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## Pediatric-inspired Therapy compared to Allografting for Philadelphia Chromosome Negative Adult ALL in First Complete Remission

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## Abstract

For adults with Philadelphia chromosome negative (Ph-) acute lymphoblastic leukemia (ALL) in first complete remission (CR1), allogeneic hematopoietic cell transplantation (HCT) is an established curative strategy. However, pediatric-inspired chemotherapy may also offer durable leukemia free survival in the absence of HCT. We compared 422 HCT recipients aged 18-50 years with Ph-ALL in CR1 reported to the CIBMTR with an age-matched concurrent cohort of 108 Ph-ALL CR1 patients who received a Dana-Farber Consortium pediatric-inspired non-HCT regimen. At four years follow-up, incidence of relapse after HCT was 24% [95% C.I. 19-28] vs. 23% [95% C.I. 15-32] for the non-HCT (“chemo”) cohort (p=0.97). Treatment-related mortality (TRM) was higher in the HCT cohort (HCT 37% [95% C.I. 31-42] vs. chemo 6% [95% C.I. 3 – 12], p<0.0001). DFS in the HCT cohort was 40% [95% C.I. 35-45] vs. 71% [95% C.I. 60-79] for chemo, p<0.0001. Similarly, OS favored chemo (HCT 45% [95% C.I. 40-50]) vs. chemo 73% [95% C.I. 63-81], p<0.0001). In multivariable analysis, the sole factor predictive of shorter OS was the administration of HCT (HR 3.12 [1.99 – 4.90], p<0.0001). For younger adults with Ph-ALL, pediatric-inspired chemotherapy had lower TRM, no increase in relapse, and superior overall survival compared to HCT.

## Keywords

Leukemia; Acute Lymphoblastic; Chemotherapy; Hematopoietic Stem Cell Transplantation; Clinical Trials

## Introduction

In Philadelphia chromosome negative (Ph-) Acute Lymphoblastic Leukemia (ALL), multi-agent chemotherapy protocols result in high complete remission rates, but for adults long-term disease-free survival (DFS) can be maintained in only about 30-45% of patients.<sup>1-3</sup> These results are in contrast to the gratifying outcomes seen in children and adolescents treated within pediatric clinical trials consortia.<sup>4,5</sup>

In younger adults who achieve 1<sup>st</sup> complete remission (CR1), two major therapeutic approaches have been administered to maintain CR and improve long-term survival. First, allogeneic hematopoietic cell transplantation (HCT) may be offered. Donor-versus no-donor trials, meta-analyses and clinical practice guidelines conclude that related donor HCT is a more efficacious therapy compared to conventional chemotherapy or autologous HCT.<sup>3,6-8</sup> Although the major published phase III trials were restricted to related donor (RD) alloHCT, recent observational data suggest that unrelated donor (URD) HCT produces similar outcomes to RD HCT.<sup>9,10</sup> Thus, HCT in CR1 has become a popular post-remission modality regardless of whether suitably matched RDs or URDs are used<sup>7</sup>.

The second post-remission approach for adult ALL patients is the administration of “pediatric-inspired” chemotherapy protocols. These regimens are more dose-intensive than

standard chemotherapy approaches for adults, particularly with respect to non-myelosuppressive agents such as corticosteroids, vincristine, and L-Asparaginase. Single arm clinical trials and cohort studies suggest that pediatric-inspired regimens offer excellent outcomes in younger adults, with long-term survival in 60-68% of patients.<sup>11-15</sup> It is plausible that pediatric-inspired chemotherapy regimens are at least as effective, and potentially superior to HCT for adults with Ph-ALL in CR1. However, these two post-remission approaches have never been directly compared. In the current study we compared outcomes in a cohort of younger adults with Ph- ALL who received HCT in CR1 to a similar population of younger adults with ALL who received one of two pediatric-inspired regimens, while adjusting for important patient-, disease-, and transplant-related variables that may affect outcomes.

## Subjects and Methods

### Inclusion Criteria

We analyzed two cohorts of contemporaneously treated Ph- ALL patients in CR1: (1) Patients who underwent a first bone marrow or peripheral blood allogeneic HLA-identical RD or URD HCT for Ph- ALL in the US or Canada, reported to the CIBMTR; (2) Patients who received pediatric-inspired chemotherapy regimens for Ph- ALL as part of the Dana-Farber Cancer Institute (DFCI) ALL consortium. Patients from both cohorts were aged 18 to 50 years and received their post-remission therapy between June 1, 2002 and December 31, 2011.

The CIBMTR cohort came from 97 reporting centers in the U.S. and Canada. We excluded patients who received HCT from RDs who were not fully matched (N=27), and URDs who were matched at <7/8 HLA loci (N=15) or whose level of HLA match was not reported (N=65). We also excluded patients without day-100 comprehensive research forms (N=13), no informed consent for research studies (N=6), and patients in whom the date of CR1 was unknown (14). This left 422 HCT recipients for further analysis. Completeness of follow-up was 93% at 5 years.

