a long lasting remission (at 5 years). The high relapse rate and high TRM rate has to be improved by preemptive DLI therapy and better supportive care.

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### Allogeneic Transplantation for Ph+ Acute Lymphoblastic Leukemia (ALL): Impact of Conditioning Intensity, Tyrosine Kinase Inhibitors (TKI) and Minimal Residual Disease (MRD)

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Allogeneic hematopoietic cell transplantation (HCT) is the only curative therapy for Ph+ ALL. Reduced intensity conditioning (RIC) has been explored to limit transplant related mortality (TRM) while allowing engraftment and the graft-versus- leukemia effect, perhaps enhanced by use of TKI and monitoring for MRD by cytogenetic and molecular techniques. Data on TKI and pre-transplant MRD on RIC HCT outcomes are lacking.

We analyzed 197 adults with Ph+ ALL in CR1 reported to CIBMTR between 2001-2009 and collected data on pre- and post-HCT TKI administration and pre-transplant MRD. Sixty-seven patients receiving RIC were matched with 130 myeloablative (MA) HCT recipients (matched for age, donor type and transplant year). Median age in RIC (54 years) was older than MA (50 years). The RIC group had more frequent pre-HCT fungal infections and a longer time from diagnosis to CR. The majority in both groups received TKI pre-transplant (RIC: 76% vs MA: 78%) while only 31% (RIC) and 17% (MA) received TKI post-transplant. Most patients had MRD monitored pre-HCT by cytogenetic testing (89%) or BCR/ABL PCR (64%).

TRM at 1 year was almost 3-fold lower following RIC compared to MA HCT (13% vs 36%; $P < .001$). In contrast, the 3-yr relapse rate was higher after RIC HCT (49% vs 28%; $P = .058$) resulting in similar 3 year overall survival (OS) and disease-free survival (DFS) following RIC and MA allograft (OS: 39% vs 35%, $P = .62$; DFS: 26% vs 28%, $P = .75$). In multivariate analysis, RIC was associated with 2 fold increased relapse risk, but had no significant impact on survival. Post-transplant TKI use and younger age (< 40 years) associated with significantly lower TRM and improved OS. Probability of grade II-IV acute GVHD was 30% and 47% in RIC and MA groups respectively ($P = .014$), while conditioning intensity did not alter the incidence of chronic GVHD.

Pre-transplant TKI therapy might influence clearance of MRD pre-HCT and risk of relapse. Among 153 patients who received pre-HCT TKI, complete molecular and cytogenetic remission was 22% (RIC) and 26% (MA); similar to pre-HCT MRD status of patients without TKI (RIC 19%; MA 18%). Importantly, in adjusted multivariate analysis, positive BCR/ABL pre-HCT was strongly associated with increased relapse (HR 2.72; $P = .003$) and use of pre-HCT TKI was associated with a 2-fold reduction in relapse (HR 0.49; $P = .003$). MRD positivity or pre-transplant TKI had no significant influence on survival.

In this matched case-control study, we demonstrated that RIC HCT yields similar survival of adults with Ph+ALL in CR1 compared to MA allografts. Importantly, relapse remains higher after RIC HCT. TKI administration prior to HCT can reduce the relapse to achieve the negative MRD status – which is the strongest predictor of leukemia recurrence. MRD reduction pre-allograft therefore remains the important target for future clinical trials, particularly for patients who are candidates for RIC HCT.

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### Aberrant Expression of Myeloid Antigens Identifies a Subgroup of Standard-Risk Adult Acute Lymphoblastic Leukemia Patients with Short Survival

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**Background:** Adult patients (pts) with acute lymphoblastic leukemia (ALL) are stratified into standard- and high-risk groups based on WBC count, karyotype and response to induction chemotherapy. Nevertheless, the standard-risk group (SR) is heterogeneous with 40%-50% of pts relapse, and the survival varies from a few months to decades. The role of immunophenotyping in further sub-stratifying the standard risk group has not been assessed in adult pts.

