conditioning in Childhood ALL: A Multinational, Randomized, Noninferiority Phase III Study. J. Clin. Oncol. JCO.20.02529.

Pochon, C., Detrait, M., Dalle, J.-H., Michel, G., Dhédin, N., Chalandon, Y., Brissot, E., Forcade, E., Sirvent, A., Izzadifar-Legrand, F., et al. (2021). Improved outcome in children compared to adolescents and young adults after allogeneic hematopoietic stem cell transplant for acute myeloid leukemia: a retrospective study from the Francophone Society of Bone Marrow Transplantation and Cell Therapy (SFGM-TC). J. Cancer Res. Clin. Oncol.

Pui, C.-H., Pei, D., Campana, D., Bowman, W.P., Sandlund, J.T., Kaste, S.C., Ribeiro, R.C., Rubnitz, J.E., Coustan-Smith, E., Jeha, S., et al. (2011). Improved Prognosis for Older Adolescents With Acute Lymphoblastic Leukemia. J. Clin. Oncol. *29*, 386–391.

Pulewka, K., Strauss, B., Hochhaus, A., and Hilgendorf, I. (2020). Clinical, social, and psycho-oncological needs of adolescents and young adults (AYA) versus older patients following hematopoietic stem cell transplantation. J. Cancer Res. Clin. Oncol.

Rank, C.U., and Schmiegelow, K. (2020). Optimal approach to the treatment of young adults with acute lymphoblastic leukemia in 2020. Semin. Hematol. *57*, 102–114.

Shago, M. (2017). Recurrent Cytogenetic Abnormalities in Acute Lymphoblastic Leukemia. Methods Mol. Biol. Clifton NJ *1541*, 257–278.

Singh, A.K., and McGuirk, J.P. (2016). Allogeneic Stem Cell Transplantation: A Historical and Scientific Overview. Cancer Res. *76*, 6445–6451.

Soulier, J., Trakhtenbrot, L., Najfeld, V., Lipton, J.M., Mathew, S., Avet-Loiseau, H., De Braekeleer, M., Salem, S., Baruchel, A., Raimondi, S.C., et al. (2003). Amplification of band q22 of chromosome 21, including AML1, in older children with acute lymphoblastic leukemia: an emerging molecular cytogenetic subgroup. Leukemia *17*, 1679–1682.

Stock, W., La, M., Sanford, B., Bloomfield, C.D., Vardiman, J.W., Gaynon, P., Larson, R.A., Nachman, J., Children's Cancer Group, and Cancer and Leukemia Group B studies (2008). What determines the outcomes for adolescents and young adults with acute lymphoblastic leukemia treated on cooperative group protocols? A comparison of Children's Cancer Group and Cancer and Leukemia Group B studies. Blood *112*, 1646–1654.

Stock, W., Douer, D., DeAngelo, D.J., Arellano, M., Advani, A., Damon, L., Kovacsovics, T., Litzow, M., Rytting, M., Borthakur, G., et al. (2011). Prevention and management of asparaginase/pegasparaginase-associated toxicities in adults and older adolescents: recommendations of an expert panel. Leuk. Lymphoma *52*, 2237–2253.

Tewari, P., Franklin, A.R., Tarek, N., Askins, M.A., Mofield, S., and Kebriaei, P. (2014). Hematopoietic stem cell transplantation in adolescents and young adults. Acta Haematol. *132*, 313–325.

Toft, N., Birgens, H., Abrahamsson, J., Griškevičius, L., Hallböök, H., Heyman, M., Klausen, T.W., Jónsson, Ó.G., Palk, K., Pruunsild, K., et al. (2018). Results of NOPHO ALL2008 treatment for patients aged 1-45 years with acute lymphoblastic leukemia. Leukemia *32*, 606–615.

Trama, A., Botta, L., Foschi, R., Ferrari, A., Stiller, C., Desandes, E., Maule, M.M., Merletti, F., Gatta, G., and EUROCARE-5 Working Group (2016). Survival of European adolescents and young adults diagnosed with cancer in 2000-07: population-based data from EUROCARE-5. Lancet Oncol. *17*, 896–906.

Wood, W., Deal, A., Whitley, J., Sharf, A., Serody, J., Gabriel, D., and Shea, T. (2011). Usefulness of the hematopoietic cell transplantation-specific comorbidity index (HCT-CI) in predicting outcomes for adolescents and young adults with hematologic malignancies undergoing allogeneic stem cell transplant. Pediatr. Blood Cancer *57*, 499–505.

Wood, W.A., Lee, S.J., Brazauskas, R., Wang, Z., Aljurf, M.D., Ballen, K.K., Buchbinder, D.K., Dehn, J., Freytes, C.O., Lazarus, H.M., et al. (2014). Survival improvements in adolescents and young adults after myeloablative allogeneic transplantation for acute lymphoblastic leukemia. Biol. Blood Marrow Transplant. J. Am. Soc. Blood Marrow Transplant. *20*, 829–836.