The chemotherapy cohort consisted of Ph- patients enrolled in two consecutively conducted DFCI ALL consortium phase II clinical trials between June 1, 2002 and December 31, 2011 (DFCI 01-0175 and 06-254).<sup>11,16</sup> There were 13 participating consortium centers in the U.S and Canada. Details regarding eligibility and treatment characteristics of DFCI 01-0175 been published elsewhere.<sup>11,16</sup> The successor protocol (DFCI 06-254) was a modified version of DFCI 01-0175, wherein the formulation of L-Asparaginase was switched from an E. Coli to a pegylated product, and 3 additional cycles of intensification chemotherapy were added after the CNS prophylaxis phase.<sup>16</sup> In the DFCI 01-0175 study (June 2002 - February 2008), 74 Ph- patients were enrolled. Of these, only the 61 patients who met criteria for CR1 within 6 weeks of treatment initiation were included in the current analysis. For the DFCI 06-254 study (March 2007 – December 2011), the acceptable time to achieve CR1 was extended from 6 to 8 weeks, based on previous studies that suggest that a dose intensive second induction cycle may permit a larger proportion of patients to achieve CR1, thus increasing the potential benefit of receiving pediatric-inspired post-remission therapy.<sup>7</sup> For the DFCI 06-254 trial, 52 Ph- patients were enrolled. Of these, 47 met criteria for CR1

within 8 weeks of treatment initiation. Combining the two trials a total of 108 patients were eligible for initial analysis. However, 1 of these patients was lost to follow-up on the day that CR1 was documented, leaving 107 chemotherapy patients for subsequent analyses.

## Endpoints

Overall survival (OS) was defined as time from CR1 to death. Disease-free survival (DFS) was defined as time from CR to treatment failure (death or relapse). Treatment-related mortality (TRM) was defined as time to death without evidence of leukemia. Relapse was defined as time to marrow or extramedullary leukemia recurrence. Patients were censored at time of last follow-up.

Variables analyzed included age at CR1 (by decades); T-cell vs. B-cell vs. unclassified; diagnostic white cell count (WBC)  $\times 10^9/L$ :  $<30$  vs.  $30-100$  vs.  $>100$ ; time to achieve CR1:  $<4$  weeks vs.  $4-8$  weeks vs.  $>8$  weeks; extramedullary disease at diagnosis: CNS involved (yes/no); cytogenetic abnormalities, according to CIBMTR risk categories: High risk [t(4;11), t(14;18), hypodiploidy ( $<46$ ), complex] vs. standard (all others).

Variables specific to the HCT cohort included months from diagnosis to transplant:  $<5$  vs.  $>5$ ; from CR1 to HCT:  $<3$  vs.  $>3$ ; conditioning regimen: total body irradiation (TBI); yes vs. no; type of donor: HLA-identical sibling vs. 8/8 HLA allele matched URD vs. 7/8 matched URD; donor-recipient gender match: F-M vs. others; donor-recipient CMV serostatus:  $-/-$  vs. others; graft source: bone marrow vs. peripheral blood stem cells; year of transplant: 2002-2007 vs. 2008-2011; GVHD prophylaxis: *ex vivo* T cell depletion vs. cyclosporine A and methotrexate vs. tacrolimus and methotrexate vs. mycophenolate mofetil and cyclosporine A or tacrolimus vs. sirolimus; anti-thymocyte globulin (ATG) or alemtuzumab: yes vs. no. Before study entry, all patients signed informed consent documents that were approved by the Institutional Review Board at each institution for treatment and subsequent data analysis.

## Statistical analyses

Study time for both cohorts began at CR1. Patients in the DFCI chemotherapy cohort who received HCT in CR1 remained in the chemotherapy cohort for this analysis, but were censored at time of HCT ( $n=10$ ). If patients in the chemotherapy cohort relapsed and received HCT beyond CR1 ( $n=4$ ), the relapse was counted as the event date for chemo outcomes including relapse and treatment failure.

Patient-, disease- and transplant- related factors were compared between treatment groups using the Chi-square test for categorical variables and the Wilcoxon two-sample test for continuous variables. Events were summarized by the cumulative incidence estimate with TRM as a competing risk for relapse and the converse. Comparing outcomes in the HCT and non-HCT groups required adjustment for differences in time to treatment using left-truncated analysis starting from CR1<sup>17</sup> and differences in baseline characteristics. Probabilities of disease-free and overall survival were calculated using the left-truncated Kaplan-Meier estimator.<sup>18</sup> Probabilities of other major endpoints included were generated using left-truncated cumulative incidence estimates to account for competing risks. To

adjust for differences in baseline characteristics, Cox proportional hazards regression was used to compare the two treatment groups. For multivariable analysis, the following variables were considered: age at CR1, by decades; T-cell vs. B-cell vs. unclassified; diagnostic WBC,  $\times 10^9/L$ : <30 vs. 30-100 vs. >100; time to achieve CR1: <4 weeks vs. 4-8 weeks vs. >8 weeks; extramedullary disease at diagnosis: CNS involved (yes/no); cytogenetic abnormalities: complex vs. standard.

The assumption of proportional hazards for each factor in the Cox model was tested and as needed non-proportional hazards were constructed using the maximized partial likelihood method to find the most appropriate breakpoint. A backward stepwise model selection approach was used to identify all significant risk factors. Each step of model building contained the main effect for treatment groups. Factors significant at a 5% level were kept in the final model. The potential interactions between main effect and all significant risk factors were tested. P values of <0.05 were considered statistically significant. All statistical analyses were performed using SAS version 9.2 (SAS Institute Inc., Cary, NC).

