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# HLA-Identical Sibling Allogeneic Transplants versus Chemotherapy in Acute Myelogenous Leukemia with t(8;21) in First Complete Remission: Collaborative Study between the German AML Intergroup and CIBMTR

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## ABSTRACT

**We studied the role of HLA-matched sibling hematopoietic cell transplantation (HCT) in treating t(8;21) acute myelogenous leukemia (AML) in first remission. Outcomes of 118 patients receiving HCT and reported to the Center for International Blood and Marrow Transplant Research were compared with 132 similar patients receiving chemotherapy selected from 8 German AML Intergroup multicenter trials. Characteristics of the cohorts were similar except that chemotherapy recipients were significantly older. To adjust for time to treatment bias, outcomes were compared using left-truncated Cox regression models. Transplants were associated with higher treatment-related mortality (TRM; relative risk [RR] 6.76, 95% confidence interval [CI] 2.95-15.45, $P < .001$), lower relapse (RR 0.47, 95% CI 0.25-0.85, $P = .01$), and similar relapse-free survival ($P = .2$). Loss of sex chromosomes (LOS) in addition to t(8;21) had a negative impact on overall survival (OS) in patients receiving chemotherapy. Patients without LOS experienced shorter survival after HCT comparing to chemotherapy (RR 3.05, $P = .02$), whereas patients with LOS had similar survival regardless of postremission therapy. In both cohorts, white blood cell count (WBC) at diagnosis $>25 \times 10^9$/L was associated with a higher relapse risk (RR = 2.09, $P = .03$), lower relapse-free (RR = 1.9, $P = .008$), and OS (RR = 1.91, $P = .01$). In this cohort of patients with t(8;21) AML, HCT did not improve OS, because reduction of relapse was offset by high TRM. In the group**

**without LOS, survival after chemotherapy was far superior to HCT. These results suggest that patients with t(8;21) AML without poor prognostic factors have higher rates of survival after chemotherapy as a post remission therapy compared to HCT.**


**KEY WORDS**
t(8;21) • AML • Hematopoietic stem cell transplantation • Chemotherapy

## INTRODUCTION

Translocation t(8;21) (q22;q22) (t[8;21]) is found in 1/3 of karyotypically abnormal and approximately 8% of all patients with acute myeloid leukemia AML [1]. This translocation is associated with secondary aberrations in 60% to 80% of cases, with loss of a sex chromosome (LOS) being the most frequent [2-4]. At the molecular level this translocation involves *RUNX1* (AML1) on chromosome 21 and *CBFA2T1* (ETO) on chromosome 8 [5]. *RUNX1* is a member of the core-binding factor alpha family (CBFα) of transcriptional regulators and, through interaction with CBFβ, allows transcription of genes required for myeloid differentiation. The *RUNX1/CBFA2T1* fusion protein acts as a dominant repressor of *RUNX1*-dependent transcription.

The role of postremission therapy in acute mylegenous leukemia (AML) is to decrease relapse and prolong survival. Outcomes after postremission therapy vary considerably by specific AML subtypes and presence of poor prognostic factors. Slovak et al. [6], from the American Intergroup study (SWOG/ECOG), observed superior overall survival (OS) after transplantation compared to chemotherapy among patients with favorable risk AML: t(8;21), t(15;17), and inv (16). Conversely, both French and German AML Intergroups showed no difference between hematopoietic stem cell transplantation (HCT) strategies and intensive chemotherapy for this group of AML patients [7,8].

Relapse varies substantially according to additional risk factors within the same cytogentically risk categories. Leukocytosis at diagnosis is associated with worse outcomes [9,10], with the French and the German AML Intergroup analyses revealing nearly identical cut points for higher risk category ($30 \times 10^9$/L and $25.4 \times 10^9$/L, respectively) [4,7,11]. Additional cytogenetic abnormalities also predict treatment outcomes but less certainly than leukocytosis. LOS in men and del(9q) are associated with shorter survival outcomes in patients with t(8;21) [3,4,12,13].

In this study we examined 2 different postremission strategies for t(8;21) AML in the first complete remission (CR1), namely, intensive chemotherapy with cytarabine-based regimes, using data from the German AML Intergroup, and HLA-matched sibling HCT using data from the Center for International Blood and Marrow Transplant Research (CIBMTR). Current practice does not suggest that t(8;21) AML in the CR1 is an indication for sibling donor HCT. We undertook this analysis to determine whether this currently held practice was evidence based, especially in the light of known prognostic factors in this specific type of AML.

