Intensity of Induction Regimen and Outcomes Among Adults with Ph+ ALL Undergoing Allogeneic Hematopoietic Stem Cell Transplantation

Marlise Luskin (marlise_luskin@dfci.harvard.edu)
Dana-Farber Cancer Institute
Hari Raman
Brigham and Women's Hospital https://orcid.org/0000-0001-6471-2144
Se Eun Kim
Dana-Farber Cancer Institute
Daniel DeAngelo
Kristen Stevenson
Dana-Farber Cancer Institute
Donna Neuberg
Dana-Farber Cancer Institute https://orcid.org/0000-0003-2566-3145
Eric Winer
Dana-Farber Cancer Institute
Martha Wadleigh
Dana-Farber Cancer Institute
Jacqueline Garcia
Dana-Farber Cancer Institute
Annette Kim
Brigham and Women's Hospital
Richard Stone
Dana-Farber Cancer Institute https://orcid.org/0000-0002-7526-2633
Vincent Ho
Dana-Farber Cancer Institute

Article

Keywords:

Posted Date: September 20th, 2022

DOI: https://doi.org/10.21203/rs.3.rs-2062860/v1

Abstract

Tyrosine kinase inhibitors are essential in treating Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph + ALL) and have allowed for effective, low intensity induction regimens. Whether the use of low intensity induction regimens impacts outcomes after allogeneic stem cell transplant (alloHSCT) is less understood. We identified consecutive adult patients with Ph + ALL undergoing alloHSCT in first complete remission (CR1) at our center from 2010 to 2021 and examined the impact of induction intensity on outcomes. Among the 87 patients, 44 (51%) received low intensity induction and 43 (49%) received induction with high intensity chemotherapy. Patients receiving low intensity induction were older (median age 60 vs. 47, $p < 0.01$). Following induction, measurable residual disease (MRD) negativity by *BCR::ABL1* RT-PCR was similar in the low and high intensity cohorts (54% and 52% respectively). There was no difference between low and high intensity induction with respect to 2-year disease-free survival (58% vs. 56%), 2-year overall survival (62% vs. 63%), 2-year cumulative incidence of relapse (9% vs. 17%), and 2-year non-relapse mortality (33% vs. 29%). Outcomes were similar when patients were segmented by induction and conditioning regimen intensities. We demonstrate that induction intensity does not impact post-transplant outcomes among Ph + ALL patients Ph + ALL transplanted in CR1.

Introduction

Philadelphia chromosome-positive (Ph+) acute lymphoblastic leukemia (ALL) is a common genetic subtype of ALL diagnosed in adults.(1, 2) The Philadelphia chromosome arises from the reciprocal translocation of chromosomes 9 and 22 [t(9;22)(q34;q11)] yielding the *BCR::ABL1* fusion gene which encodes a constitutively active ABL kinase. Adding ABL tyrosine kinase inhibitors (TKIs) to chemotherapy improves outcomes compared with chemotherapy alone in patients with Ph + ALL.(3, 4) Currently, a TKI is the central component of treatment regimens for Ph + ALL.(5, 6)

In the TKI era, high-dose induction chemotherapy is no longer needed to achieve initial complete remission (CR). The GRAAPH-2005 trial randomized patients aged 18–60 years with newly diagnosed Ph + ALL to high intensity or reduced intensity induction chemotherapy in combination with imatinib and demonstrated that reduced intensity induction was associated with fewer induction deaths and a higher rate of CR.(7) Chemotherapy-free induction regimens of TKI plus corticosteroids have similarly demonstrated low toxicity and high CR rates.(8–11)

Among eligible patients with Ph + ALL in CR1, allogeneic hematopoietic stem cell transplant (alloHSCT) remains a reasonable consolidation approach due to evidence it reduces relapse and improves OS.(7, 12–15) While some studies have questioned the incremental benefit of alloHSCT following later-generation TKIs plus intensive chemotherapy in patients achieving deep molecular remissions, alloHSCT remains an accepted consolidation approach for patients with Ph + ALL even in patients consolidated with novel agents such as blinatumomab.(10, 13, 14, 16–18)

Although the ability of reduced intensity induction regimens to induce CR with less toxicity has been demonstrated, the impact of initial therapeutic de-intensification on long-term outcomes of patients who proceed to alloHSCT is less understood. In the GRAAPH-2005 trial, patients receiving reduced intensity induction had equivalent 5-year event-free survival (EFS) and overall survival (OS) compared to patients receiving standard intensity induction, but all patients received high-dose cytarabine consolidation prior to alloHSCT.(7) The GIMEMA LAL1509 protocol demonstrated the feasibility of a chemotherapy-free induction with dasatinib followed by alloHSCT for persistent molecular disease without therapeutic intensification prior to transplant.(19)

In the absence of a randomized trial, alloHSCT remains a standard treatment option for eligible patients with Ph + ALL in CR1. Due to heterogeneity and evolution of local and regional practice patterns, the intensity of induction chemotherapy in patients with Ph + ALL prior to alloHSCT is highly variable. Therefore, we report on the outcomes of Ph + patients receiving alloHSCT in CR1 at our center over a 10-year period to assess the impact of pre-transplant induction treatment intensity on post-alloHSCT outcomes.

