Effect of allogeneic hematopoietic cell transplantation in first complete remission on post-relapse complete remission rate and survival in acute myeloid leukemia

Several studies have shown that allogeneic hematopoietic cell transplantation (HCT) in first complete remission (CR1) of AML reduces the risk of relapse and improves relapse-free survival in intermediate- and poor-risk AML.[1] Benefits in (overall) survival are less obvious.[1,2] One possible explanation is that following the occurrence of relapse, previous receipt of allogeneic HCT in CR1 is associated with shorter survival, with a lower CR rate following therapy for relapse (salvage therapy) being a possible contributing factor. Breems et al. reported that in 667 adults age < 60, HCT in CR1 was independently associated with shorter survival after subsequent relapse, with 58 patients receiving allogeneic and 102 autologous HCT.[3] Second CR rate was 33% when HCT had been done in CR1, and 49% if it had not. Burnett *et al*. noted that survival after relapse was shorter in their 1,064 patients receiving HCT in CR1 than in patients not transplanted in CR1; 23% of the 1,064 patients received autologous HCT and CR rates in these 1,064 were not reported.[4] The aims of our study were to analyze the effect of, specifically, allogeneic HCT in CR1 on the probabilities of (a) achieving second CR (CR2) with first salvage therapy, and (b) survival from first salvage.

We identified 173 consecutive patients with AML (APL excepted) or MDS with 10-19% blasts who, after achieving CR1 (< 5% morphologic blasts in marrow, ANC > 1,000 and platelets > 100,000 micro/L) with initial treatment, relapsed (> 5% blasts in marrow and/or blood unrelated to recovery of blood counts) between 2008 and 2013 at our center. 161 of the 173 received first salvage therapy. From these 161, we collected data on: (1) age, (2) secondary *vs. de novo* AML, (3) CR1 duration, (4) number of initial induction courses, (5) number of post-remission courses, (6) ECOG performance status at relapse, (7) cytogenetic category (ELN criteria for adverse, intermedi-

Table 1. Pre-1st salvage therapy patient characteristics of cohort, stratified by HCT status in CR1 (No-HCT *vs.* MA HCT *vs.* RI HCT).

	All (n=161)	No-HCT (n=116)	MA (n=26)	RI (n=19)	*P**
Median Age at 1st relapse, year (range)	53 (20-82)	54 (20-82)	46.5 (20-59)	61 (21-75)	< 0.001
Secondary AML, n (%)	47 (29%)	31 (27%)	6 (23%)	10 (53%)	0.068
No. of induction courses to attain CR1, n (%)					0.027
1	134 (83%)	102 (88%)	18 (69%)	14 (74%)	
2	27 (17%)	14 (12%)	8 (31%)	5 (26%)	
Post-remission therapy in CR1, n (%)					0.064
No	25 (16%)	14 (12%)	8 (31%)	3 (16%)	
Yes	136 (84%)	102 (88%)	18 (69%)	16 (84%)	
No. of post-remission courses in CR1, n (%)					0.003
0	25 (16%)	14 (12%)	8 (31%)	3 (16%)	
1	35 (22%)	20 (17%)	7 (27%)	8 (42%)	
2	36 (22%)	26 (22%)	6 (23%)	5 (26%)	
3	65 (40%)	59 (49%)	5 (19%)	3 (16%)	
Median CR1 duration, m (range)	8.0 (0.5-163)	6.4 (0.5-79.5)	11.6 (3.9-163)	10.0 (3.4-82)	< 0.001
Performance status at 1st relapse, n (%)					0.042
0-1	129 (81%)	97 (84%)	21 (81%)	11 (60%)	
2	32 (19%)	19 (16%)	5 (19%)	8 (40%)	
Cytogenetics at 1st relapse, n (%)					0.35
Favorable	11 (7%)	10 (9%)	1 (4%)	0 (0%)	
Intermediate	94 (58%)	70 (60%)	13 (50%)	11 (58%)	
Adverse	34 (21%)	24 (21%)	7 (27%)	3 (16%)	
Missing/Insufficient	22 (14%)	12 (10%)	5 (19%)	5 (26%)	
Molecular studies at 1st relapse					
FLT3, n (%)					0.78
Positive	22 (13.5%)	18 (15.5%)	3 (11.5%)	1 (5%)	
Negative	64 (40%)	47 (40.5%)	9 (34.5%)	8 (42%)	
N/A	75 (46.5%)	51 (44%)	14 (54%)	10 (53%)	
NPM1, n (%)					0.05
Positive	20 (12.5%)	19 (16%)	1 (4%)	0 (0%)	
Negative	33 (20.5%)	24 (21%)	3 (11.5%)	6 (31.5%)	
N/A	108 (67%)	73 (63%)	22 (84.5%)	13 (68.5%)	
Intensity of 1st salvage therapy, n (%)					0.062
High intensity	86 (53%)	69 (59%)	12 (46%)	5 (26%)	
Average intensity	29 (18%)	17 (15%)	6 (23%)	6 (32%)	
Low intensity	46 (29%)	30 (26%)	8 (31%)	8 (42%)	