## MATERIAL AND METHODS

### Data Sources

**Transplant cohort.** The CIBMTR is a voluntary working group of more than 400 centers worldwide. Participating centers register basic information on all consecutive transplant recipients. Comprehensive demographic and clinical data are collected on a representative sample of registered patients selected using a weighted randomization scheme. Patients are followed longitudinally, with yearly follow-up.

Computerized checks for errors, physician reviews of submitted data, and on-site audits of participating centers ensure the quality of data. Studies utilizing CIBMTR data are approved by the Medical College of Wisconsin Internal Review Board.

**Chemotherapy cohort.** The data from patients who received chemotherapy were obtained from the German AML Intergroup database using data from 8 multicenter prospective clinical trials [4]: SHG-Hannover-AML-2/95 [14], SHG-Hannover-AML-1/99, SHG-Dresden-AML-96 [15], AMLSG ULM AMLHD93 [8], AMLSG ULM AML-HD 98A, AMLCG92 [16], AMLCG99 [17], and OSHO AML-96. All trials enrolled AML patients and included double-induction chemotherapy followed by different postremission strategies including different dose levels of cytarabine-based chemotherapy, autologous, and allogeneic HCT.

### Eligibility Criteria

The study included patients with t(8;21) AML in morphologic CR1, aged 16 to 60 years, who underwent an HLA-identical sibling HCT with myeloablative conditioning regimen reported to the CIBMTR from 1990 to 2002 or who received chemotherapy in 1 of the German trials noted above from 1993 to 2002. One hundred ninety-seven patients with t(8;21) AML enrolled in the German trials. Thirty-one were excluded for not achieving remission, 7 for not receiving postremission therapy, and 27 for receiving an allogeneic (n = 9) or an autologous (n = 18) HCT. Thus, 132 patients were eligible for this study. Among the 124 patients receiving HLA-identical

sibling transplants for t(8;21) AML and reported to the CIBMTR, 2 were excluded for receiving reduced-intensity conditioning regimens and 4 from inactive transplant centers for insufficient post transplant follow-up data, leaving a total of 118 eligible patients, contributed by 66 centers in 26 countries (Table 1).

### Cytogenetic Analysis and Review

All cytogenetic and molecular analyses in the chemotherapy cohort except for the OSHO trial were performed in central reference laboratories per protocol requirements. In the OSHO trial, cytogenetic analyses were required prior to study entry but there was no central review (n = 9). The CIBMTR requests information on cytogenetic testing performed at diagnosis, prior to transplantation and at relapse, but not all patients had these analyses performed. Only cases reporting the presence of t(8;21) were included. Cytogenetic reports were available for review and confirmation for 69 of 118 patients in the transplant cohort. Descriptions of karyotypic abnormalities adhered to the International System for Human Cytogenetic Nomenclature [18]. Five patients in the chemotherapy and 1 patient in the HCT group without evaluable metaphases had confirmed t(8;21) through AML1/ETO molecular analysis.

The most frequent additional cytogenetic change observed in both groups was LOS chromosomes (−X or −Y). Three groups were analyzed: t(8;21) alone, t(8;21) and LOS with or without other cytogenetic changes, and t(8;21) with other cytogenetic changes excluding LOS. Deletion 9q was present in only a small proportion of patients (chemotherapy, n = 21 and HCT, n = 9), precluding separate analysis.

### Outcomes

Treatment-related mortality (TRM) was defined as deaths occurring during the CR1 as calculated by the cumulative incidence estimate, with relapse as the competing risk. Patients were censored at time of last follow-up. Relapse was defined as morphologic leukemia recurrence at any site by the cumulative incidence estimate, with death in remission as the competing risk. Patients were censored at death in the CR1 or surviving in continuous CR at last contact. Relapse-free survival (RFS) and OS were defined, respectively, as survival in complete CR and survival, with censoring at last follow-up [19]. For OS, death from any cause was considered an event. For RFS (ie, treatment failure), relapse or death was considered an event.

### Statistical Analysis

Variables related to patient and disease characteristics were compared between groups using the chi-square statistic or Fishers exact test, if appropriate, for categoric variables and the Kruskal-Wallis test for continuous variables. The median follow-up time was calculated utilizing the Kaplan-Meier estimate for the censoring distribution.

When comparing outcomes of transplant versus nontransplant groups, differences in time to treatment and differences in patient baseline characteristics are potential sources of bias and require appropriate adjustments. As transplant recipients must survive long enough to undergo transplantation, they may represent population with inherently better outcome. To address this potential bias, left-truncated Cox regression models and left-truncated cumulative incidence estimates were used. At each time point in this model, the risk set in the chemotherapy cohort consisted of all patients, whereas the risk set in the transplant cohort included only those whose waiting time to transplant was less than this time point [20].