## Results

The characteristics of the 422 HCT patients and 108 chemotherapy patients are summarized in Table 1. Median follow-up time of living patients was 65 months (range 6-130) in the HCT group and 48 months (<1-94) in the chemotherapy group. The HCT group was characterized by a higher median age (34 vs. 30 years,  $p=0.001$ ) and lower proportion of T-cell ALL (14% vs. 22%,  $p=0.03$ ). CNS disease at diagnosis was less frequent in the HCT cohort (HCT 6% vs. chemo 11%,  $p<0.001$ ). Cytogenetic risk groups were similar between the cohorts. Minimal residual disease testing was not reported in the majority of patients in both cohorts, and was thus not analyzed.

Median time to achieve CR1 was longer in the HCT group (8 weeks, interquartile range 4-14) vs. (chemo 4 weeks, interquartile range 4-5,  $p<0.001$ ). Within the HCT cohort, conditioning regimen intensity was myeloablative for 94%, and 86% of all HCT recipients received TBI. RDs comprised 42% of HCTs, with the remainder consisting of HLA 8/8 matched URD (40%) or 7/8 matched (18%). Hematopoietic cell source was peripheral blood in 79%. For GVHD prophylaxis 15% of HCT recipients received *in vivo* T cell depletion with ATG or alemtuzumab and an additional 2% underwent *ex vivo* T cell depletion.

Ten of the chemotherapy patients were taken off protocol and censored at the time they underwent HCT in CR1 at investigator discretion; two of these patients relapsed 102 and 305 days post-HCT. Eight remaining patients were alive in CR1 with median follow-up time of 33 months (range 11-68) post-HCT.

Causes of death for both cohorts are listed in the supplementary online document. Within the chemotherapy cohort, 5 patients experienced lethal toxicities during post-remission chemotherapy. Relapse accounted for 69% of the deaths in the chemotherapy cohort, with 23% from non-relapse causes. In contrast, within the HCT cohort, 28% of the deaths were related to leukemic relapse and 70% were attributable to HCT-related toxicities.

In univariate comparisons at 4 years of follow-up, cumulative incidence of relapse was similar in both groups (HCT 24% [19-28] vs. chemo 23% [15-32]  $p=0.97$ ). TRM was higher in the HCT cohort (HCT 37% [31-42] vs. chemo 6% [3 – 12],  $p<0.0001$ ). DFS favored the chemo cohort (HCT 40% [35-45] vs. chemo 71% [60-79],  $p<0.0001$ ). OS was also in favor of chemo (HCT 45% [40-50] vs. chemo 73% [63-81],  $p<0.0001$ ).

### Multivariable Analysis

The single independent factor predictive of treatment failure (relapse or death) was HCT (HR 3.10 [2.04 – 4.70],  $p<0.001$ ) (Table 2). HCT was also independently associated with poorer OS (HR 3.12 [1.99 – 4.90],  $p<0.0001$ ). Factors significantly associated with relapse were HCT (HR 1.77 [1.07 – 2.94]) and CNS involvement at diagnosis (HR 1.90 [1.07 – 3.40]). TRM was associated with HCT (HR 6.88 [3.02 – 15.70]), older age (HR 1.69 [1.16 – 2.44]), and B cell phenotype (HR 2.26 [1.30 – 3.93]).

As a sensitivity analysis, we excluded the 10 patients in the chemo cohort who underwent HCT in CR1. This did not change the key outcomes. Similar to the primary analysis, treatment failure (relapse or death) was higher in the HCT cohort (HR=3.05 [2.00 – 4.63],  $P<0.0001$ ). Relapse and TRM were greater in the HCT cohort (HR 1.75 [1.05 – 2.90],  $p=0.0308$ , and HR=6.74 [2.96 – 15.37], respectively). Overall Survival favored the chemotherapy cohort (HR=3.08[1.96 –4.83],  $P<0.0001$ ).

Figures 2a and 2b show left-truncated Kaplan-Meier DFS and OS curves comparing outcomes of chemotherapy and HCT. Hazard Ratios for these outcomes favor the chemo cohort (3.10 [2.04-4.70] and 3.12 [1.99-4.90], respectively). Figures 2c and 2d demonstrate left-truncated cumulative incidence of relapse and TRM. In these analyses, both relapse and TRM were inferior in the HCT cohort (HR=1.77 [1.07-2.94] and HR=6.88 [3.02-15.70], respectively).

Exploratory multivariable regression analysis was performed within the HCT cohort in order to establish predictors of outcome for these patients. Time to CR of >8 weeks and the use of HLA mismatched URDs (7/8) were significantly associated with inferior OS after HCT. These factors were then adjusted for in the analysis of HCT vs. chemo outcomes (supplementary online material). This demonstrated that the better OS associated with chemotherapy was maintained (HCT HR 2.14 [1.36-3.35]) even when restricting the HCT cohort to only those recipients using RDs or 8/8 URDs and those with time from diagnosis to CR1 <8 weeks (Figure 2e).

