

Do liberal thresholds for red cell transfusion result in improved quality of life for patients undergoing intensive chemotherapy for acute myeloid leukemia? A randomized crossover feasibility study

Patients with acute myeloid leukemia (AML) on intensive treatment are dependent on red blood cell (RBC) transfusion, but the evidence base defining optimal transfusion threshold support in AML is very weak. We conducted a multicenter, randomized controlled feasibility trial in patients transfused below 70 (restrictive, R) or 90g/L (liberal, L) hemoglobin. The aim of the study was to assess the feasibility of randomizing to two hemoglobin thresholds in the setting of AML and assessing quality of life (QoL) among participants. We incorporated a novel crossover design between cycles of intensive chemotherapy, thus

allowing patients to serve as their own control, and assessed QoL at multiple intervals.

Patients were eligible if ≥ 18 years, and treated with curative intent for newly diagnosed or relapsed AML, or myelodysplasia with excess of blasts (MDS-EB). Patients with prior MDS were excluded. Participants were randomized (1:1, web-based service, stratified by center) by day 5 of chemotherapy in cycle 1, to restrictive transfusion (threshold 70 g/L; target 71-80 g/L) or liberal transfusion (threshold 90 g/L, target 91-100 g/L); participants then crossed over to the alternative policy for the second cycle

Table 1. Baseline characteristics.

Baseline characteristics - N (%) or median (q1-q3)			
	Restrictive then liberal (n=21)	Liberal then restrictive (n=22)	Total (n=43)
Age (years)	62 (46-68)	61 (52-68)	61 (48-68)
Male	8 (38)	14 (64)	22 (51)
Ethnic origin			
Caucasian	19 (90)	19 (86)	38 (88)
Black	0 (0)	1 (5)	1 (2)
Hispanic	1 (5)	0 (0)	1 (2)
Asian	1 (5)	2 (9)	3 (7)
ECOG status			
0	13 (62)	13 (59)	26 (60)
1	8 (38)	8 (36)	16 (37)
2	0 (0)	0 (0)	0 (0)
3	0 (0)	0 (0)	0 (0)
4	0 (0)	1 (5)	1 (2)
Cytogenetic category			
Not reported	1 (5)	0 (0)	1 (2)
Favorable risk	2 (10)	2 (9)	4 (9)
Standard risk	11 (52)	14 (64)	25 (58)
Poor risk	7 (33)	6 (27)	13 (30)
AML subtype			
First presentation	21 (100)	20 (91)	41 (95)
Relapsed	0 (0)	2 (9)	2 (5)
Hemoglobin (g/L)	82 (77-92)	80 (74-94)	81 (75-94)
Platelets ($\times 10^9/L$)	55 (25-112)	75 (26-154)	55 (25-139)
White cell count ($\times 10^9/L$)	5 (2-23)	2 (1-14)	2 (1-20)
Total RBC units in 8 weeks prior to randomisation	2 (1-2)	1 (0-2)	1 (0-2)
Received RBC transfusion prior to randomisation, n (%)	9 (43)	7 (32)	16 (37)

ECOG: Eastern Cooperative Oncology Group Performance Status; RBC: red blood cells; q1-q3= quartile 1 to quartile 3; AML: acute myeloid leukemia.