To adjust for differences in baseline characteristics, multivariate Cox proportional hazards regression models were used [21]. First, associations between each outcome and potential prognostic variables (listed in Table 2) were evaluated using a stepwise approach. Variables significantly associated with each outcome event ($P < .05$) were included as covariate factors in the subsequent comparisons. The proportionality assumption of the Cox model was tested by adding separately for each outcome event a time-dependent covariate for each of the covariates tested. Presence of LOS in the OS model was the only variable demonstrating significant interaction with type of postremission therapy. Adjusted probabilities of RFS and OS were then generated from the final Cox models stratified on postremission therapy. Results were expressed as relative risks (RR) of each outcome after transplantation versus after chemotherapy. *P*-values are 2-sided. Analyses were performed using SAS software, version 9.2 (SAS Institute, Cary, NC).

## RESULTS

### Patient Characteristics

Table 1 shows patient, disease, and treatment-related characteristics by postremission therapy. Transplant recipients were younger than chemotherapy recipients (median age 32 versus 42 years, $P < .001$). We considered patients as having high-risk leukocytosis, if their WBC count at diagnosis was $>25 \times 10^9$/L [4]. Cytogenetic abnormalities detected in addition to the t(8;21) were frequently observed in both groups. Fifty-two percent of HCT patients received TBI-based conditioning regimens and 88% received bone marrow grafts. None of the HCT recipients received donor lymphocyte infusions either as a planned therapy or for recurrent leukemia. Most transplants were performed prior to 1994; consequently, median follow-up times of survivors were 48 and 94 months after chemotherapy and HCT, respectively. Nevertheless, 66% of

**Table 1.** *Characteristics of Patients 16-60 years of Age with t(8;21) AML in First Complete Remission Who Either Received a Cytarabine-Based Chemotherapy or an HLA-Identical Sibling Transplant*

| | Chemotherapy | | Transplant | | |
|---|---|---|---|---|---|
| **Characteristics of Patients** | **N Eval** | **N (%)** | **N Eval** | **N (%)** | ***P*-Value** |
| Number of patients | | 132 | | 118 | |
| Number of multicenter trials*/ centers | | 8 | | 66 | |
| Age at first CR, median (range), years | 132 | 42 (17-60) | 118 | 32 (16-52) | <.001 |
| Age at first CR | 132 | | 118 | | <.001 |
| 16-19 y | | 6 (5) | | 10 (8) | |
| 20-29 y | | 18 (14) | | 44 (37) | |
| 30-39 y | | 27 (20) | | 38 (32) | |
| 40-49 y | | 44 (33) | | 23 (20) | |
| ≥50 y | | 37 (28) | | 3 (3) | |
| Male sex | 132 | 81 (61) | 118 | 73 (62) | .94 |
| FAB subtype | 129 | | 118 | | .09 |
| M1 | | 6 (5) | | 10 (9) | |
| M2 | | 111 (86) | | 92 (78) | |
| M3 | | 3 (2) | | 0 | |
| M4 | | 7 (5) | | 12 (10) | |
| RAEBT | | 1 (1) | | 0 | |
| Other | | 1 (1) | | 4 (3) | |
| WBC at diagnosis, $\times 10^9$/L, median (range) | 130 | 9 (1-152) | 114 | 11 (2-260) | .17 |
| WBC at diagnosis $>25.4 \times 10^9$/L | 130 | 21 (16) | 114 | 24 (21) | .32 |
| Year of diagnosis | 132 | | 118 | | <.001 |
| 1989-1990 | | 0 | | 19 (16) | |
| 1991-1992 | | 0 | | 30 (26) | |
| 1993-1994 | | 1 (<1) | | 21 (18) | |
| 1995-1996 | | 26 (20) | | 18 (15) | |
| 1997-1998 | | 34 (26) | | 12 (10) | |
| 1999-2000 | | 33 (25) | | 10 (8) | |
| 2001-2002 | | 38 (29) | | 8 (7) | |
| Cytogenetics | 127 | | 118 | | |
| t(8;21) as the sole change | | 43 (34) | | 53 (45) | .30 |
| Additional LOS | | 58 (46) | | 48 (41) | |
| −X ± other | 50 | 19 (38) | 45 | 16 (35) | |
| −Y ± other | 77 | 39 (50) | 73 | 32 (44) | |
| Other | | 26 (20) | | 17 (14) | |
| Blast in bone marrow, median % (range) | 123 | 60 (7-100) | 104 | 59 (8-100) | .32 |
| Extramedullary disease at diagnosis | 130 | 8 (6) | 118 | 14 (12) | .11 |
| Consolidation therapy | 132 | | 117 | | — |
| Standard Ara-C | | 2 (2) | | 42 (36) | |
| Intermediate Ara-C | | 25 (19) | | 0 | |
| High-dose Ara-C | | 105 (79) | | 30 (25) | |
| Other consolidation | | 0 | | 23 (20) | |
| None | | 0 | | 22 (19) | |
| Number of consolidation cycles | 132 | | 118 | | — |
| 0 | | 0 | | 22 (19) | |
| 1 | | 3 (2) | | 39 (33) | |
| 2 | | 52 (40) | | 21 (18) | |
| 3 | | 77 (58) | | 7 (6) | |
| 4 | | 0 | | 2 (1) | |
| Missing | | 0 | | 27 (23) | |
| Conditioning regimen | NA | | 118 | | — |
| Bu + Cy ± other | | | | 54 (46) | |
| Cy + TBI ± other | | | | 50 (42) | |
| TBI ± other | | | | 12 (10) | |
| Other† | | | | 2 (2) | |
| Duration of postremission treatment, months | 132 | 3 (<1-14) | NA | | — |
| Time from first CR to transplant, months | NA | | 118 | 3 (<1-12) | — |
| Time from diagnosis to last treatment/ HCT, months | 132 | 5 (1-16) | 118 | 5 (2-16) | .67 |
| Donor-recipient sex match | NA | | 118 | | — |