*HCT: hematopoietic cell transplantation; CR1: first complete remission; MA: myeloablative; RI: reduced intensity; N/A: not available. *For the comparison of No-HCT in CR1 vs. MA HCT in CR1 vs. RI HCR in CR1.*

ate, "favorable", and "missing"5) at relapse, (8) *FLT3* ITD and *NPM1* status at relapse, (9) allogeneic HCT in CR1 (yes *vs.* no, and subsequently myeloablative (MA) *vs.* reduced intensity (RI) *vs.* none), (10) intensity of first salvage therapy and (11) HCT in CR2. Cytarabine at ≥ 1 g/m^2/dose +/- other drugs or allogeneic HCT were considered "high intensity", "3+7" +/- other drugs as average intensity, and other salvage treatments (typically low-dose cytarabine, or azacitidine) as low intensity. First salvage regimens were chosen informally by attending physicians, as were post-remission regimens which included HiDAC, repeats of initial treatment or allogeneic HCT.

45/161 (28%) of patients received HCT in CR1, with 26 being given a MA and 19 RI HCT. In 60 of the 116 patients who did not receive HCT in CR1, the decision seemed based on the following criteria: (a) the lack of a matched sibling or unrelated donor, (b) the relatively low risk of relapse given "favorable" cytogenetics or *NPM1* positive/*FLT3* ITD negative status, (c) the relatively high risk of non-relapse mortality based on age > 75 or HCT co-morbidity index 2-5, and (d) the discovery of relapse in 28 of the patients at the pre-HCT evaluation. The reasons for the decision not to proceed to HCT were unclear in almost half the patients (56/116) who did not receive HCT in CR1.

Survival was measured from date of first salvage therapy and analyzed using log-rank tests. Univariate logistic (for CR2 after relapse) and Cox regression (for survival) analyses were performed for the covariates noted above, with HCT in CR2 treated as time-dependent covariate. Variables among those noted in the 2nd paragraph, significant at P<0.10 in univariate analyses, were included in multivariable logistic and Cox regression models. The study was approved by the relevant Institutional Review Boards and conducted in accordance with the Declaration of Helsinki.

Table 1 shows patient characteristics. MA patients were the youngest and RI patients the oldest (P<0.001). Since they were often in relapse at pre-HCT evaluation, no-HCT patients had shorter CR1 durations than the MA or RI groups (P<0.001), but received more post-remission courses. Perhaps, reflecting their older age, RI patients tended to have poorer performance status and to receive

Table 2A. Multivariable logistic regression model for CR2 with first salvage (n=161).

	OR	95% CI	P
HCT in CR1 (ref = No-HCT)	1.5	(0.64, 3.51)	0.35
High intensity salvage (ref = average intensity)	1.2	(0.46, 3.09)	0.71
Low intensity salvage (ref = average intensity)	0.39	(0.13, 1.18)	0.095
Length of CR1 (months)	1.02	(1, 1.04)	0.019
PS 2+ (ref = PS 0-1)	0.44	(0.16, 1.19)	0.11
Age (years)	1.02	(0.99, 1.04)	0.24
Favorable cyto (ref = Adverse)	5.45	(1.17, 25.4)	0.031
Intermediate cyto (ref = Adverse)	1.73	(0.68, 4.37)	0.25
Insufficient/Missing cyto (ref = Adverse)	0.93	(0.25, 3.44)	0.91

Table 2B. Multivariable Cox regression model for survival after first salvage.