### Discussion

In younger adults with Ph- ALL in CR1, we show that the administration of a non-HCT, pediatric-inspired chemotherapy regimen resulted in clinical outcomes that were superior to allogeneic HCT. A striking finding was that HCT did not appear to reduce relapse rates as compared to the non-HCT approach. The HCT also patients experienced higher TRM. Overall, this resulted in poorer DFS and OS compared to patients who received the pediatric-inspired regimen.

Our results differ from the largest donor-versus-no donor clinical trial conducted in adults with ALL in CR1 that demonstrated better overall survival for HCT recipients.<sup>3</sup> The value of HCT has been further supported by meta-analyses, suggesting that for adults with Ph-ALL in CR1, HCT offers an OS advantage of approximately 10% compared to non-HCT therapy.<sup>6,8</sup> The contradictory findings in our current study are likely to be a consequence of the characteristics of the non-HCT chemotherapy arm, which is adopted from the intensive approach offered to children and adolescents with high-risk ALL.<sup>4,5</sup> The DFCI regimen, similar to other pediatric regimens for ALL, offers a prolonged (> 2 years), intensive protocol, with particular emphasis on the post-remission administration of high cumulative doses of non-myelosuppressive agents including corticosteroids, vincristine, and L-Asparaginase. In addition, this regimen includes extensive CNS prophylaxis with intrathecal chemotherapy, cranial irradiation, and high dose intravenous methotrexate.<sup>4,5,7</sup> When comparing outcomes of adolescents and younger adults who have received pediatric regimens to those of similar age who received less intensive regimens at adult ALL centers, the intensive approach has consistently resulted in better prevention of relapse and more favorable clinical outcomes.<sup>19-21</sup> Pediatric-inspired regimens have recently been evaluated for adults as old as 60 years, with promising outcomes in both clinical trial and regular hospital settings.<sup>7,11-14</sup>

This study was not a randomized controlled trial, and thus we actively addressed potential biases that may result from measurable differences in baseline clinical characteristics and in time to definitive post-remission treatment. We selected patients who were treated over the same time period (2002-2011) and geographic regions (Canada and US) with identical eligibility criteria for age (18-50). We then deployed multivariable Cox regression analysis to account for imbalances between the two cohorts including age, baseline white blood cell count, and cytogenetic risk category. We also used left-truncation to adjust for a time bias which might favor HCT patients, as these patients would need to survive in CR1 long enough to receive the HCT.

Within the HCT cohort, a longer time from diagnosis to CR1 may have been an indication of patients who required several cycles of chemotherapy to achieve CR1; this may adversely influence outcomes for the HCT cohort. However, when we limited the HCT cohort only to those whose time from diagnosis to CR1 was less than 8 weeks, the key clinical outcomes still favored the chemotherapy cohort.

The advantage of pediatric-inspired chemotherapy over HCT was noted regardless of donor type in the HCT arm. Because the use of a partially HLA matched (7/8) URD may confer poorer outcomes after HCT, we performed a subgroup analysis restricted to RD or only 8/8 URD. Using this adjustment, our results still showed a survival advantage for the chemotherapy cohort.

Although follow-up in the chemo group was shorter than in the HCT cohort (48 vs. 65 months), the majority of events related to relapse or to TRM occurred within the first 48 months in both cohorts. Thus, the shorter median follow-up time in the chemo cohort is unlikely to change the key results in this study. Overall, adjusting for all of potential biases



that we could recognize, we continued to find a significant advantage in favor of chemotherapy compared to HCT, the latter offering no reduction in relapse risk.

HCT outcomes were limited by excess TRM. Lethal toxicities following HCT, primarily as a result of GVHD or infection, remain major limiting factors to HCT for ALL. Thankfully, improvements in survival following HCT have been noted,<sup>22</sup> although outcomes after HCT for adults with ALL do not appear to have improved as much as those seen in children and adolescents.<sup>23</sup> The BFM group have demonstrated that for children with ALL who received an allogeneic HCT, TRM as low as 4% after related donor transplants and 10% after unrelated donor transplants can be achieved<sup>24</sup>. This suggests that young adults tolerate allogeneic HCT much more poorly than in children, further emphasizing our concerns about the risks of HCT in younger adults with ALL. However, regardless of any foreseeable improvements in TRM after HCT, this procedure did not appear to reduce the relapse rate, and hence the added risk of TRM was not counterbalanced by a reduction in ALL relapse.

Older age (>30 years) was independently associated with excess TRM. This is not surprising, and highlights the need for greater attention to the management of co-morbidities, and general supportive care regardless of whether patients are assigned to a HCT or a non-HCT post-remission strategy. For the HCT cohort, selection of the optimal conditioning regimens is important. The majority of the HCT patients in the current analysis underwent myeloablative conditioning, which has been shown in some<sup>25</sup> but not all<sup>26</sup> studies to pose a higher risk of TRM compared to reduced intensity conditioning (RIC) approaches in adult ALL. With increasing use of RIC approaches that lack TBI, especially those who are older than 40 to 50 years or with comorbidities, the outcomes of ALL patients undergoing HCT may improve, necessitating further analyses of post-HCT outcomes in the RIC era.<sup>27,28</sup> Although the incidence of post-remission TRM was significantly lower in the chemo cohort, it was still at an appreciable level (6%). Pediatric-inspired regimens require vigilance with respect to infectious, venous thromboembolic, and other complications.<sup>7</sup> Centers that choose to use such regimens need to build rigorous supportive care strategies into their protocols.