(*Continued*)

**Table 1.** *Continued*

| Characteristics of Patients | Chemotherapy N Eval | Chemotherapy N (%) | Transplant N Eval | Transplant N (%) | *P*-Value |
|---|---|---|---|---|---|
| Male donor/male recipient | | | | 31 (26) | |
| Male donor/female recipient | | | | 24 (20) | |
| Female donor/male recipient | | | | 42 (36) | |
| Female donor/female recipient | | | | 21 (18) | |
| CMV status | NA | | 111 | | — |
| Donor (+)/recipient (+) | | | | 47 (42) | |
| Donor (+)/recipient (−) | | | | 12 (11) | |
| Donor (−)/recipient (+) | | | | 25 (23) | |
| Donor (−)/recipient (−) | | | | 27 (24) | |
| Graft type | NA | | 118 | | — |
| Bone marrow | | | | 104 (88) | |
| Peripheral blood | | | | 14 (12) | |
| GVHD prophylaxis | NA | | 118 | | — |
| CsA + MTX ± other | | | | 92 (78) | |
| CsA ± other, tacrolimus ± other | | | | 17 (14) | |
| T-cell depletion ± other | | | | 9 (8) | |
| Median follow-up of survivors, months | | 43 (2-108) | | 77 (14-178) | |

EVAL indicates evaluable; FAB, French-American-British classification; WBC, white blood cell count; CR, complete remission; Bu, busulfan; Cy, cyclophosphamide; TBI, total body irradiation; CMV, cytomegalovirus; CsA, cyclosporine; MTX, methotrexate; LOS, loss of sex chromosome; HCT, hematopoietic stem cell transplant.

*SHG-Hannover-AML-2/95 (n = 22); SHG-Hannover-AML-1/99 (n = 7); AMLHD93 (n = 13); AMLHD98A (n = 26); AMLCG92 (n = 15); AMLCG99 (n = 13); OSHO-AML-96 (n = 9); SHG-D (n = 27).

†Other conditioning regimen were: busulfan + melphalan (1); bleomycin + cyclophosphamide (1).

chemotherapy and 87% of transplant recipients were followed for ≥5 years and the completeness of follow-up (the ratio of the sum of the observed follow-up time to the sum of the potential follow-up time for all patients in the study) [22] was 86% for both treatment groups. The rate of grade II-IV acute graft-versus-host disease (aGVHD) at day 100 after HCT was 9% (95% confidence intervals [CI] 5%-15%] and chronic GVHD (cGVHD) at 1 and 3 years were 27% (95% CI 19%-35%) and 37% (95% CI 29%-46%).

## TRM

Risks of TRM were significantly higher after HCT than after chemotherapy (Table 3). The 5-year cumulative incidences of TRM were 6% (95% CI 2%-11%) and 32% (95% CI 22%-44%) after chemotherapy and HCT, respectively (Figure 1).