Covariate	HR	95% CI	P
HCT in CR1 (ref = No-HCT in CR1)	0.79	(0.48, 1.28)	0.34
High intensity salvage (ref = average intensity)	0.84	(0.47, 1.52)	0.57
Low intensity salvage (ref = average intensity)	1.49	(0.82, 2.69)	0.19
Length of CR1 (months)	0.99	(0.98, 1)	0.13
PS 2+ (ref = PS 0-1)	1.86	(1.13, 3.06)	0.015
Age (years)	1	(0.98, 1.02)	0.99
Favorable cyto (ref = Adverse)	0.37	(0.15, 0.94)	0.036
Intermediate cyto (ref = Adverse)	0.68	(0.41, 1.12)	0.13
Insufficient/Missing cyto (ref = Adverse)	0.77	(0.39, 1.53)	0.46
HCT in CR2 (ref = No-HCT in CR2)	0.55	(0.28, 1.06)	0.075

**Time-dependent Cox regression analyses with the covariate of HCT in CR2.*

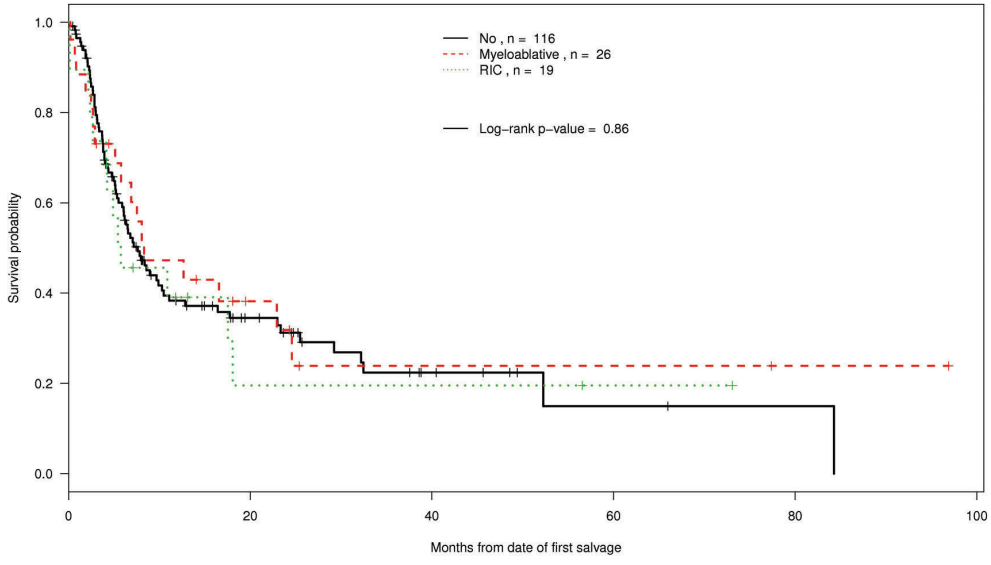

Figure 1. Overall survival after first salvage therapy, stratified by HCT status in CR1. No-HCT (n=116, black line), myeloablative HCT (n=26, red line), and reduced intensity HCT (n=19, green line). Log rank P=0.86.

intensive therapy less often at relapse. The CR2 rate with first salvage therapy was essentially similar in the 3 groups: 43/116 (37%) for no-HCT, 11/26 (42%) for MA, and 8/19 (42%) for RI. 50/116 patients in the no-HCT in CR1 group received HCT after first relapse; half the time this was done in CR2 (25/50). Only 9/45 patients who received HCT in CR1 also received HCT after relapse; in 5 patients HCT was done in CR2 (5/9). Paralleling the similar CR2 rates, survival after first salvage was largely identical in the 3 groups (Figure 1, *P*=0.86), with medians of 8 months for no-HCT and MA, and 6 months for RI.

