Synergistic Effect of Anti-Thymocyte Globulin Combined with Post-Transplant Cyclophosphamide for Dual T Cell Modulation in Haploidentical Stem Cell Transplantation for Poor Prognosis Acute Leukemia.

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Abstract

Background: In the evolution of haploidentical stem cell transplantation (haplo-SCT), the implementation of anti-thymocyte globulin (ATG)-based and high-dose posttransplant cyclophosphamide (PTCy)-based regimens has improved patient outcomes. We hypothesized that the combination of ATG and PTCy in the correct sequence and with proper timing has a synergistic effect on immune tolerance. The *purpose* of the study *was* to discover whether the concomitant use of ATG and PTCy would *be* advantageous for haplo-SCT and which subgroup of patients would receive the most benefit.

Methods: This cohort was conducted on 119 patients with poor prognosis acute myeloid leukemia (AML) or acute lymphoblastic leukemia (ALL) who underwent haplo-SCT with peripheral blood stem cell (PBSC) sources and myeloablative conditioning (MAC) regimens using a uniform protocol in our center from 2010 to 2019. The outcomes of patients who received a combination of rabbit ATG (2.5 mg/kg/d for three days) plus modified PTCy (40 mg/kg/d on days +3 and +4) (n=100) was compared with those of patients who received an ATG-only regimen (n=19). The median follow-up was 35.8 months. Both arms shared similar characteristics, except for the median donor age, the distribution of relationships, and the median time between diagnosis and transplantation.

Results: The cumulative incidence of acute graft versus host disease (aGvHD) grade II-IV was significantly lower in the ATG-PTCy group ($P < 0.0001$), although the incidence of 30-day neutrophil engraftment was higher in the ATG group ($P = 0.036$). The overall outcome was not significantly different between the two arms. Subgroup analyses stratified by disease status separately for AML and ALL indicated 3-year leukemia-free survival rates of 72% and 24.6% for the first remission of intermediate-high risk AML and ALL; 34.4% and 34.5% for recurrent disease; and 46% and 33.3% for refractory disease.

Conclusion: Our experience indicates that the combination of ATG +PTCy in the context of MAC and PBSC sources offers satisfactory outcomes for patients with intermediate-high risk AML receiving haplo-SCT during the first remission; however, some modifications are recommended to improve the results of other subgroups.

Introduction

Despite many advances in bone marrow transplantation procedures and supportive measures over recent years (1, 2), selecting a suitable alternative donor at the optimal time is one of the fundamental challenges of HSCT centers when an HLA-matched donor is not available.

Haploidentical transplant outcomes have significantly improved, now resembling those of matched unrelated transplant recipients (3, 8, 9). In addition, the possibility of accessing an available and inexpensive donor (4) quickly and the ability of repeating stem cell collection if indicated (5, 6) have led to a significant expansion of the use of haplo-SCT (7, 10).

In recent years, during the evolution of haplo-SCT, the implementation of two different methods, in vivo T cell depletion by an anti-thymocyte globulin (ATG)-based regimen and induction of immune tolerance by high-dose posttransplant cyclophosphamide (PTCy), has had a great impact on improving haplo-SCT outcomes (11–13). Administration of PTCy over a specific time frame early after graft infusion (50 mg/kg, days + 3, +4) prevents GvHD by selectively attenuating rapidly proliferating alloreactive T cells after antigen exposure. Interestingly, regulatory T cells, which play an influential role in preventing GvHD, are resistant to PTCy due to the high expression of aldehyde dehydrogenase (14–16).

When administered as a part of the conditioning regimen for T-cell replete (TCR) haplo-SCT, ATG at a dose of 2.5 mg/kg/day (-3, -2, -1) has been shown to facilitate engraftment and reduce rejection by depleting recipient T cells (17, 18). It has also been reported to decrease the chronic GvHD incidence after unrelated transplantation (19).

According to some retrospective studies, the concomitant use of PTCy + ATG in the proper sequence and with optimal timing had a synergistic effect on reducing GvHD compared to other protocols (20–22); however, it could also increase the rate of CMV reactivation, graft failure, or delayed engraftment (20, 23, 24). Thus, some researchers prefer adjusting the to prevent related complications while maintaining anti-GvHD effects (20, 21, 23).