## Leukemia Relapse

Risks of leukemia relapse were significantly lower after HCT than after chemotherapy (Table 3). The 5-year probabilities of relapse was 29% (95% CI 21%-37%) and 14% (95% CI 8%-21%) after chemotherapy and HCT, respectively ($P = .005$) (Figure 2). Risks of relapse were significantly higher in patients with WBC $>25.4 \times 10^9$/L at diagnosis in both cohorts (Table 3).

## RFS

Risks of treatment failure (relapse or death) were similar after chemotherapy and HCT (Table 3). The 5-year probabilities of RFS were 64% (95% CI 53%-73%) and 55% (95%CI 45%-65%) after chemotherapy and HCT, respectively ($p = .2$) (Figure 3). Risks

**Table 2.** *Variables Tested in Cox Proportional Hazards Regression Models*

| |
|---|
| **Main Effect Variable:*** |
| **Postremission treatment: cytarabine-based chemotherapy versus HLA-identical sibling transplant** |
| **Patient-related variables:** |
| **Age at first CR: continuous** |
| **Sex: female versus male** |
| **Disease-related variables at diagnosis:** |
| **WBC at diagnosis: ≤25.4 × $10^9$/L versus >25.4 × $10^9$/L versus missing** |
| **Blast in BM: ≥60% versus 60% versus unknown** |
| **Year of diagnosis: continuous** |
| **Additional cytogenetics abnormalities: t(8;21) alone versus t(8;21) and LOS ± other versus t(8;21) and other additional not LOS** |
| **Disease-related variables at transplant:** |
| **Extramedullary disease at diagnosis: yes versus no** |
| **Time from diagnosis to first CR** |
| **Chemotherapy-related:** |
| **German AML Intergroup clinical trial** |
| **Treatment-related (*for transplant group only*):** |
| **Conditioning regimen: Bu + Cy ± other versus Cy + TBI ± other versus others** |
| **Donor age** |
| **Donor-recipient sex match: match versus mismatch** |
| **Donor-recipient CMV status: −/− versus others** |
| **Graft type: bone marrow versus peripheral blood** |

CR indicates complete remission; WBC, white blood cell count; BM, bone marrow; LOS, loss of sex chromosome; Bu, busulfan; Cy, cyclophosphamide; TBI, total body irradiation; CMV, cytomegalovirus.

*Included in all models.

**Table 3.** *Relative Risk of Treatment-Related Mortality, Relapse, Leukemia-Free Survival, and Overall Survival in Patients Receiving HCT versus Chemotherapy for Postremission Treatment*

| Outcome | N Evaluable | Relative Risk (95% Confidence Interval) | *P*-Value |
|---|---|---|---|
| **Treatment related mortality** | | | |
| Chemotherapy | 132 | 1.00* | |
| Transplant | 118 | 6.76 (2.95-15.45) | <.001 |
| **Other significant covariates:†** | | | |
| **Blast in bone marrow** | | | |
| <60 % | 109 | 1.00* | |
| ≥60% | 118 | 2.64 (2.95-15.45) | .005 |
| **Relapse** | | | |
| Chemotherapy | 132 | 1.00* | |
| Transplant | 118 | 0.47 (0.25-0.85) | .014 |
| **Other significant covariates:** | | | |
| **WBC at diagnosis** | | | |
| $\leq 25 \times 10^9$/L | 199 | 1.00* | |
| $>25 \times 10^9$/L | 45 | 2.09 (1.09-4.04) | .028 |
| **Relapse-free survival‡** | | | |
| Chemotherapy | 132 | 1.00* | |
| Transplant | 118 | 1.29 (0.84-1.98) | .24 |
| **Other significant covariates:** | | | |
| **WBC at diagnosis** | | | |
| $\leq 25 \times 10^9$/L | 199 | 1.00* | |
| $>25 \times 10^9$/L | 45 | 1.90 (1.18-3.05) | .008 |
| **Overall survival§** | | | |
| **No LOS** | | | |
| Chemotherapy | 69 | 1.00* | |
| Transplant | 70 | 3.05 (1.51-6.15) | .002 |
| **LOS** | | | |
| Chemotherapy | 58 | 1.00* | |
| Transplant | 48 | 0.90 (0.47-1.70) | .74 |
| **WBC at diagnosis** | | | |
| $\leq 25 \times 10^9$/L | 199 | 1.00* | |
| $>25 \times 10^9$/L | 45 | 1.91 (1.16-3.15) | .012 |

LOS indicates loss of sex chromosome.
*Reference group.
†WBC was not a significant covariate (RR = 1.52, 95% CI 0.81-2.86, $P = .19$).
‡Relative risk of relapse or death.
§Relative risk of death.

of treatment failure were higher in patients with a diagnostic WBC $>25 \times 10^9$/L in both cohorts (Table 3).