As expected, univariate analyses indicated that the principal predictor of CR2 achievement was longer CR1 duration (OR 1.03, *P*=0.01). Also associated was the receipt of average or high, rather than low, intensity salvage (OR 2.5, *P*=0.04). Both these covariates were associated with longer survival after first salvage, (HR 0.99, p = 0.06, HR 0.62, *P* =0.04) respectively. However the major predictor of longer survival after first salvage was HCT in CR2 *vs.* no-HCT in CR2 (HR 0.42, *P*=0.008).

Multivariable analyses (Table 2A-B) showed that HCT in CR1 had no significant effect on CR2 rate (OR 1.5, *P*=0.35) or OS (HR 0.79, *P*=0.34). In contrast, CR1 duration, cytogenetics, and performance status at relapse were independently associated with these outcomes. An analysis of MA *vs.* RI *vs.* no-HCT led to similar conclusions (*Online Supplementary Tables S1 and S2*), as did an analysis of low intensity salvage *vs.* that of average- or high-intensity (*Online Supplementary Tables S3 and S4*). Of particular note is that the multivariate analyses suggested that if anything the effect of HCT in CR1 on both CR2 (OR 1.50) and OS (HR 0.79) was favorable. Although not statistically significant, it thus seems unlikely that the effect of HCT in CR1 was unfavorable. Furthermore, patients receiving HCT in CR1 did not have poorer OS, although HCT in CR2, which was strongly associated with survival from first salvage, was essentially restricted to patients who did not have HCT in CR1.

The differences between our findings and those of Breems *et al*. may reflect different practices after relapse. A higher proportion of our patients received first salvage than did those of Breems *et al*.: 93% *vs.* 81%. Because we were interested in CR2 rate, we included only the 161 patients who were treated in our survival analysis, while Breems *et al*. included all relapsed patients. 91% of the patients treated by Breems *et al*. received intensive salvage therapy including 36% who were given an allogeneic or autologous transplant. In contrast, 53% of our patients received high intensity first salvage (with only 2% receiving allogeneic HCT as first salvage therapy) and 29% receiving low intensity salvage. While suggesting that a deleterious effect of HCT in CR1 on outcome of salvage therapy might be limited to patients receiving intense salvage therapy, we could not, within the limits of our patient numbers, identify an interaction between effect of each type of HCT in CR1 and intensity of salvage therapy. Patients of Breems *et al*. were age < 60 (median age approximately 45), and more often received autologous rather than allogeneic HCT in CR1 (although they did not separately assess the risks of each type of HCT), while our patients were older (median age 53) and only received allogeneic HCT. Patients of Burnett *et al*. were all age < 50 with 23% receiving autologous HCT. Finally, a reduction in allogeneic HCT-related mortality has occurred over the past decade with the patients of Breems *et al*. having been treated from 1987-2001, those of Burnett *et al*. from 1988-2009 (62% from 1988-2002) and ours from 2008-2013.[6] Hence, the lack of effect of HCT in CR1 on survival after relapse in our study, but not in that of Breems *et al*. nor that of Burnett *et al*., may simply reflect an improved ability to manage post allogeneic HCT complications.

The proportion of patients receiving HCT beyond first relapse was similar in our study and that of Breems *et al*. (37% *vs.* 33%), as was the proportion of patients receiving HCT beyond first relapse having not received previous HCT either in our study or in that of Burnett *et al*. (each 43%). Nonetheless our study was smaller than both those of Breems *et al*. and Burnett *et al*., and like these studies could have been affected by various selection biases, even after accounting for a relatively large number of covariates (paragraph 2). For example, the reason for no-HCT in CR1 was unclear in almost half our patients. While, optimally, the effect of HCT in CR1 on outcome after relapse would be addressed via a trial randomizing patients in CR1 between immediate HCT and HCT only should relapse occur, such a trial is unlikely to be done given such biases. With these constraints our results suggest that the effect of HCT in CR1 can be relatively small, and certainly less than those of CR1 duration, cytogenetics and performance status.

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