**Patients and Methods:** Out of 161 adult ALL pts diagnosed and treated at the L/BMT Program of BC between 1989 and 2010, 81 SR pts were separated out based on: WBC $\leq 50X10^9$/L (B-ALL) or $\leq 100X10^9$/L (T-ALL), absence of adverse cytogenetics (i.e. t(9;22), *BCR-ABL fusion*, complex karyotype ($\geq$5 abnormalities), t(4;11), t(1;19), low hypodiploid/near triploid), and complete remission (CR) following induction chemotherapy. The immunophenotype of this group was reviewed, reanalyzed, and correlated with CR, relapse, relapse-free survival (RFS), and overall survival (OS). Pts were treated with a consistent chemotherapy regimen: Induction consisted of prednisone, vincristine and daunorubicin ± L-asparaginase. A second phase of induction comprised of cyclophosphamide, cytarabine, methotrexate and mercaptopurine. Intensification was with dexamethasone, vincristine, daunorubicin, cyclophosphamide, cytarabine and thioguanine. Four cycles of consolidation with cytarabine and tenoposide were given followed by 2-year maintenance oral chemotherapy with methotrexate and mercaptopurine.

**Results:** Eighty-one standard-risk adult ALL pts (62 B-ALL, 19 T-ALL) were identified, (50 males , 31 females), median age 33 years (16-66). With a median follow up of 30 months (3-235), 32 pts (40%) relapsed within 1-136 months. The median OS and RFS were 30 months (3-235) and 26 months (1-235) respectively. CD13, CD33 and CD117 data was available in 59, 58 and 50 pts respectively. They were positive in 17 (29%), 13 (22%) and 0 (0%) pts respectively. At least one of CD13 or 33 or 117 was available in 61, and positive in 25 of them (41%). Aberrant expression of myeloid antigens was associated with early relapse (median 8 vs 16 months), shorter survival (median 11 vs 28 months). OS at 24 months and 60 months and RFS at 24 months were inferior in ALL patients expressing myeloid antigens (Table 1).

**Conclusion:** In adult patients with standard-risk ALL, aberrant expression of myeloid antigens indicates early relapse,

**Table 1**
Association of Expression of Myeloid Antigens with Survival in Adult ALL

| Short Survival | CD13 | CD33 | CD13 or 33 or 117 |
|---|---|---|---|
| RFS ≤24 months | 44% vs 16%, $P = .014$ | 35% vs 13%, $P = .044$ | 57% vs 27%, $P = .018$ |
| OS ≤24 months | 50% vs 16%, $P = .006$ | 35% vs 16%, $P = .095$ | 64% vs 28%, $P = .006$ |
| OS ≤60 months | 34% vs 8%, $P = .979$ | 24% vs 17%, $P = .591$ | 46% vs 23%, $P = .138$ |

and inferior RFS and OS at 24 and 60 months. More aggressive therapy may be considered in this subgroup.

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### Early Versus Late Allogeneic Hematopoietic Cell Transplantation in Patients with AML - Results From the Randomized AML 2003 Trial