## OS

OS after HCT versus chemotherapy differed in the presence or absence of LOS in addition to t(8;21). Risks of overall mortality were significantly higher after HCT than after chemotherapy in patients with t(8;21) and no LOS; risks of overall mortality were similar after HCT and chemotherapy in patients with t(8;21) and LOS (Figure 4). WBC $>25.4 \times 10^9$/L

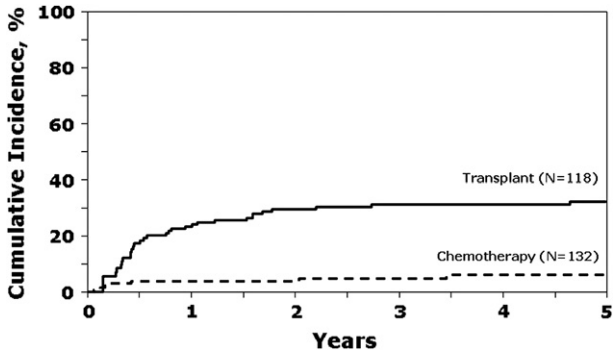


**Figure 1.** Cumulative incidence of TRM after chemotherapy and HLA-matched sibling hematopoietic stem cell transplant for patients with t(8;21) AML in CR1, by postremission treatment.

was associated with higher risk of overall mortality after both chemotherapy and HCT (Table 3).

## Causes of Death

The most common cause of death in both treatment groups was recurrent leukemia, accounting for 70% of deaths after chemotherapy and 24% of deaths after HCT. Nonrelapse causes of death after chemotherapy included infection (21%), organ failure (3%), secondary malignancy (3%), and other causes (3%). Nonrelapse causes of death after HCT were infection (16%), interstitial pneumonitis (6%), acute respiratory distress syndrome (8%), aGVHD (2%), cGVHD (10%), interstitial pneumonitis and GVHD (6%), organ failure (10%), secondary malignancy (6%), hemorrhage (4%), and other causes (2%). The cause of death was unknown for 3 patients (6%) in the HCT cohort.

## DISCUSSION

This study shows that HLA-matched sibling HCT for t(8;21) AML in the CR1 for patients between 16 and 60 years is associated with lower relapse rates,

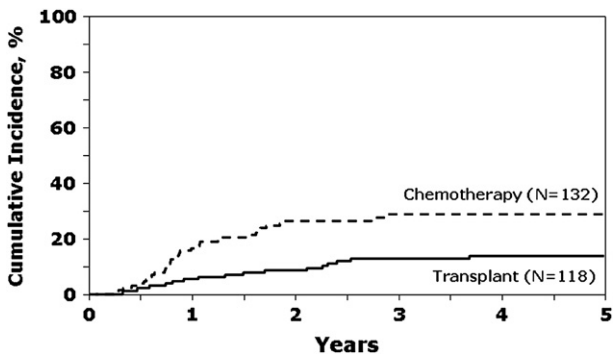


**Figure 2.** Cumulative incidence of relapse after chemotherapy and HLA-matched sibling hematopoietic stem cell transplant for patients with t(8;21) AML in CR1, by postremission treatment.

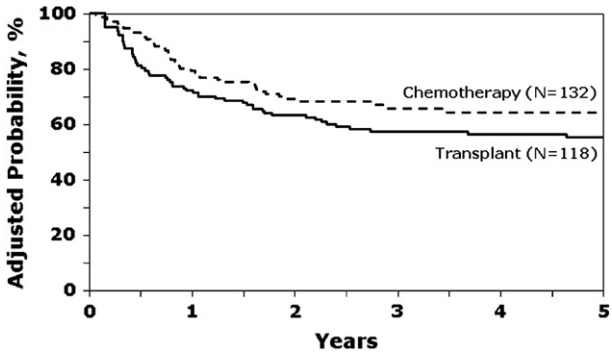


**Figure 3.** Adjusted probability of RFS after chemotherapy and HLA-matched sibling hematopoietic stem cell transplant for patients with t(8;21) AML in CR1, by postremission treatment.