Too few data were available regarding the use of alternative graft sources (umbilical cord blood or haploidentical donors) to include in this analysis. Recently, registry studies and clinical trial outcomes have suggested that HCTs using such cell sources are promising modalities, albeit in need of further study.<sup>29-31</sup>

Unfortunately, we lacked data for either cohort on novel molecular markers in ALL, such as *IKZF1*<sup>32</sup>; however, in North American leukemia centers, these tests were unlikely to have been performed frequently over the time period of study and thus would not have influenced assignment to either chemotherapy or HCT.

In ALL, MRD is an important predictor of subsequent relapse.<sup>32-34</sup> Data on post-treatment MRD (as a measure of the depth of remission) were unfortunately not available for the majority of patients in either the HCT or chemotherapy arms. It is possible that the 10 patients in the chemo cohort who proceeded to HCT while in CR1 represented a subgroup at particularly high risk for relapse (e.g. MRD positivity or other adverse molecular markers).

As a sensitivity analysis, we removed these patients from the chemo cohort. Outcomes continued to show no advantage to receiving HCT in CR1 in terms of relapse risk, TRM, DFS, or OS. MRD guided therapy, although popular in pediatric ALL, was not widely applied for adults during the period of study and thus could not further inform the reported comparisons.<sup>35</sup> Future studies will need to incorporate MRD reporting into their results.