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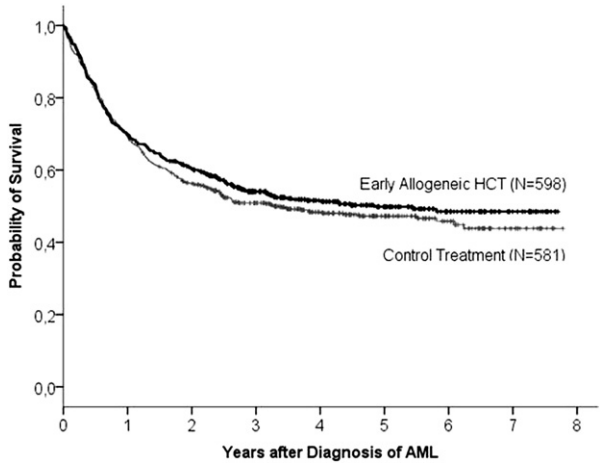
The optimal timing of hematopoietic cell transplantation (HCT) in AML is still under debate. We addressed this question in the AML 2003 study, a large, multicenter, open-label, randomized study of the German SAL group. All patients received one cycle of induction therapy (IT). Upfront molecular characterization, HLA typing and donor search were performed. The transplant strategy was tailored to AML risk and to donor availability. Patients aged 18-60 years were randomly assigned upfront 1:1 to either one of two transplant strategies: In the control arm HLA-identical sibling HCT was scheduled in first complete remission for patients with intermediate cytogenetic risk AML and related or unrelated compatible HCT for patients with a complex karyotype (CK). In the experimental arm the indication for allogeneic HCT was extended to patients with an FLT3-ITD allelic ratio >0.8 (mutant/wild type), >10% marrow blasts on day 15 after IT1 and patients with adverse karyotypes, including: -7, -5, del(5q), inv(3q), t(3;3), t(6;9), t(6;11), t(11;19) (q23;p13.1). Furthermore, HCT was scheduled earlier, i.e. in aplasia after the first or the second cycle of IT.

Between December 1st, 2003 and November 26th, 2009 1179 patients were assigned randomly either to the experimental (N=598) or the control intervention (N=581). The median age was 48 years (range, 18 to 60 years) and the median observation time now is 52 months. In the intent-to-treat analysis the hazard ratio of the treatment effect (experimental versus control) was 0.92 (95% CI, 0.75 to 1.14; $P = .45$) for the primary endpoint overall survival (OS) and 0.85 (95% CI, 0.71 to 1.02; $P = .08$) for the secondary endpoint event-free survival (EFS). However, the rate of patients who received allogeneic HCT as first post-remission therapy was only 39% in the experimental arm and 20% in the control arm. Thus, the analysis according to the intent-to-treat could not discriminate appropriately between the two treatment strategies. In an exploratory analysis, we therefore analyzed the effect of allogeneic HCT as a time-dependent covariate in a Cox-regression model. We adjusted for the cytogenetic risk, age, ECOG performance status, white blood cell count, and LDH at diagnosis. In this as-treated analysis the adjusted hazard ratio for the treatment (allogeneic HCT versus chemotherapy) was 0.73 (95% CI, 0.59 - 0.89; $P = .002$) for OS and 0.67 (95% CI, 0.55 - 0.82; $P < .001$) for EFS. This analysis corrects appropriately for a classical time-selections bias. However, a patient selection based on comorbidity or fitness cannot be ruled out.

In conclusion, a survival benefit from early compared to late allogeneic HCT could not be shown in the intent-to-treat analysis of this large randomized trial using a risk-adapted transplant strategy. However, the results of the as-treated analysis suggest a substantial benefit from allogeneic HCT in first remission versus chemotherapy.

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### Mixed Phenotype Acute Leukemia: Patient Outcomes According to the WHO 2008 Classification

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Mixed phenotype acute leukemia (MPAL) is a rare leukemia with features of both myeloid and lymphoid lineage. The 2008 World Health Organization (WHO) definition of MPAL is based on the expression of strictly specific T-lymphoid (cytoplasmic CD3) and myeloid (myeloperoxidase) antigens, and B-cell lineage assignment relies on the expression of CD19 together with other B cell–associated markers (Borowitz et al. World Health Organization Classification of Tumours: Pathology and Genetics of Tumours of Haematopoietic and Lymphoid Tissues. 2008). In this retrospective review, we analyzed the clinical features and treatment outcomes of patients treated at MDACC between 5/2004 and 6/2012 who fulfilled the diagnostic criteria for MPAL. We identified a total of 41 patients with a median age of 47 years (range 9 – 82; 63% male) with characteristics described in the table below. Twenty one (51%) patients had leukemia with myeloid plus B-lymphoid (M/B) markers, 18 (44%) with myeloid plus T-lymphoid (M/T) markers, and 2 (5%) with B-lymphoid plus T-lymphoid (B/T) markers. Cytogenetic analysis showed 31 patients (76%) had an abnormal