Methods

The DFCI transplant database was queried to identify all adult patients (aged ≥ 18 years) with Ph + ALL who underwent alloHSCT between January 1, 2010 and April 31, 2021 in CR1. Patient demographics, disease and clinical characteristics, and pre-transplant chemotherapy regimen details and associated responses were obtained from the electronic medical record. Transplant details and post-transplant clinical outcomes including hematologic and molecular relapse, the development and severity of graft-versus-host disease (GVHD), and survival were collected from the DFCI transplant data repository and supplemented by chart review.

Diagnosis of Ph + ALL and Determination of MRD Status

Patients were determined to be Ph + at diagnosis through karyotype, fluorescence in situ hybridization analysis, and/or *BCR::ABL1* fusion transcript detection with reverse-transcriptase polymerase chain reaction (RT-PCR). Measurable residual disease (MRD) status at time of alloHSCT was determined by either the absence of detectable *BCR::ABL1* p190 transcript on a qualitative assay with a sensitivity of 1:100,000 cells (until 12/2019) or a quantitative assay with a sensitivity of 1:50,000 cells (since 12/2019), *BCR::ABL1* p210 transcript on a quantitative assay with a sensitivity of at least 4.7 logs, or via multi-parameter flow cytometry with the absence of detectable immature lymphoid cells at a level < 0.01%.

Pre-Transplant Treatment Intensity

The induction therapy received at the time of Ph + ALL diagnosis was classified as either low intensity or high intensity. Regimens consisting of a TKI, corticosteroids, with or without vincristine were classified as low intensity, while all other chemotherapeutic regimens with concurrent TKI use and including but not

limited to hyper-CVAD, asparaginase, or anthracycline-based therapies were classified as high intensity. Patients receiving low intensity induction continued a low intensity approach until transplant unless additional “salvage” therapy was required for management of refractory disease prior to entering CR1. These patients remained in the low intensity cohort for analysis. All patients received central nervous system (CNS) prophylaxis with intra-thecal chemotherapy and in some cases prophylactic cranial irradiation.

Allogeneic Hematopoietic Stem Cell Transplantation

Prior to transplant, the hematopoietic cell transplantation-specific comorbidity index (HCT-CI) score was calculated for all patients through chart review and laboratory data.(20) Following transplant, the presence of acute GVHD (aGVHD) was scored according to standard Keystone criteria.(21) Chronic GVHD (cGVHD) was graded on the conventional scale of limited versus extensive disease on the basis of severity and organ involvement.(22) Choice and conditioning regimen, conditioning intensity, and GVHD prophylaxis was determined by the transplant physician based on patient age, co-morbidities, performance status, and donor source/match. Myeloablative conditioning (MAC) regimens for transplantation for ALL predominantly included high dose fractionated total body irradiation (TBI) ≥ 1200 cGy given in 6 fractions. Reduced intensity conditioning (RIC) regimens predominantly included fludarabine with intravenous busulfan 6.4 mg/kg or melphalan ≤ 140 mg/kg.(23) Post-transplant maintenance therapy with a TKI starting before day + 100 became a standard practice starting around 2015.

Statistical Analysis

Patients who experienced induction failure (n = 2) or were transplanted outside of CR1 (n = 8) were excluded. Comparisons between categorical variables were assessed using a Fisher exact test, and continuous variable comparisons were performed using a Wilcoxon rank-sum test. For all time-to-event assessments, those alive without the event of interest were censored at date last known alive. Overall survival (OS) is defined as time from transplant to date of death. Disease-free survival (DFS) for hematologic relapse is defined as time from transplant to date of hematologic relapse or death. One patient with missing MRD at transplant was excluded from OS and DFS analyses relating to MRD but included the overall outcome analyses. One patient who had “cord blood” for stem cell source was excluded from OS and DFS analyses. The above analyses were performed using Cox proportional hazards regression, and differences were assessed using the log rank test. The cumulative incidence of relapse (CIR) was calculated and compared between the high versus low intensity induction therapy groups from the time of transplant to time of relapse, with NRM as a competing event. Additionally, the cumulative incidence of molecular relapse was also estimated, as determined by the presence of detectable *BCR::ABL1* transcript on PCR without morphologic evidence of relapse. The cumulative incidence of grade II-IV aGVHD and cGVHD were also calculated with morphologic relapse or death as competing events. These analyses were performed using the Fine and Gray regression models, and differences were assessed using the Gray test. Lastly, analysis with a composite variable that combined induction intensity and transplant intensity (high/MAC, high/RIC, low/MAC, low/RIC) was explored for all

endpoints. All p-values are two-sided and considered significant at a 0.05 level. R version 4.0.5 was used for all analyses.

Results

Patient Characteristics

There were 87 patients with Ph + ALL who underwent alloHSCT in CR1 at the Dana-Farber Cancer Institute/Brigham and Women's Cancer Center between January 2010 and April 2021, with 44 and 43 patients receiving low intensity and high intensity induction following ALL diagnosis, respectively. Patient demographics, era of diagnosis, and baseline disease characteristics are listed in Table 1 organized by induction intensity. Patients receiving low intensity induction regimens were significantly older (median age 60 vs. 47 years, p = 0.005), and were more likely to be diagnosed after 2015 than those receiving high intensity induction regimens (73% vs. 33%, p < 0.001). Other clinical and pathologic characteristics did not differ between the two induction intensity groups including initial white blood cell (WBC) count, presence of central nervous system (CNS) disease, type of *BCR::ABL1* fusion transcript (p190 vs. p210), and presence of additional cytogenetic abnormalities.