In summary, we show that a pediatric-inspired chemotherapy regimen for adults with Ph-ALL results in durable leukemia-free survival, and is associated with superior outcomes compared to allogeneic transplantation. These findings should help to inform health care providers and patients about the relative merits of HCT versus intensive, non-HCT approaches in adult Ph-ALL, and will also provide rationale for the development of prospective clinical trials in this area.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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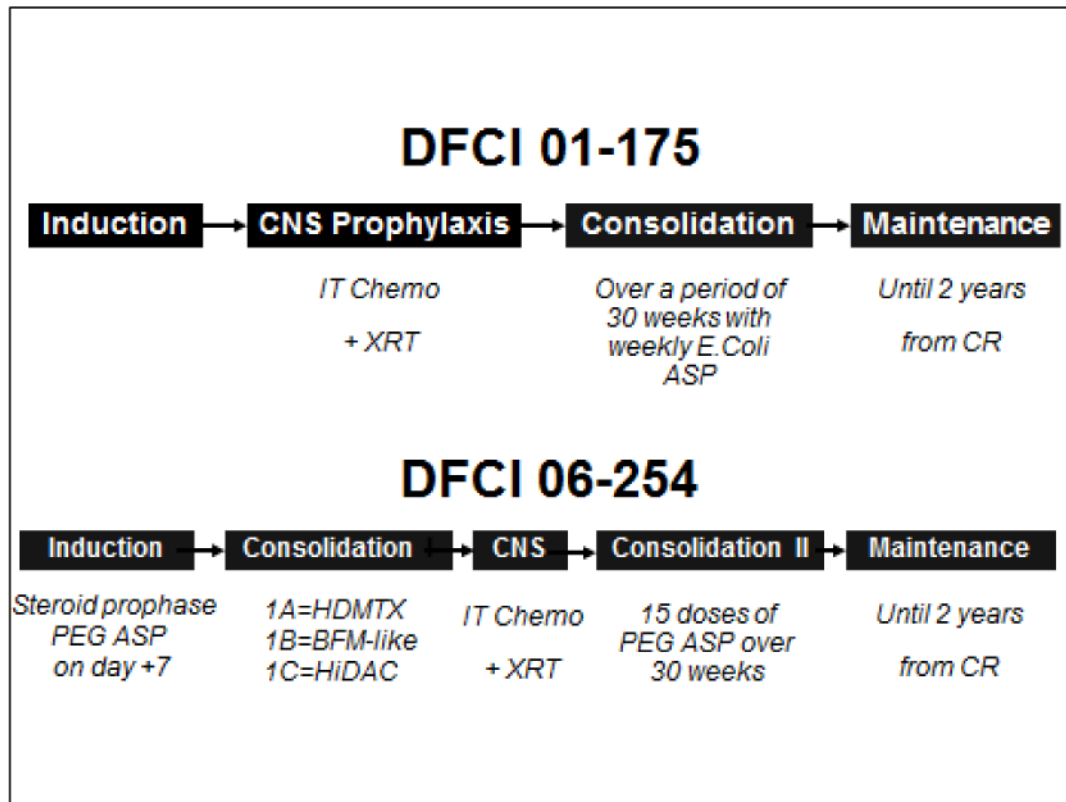
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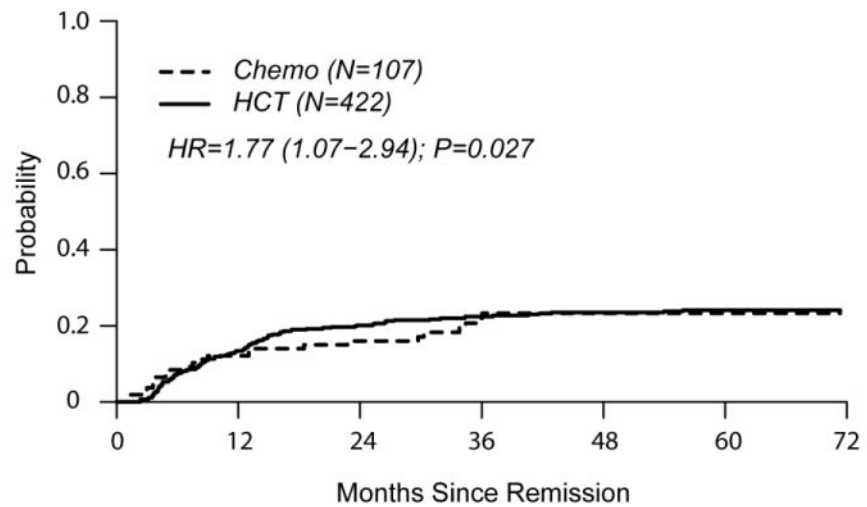
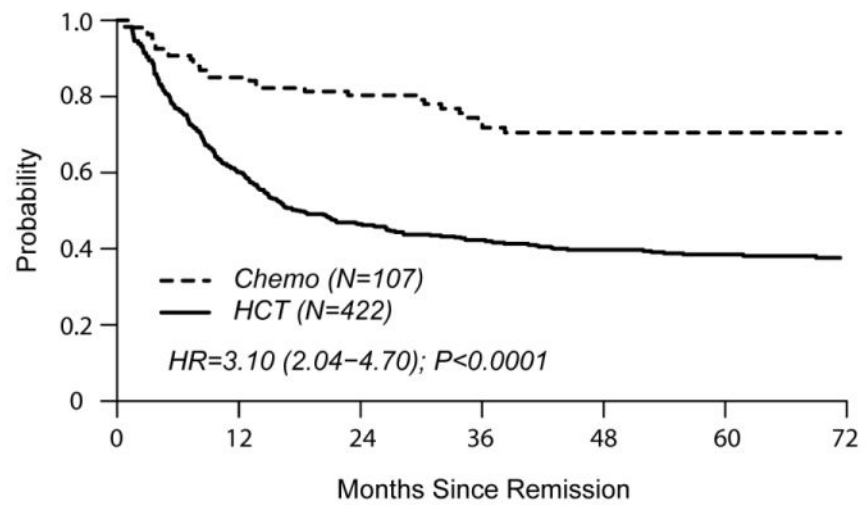
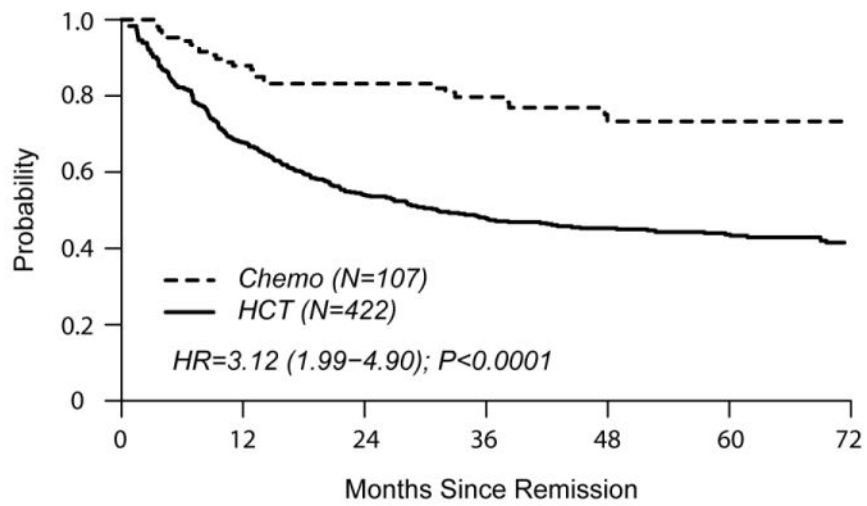
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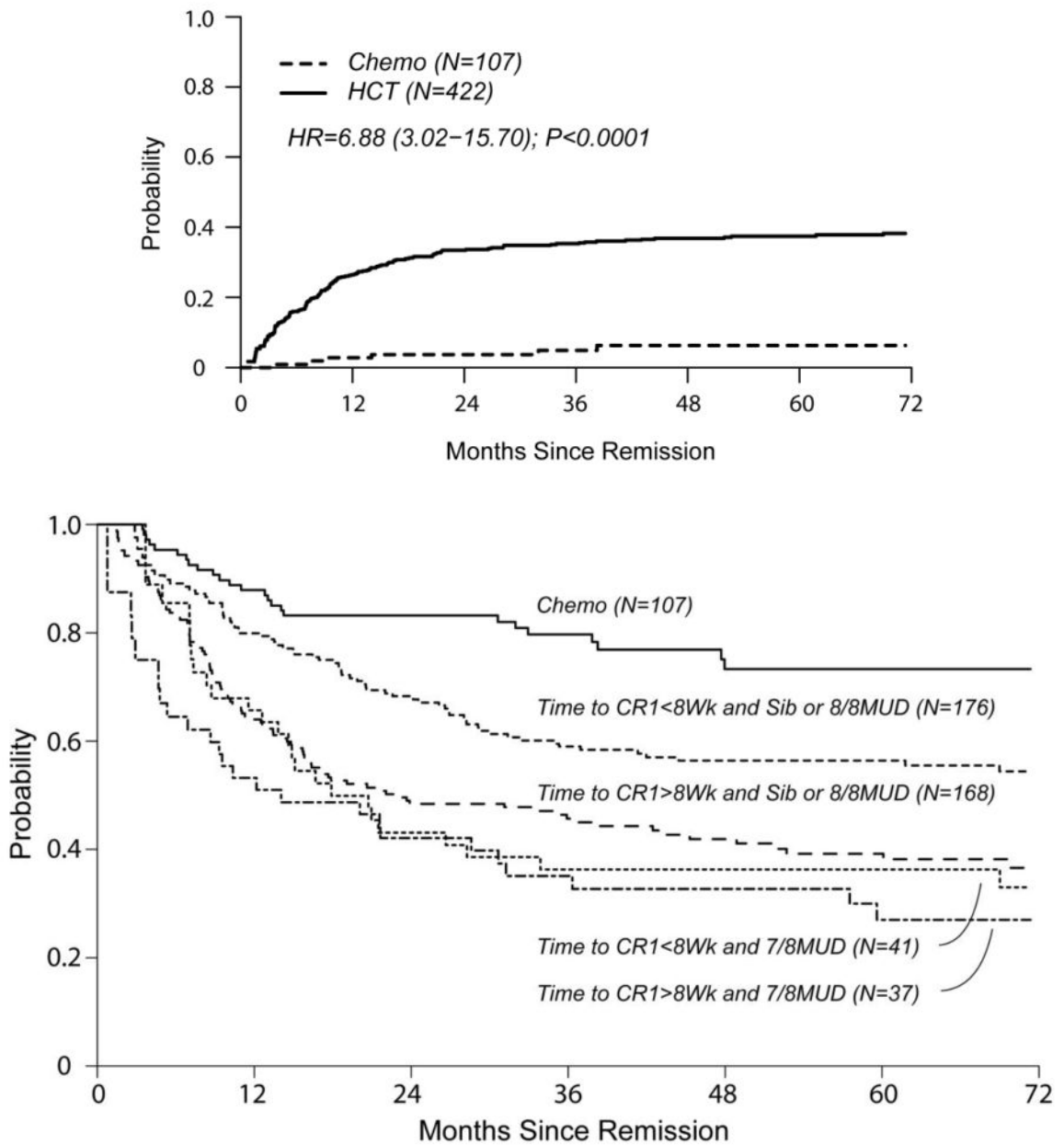
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**Figure 1.**