In the present study, we report the outcomes of acute leukemia patients with a poor prognosis who underwent G-CSF-mobilized PBSC grafts from haplo donors after the MAC regimen and received a combination of conventional-dose ATG plus a modified dose of PTCy.

Material And Methods

Data collection and ethical considerations

The ethical committee of the Hematology, Oncology and Stem Cell Transplantation Research Center (HORCSCT), affiliated with Tehran University of Medical Sciences (TUMS), approved the study (reference IR.TUMS.HORCSCT.REC.1399.011). The work was carried out in accordance with relevant guidelines and regulations. All of the patients gave informed and written consent to the transplantation procedure and use of their data.

Demographic, clinical, and laboratory data of patients and donors were collected from their medical profiles using a checklist. We updated the data and followed the patients until late April 2020.

Transplant procedures and study design

Recipients of haplo-SCT received unmanipulated G-CSF-mobilized peripheral blood grafts after MAC regimens that consisted of Bu/Cy; Busulphan (3.2 mg/kg on days −6 through −3) and cyclophosphamide (40 mg/kg on days – 3 and – 2). GvHD prophylaxis for haplo-SCT recipients consisted of cyclosporine A (CyA; 1.5 mg/kg on days − 6 through – 2 and then 3 mg/kg/day), rabbit ATG (2.5 mg/kg on days -3, -2, -1), and a modified dose of PTCy (40 mg/kg on days +3 and +4). The above strategy has been used since

2015 as the *standard protocol of our center* for haplo-SCT recipients based on our previous prospective study that was published as an abstract in BMT 2015 (38).

Supportive care:

All patients received standard prophylaxis regimens including acyclovir, fluconazole, and trimethoprim/ sulfamethoxazole to prevent herpes simplex virus, fungal infection, and Pneumocystic jivecii infection. Preemptive therapy with ganciclovir for cytomegalovirus disease prevention was performed based on viral load measurements. Patients with relapsed/refractory leukemia often received a single course of salvage therapy such as FLAG±M (fludarabine, high-dose cytarabine, G-CSF ± mitoxantrone) to decrease disease burden before transplant.

Outcomes and definitions

The primary endpoints were the probability of disease-free survival (DFS) and cumulative incidences (CI) of grades II-IV acute graft versus host disease (aGvHD). Secondary endpoints were overall survival (OS), the cumulative incidences of nonrelapse mortality (NRM), relapse, and engraftment.

OS was defined as the time between HSCT to death or last contact. DFS was defined as the length of time after transplantation during which no disease was found. Neutrophil engraftment was defined as ANC (absolute neutrophil count) ≥ 500 cells/μL in three consecutive days.

Acute and chronic GVHD were graded according to the modified and revised Seattle criteria (25, 26). The incidence of aGvHD was defined as the development of aGvHD within 100 days after HSCT when death and relapse were considered competing risks. Relapse incidence (RI) was defined as the time to disease recurrence or reappearance of blasts (>5%), given that the patient was previously in remission. NRM was defined as death without relapse and was considered a competing event for relapse. Poor-prognosis acute leukemia included the first remission event of intermediate or high-risk AML and ALL according to the 2010 ELN recommendations and ALL risk stratification (27, 28), recurrent disease, and primary refractory AML/ALL.

Statistical analysis

All demographic, clinical, and laboratory characteristics were compared between two groups (ATG and ATG +PTCy) using the Mann-Whitney test for continuous variables and the chi-square test for categorical variables.

Patients who were followed beyond three years were censored for a better comparison of the two groups, as crucial differences between follow-up periods can cause serious bias. The median follow-up time was calculated by the reverse Kaplan-Meier method. OS and DFS rates were estimated by the Kaplan-Meier method and compared among different categories for each covariate using the log-rank χ^2 test. The CIs of ANC recovery, aGvHD, relapse, and NRM were calculated and compared by the Gray test.

A Cox proportional hazard regression model was used for univariable and multivariable analyses of OS and DFS. The assumption of proportionality of hazards was tested for each covariate using Schoenfeld's residuals and plotting criteria. Univariable and multivariable Fine and Gray proportional subdistribution hazard regression models were applied to test the associations of covariates with relapse and NRM incidence.