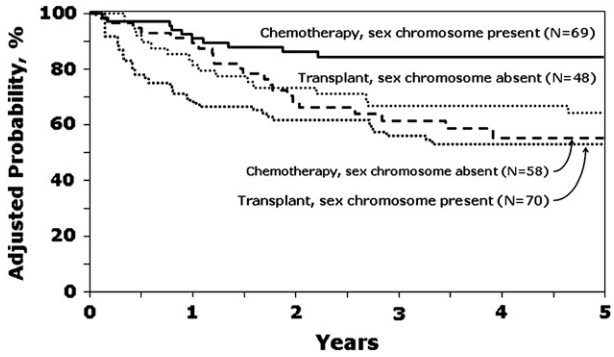


**Figure 4.** Adjusted probability of OS after chemotherapy and HLA-matched sibling hematopoietic stem cell transplant for patients with t(8;21) AML in CR1, by postremission treatment and presence of sex chromosome.

higher TRM, and similar RFS compared to cytarabine-based postremission chemotherapy. This is consistent with reports of unselected groups of AML patients treated in the CR1. Reported relapse rates after allogeneic HCT for AML in CR1 range from 24% to 37% [23-26] compared to much higher rates after chemotherapy (36%-60%) [23-27]. This advantage (ie, fewer relapses after HCT) does not always translate into longer RFS or OS because of higher rates of TRM after HCT. We observed 1-year TRM rates of 23% after HCT, compared to 4% after chemotherapy. Most transplants were performed in the early 1990s; however, the year of transplantation did not significantly impact the rate of TRM. Despite changes in transplant practice in the last decade, TRM remains a major challenge in transplantation. The majority of patients in the HCT cohort received bone marrow grafts, which differs from the current practice of utilizing mobilized peripheral blood stem cells (PBSC) [28]. The selection of graft source is likely to influence hematopoietic recovery and incidence of cGVHD. However, in patients with AML in CR1, rates of TRM are similar after bone marrow and peripheral blood stem cells transplants [29-32].

The MRC 10 prospectively compared allogeneic HCT with chemotherapy allocating patients with a matched sibling donor to HCT (biologic assignment) [33]. Patients within the favorable risk category had similar rates of leukemia-free and OS, regardless of donor availability. This observation and the overall favorable responses with standard dose chemotherapy led to recommendations against HCT for patients with favorable risk AML in CR1. In contrast, the American Intergroup (SWOG/ECOG) performed a similar subset analysis by postremission therapy and showed better survival in favorable risk patients undergoing either autologous or allogeneic HCT versus those receiving chemotherapy [6]. Importantly, despite large numbers of patients in these landmark studies, the groups with specific cytogenetic changes were small and imbalances between comparison groups become significant. The French AML Intergroup analysis of t(8;21) AML demonstrated similar rates of leukemia-free survival with allogeneic HCT and chemotherapy. Thirty-seven of 154 patients in the French study underwent HLA-matched sibling HCT and 5-year probabilities of LFS were 56% and 52% for the transplant and chemotherapy groups, respectively [11].

Treatment outcomes after chemotherapy or HCT in patients with t(8;21) and additional cytogenetic abnormalities are mixed. The MRC and SWOG/ECOG cytogenetic classifications addressed this issue differently. The MRC included t(8;21) plus any additional changes in the favorable risk group because a separate analysis showed no significant impact of additional cytogenetic abnormalities on survival. In contrast, SWOG/ECOG excluded cases with cytogenetic abnormalities in addition to t(8;21) from the favorable risk group. The current study showed LOS to be an important predictor of overall mortality when present in addition to t(8;21) in patients receiving chemotherapy. Deletion of chromosome Y was the most frequent LOS and the main factor associated with poorer survival. Subset analysis on a group of patients with −X (chemotherapy, n = 18 and HCT, n = 16) did not show the same association. As the number of patients with −X was small, this interpretation deserves caution. Furthermore, the presence of additional cytogenetic abnormalities to t(8;21) other than LOS did not affect any outcomes analyzed, and thus were combined to the group of patients with t(8;21) as a sole cytogenetic abnormality. Patients with t(8;21) alone or t(8;21) with additional cytogenetic abnormalities other than LOS had longer survival after chemotherapy than HCT, whereas among those with LOS, there was no significant difference in survival after chemotherapy or HCT. These findings contrast other reports [3,11]. The French Intergroup trial, in which 43% of patients had LOS and 8% had del(9q), showed no significant impact of these abnormalities on survival. A