Zheng, C., Zhu, X., Tang, B., Yao, W., Song, K., Tong, J., Geng, L., Liu, H., and Sun, Z. (2015). Comparative analysis of unrelated cord blood transplantation and HLA-matched sibling hematopoietic stem cell transplantation in children with high-risk or advanced acute leukemia. Ann. Hematol. *94*, 473–480.

Figures

Figure 1

Comparisons between Adolescents and Young Adults (AYA) (blue curve) and Children (Ped) (red curve) of Overall Survival probability (OS) (A), GvHD and Relapse Free Survival probability (GFRS) (B), Cumulative Incidence of relapse (CIR) (C), Treatment Related Mortality cumulative incidence (TRM) (D) and chronic GvHD incidence (cGvHD) (E).

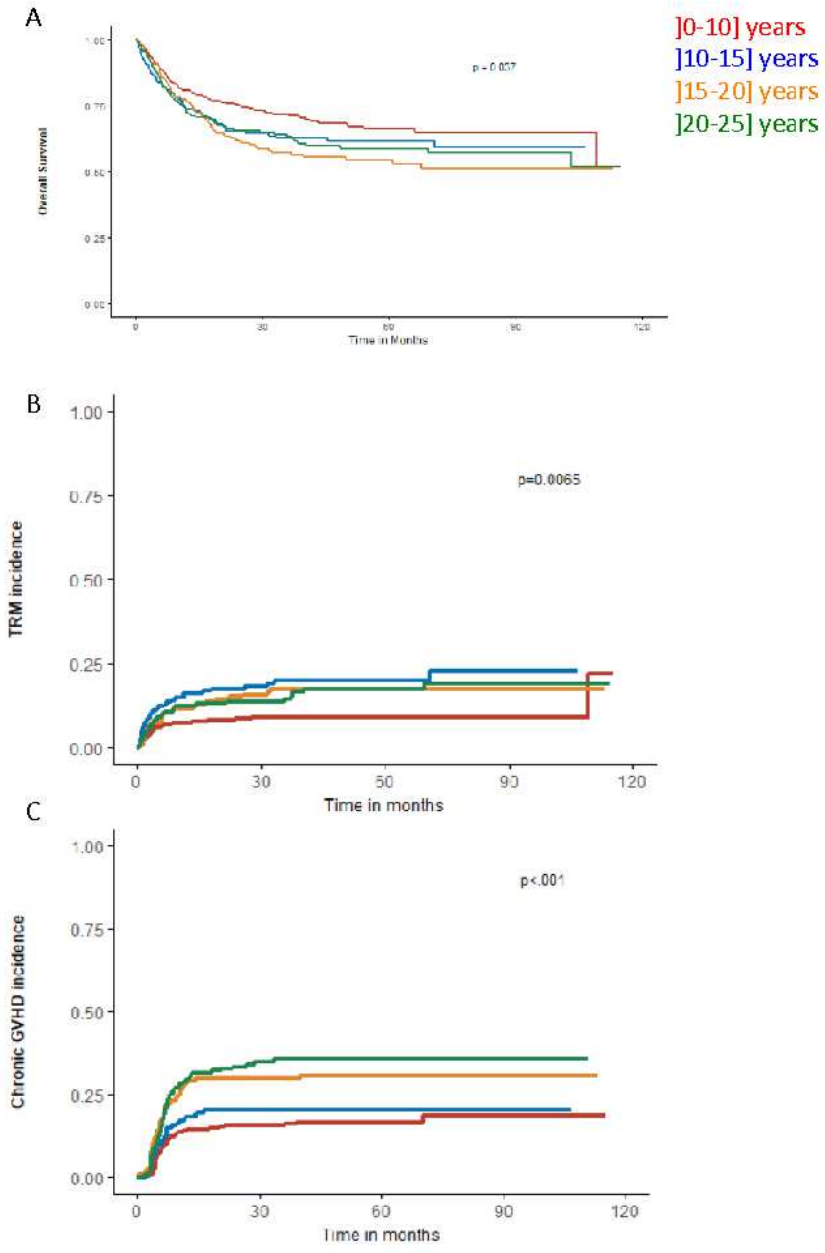

Figure 2

Subgroup analysis, excluding patients with refractory diseases at transplant, and comparing Overall Survival (OS) (A), Treatment Related Mortality cumulative incidence (TRM) (B) and cGVH cumulative incidence (C) between each age-groups:]0-10] years (red) ;]10-15]years (blue) ;]15-20] years (yellow) ;]20-25] years (green).

Figure 3

Multivariate analysis of overall survival (OS) (A), Cumulative Incidence of Relapse (CIR) (B) Treatment Related Mortality (TRM) (C) and chronic Graft versus Host Disease incidence (cGvHD) (D). Results are presented with Hazard Ratio (HR) and 95% confidence interval (IC95). RIC: Reduced Intensity Conditioning; AYA: Adolescents and Young Adults; TBI: Total Body Irradiation; PBSC: Peripheral Blood Stem Cells; CB: Cord Blood; HR: High Risk

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