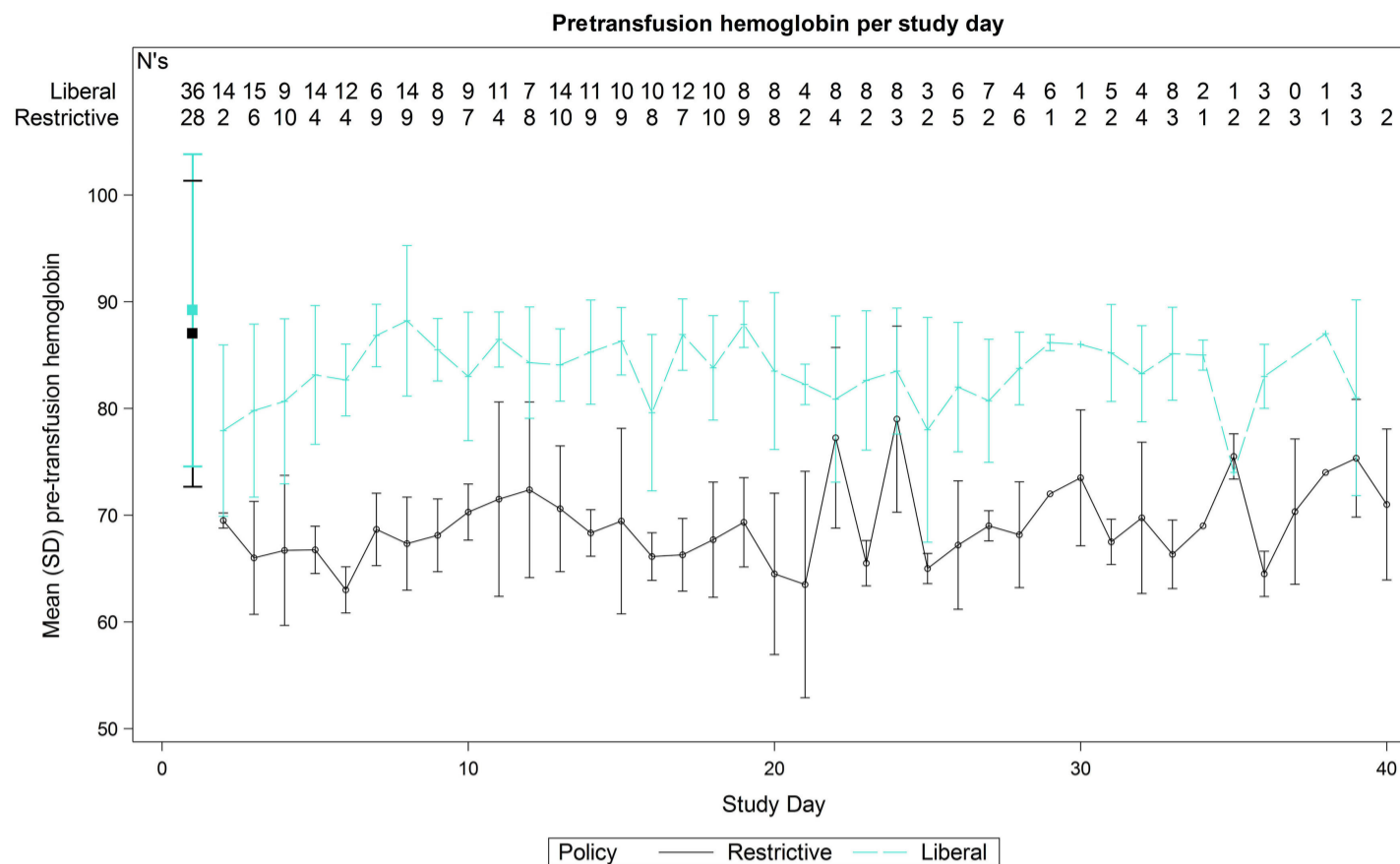


Figure 1. Pretransfusion hemoglobin.

(groups R/L and L/R, respectively). Follow-up was until the end of the second cycle, or 42 days from start of cycle two, whichever was earlier.

Primary outcomes were: i) percentage pretransfusion hemoglobins below threshold of the assigned strategy (predefined compliance $\geq 70\%$); and ii) difference of at least 15g/L between mean pretransfusion hemoglobin in the two strategies.

Secondary outcomes included adherence to protocol and QoL; survival at 3 months; transfusion related adverse events. QoL questionnaires EORTC QLQ-C30 and EQ-5D-5L were administered before, during and following each cycle. Participants also completed daily QoL scores (adapted from ECOG score¹ and from EQ 5D-5L²). Participants were blinded.

The sample size was 36, based on 10% attrition and the need for 31 patients to detect 15g/L difference between the two strategies (estimated group standard deviation 20 g/L, 90% power, intraclass correlation coefficient 0.25 and significance level 0.05; *t*-test). The analysis was intention to treat. A mixed linear regression model, with a random participant and period effect, was used to test for a difference between the groups and for evidence of a period effect. Secondary outcomes were analyzed using summary statistics. All participants completing at least one QoL questionnaire at baseline and at least one other were included in QoL analysis.

43 patients were randomized from 84 eligible (51.2%), receiving 75 chemotherapy cycles at eight UK hospitals between May 2017 to August 2018 (*Online Supplementary*

Figure S1). Twenty-one participants were allocated to group R/L and 22 to group L/R. Overall, 37 participants followed the restrictive strategy and 38 the liberal strategy. Baseline characteristics were similar between the two groups (Table 1).

Pretransfusion hemoglobin was below threshold in 91% of all transfusion episodes; 77.2% for transfusions in restrictive (95% confidence interval [CI]: 70.7-82.8) and 99.3% in liberal (95% CI: 97.6-99.9) cycles. As both groups had compliance $\geq 70\%$, this demonstrates predefined feasibility.