Treatment Characterization and Oncologic Outcomes

Pre-alloHSCT Induction Treatment and Response

Tyrosine kinase inhibitor received, response to treatment, pre-alloHSCT MRD status and alloHSCT characteristics are shown in Table 2 organized by pre-transplant induction intensity. Dasatinib was the most frequently used TKI in both groups but was more common in the low intensity induction group: 95% compared to 65% in the low and high intensity groups, respectively (p = < 0.001), with the remainder mostly receiving imatinib. Most patients proceeded directly to alloHSCT after their initial treatment regimen with similar time to alloHSCT from Ph + ALL diagnosis in both low and high intensity groups (4 vs. 5 months, p = 0.93). Similar numbers of patients in both the low and high intensity induction groups received at least one additional "salvage" regimen for management of refractory disease prior to entering CR1 (14% vs. 16%, p = 0.77). Salvage regimens varied among patients, but included hyper-CVAD, high-dose cytarabine (HiDAC), asparaginase-based therapy, or blinatumomab. Pre-transplant MRD status by *BCR::ABL1* RT-PCR was available for 73 patients and showed similar rates of molecular MRD negativity between the two groups (54% vs. 52%, p = 0.99). Similarly, pre-transplant MRD negativity determined by flow cytometry was done in 79 patients and was not significantly different between groups (78% vs. 84%, p = 0.57).

Transplant Characteristics

Transplant characteristics are shown in Table 2 organized by pre-transplant induction intensity. Most patients received myeloablative conditioning prior to transplant, including 81% of patients who received a high intensity induction and 61% of patients who received a low intensity induction (p = 0.05). There were

more patients receiving stem cells from a matched unrelated donor in the low intensity induction group (75% vs. 51%, p = 0.013). There were no significant differences in distribution of stem cell sources between the low vs. high intensity induction groups. The majority of patients received tacrolimus-based GVHD prophylaxis in both groups (82% and 95% respectively, p = 0.12).

Post-Transplant Oncologic Outcomes by Pre-Transplant Chemotherapy Intensity

Post-transplant outcomes stratified by initial induction intensity are described in Table 3. At a median follow-up of 21 months, there were no significant differences in the 2-year DFS (58% vs. 56%, p = 0.58) or 2-year OS (62% vs. 63%, p = 0.46) as measured from date of transplant between the low and high intensity induction groups, respectively. Patients in low and high intensity induction groups also experienced comparable rates of RT-PCR detected molecular relapse (34% vs. 33%, p = 0.60) and hematologic relapse (9% vs. 17%, p = 0.78) by 2 years. The cumulative incidence of NRM at 2 years was not different in the low and high intensity induction groups, 33% and 29% respectively (p = 0.54). Similar results in DFS, OS, hematologic relapse, and NRM were achieved when restricting the cohort to patients who did not require any “salvage” therapies prior to transplant. Lastly, there were no statistically significant differences in the cumulative incidence of either acute or chronic GVHD between the two cohorts.

Factors Associated with Outcome

We conducted a univariate analysis to identify factors associated with OS, DFS, cumulative incidence of relapse (CIR), and NRM with results shown in Table 4, Table 5, and Fig. 1. With respect to CIR, RIC versus MAC conditioning intensity (HR, 2.92; 95% CI, 1.04–8.19, p = 0.042) and HCT-CI score of > 3 vs. 0–1 (HR, 4.59; 95% CI, 1.17-18.00; p = 0.029) were statistically significant factors associated with higher CIR. There was a trend toward higher CIR for those with CNS involvement at the time of diagnosis, but did not reach statistical significance (HR, 2.61 95% CI, 0.54–12.50; p = 0.23). Regarding NRM, patients aged 50–59 years had significantly higher NRM compared to those aged 40–49 years (HR, 3.15; 95% CI, 1.16–8.61; p = 0.025). Notably, while RIC vs. MAC transplant conditioning was associated with a higher incidence of relapse, initial induction intensity (low vs. high) was not significantly associated with OS (HR, 1.28; 95% CI, 0.66–2.49, p = 0.46), DFS (HR, 1.19; 95% CI, 0.64–2.20; p = 0.58), CIR (HR, 1.23; 95% CI, 0.43–3.57; p = 0.70) or NRM (HR, 0.80; 95% CI, 0.38–1.67; p = 0.55).

Long-term Outcomes by “Total” Treatment Approach.

We grouped patients by combining pre-transplant induction intensity and alloHSCT conditioning regimen intensity as shown in Fig. 2. Log-rank tests across the four categories showed no statistically significant difference between groups for OS, DFS, CIR, and NRM (p = 0.19, p = 0.40, p = 0.21, and p = 0.76 respectively). A comparison among the low intensity induction subgroup receiving MAC vs. RIC conditioning further showed no statistically significant difference in OS (HR, 1.02; 95% CI, 0.41–2.54; p = 0.97). Patients receiving high intensity pre-transplant induction chemotherapy followed by RIC alloHSCT

had an inferior OS compared to patients receiving high intensity induction followed by MAC alloHSCT (HR, 2.92; 95% CI, 1.08–7.94; p = 0.027), however these results should be interpreted with caution as only 8 patients received this combination.