All variables with a p-value < 0.2 in the univariable analyses were incorporated in the multivariable analysis. A significance level of 0.05 was used for all analyses. Analyses were conducted using Stata (version 11.2, Stata Corp LP, College Station, TX, USA) and Packages "survival," "cmprsk," and "coxphf" in R software version 3.3.1.

Results

Patient characteristics

The study population included patients (total=119) with poor-prognosis AML (n=76) or ALL (n=43) who had no matched available donor and underwent haplo-SCT from mismatched first-degree relatives from Jan. 2010 to Dec. 2019 at the HORCSCT, a tertiary referral center in Tehran, Iran.

Baseline demographic characteristics are shown in Table 1. One hundred patients received the ATG plus PTCy regimen, and 19 patients received the ATG-based protocol. Among patients with AML and ALL, 24 (31.5%) and 17 (39.5%) were transplanted during the first remission, 44 (57.8%) and 17 (39.5%) received haplo-SCT after recurrent disease, and 8 (10.5%) and 9 (20.9%) received haplo-SCT after refractory leukemia.

Except for median donor age, the distribution of relationships, and the median time between diagnosis and HSCT, which were significantly different, there was no other statistically significant difference between the two arms. Infection and relapse were the two common causes of death in total (accounting for 44.44% and 22.22%, respectively), with a normal distribution between the two groups (P = 0.772).

Engraftment and acute graft-versus-host disease (aGvHD)

The CI of ANC engraftment at day 30 was 94.74% [95% confidence interval (95% CI): 50.47 - 99.57] in ATG arm and 83.00% (95% CI: 73.96 - 89.13) in ATG plus PTCy (P = 0.036). As shown in the Figure 1A, the 100-day CI of aGvHD (grade II-IV) was much lower in ATG plus PTCy arm than ATG alone (P < 0.0001). The rate of extensive chronic GVHD was also significantly higher in the ATG arm (n=15, 93.7%) than PTCy plus ATG (n=35, 69%) (P= 0.004). Figs 1B, 1C give the pictures of the aGvHD incidence separately for AML and ALL, stratified by disease status before transplant.

Overall Survival, Disease-free Survival, Relapse Incidence, and Nonrelapse Mortality

The median follow-up times were 3 and 2.54 years in the ATG and ATG plus PTCy arms, respectively. By the end of the follow-up time, 52.94% of patients (n= 63) died (47.37% and 54.00% in the ATG and ATG

plus PTCy arms, respectively). Only 17 patients relapsed, with two relapsed patients in the ATG arm and the rest in the ATG plus PTCy arm.

The three-year OS and DFS rates together with the log-rank test results for different groups of covariates were calculated and are depicted in Supplementary Table 1. There were no statistically significant differences in 3-year OS and DFS (P = 0.19 and P = 0.23, respectively) or 3-year RI and NRM (P = 0.49 and P = 0.45, respectively) between the two arms (Figs 2A, 3A, and Supplementary Figs 1A, 2A).

The three-year OS, DFS, RI, and NRM for AML and ALL patients stratified by disease status before transplantation are shown in Table 3, Figs 2 and 3 (B, C) and Supplementary Figs 1 and 2 (B, C).

Univariable and multivariable modeling of OS, DFS, relapse incidence, and NRM

The multivariable modeling analyses of OS, DFS, relapse, and NRM are shown in Table 2, and the univariable analyses are shown in Supplementary Table 2. Multivariable Cox regression analysis of OS and DFS indicated that donor age was a statistically significant hazard factor for OS and DFS, increasing by 6% every year (HR: 1.06; P = 0.012).

Compared to sibling donor (reference), offspring was a hazard factor associated with worse OS and DFS (HR: 5.27; P =0.044 & HR: 5.78; P =0.031) while father as donor, was a protective factor for OS and DFS which declined the risk of death or relapse up to 88 percent. AML rather than ALL (HR: 0.50; P = 0.025 & HR: 0.47; P =0.017) and experiencing aGvHD (HR: 0.47; P = 0.014 & HR: 0.45; P = 0.010 respectively) both had independent protective effects on the OS and DFS.