Overall Schema of the Dana Farber Cancer Institute (DFCI) adult ALL Consortium regimens in trials 01-175 and 06-254 trials<sup>11,16</sup>

CNS: Central Nervous System; IT: Intrathecal; XRT: Cranial Irradiation; ASP: L-Asparaginase; CR: Complete Remission; PEG: Pegylated; HDMTX: High dose Methotrexate; BFM: Berlin-Frankfurt-Münster; HiDAC: High dose cytarabine;





**Figure 2.** Comparison of outcomes of Chemotherapy only regimen (chemo) and allogeneic hematopoietic cell transplantation (HCT)  
(a) Overall Survival  
(b) Disease Free Survival  
(c) Cumulative Incidence of Relapse  
(d) Cumulative Incidence of Treatment Related Mortality  
(e) Kaplan Meier Estimate of Overall Survival Comparing Chemotherapy Patients To Sub-Groups Of HCT Recipients



**Table 1**  
**Characteristics of study population**

Variable	HCT	Chemo	p-value
Number of patients	422	108 <sup>d</sup>	
Number of centers	97	13	
Age in decades			0.05
Median (range)	34 (18-50)	30 (18-50)	0.001
18-29	161 (38)	54 (50)	
30-39	126 (30)	30 (27)	
40-50	135 (32)	24 (23)	
Gender			0.67
Male	253 (60)	68 (62)	
Female	169 (40)	40 (38)	
Immunophenotype			0.03
T-cell	61 (14)	24 (22)	
B-cell	343 (81)	84 (78)	
Unspecified	18 (4)	0	
WBC at diagnosis ( $\times 10^9/L$ )			<0.001
Median (range)	12 (<1-515)	8 (1-1424)	0.30
$\leq 30$	238 (56)	80 (74)	
30 – 100	67 (16)	13 (13)	
> 100	53 (13)	14 (13)	
Missing	64 (15)	1 (<1)	
CNS involvement at diagnosis			<0.001
No	392 (93)	90 (83)	
Yes	27 (6)	12 (11)	
Missing	3 (<1)	6 (6)	
Cytogenetic abnormalities			0.30
t(4;11) or MLL rearranged	34 (8)	11 (10)	
t(1;19)	7 (2)	4(4)	
Others <sup>d</sup>	268 (63)	71 (66)	
Missing	113 (27)	22 (20)	
Cytogenetic risk group			0.01
High risk (t(4;11)/t(14;18)/hypodiploidy/complex)	48 (12)	24 (22)	
Standard	261 (62)	62 (57)	
Missing	113 (27)	22 (20)	
Time to achieve CR1 (weeks)			<0.001
Median (interquartile range)	8 (4-14)	4 (4-5)	<0.001
<4 weeks	48 (11)	8 (7)	
4-8 weeks	169 (39)	99 (92)	
$\geq 8$ weeks	205 (47)	1 (<1)	
Time from diagnosis to HCT (months)		N/A	