Discussion

Our study shows that favorable long-term outcomes can be achieved for adults with Ph + ALL consolidated with alloHSCT in CR1 regardless of the intensity of the initial induction regimen. The 2-year OS of 62% and 63% in the low and high intensity induction groups in our cohort compares favorably to other recent series of Ph + ALL patients undergoing HSCT.(4, 9, 11–14, 16, 24–26)

There has been a paradigm shift towards the use of less intensive and chemotherapy-free induction regimens for Ph + ALL over the last decade. Multiple studies have confirmed that in patients with newly diagnosed Ph + ALL, the combination of a TKI, corticosteroids, and minimal (or no) chemotherapy can reliably induce deep remissions with minimal toxicity.(9, 10, 19, 27–31) Less understood is whether chemotherapy intensification prior to alloHSCT is needed after a low intensity induction, and whether the need for chemotherapy intensification depends on intensity of subsequent alloHSCT conditioning.

Our study included all patients with Ph + ALL consolidated with an alloHSCT in CR1 over a 10-year period at our center. Many patients received one or more cycles of intensive chemotherapy, most commonly hyper-CVAD plus TKI, prior to alloHSCT. However, there were also a large number of patients who received minimal or no chemotherapy prior to alloHSCT, bridging directly from remissions achieved by TKIs and corticosteroids to alloHSCT, similar to the strategy described by the GIMEMA LAL1509 as well as the CALGB 10701 approach.(19, 31) Patient age and comorbidities determined intensity of transplant conditioning strategy. Intensity of chemotherapy induction was dictated by age, comorbidities, but also changing practice patterns in the setting of new data. This heterogeneity allowed us to explore factors impacting long-term outcomes, including pre-transplant chemotherapy intensity and transplant conditioning.

We found no difference in OS, DFS, CIR, and NRM at 2 years between patients who received low versus high intensity chemotherapy prior to transplant, despite the older median age of the low intensity cohort. Our data suggest that low intensity chemotherapy followed by alloHSCT consolidation results in excellent outcomes, equivalent to outcomes achieved by patients who receive more intensive pre-transplant chemotherapy. These findings are encouraging as lower intensity regimens are well-tolerated with lower treatment-related mortality, maximizing the number of patients able to achieve adequate disease response with sufficient performance status to be considered for curative alloHSCT.(5, 7)

Multiple studies have demonstrated that low MRD status prior to alloHSCT is associated with lower risk of relapse and improved OS in Ph + ALL.(26, 32) The high rate of MRD negativity by flow cytometry in both cohorts in our study when compared to rate of MRD negativity by RT-PCR is concordant with previous literature, likely reflective of the increased sensitivity of RT-PCR and, in some cases, presence of *BCR-ABL* clonal hematopoiesis in other hematopoietic compartments.(33) While the sample size of our

cohort made the significance of MRD status on outcome less certain, the older patient cohort receiving low intensity induction had similar rates of pre-AlloHSCT MRD negativity compared to the younger cohort largely undergoing intensive induction, supporting the effectiveness of a TKI-based approach without the need for intensive chemotherapy in achieving deep remissions before alloHSCT.

We further examined patient outcomes by combining pre-transplant induction intensity and intensity of transplant conditioning regimens and found excellent outcomes among all of the subgroups of patients. The subgroup of patients receiving high intensity induction chemotherapy and myeloablative conditioning had a 2-year OS of 72.5%, while the cohort of patients receiving low intensity induction therapy and myeloablative pre-transplant conditioning had a similar 2-year OS of 63.0% ($p = 0.19$). This supports an approach of treating younger, fit patients with a lower intensity induction prior to transplant. Particularly intriguing is that patients receiving low intensity induction therapy followed by a RIC alloHSCT also had a statistically similar 2-year OS of 59.9% ($p = 0.19$), suggesting a minimally toxic approach with both low intensity induction and RIC transplantation can still offer high rates of cure for older and less fit patients with Ph + ALL.

There are several limitations to our study. While several studies have demonstrated that the presence of additional cytogenetic abnormalities, CNS involvement at diagnosis and MRD status at the time of alloHSCT influence OS and DFS, the limited sample size in this study limited our ability to detect the influence of these factors.(5, 24, 25) Additionally, as this dataset was comprised of patients referred for consideration of alloHSCT, we are not able to assess the full impact of high vs. low intensity induction based on intention to treat, and do not know how many patients who received induction were never referred for transplantation because they either developed treatment complications that precluded their transplant candidacy, died from the induction before transplant, or pursued an alternative treatment approach. However, our data is broadly applicable given that this study represents an unselected experience of a heterogenous cohort referred to a large, NCI designated transplant center. Furthermore, our findings are consistent with the result of the GRAAPH-2014 study which reported similar outcomes of transplanted patients regardless of treatment intensity prior to alloHSCT.(34)

In summary, our data demonstrate that in adult Ph + ALL patients who undergo consolidation with alloHSCT in CR1, the intensity of initial induction regimen at diagnosis does not significantly impact overall survival or molecular and hematologic relapse following alloHSCT, and that low dose induction should be considered even in young and fit patients diagnosed with Ph + ALL. Our data further suggests that excellent outcomes can be achieved by an entirely reduced intensity approach of low dose induction and RIC transplantation in patients who are too old or unfit to undergo myeloablative transplantation, and worthy of further study in younger and fit patients.