The multivariable analysis of RI demonstrated that mother and offspring in comparison with sibling donors had a significant association with a higher RI (HR: 2.61, P = 0.032 & HR: 5.35, P = 0.017, respectively). Moreover, minor ABO mismatched compared to ABO matched (P = 0.005) and receiving HSCT for refractory disease compared with CR1 status were also correlated with higher RI by nearly four times (P =0.009). The results showed that experiencing aGvHD after HSCT significantly decreased the RI by approximately 80% (HR: 0.21, P =0.005). A higher NRM was significantly associated with increasing recipient age and recurrent disease, while a higher CD34 dose and AML (compared to ALL) had incredibly protective associations with NRM.
Multivariable modeling analyses of OS and DFS, separately for AML and ALL, demonstrated that receiving haplo-SCT in recurrent or refractory disease status in comparison with the first remission of intermediate-high risk disease (reference), was independently associated with lower OS and DFS in AML (HR: 3.42; 95%CI: 1.23 – 10.46, P = 0.022 & HR: 4.48; 95%CI: 0.98 – 17.54, P = 0.042 respectively), while this is not true in patients with ALL. Compared to ABO matched (reference), major ABO mismatched was a hazard factor associated with worse OS and DFS in patients with AML (HR: 2.84; 95%CI: 1.01 – 7.97, P = 0.047 & HR: 2.82; 95%CI: 0.99 – 8.02, P = 0.050 respectively) (Supplementary Table 3).

Discussion

According to our center's strategy, haplo-SCT has primarily been used for patients with relapsed, refractory, or high-risk acute leukemia in the absence of a matched donor. Therefore, a myeloablative conditioning regimen to remove residual disease and TCR-PBSC sources to improve engraftment and GVL effects were administered. Subsequently, the expectation of a high incidence of acute and chronic GvHD related to a mismatched donor, MAC, and the PBSC source (29) motivated us to design a combination regimen consisting of standard-dose ATG plus a modified dose of PTCy (in addition to cyclosporine A) for stronger GvHD prophylaxis (30–32).

The rationale for using the lower dose of PTCy (40 mg/kg, days + 3, +4) in combination with ATG in the context of MAC with PBSCs as the "standard protocol of the center" for all haplo-SCT recipients was based on a prospective study that was conducted on 40 haplo-SCT recipients in our center between 2010 and 2015 and reported as an abstract in BMT 2015 (38).

In this retrospective and single-center cohort, we evaluated the posttransplant outcomes of patients with poor-prognosis acute leukemia undergoing haplo-SCT with our center protocol who received the combination of ATG/PTCy compared with a smaller group with similar characteristics who received the ATG-only protocol. Moreover, to evaluate whether the effect of this protocol is more prominent in myeloid or lymphoid subsets, patients with AML and ALL were separately analyzed after stratification by disease status.

The essential findings of the comparisons between the two arms are as follows: the comparison of outcome events (three-year OS, DFS, RI, and NRM) between the two arms showed that neither arm showed superiority, as the association was not statistically significant, which may be due to the small number of patients in the ATG-based arm. The CI of aGVHD (grade II-IV) was significantly lower in the ATG-PTCy group, although the CI of ANC engraftment at day 30 was better in the ATG group.

Despite a relatively high incidence of aGvHD for all subjects, the occurrence of severe types was infrequent, so aGvHD remained a rare cause of posttransplant mortality, accounting for only 7.41% and 11.1% in the ATG-PTCy and ATG groups, respectively. Interestingly, experiencing aGvHD was an independent protective factor for OS and DFS by preventing relapse (Table 2).

Our results are in agreement with the findings of previous studies comparing the ATG/PTCy combination with other GvHD prophylaxis regimens on posttransplant outcomes, which showed a significant reduction in aGvHD incidence with the combination regimen; nevertheless different doses of ATG or PTCy were used, and there was heterogeneity in the transplant protocols (21, 22, 30–34).

The following articles have explored different doses of ATG/PTCy in combination for haplo-SCT: A low-dose ATG (4.5 mg/kg, total) plus standard-dose PTCy regimen was reported by Law et al. in patients with a low incidence of acute and chronic GvHD (20%, 15%); the 1-year DFS, RI, and NRM were 35.7%, 16%, and 38.2%, respectively (23). Another study demonstrated that standard-dose ATG in conjunction with low-dose PTCy (14.5 mg/kg, days + 3, +4) was associated with reduced GvHD and NRM incidence compared with an ATG-based regimen (20). Yang J et al. applied a different form of combination regimen

consisting of a low dose of both ATG (5 mg/kg, total) and PTCy (50 mg/kg, one day) combined with unrelated cord blood that was associated with a lower incidence of GvHD and NRM in comparison to the ATG-based protocol (21).