Variable	HCT	Chemo	p-value
Median (range)	5 (2-31)		
<5 months	164 (39)		
>=5 months	258 (61)		
Time from CR1 to HCT (months)		N/A	
Median (range)	3 (<1-30)		
<3 months	201 (47)		
>=3 months	223 (53)		
KPS (%) pre HCT			
<80	25 (6)		
>=80	372 (88)		
Missing	25 (6)		
Conditioning intensity			
Myeloablative	396 (94)	N/A	
RIC/NMA	17 (4)		
Missing	8 (2)		
Total body irradiation		N/A	
No	58 (14)		
Yes	364 (86)		
Type of donor		N/A	
HLA-identical sibling	176 (42)		
Unrelated HLA 8/8 allele matched	168 (40)		
Unrelated HLA 7/8 allele matched	78 (18)		
HLA-identical sib donor age		N/A	
Median (range)	35 (13-61)		
Unrelated donor age			
Median (range)	35 (19-61)		
Donor/Recipient sex match		N/A	
M/M	168 (40)		
M/F	87 (21)		
F/M	84 (20)		
F/F	81 (19)		
Missing	2 (<1)		
Donor/Recipient CMV serostatus		N/A	
D+/R+	113 (27)		
D+/R-	125 (29)		
D-/R+	59 (14)		
D-/R-	110 (26)		
Missing	15 (4)		
Graft type		N/A	
Bone marrow	86 (21)		
Peripheral blood	336 (79)		
GVHD prophylaxis		N/A	

Variable	HCT	Chemo	p-value
Ex-vivo TCD or CD34 selection	12 (2)		
CsA + MTX	91 (21)		
Tacrolimus + MTX	195 (46)		
CsA/Tac + MMF	58 (14)		
Tac + Sirolimus	29 (7)		
Others <sup>b</sup>	37 (9)		
ATG/Alemtuzumab		N/A	
ATG alone	53 (13)		
Alemtuzumab alone	9 (2)		
No ATG or alemtuzumab	360 (85)		
Year			
2002-2007	318 (75)	72 (65)	
2008-2011	104 (25)	36 (35)	
Median follow-up of survivors (range), months <sup>c</sup>	65 (6-130)	48 (<1-94)	

<sup>a</sup> other cytogenetic abnormalities for HCT cohort include: hypodiploidy, n=7; hyperdiploidy, n=11; more than 3 complexity, n=7; normal karyotype, n=54; other specified, n=189.

<sup>b</sup> other GVHD prophylaxis include: cyclophosphamide alone, n=3; FK506 + others, n=9; FK506 alone, n=11; CsA based, n=7; unknown, n=7

<sup>c</sup> Median follow-up of survivors counted from date of 1<sup>st</sup> complete remission HCT: Hematopoietic Cell Transplantation; Chemo: chemotherapy cohort; CR: Complete Remission; MTX: Methotrexate; MMF: Mycophenolate Mofetil; Tac: CsA: cyclosporine A; Tacrolimus; CMV: cytomegalovirus; ATG: Anti-thymocyte globulin; TCD: T cell depletion.

<sup>d</sup> 108 cases in chemo cohort but 1 lost to follow-up on day of CR1, so 107 were included in all analyses.

**Table 2**  
**Multivariable Analyses**

Outcome	Number	Hazard Ratio (95% CI)	p-value
<b>TRM</b>			
Main: Chemo	107	1.00	
HCT	422	6.88 (3.02 – 15.70)	<0.01
Age: 19 - 29	214	1.00	
30 - 50	315	1.69 (1.16 – 2.44)	<0.01
FAB: T-cell/Unspecified	102	1.00	
B-cell	427	2.26 (1.30 – 3.93)	<0.01
<b>Relapse</b>			
Main: Chemo	107	1.00	
HCT	422	1.77 (1.07 – 2.94)	0.03
CNS Involvement: No	481	1.00	
Yes	39	1.90 (1.07 – 3.40)	0.03
Missing	9	3.51 (1.35 – 9.16)	0.01
<b>Treatment Failure (inverse of DFS)</b>			
Main: Chemo	107	1.00	
HCT	422	3.10 (2.04 – 4.70)	<0.01
CNS Involvement: No	481	1.00	
Yes	39	1.53 (0.99 – 2.35)	0.05
Missing	9	2.21 (0.88 – 5.57)	0.09
<b>Overall Mortality</b>			
Main: Chemo	107	1.00	
HCT	422	3.12 (1.99 – 4.90)	<0.01

TRM: treatment related mortality; N: Number; Chemo; Chemotherapy cohort; HCT: Hematopoietic Cell Transplant; DFS: disease-free survival; OS: overall survival; CI: Confidence Interval; CNS: Central Nervous System.