Declarations

Competing Interests: No associated clinical trial or external funding source was utilized in this research study. Please see individual competing interests for authors at the end of the manuscript.

Author Contributions: H.S.R and M.R.L designed the study, performed the research and wrote the paper. D.J.D, V.T.H and A.S.K designed the study and edited the manuscript. S.E.K, K.E.S, and D.N analyzed the data. E.S.W, M.W, J.S.G, and R.M.S edited the manuscript and wrote the paper.

Competing Interests: D.J.D. receives consultancy funding from Amgen, Autolos, Agios, Blueprint, Forty-Seven, Gilead, Incyte, Jazz, Novartis, Pfizer, and Takeda; and research funding from Abbvie, Blueprint, Glycomimetics, and Novartis. E.S.W. receives consultancy funding from Abbvie, Novartis, and Takeda. J.S.G. serves on the advisory board of Abbvie; receives consultancy funding from Abbvie, Astellas, and Takeda; and research funding from Abbvie, AstraZeneca, Genentech, Pfizer, and Prelude. A.S.K. receives consultancy funding from LabCorp and research funding from the Multiple Myeloma Research Foundation. R.M.S. receives consultancy funding from Abbvie, Actinium, Agios, Astellas, Biolinerx, Celgene, Daiichi-Sankyo, Elevate, Gemoab, Janssen, Jazz, Macrogenics, Novartis, OncoNova, Syndax, Syntrix, Syros, Takeda, Trovagene, BerGenBio, Foghorn Therapeutics, Glaxo Smith Kline, Aprea, Innate, Amgen, Boston Pharmaceuticals, Apteva, Epizyme, and Kura Oncology; and research funding from Abbvie, Agios, Arog, and Novartis. V.T.H. receives consultancy funding from Alexion, Allovir, and Omeros; and research funding from Jazz. M.R.L. serves on the advisory board of Pfizer; and receives research funding from Abbvie and Novartis. The remaining authors declare no competing financial interests.

Data Availability Statement: The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request

References

1. Burmeister T, Schwartz S, Bartram CR, Gökbuget N, Hoelzer D, Thiel E. Patients' age and BCR-ABL frequency in adult B-precursor ALL: a retrospective analysis from the GMALL study group. Blood. 2008;112(3):918–9.
2. Chiaretti S, Vitale A, Cazzaniga G, Orlando SM, Silvestri D, Fazi P, et al. Clinico-biological features of 5202 patients with acute lymphoblastic leukemia enrolled in the Italian AIEOP and GIMEMA protocols and stratified in age cohorts. Haematologica. 2013;98(11):1702–10.
3. Tanguy-Schmidt A, Rousselot P, Chalandon Y, Cayuela J-M, Hayette S, Vekemans M-C, et al. Long-Term Follow-Up of the Imatinib GRAAPH-2003 Study in Newly Diagnosed Patients with De Novo Philadelphia Chromosome-Positive Acute Lymphoblastic Leukemia: A GRAALL Study. Biology of Blood and Marrow Transplantation. 2013;19(1):150–5.
4. Fielding AK, Rowe JM, Buck G, Foroni L, Gerrard G, Litzow MR, et al. UKALLXII/ECOG2993: addition of imatinib to a standard treatment regimen enhances long-term outcomes in Philadelphia positive acute lymphoblastic leukemia. Blood. 2014;123(6):843–50.
5. Fielding AK. Curing Ph + ALL: assessing the relative contributions of chemotherapy, TKIs, and allogeneic stem cell transplant. Hematology Am Soc Hematol Educ Program. 2019;2019(1):24–9.
6. Ravandi F. How I treat Philadelphia chromosome-positive acute lymphoblastic leukemia. Blood. 2019;133(2):130–6.