Subgroup analyses to evaluate AML and ALL patient outcomes stratified by disease status indicated that the 3-year DFS rates of recurrent and refractory disease in patients with ALL (34.5%, 33.3%) were better than those in patients experiencing their first remission of intermediate-high risk ALL (24.6%). We have no explanation for this finding; this discrepancy may be due to the small number of patients in these subsets.

After adjustment of the multivariate model, patients with intermediate- or high-risk AML who received haplo-SCT during the first CR had significantly better outcomes than patients with relapsed and refractory disease. Since all but one intermediate-high risk AML patient who was transplanted in the first remission was included in the ATG/PTCy arm, we compared outcomes (3-year DFS, NRM, and RI of 72%, 23%, and 5%) with two reports of EBMT that were conducted on similar risk groups, as follows:

In the first paper, the 2-year LFS, NRM, and RI of patients with adverse-karyotype AML receiving haplo-SCT during the first CR with different protocols were 53%, 19%, and 27% (8), and in the second report, the 2-year LFS, NRM, and RI were 58%, 23% and 19%, respectively, for patients with intermediate- or high-risk AML receiving haplo-SCT during the first remission (35).

Taken together, the results indicate that patients with intermediate-high risk AML undergoing haplo-SCT during the first CR using our center protocol had better outcomes than other subgroups in the present study and similar populations in other studies (8, 35).

Patients who received haplo-SCT beyond first CR (recurrent disease) were at higher risk for transplant-related morbidity, with the incidence of NRM exceeding 50% and 40% for AML and ALL, respectively (Table 3). In this regard, considering a lower intensity conditioning regimen to reduce the NRM in recurrent patients may be effective, provided there is no residual disease (36).

Given that infectious diseases were the most common cause of death in our study subjects and the high rate of posttransplant CMV reactivation, it seems that an adjustment in the immunosuppression protocol for certain patients (20, 21) and the design of a CMV prophylactic regimen suitable for high-risk transplants (37) could potentially improve NRM by decreasing infectious complications. Moreover, in the refractory group, increased mortality was secondary to increased relapse incidence.

Regarding donor selection for haplo-SCT, it should be noted that the assessment of donor-specific anti-HLA antibodies (DSAs) has been available at our center during the last few years and has produced changes in the donor selection process over time; for example, in the early ATG cohort, there was an extensive use of mothers as donors, whereas in the more recent cohort, siblings were the most commonly used donors.

Conclusion

In summary, the most important finding of the present study is that ATG + PTCy in the context of myeloablative conditioning with a PBSC source offers satisfactory results for patients with intermediate-high risk AML receiving haplo-SCT during the first remission; however, some modifications are warranted to improve the outcome of other subgroups. Further prospective research is warranted to determine which group of haplo-SCT patients would benefit most from the concomitant use of ATG and PTCy and what range of doses is more suitable for the combination protocol.

Limitations

This study had certain limitations, including its retrospective nature, single-center design, and small sample size, with even fewer events in the ATG arm, which made it relatively difficult to interpret the Cox regression analyses as well (as evidenced by the wide confidence intervals). Moreover, we could not determine the cumulative incidence of cGvHD because of insufficient data regarding the exact time of chronic GvHD onset. Our findings need to be confirmed by a large prospective study, which is now ongoing at our center.

Abbreviations

aGVHD: acute Graft-versus-Host Disease

ALL: Acute Lymphoblastic Leukemia

AML: Acute Myeloid Leukemia

ANC: Absolute Neutrophil Count

ATG: Anti-Thymocyte Globulin

cGVHD: chronic Graft-versus-Host Disease

CI: Confidence Interval

CR: Complete Remission

haplo-SCT: Haploidentical Stem Cells Transplantation

HR: Hazard Ratio

LFS: Leukemia-Free Survival

MAC: Myeloablative Conditioning

NRM: Non-Relapse Mortality

OS: Overall Survival

PBSC: Peripheral Blood Stem Cell

PTCy: post-Transplant Cyclophosphamide

RI: Relapse Incidence

Declarations

Availability of data and materials

The datasets generated during the current study are available from the corresponding author on a reasonable request.