CALGB analysis of CBF-AML identified 69% with cytogenetic abnormalities in addition to t(8;21), of which 90% were LOS and 17.4% del(9q). LOS did not impact survival, although in a subset of non-White patients, the presence of del(9q) was associated with longer OS. These discrepancies may represent inherent differences in study populations and methods of analyses. In the French study, the subset analysis did not specify additional cytogenetic changes among treatment groups. The majority of patients (61%) in the CALGB study presented with additional LOS and the 5-year probability of OS for t(8;21) AML patients was 46% (95% CI 37%-55%). This survival probability is similar to the chemotherapy cohort with additional LOS (55%, 95% CI 41%-69%) from our study. Small numbers of patients with normal sex chromosomes in the CALGB study may explain why LOS had no detectable impact on survival. Appelbaum et al. [2] also analyzed the effect of additional cytogenetic changes in the outcome of patients with t(8;21) AML. The most common additional abnormality was LOS, and most patients received chemotherapy as postremission therapy. Neither LOS nor del(9q) were significantly associated with OS or any other outcomes. Patients with trisomy 8 or with 3 or more cytogenetic abnormalities had worse survival [2]. The results on the impact of additional cytogenetic abnormalities to t(8;21) are conflicting, and represent the heterogeneity of this patient population. More importantly, this illustrates that background molecular factors such as c-KIT expression and others may play a greater prognostic role; the presence or absence of certain cytogenetic markers may reveal to be more as confounders than biologically relevant.

In our study, despite the association of LOS with lower survival in the chemotherapy cohort, it was not significantly associated with TRM, relapse, or RFS. This might be explained by poor survival postrelapse of patients with LOS. The CALGB study and others demonstrated shorter postrelapse survival in patients with t(8;21) compared to those with inv(16) [2,3]. A German meta-analysis also demonstrated shorter postrelapse survival for patients with t(8;21) and LOS [4]. Whether this represents an effect of LOS or an inherent characteristic of t(8;21) AML remains undetermined.

Extreme leukocytosis at diagnosis, although uncommon in t(8;21) AML, is considered a poor prognostic factor. Several studies, including this analysis, confirmed the adverse impact of leukocytosis and higher marrow blast percentage on treatment outcome [2,9,10]. Our study demonstrated that leukocytosis was associated with higher relapse rates, shorter RFS, and shorter OS irrespective of postremission therapy. A high percent of blasts in the bone marrow at diagnosis was associated with the worse TRM. Both leukocytosis and percent marrow blasts reflect disease burden. The association between high disease burden and TRM is unclear. Other reports showed an association between percent of bone marrow blast at diagnosis and lower CR rates after induction therapy in t(8;21) AML [3,11]. The association of leukocytosis and survival in CBF AML is likely to be explained by overexpression of tyrosine kinase genes related to AML1/ETO. Gain-of-function mutations of c-KIT are associated with high disease burden at diagnosis and significantly impact on survival because of high relapse rates [34-36].

In summary, we report a large comparison of postremission therapy in a homogenous population of AML with t(8;21). We acknowledge potential biases, which may affect the outcomes described. The chemotherapy group includes participants in several clinical trials, and patient accrual was determined by trial specific eligibility criteria. Although all received cytarabine-based chemotherapy, which was administered in a spectrum of doses along with other antileukemic agents, the chemotherapy regimens considered in regression models did not influence any of the endpoints studied. Furthemore, the chemotherapy regimens used as postremission therapy differs from the 4 cycles of high-dose cytarabine (HiDAC) consolidation commonly utilized in current clinical practice in North America. Despite the results from the CALGB study on HiDAC on this patient population being similar to the chemotherapy group [37], such differences in practice should be considered. For the HCT group, the decision to transplant and all aspects of transplant procedure (ie, conditioning regimen, GVHD prophylaxis, donor selection) were at the discretion of the transplant center and reflect routine clinical transplant practices. HCT-related variables were tested in the regression model and did not affect the comparisons with chemotherapy. Last, we combined leukocytosis and LOS to assess the impact of both significant covariates on survival; however, the groups with both prognostic factors were too small for a meaningful comparison, and thus it was omitted from the analysis.

AML with t(8;21) is regarded as favorable risk based on response to initial therapy and longer OS. This study confirms that cytarabine-based chemotherapy offers results similar or better than HLA-matched sibling HCT in first remission. LOS negatively affected survival in patients who received chemotherapy as postremission therapy, but survival was still similar to that achieved with HCT. In patients with t(8;21) but without LOS, OS was longer after chemotherapy compared to HCT. Higher WBC counts at diagnosis were associated with worse outcomes after both chemotherapy and HCT. Selection of the best postremission therapy for patients with t(8;21) and poor prognostic features would be best addressed in a risk-adapted clinical trial.

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