7. Chalandon Y, Thomas X, Hayette S, Cayuela J-M, Abbal C, Huguet F, et al. Randomized study of reduced-intensity chemotherapy combined with imatinib in adults with Ph-positive acute lymphoblastic leukemia. Blood. 2015;125(24):3711–9.
8. Vignetti M, Fazi P, Cimino G, Martinelli G, Di Raimondo F, Ferrara F, et al. Imatinib plus steroids induces complete remissions and prolonged survival in elderly Philadelphia chromosome-positive patients with acute lymphoblastic leukemia without additional chemotherapy: results of the Gruppo Italiano Malattie Ematologiche dell'Adulto (GIMEMA) LAL0201-B protocol. Blood. 2007;109(9):3676–8.
9. Foà R, Vitale A, Vignetti M, Meloni G, Guarini A, De Propris MS, et al. Dasatinib as first-line treatment for adult patients with Philadelphia chromosome-positive acute lymphoblastic leukemia. Blood. 2011;118(25):6521–8.
10. Foà R, Bassan R, Vitale A, Elia L, Piciocchi A, Puzzolo MC, et al. Dasatinib-Blinatumomab for Ph-Positive Acute Lymphoblastic Leukemia in Adults. N Engl J Med. 2020;383(17):1613–23.
11. Short NJ, Kantarjian H, Konopleva M, Desikan SPP, Jain N, Ravandi F, et al. Updated Results of a Phase II Study of Ponatinib and Blinatumomab for Patients with Philadelphia Chromosome-Positive Acute Lymphoblastic Leukemia. Blood. 2021;138(Supplement 1):2298-.
12. Ravandi F, Othus M, O'Brien SM, Forman SJ, Ha CS, Wong JYC, et al. US intergroup study of chemotherapy plus dasatinib and allogeneic stem cell transplant in Philadelphia chromosome positive ALL. Blood Advances. 2016;1(3):250–9.
13. Kim DY, Joo YD, Lim SN, Kim SD, Lee JH, Lee JH, et al. Nilotinib combined with multiagent chemotherapy for newly diagnosed Philadelphia-positive acute lymphoblastic leukemia. Blood. 2015;126(6):746–56.
14. Chiaretti S, Vitale A, Vignetti M, Piciocchi A, Fazi P, Elia L, et al. A sequential approach with imatinib, chemotherapy and transplant for adult Ph + acute lymphoblastic leukemia: final results of the GIMEMA LAL 0904 study. Haematologica. 2016;101(12):1544–52.
15. Fielding AK, Rowe JM, Richards SM, Buck G, Moorman AV, Durrant IJ, et al. Prospective outcome data on 267 unselected adult patients with Philadelphia chromosome-positive acute lymphoblastic leukemia confirms superiority of allogeneic transplantation over chemotherapy in the pre-imatinib era: results from the International ALL Trial MRC UKALLXII/ECOG2993. Blood. 2009;113(19):4489–96.
16. Short NJ, Jabbour E, Sasaki K, Patel K, O'Brien SM, Cortes JE, et al. Impact of complete molecular response on survival in patients with Philadelphia chromosome-positive acute lymphoblastic leukemia. Blood. 2016;128(4):504–7.
17. Jabbour E, Short NJ, Ravandi F, Huang X, Daver N, DiNardo CD, et al. Combination of hyper-CVAD with ponatinib as first-line therapy for patients with Philadelphia chromosome-positive acute lymphoblastic leukaemia: long-term follow-up of a single-centre, phase 2 study. Lancet Haematol. 2018;5(12):e618-e27.

18. Ghobadi A, Slade M, Kantarjian HM, Alvarenga J, Aldoss I, Mohammed K, et al. The Role of Allogeneic Transplant for Adult Ph + ALL in CR1 with Complete Molecular Remission: A Retrospective Analysis. Blood. 2022.
19. Chiaretti S, Ansuinelli M, Vitale A, Elia L, Matarazzo M, Piciocchi A, et al. A multicenter total therapy strategy for de novo adult Philadelphia chromosome positive acute lymphoblastic leukemia patients: final results of the GIMEMA LAL1509 protocol. Haematologica. 2021;106(7):1828–38.
20. Sorror ML, Maris MB, Storb R, Baron F, Sandmaier BM, Maloney DG, et al. Hematopoietic cell transplantation (HCT)-specific comorbidity index: a new tool for risk assessment before allogeneic HCT. Blood. 2005;106(8):2912–9.
21. Przepiorka D, Weisdorf D, Martin P, Klingemann HG, Beatty P, Hows J, et al. 1994 Consensus Conference on Acute GVHD Grading. Bone Marrow Transplant. 1995;15(6):825-8.
22. Socié G, Ritz J. Current issues in chronic graft-versus-host disease. Blood. 2014;124(3):374–84.
23. Leonard JT, Hayes-Lattin B. Reduced Intensity Conditioning Allogeneic Hematopoietic Stem Cell Transplantation for Acute Lymphoblastic Leukemia; Current Evidence, and Improving Outcomes Going Forward. Curr Hematol Malig Rep. 2018;13(4):329–40.
24. Saini N, Marin D, Ledesma C, Delgado R, Rondon G, Popat UR, et al. Impact of TKIs post–allogeneic hematopoietic cell transplantation in Philadelphia chromosome–positive ALL. Blood. 2020;136(15):1786–9.
25. Webster JA, Luznik L, Tsai HL, Imus PH, DeZern AE, Pratz KW, et al. Allogeneic transplantation for Ph + acute lymphoblastic leukemia with posttransplantation cyclophosphamide. Blood Adv. 2020;4(20):5078–88.
26. Bachanova V, Marks DI, Zhang MJ, Wang H, de Lima M, Aljurf MD, et al. Ph + ALL patients in first complete remission have similar survival after reduced intensity and myeloablative allogeneic transplantation: impact of tyrosine kinase inhibitor and minimal residual disease. Leukemia. 2014;28(3):658–65.
27. Martinelli G, Piciocchi A, Papayannidis C, Paolini S, Robustelli V, Soverini S, et al. First Report of the Gimema LAL1811 Phase II Prospective Study of the Combination of Steroids with Ponatinib As Frontline Therapy of Elderly or Unfit Patients with Philadelphia Chromosome-Positive Acute Lymphoblastic Leukemia. Blood. 2017;130(Supplement 1):99-.
28. Rousselot P, Coudé MM, Gokbuget N, Gambacorti Passerini C, Hayette S, Cayuela JM, et al. Dasatinib and low-intensity chemotherapy in elderly patients with Philadelphia chromosome-positive ALL. Blood. 2016;128(6):774–82.
29. Ottmann OG, Pfeifer H, Cayuela J-M, Spiekermann K, Jung W, Beck J, et al. Nilotinib (Tasigna®) and Low Intensity Chemotherapy for First-Line Treatment of Elderly Patients with BCR-ABL1-Positive Acute Lymphoblastic Leukemia: Final Results of a Prospective Multicenter Trial (EWALL-PH02). Blood. 2018;132:31.
30. Sugiura I, Doki N, Hata T, Cho R, Ito T, Suehiro Y, et al. Dasatinib-based 2-step induction for adults with Philadelphia chromosome–positive acute lymphoblastic leukemia. Blood Advances.