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Authors' Contributions

A.G., M.B., and A.K. conceived the concept and designed the research. M.B. and S.A.M. collected the data. M.B. and A.K. prepared the original draft and wrote the manuscript. A.K. did the statistical analysis. All authors read and approved the final manuscript.

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Availability of Data and Materials

The datasets generated during the current study are available from the corresponding author on a reasonable request.

Ethics Approval and Consent to Participate

Ethical issues (including plagiarism, informed consent, misconduct, data fabrication and/or falsification, double publication and/or submission, redundancy) have been completely observed by the authors.

Consent for Publication

Informed consent was obtained from all subjects whose clinical data has been used in this study.

Competing Interests

The authors declare that they have no competing interests.

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Tables

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Figures

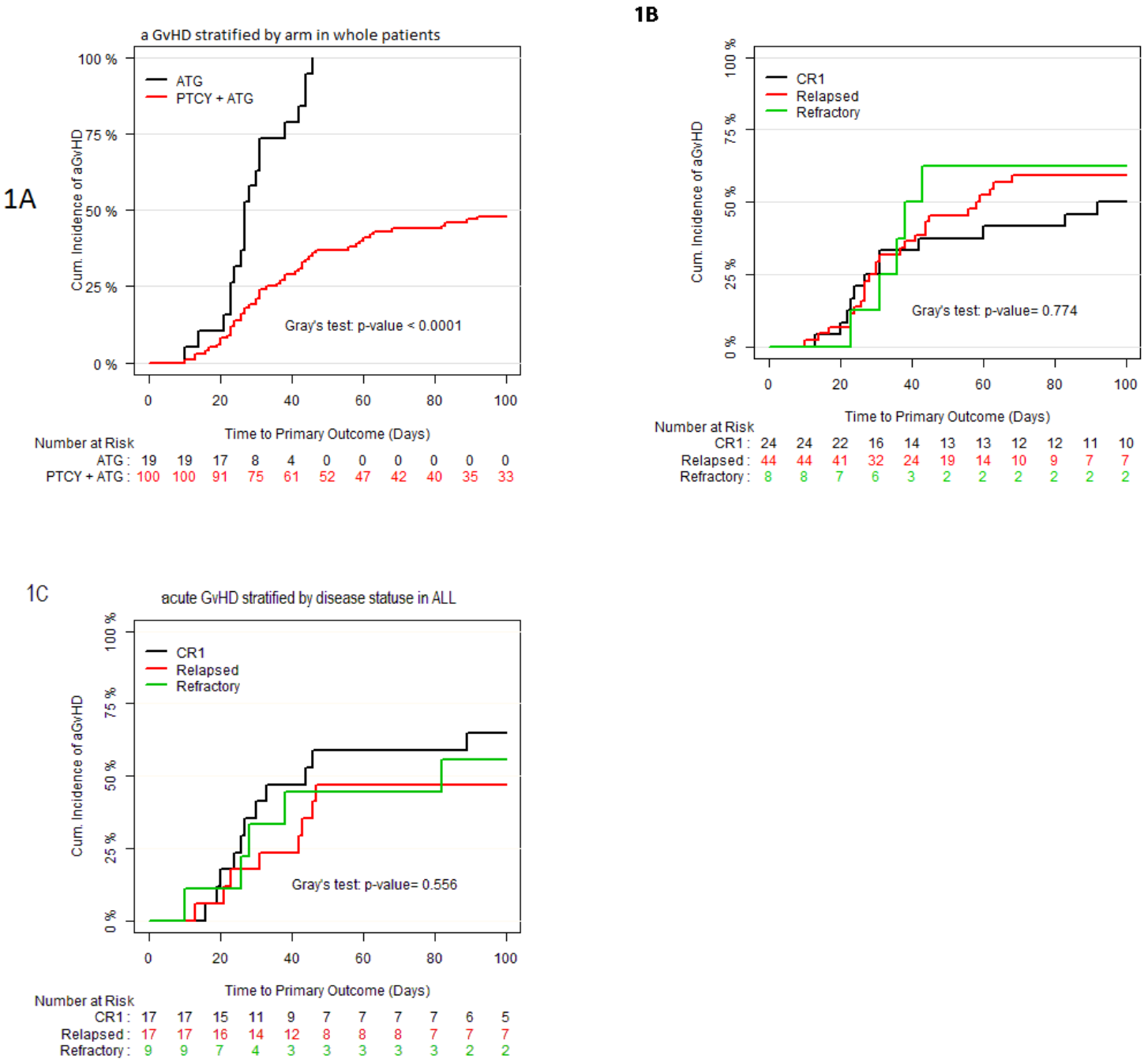
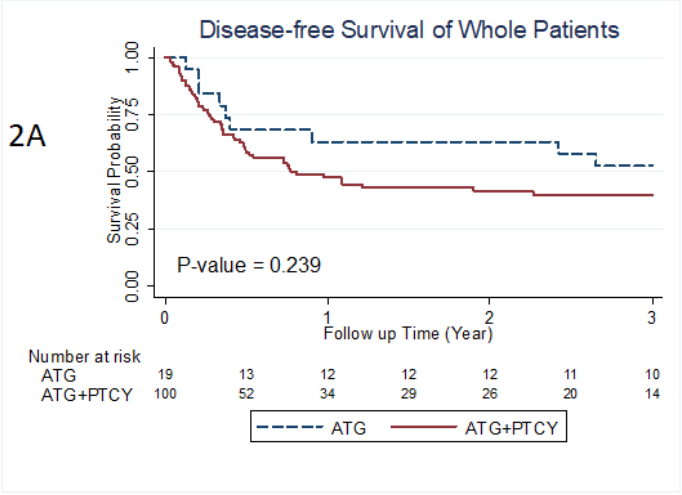
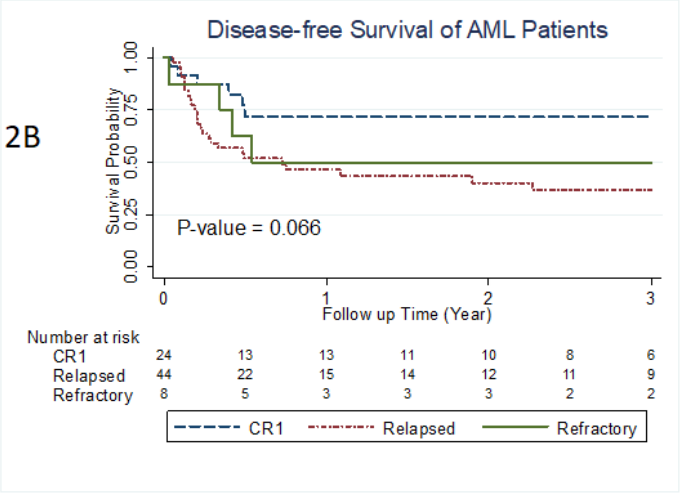