The unadjusted mean pretransfusion hemoglobin was 68.7 g/L and 83.4 g/L for the restrictive and liberal strategies respectively. After adjusting for participant as a random effect and the period effect (which was found to be significant ($P=0.01$), with hemoglobin values lower in cycle 1 than 2) the adjusted mean difference was 15.1 g/L (95% CI: 13.9-16.2; $P<0.001$) (Figure 1). No statistically significant carry-over effect was found ($P=0.2$).

Greater numbers of transfusions were required in the liberal arm to maintain the higher hemoglobin compared to restrictive arm. Median RBC units transfused per participant over all cycles was 13 (inter quartile range [IQR], 10-17), with six units (IQR, 4-9) for the restrictive strategy and nine (IQR, 7-11) liberal. Fourteen transfusions were given for symptoms above the designated hemoglobin threshold during the restrictive strategy and none during the liberal strategy. Numbers of transfusions given according to protocol, based on hemoglobin, were 447 of 537 (83.2%); 152 (70.7%) for the restrictive strategy and 295 (91.6%) liberal.

Table 2. Secondary outcomes.

	Restrictive	Liberal	Overall
Red cell usage			
Transfusion episodes			
Cycle 1	155	258	413
Cycle 2	91	108	199
Median (IQR) RBC transfused per participant	6 (4-9)	9 (7-11)	13 (10-17)
Participants with ≥1 transfusion, n (% of all participants)			
Cycle 1	21 (100.0)	22 (100.0)	43 (100.0)
Cycle 2	13 (81.3)	16 (100.0)	29 (90.6)
RBC given as an inpatient, %	98.5%	97.0%	97.6%
RBC given as single units, % of inpatient transfusions	84.9%	87.2%	86.3%
Number of transfusions given for symptoms	14	0	14
Median (IQR) self-evaluated health score for symptomatic transfusions			
Prior to transfusion ^a	52 (40-65)	-	52 (40-65)
Post transfusion ^b	55 (42.5-65)	-	55 (42.5-65)
Median (IQR) self-evaluated health score for non-symptomatic transfusions			
Prior to transfusion ^a	55 (40-75)	65 (45-80)	60 (42-80)
Post transfusion ^b	55 (37-78)	65 (45-80)	60 (40-80)
Protocol deviations			
Transfusions given according to hemoglobin trigger, n (%)	152 (70.7%)	295 (91.6%)	447 (83.2%)
Safety and other outcomes^c			
All cause mortality at 3 months, % (95% CI)	-	-	18% (9-34)
Thrombotic events, n (%)	0 (0.0)	2 (5.3)	2 (4.7)
Grade 3 or 4 bleeding, n (%)	1 (2.7)	2 (5.3)	3 (4.0)
Syncopal events, n (%)	0 (0.0)	0 (0.0)	0 (0.0)
≥1 blood culture verified bacterial infection, n (%)	16 (43.2%)	22 (57.9%)	27 (62.8)
Platelet units transfused, n	298	369	667
Median (IQR) platelet units transfused per participant	7 (6-10)	8 (4-14)	8 (5-12)

^awithin 24 hours; ^bat least 24 hours; ^cSerious adverse events defined as: death, life threatening adverse event, events requiring admission to hospital or prolongation of hospitalization, or resulting in significant disability, including severe sepsis, admission to intensive care unit, major organ dysfunction (single or multi-organ), transient ischemic attack, thromboembolic and ischemic events and acute transfusion reactions. RBC: red blood cells; IQR: interquartile range; CI: confidence interval.

When the hemoglobin was below threshold, transfusions were given on 152 of 187 (81.3%) and 295 of 447 (66.0%) occasions for the restrictive and liberal strategies respectively.

Completion rate for QoL questionnaires was high but reduced over time; 93.0% participants completed both questionnaires at the start and 55.2% at the end. Compliance was similar for both questionnaires. Daily visual analogue scores were completed on 70.3% occasions. No clear overall correlations between daily hemoglobin and daily QoL scores were found, although in an exploratory analysis, QoL scores appeared to favor the liberal threshold in the second treatment cycle (*Online Supplementary Figure S2*). There was little change in the self-evaluated visual analogue score prior to and post symptom-triggered transfusion; median score 52 (IQR, 40.0-65.0) pre

and 55 (IQR, 42.5-65.0) post. For non-symptomatic transfusions the score was 60 (IQR, 42-80) pre and 60 (IQR, 40-80) post (see Table 1).

Safety and other secondary outcomes are reported in Table 2. Numerically higher numbers of culture-verified infections, thrombotic events and grade 3 or 4 bleeding were seen during liberal cycles, although numbers are small.