2022;6(2):624–36.

31. Wieduwilt MJ, Yin J, Wetzler M, Uy GL, Powell BL, Kolitz JE, et al. Dasatinib and dexamethasone followed by hematopoietic cell transplantation for adults with Ph-positive ALL. Blood Adv. 2021;5(22):4691–700.
32. Nishiwaki S, Imai K, Mizuta S, Kanamori H, Ohashi K, Fukuda T, et al. Impact of MRD and TKI on allogeneic hematopoietic cell transplantation for Ph + ALL: a study from the adult ALL WG of the JSHCT. Bone Marrow Transplantation. 2016;51(1):43–50.
33. Zhao X, Zhao X, Chen H, Qin Y, Xu L, Zhang X, et al. Comparative Analysis of Flow Cytometry and RQ-PCR for the Detection of Minimal Residual Disease in Philadelphia Chromosome–Positive Acute Lymphoblastic Leukemia after Hematopoietic Stem Cell Transplantation. Biology of Blood and Marrow Transplantation. 2018;24(9):1936–43.
34. Rousselot P, Chalandon Y, Chevret S, Cayuela J-M, Huguet F, Chevallier P, et al. The Omission of High-Dose Cytarabine during Consolidation Therapy of Ph-Positive ALL Patients Treated with Nilotinib and Low-Intensity Chemotherapy Results in an Increased Risk of Relapses Despite Non-Inferior Levels of Late BCR-ABL1 MRD Response. First Results of the Randomized Graaph-2014 Study. Blood. 2021;138:512.

Tables

Tables 1 to 6 are available in the Supplementary Files section.