Figure 1

Cumulative incidence of 100-day acute GvHD, (A) according to ATG +PTCy vs. ATG arm in the whole population, (B) according to disease status in patients with acute myeloid leukemia (AML), (C) according to disease status in patients with acute lymphoblastic leukemia (ALL).





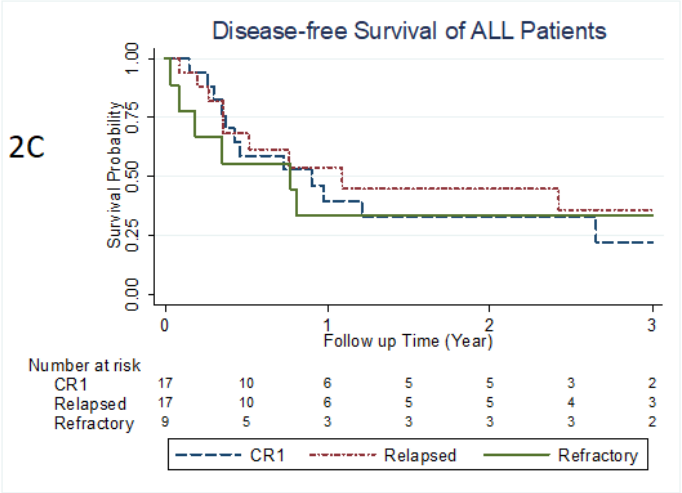


Figure 2

3-year Disease-free survival (DFS) (A) according to ATG +PTCy vs. ATG arm in the whole population, (B) according to disease status in patients with acute myeloid leukemia (AML), (C) according to disease status in patients with acute lymphoblastic leukemia (ALL).