We have previously identified the need for further trials to identify optimal transfusion support for patients with AML.³ In our study, we have successfully recruited patients with AML to follow liberal or restrictive transfusion strategies and demonstrated feasibility of a randomized crossover trial. Only two earlier small randomized trials to date have explored the impact of transfusion thresholds on outcomes in AML. A feasibility trial of patients with

acute leukemia compared thresholds of 80 g/L *versus* 120 g/L, but no QoL measures were compared, and the liberal thresholds would be considered high by current standards.⁴ Another small study compared 70 g/L *versus* 80 g/L, but the hemoglobin differences between arms appeared too small to generate separation between arms.⁵ The TRIST study examined hemoglobin thresholds of 70 g/L *versus* 90 g/L in 300 patients undergoing stem cell transplantation, but the findings cannot be extrapolated to patients with AML.⁶

Recommendations in guidelines generally advocate for restrictive transfusion policies^{7,8,9} but QoL is a critical outcome in transfusion-dependent patients with bone marrow failure. Risks including bleeding, thrombosis and immunomodulatory effects need to be weighed against potential QoL benefits for higher hemoglobin thresholds. The numerically higher rate of culture-verified infections in patients on the liberal transfusion strategy needs to be assessed in further studies applying consistent definitions, and of note, in one previously published meta-analysis of health-care associated infection, rates were also reported to be higher in liberal transfusion threshold arms.¹⁰

A number of additional learning points were identified that may help inform the design of further studies based on our results. We anticipated some hesitancy to consent and hence allowed 5 days from the start of treatment until randomization; 60.9% declined consent at the outset, the reasons reflecting the burden of decisions at diagnosis (*Online Supplementary Table S1*). Four participants declined to continue with the study after recruitment, most commonly following at least one cycle of chemotherapy, at one recruiting site, and seemingly because of a perception that the 70 g/L threshold was too difficult to tolerate. Our study re-iterates the importance of support for clinical teams and close monitoring to support protocol adherence. Our study also supports a need for economic evaluations in larger studies. Numerically the excess transfusions in the liberal arm exceeded the two units that may have been anticipated to initially raise the hemoglobin from 70 g/L to 90 g/L, suggesting there may be other on-going contributing factors to RBC requirements. This observation is a recurrent finding,¹¹ and requires investigation regarding RBC loss and/or suppression of erythropoiesis when the hemoglobin is maintained at a higher level.

In summary, we have demonstrated the feasibility of randomizing to two hemoglobin thresholds in patients with AML treated with intensive chemotherapy. Given the subjectivity of QoL measurement, the ability for each participant to serve as their own control was an advantage of our study. The findings from our crossover study may be used to inform a larger definitive threshold study addressing QoL as a primary outcome.

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<https://doi.org/10.3324/haematol.2021.279867>

Received: October 12, 2021.

Accepted: February 16, 2022.

Prepublished: February 24, 2022.

Disclosures

No conflicts of interest to disclose.

Contributions

SS, SM and MS designed and analyzed the study; RH and VH provided database support; CH and JP performed statistical analysis; HS and AM managed the trial. All authors approved the manuscript.

Acknowledgments

The authors would like to thank the hospital staff and research teams who conducted this trial and all recruited participants. Participating sites and investigators: Royal Stoke University Hospital: J. Graham; Norfolk and Norwich University Hospitals: H. Lyall; Queen Elizabeth Hospital Birmingham: S. Morton; Russells Hall Hospital: C. Taylor; Sandwell General Hospital: S. Pancham; Royal Oldham Hospital: A. Allameddine; Torbay Hospital: P. Roberts; University College Hospital London: M. Sekhar. We acknowledge A. Newland, P. White, G. Murphy (Data and Safety Monitoring Committee) and S. Knapper, J. Birchall, H. Kaur (Trial Steering Committee).

Funding

The study was supported by the NHS Blood and Transplant Clinical Trials Unit (H. Thomas, A. Deary, L. Pankhurst). The study was registered (clinicaltrials.gov. Identifier: ISRCTN 96390716), received ethics approval (REC number 16/WM/0406) and adopted onto the UK's National Institute for Health Research (NIHR) Clinical Research Network Portfolio. This manuscript is independent research funded by

NHS Blood and Transplant (REF15/86). The views expressed in this publication are those of the author(s) and not necessarily those of NHS Blood and Transplant.

Data-sharing statement

The datasets generated during and/or analysed during the current

study will be available upon request from the NHSBT Clinical Trials Unit after de-identification (text, tables, figures and appendices) 9 months after publication and ending 5 years following article publication. Data will be shared with investigators whose use of the data has been assessed and approved by an NHSBT review committee as a methodologically sound proposal.

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