Figures

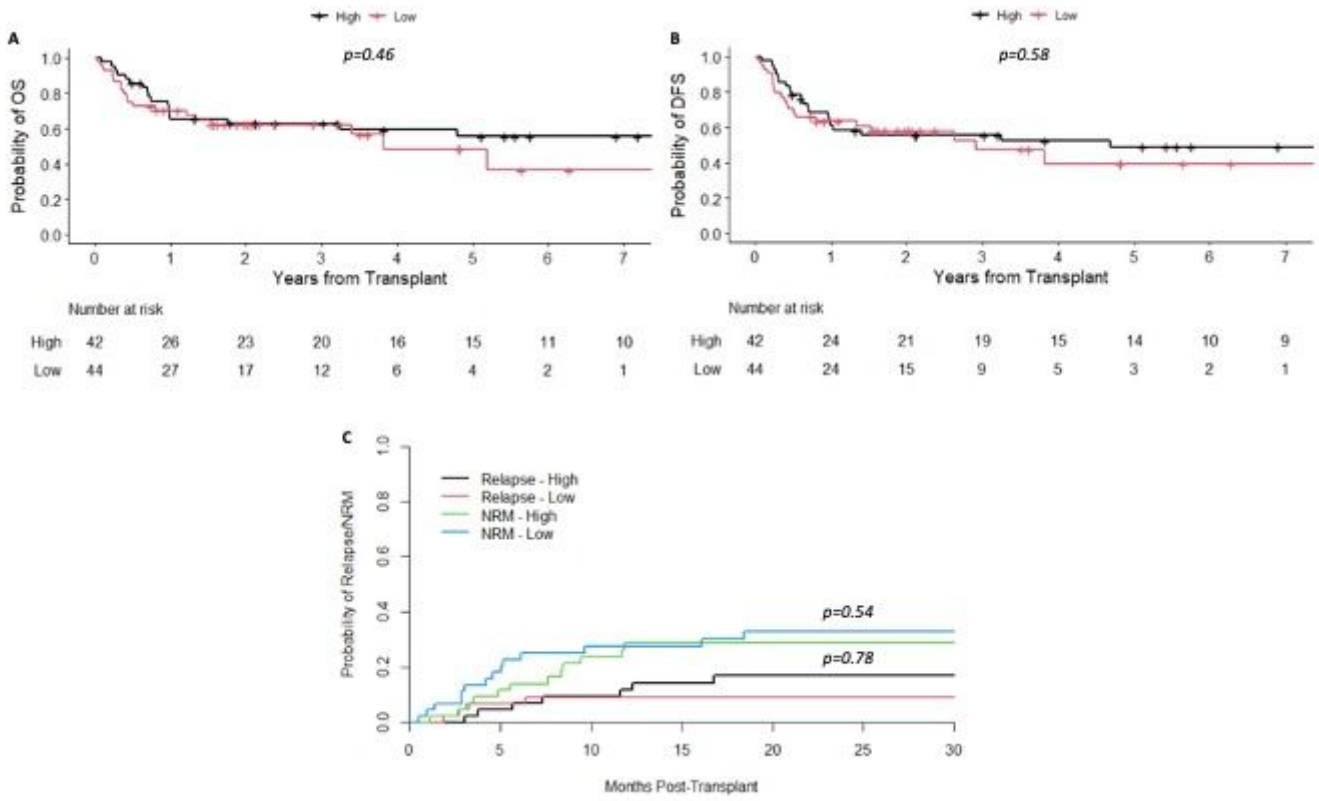

Figure 1

Outcomes based on induction intensity with Kaplan-Meier plots of oncologic outcomes. (A) OS for whole cohort separated by pre-transplant induction regimen intensity. (B) DFS for whole cohort separated by pre-transplant chemotherapy intensity. (C) CIR and NRM for whole cohort separated by pre-transplant intensity.

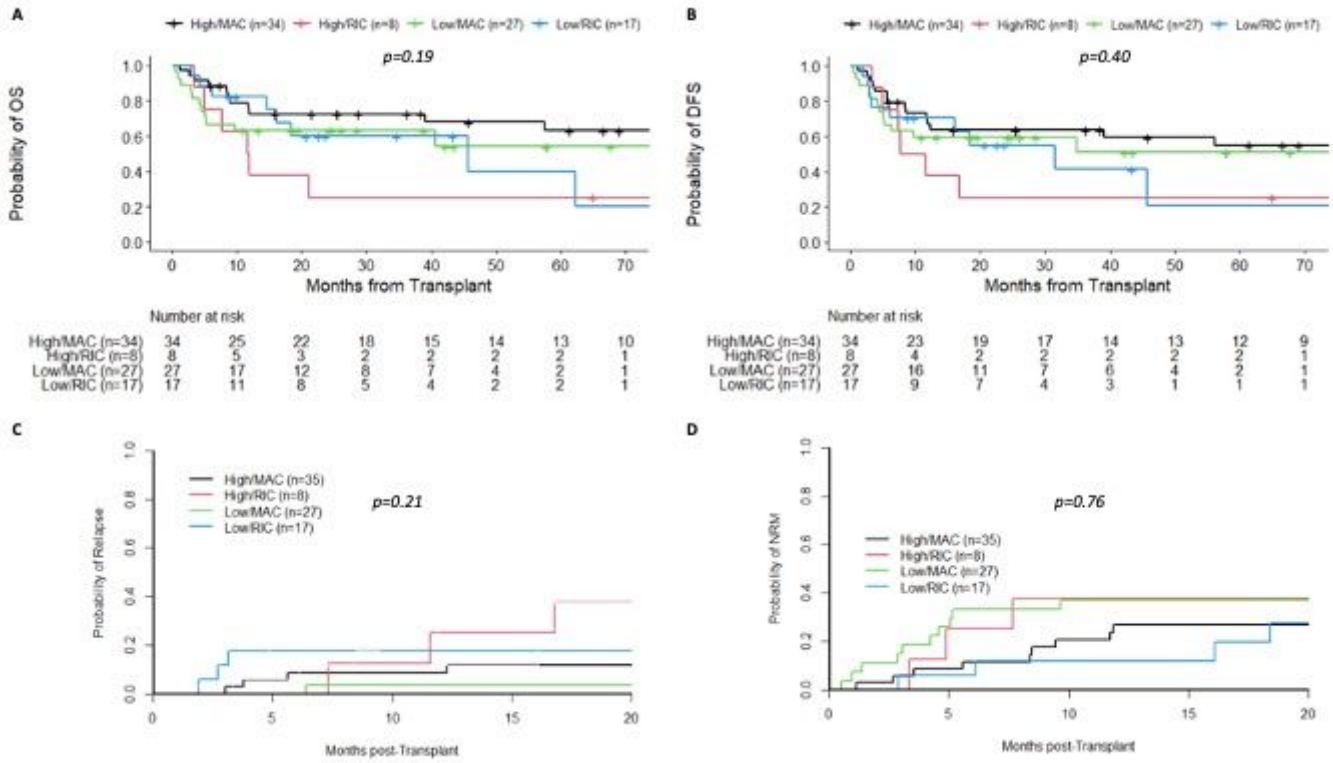

Figure 2

Outcomes based on both induction and transplant conditioning regimens with Kaplan-Meier plots of oncologic outcomes by pair subgroup. (A) OS separated by paired cohorts. (B) DFS separated by paired cohorts. (C) CIR separated by paired cohorts. (D) NRM separated by paired cohorts.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Table1.xlsx
- Table2.xlsx
- Table3.xlsx
- Table4.xlsx
- Table5.xlsx
- Table6.xlsx
- TreatmentSupplement.pdf