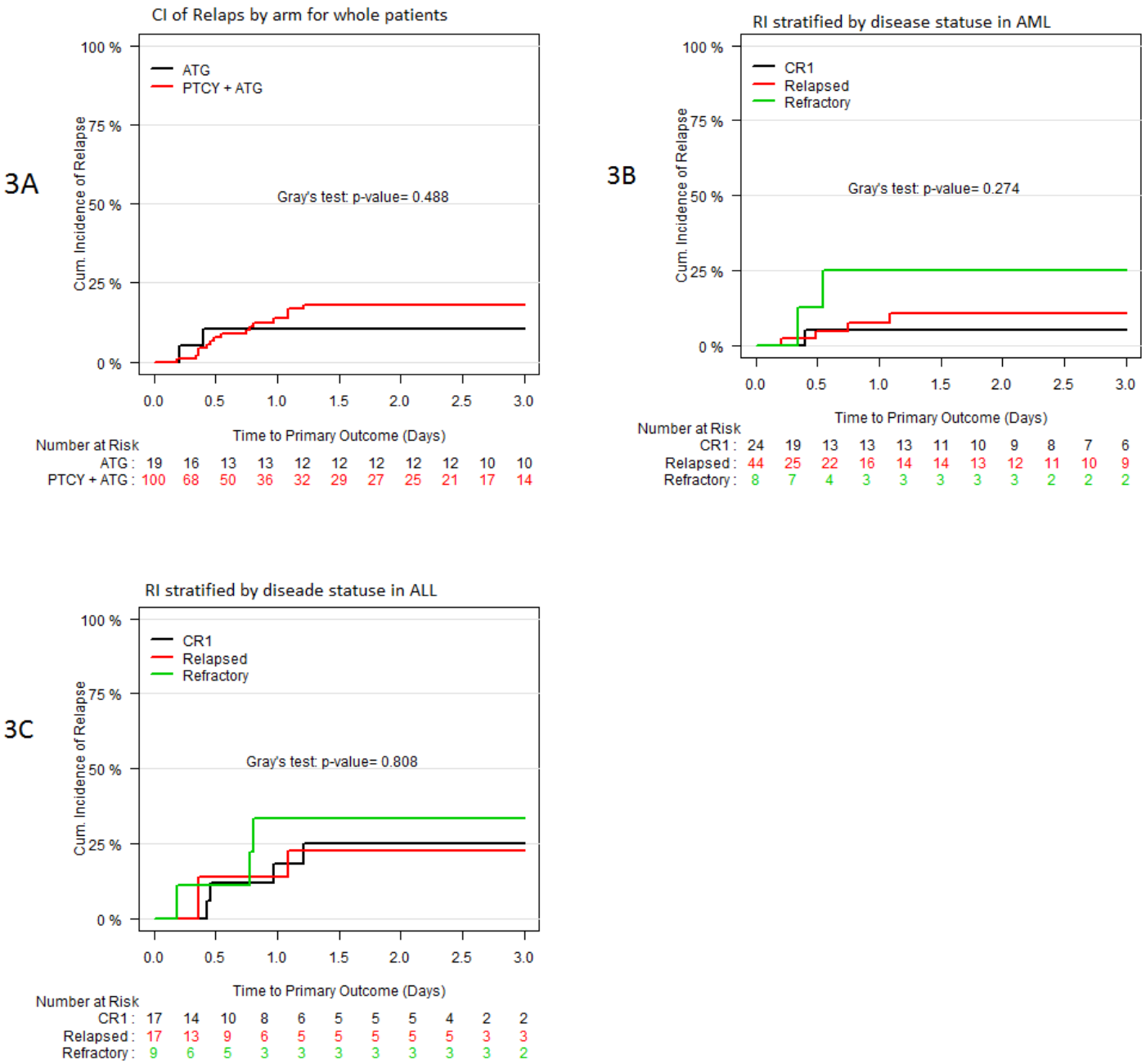


Figure 3

Cumulative incidence of 3-year Relapse-incidence (A) according to ATG +PTCy vs. ATG arm in the whole population, (B) according to disease status in patients with acute myeloid leukemia (AML), (C) according to disease status in patients with acute lymphoblastic leukemia (ALL).

Supplementary Files

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