Liberal versus restrictive red cell transfusion thresholds in hematopoietic stem cell transplantation (TRIST): a randomized, open label, phase 3, non-inferiority trial

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Manuscript Details

Research In Context Word Count:	308
Abstract Word Count:	300
Manuscript Word Count:	3780
Tables:	8
Figures:	3

RESEARCH IN CONTEXT

Evidence before this study

Red cell transfusions are part of the routine supportive care following hematopoietic stem cell transplantation. There is increasing evidence from randomised controlled trials demonstrating that restrictive transfusion thresholds are equivalent to liberal thresholds in other patient populations, specifically critical care and surgical patients. Few studies have specifically evaluated the clinical benefits and potential harms of red cell transfusions in the hematopoietic stem cell transplantation setting.

Added value of this study

This Canadian Mulitcentre (4) randomised trial involving 300 patients undergoing hematopoietic cell transplantation (HCT) compares the use of a restrictive red cell transfusion strategy (70g/L) with a liberal red cell transfusion strategy (90g/L). In patients undergoing HCT, the use of a restrictive red cell transfusion strategy as compared to a liberal red cell transfusion strategy results in similar quality of life and HCT outcomes with fewer transfusions. Adopting a restrictive red cell transfusion strategy is reasonable in the General Oncology setting given the less intense nature of chemotherapy received as compared with patients in the HCT setting.

Implications of all the available evidence

There have been a large number of studies in several clinical settings examining the effects of restrictive versus liberal red cell transfusion thresholds. These studies have been recently summarized by a Cochrane review that identified 31 randomized clinical trials. The results of the meta-analysis for 30-day mortality, which included more than 12,000 patients, did not show any

differences for restrictive transfusion strategies as compared with a liberal transfusion strategy; the relative risk was 0.97 (95% CI 0.81 to 1.16). However, the subgroup of malignancy, the two pilot trials included only a small number of patients (n=149) and the risk ratio for 30-day mortality was 0.37 with a wide 95% confidence interval (0.07 - 1.95). Our study fills this knowledge gap and supports adopting a restrictive transfusion strategy in an oncologic setting.

ABSTRACT

Background Evidence regarding red blood cell (RBC) transfusion practices in Hematopoietic Cell Transplantation (HCT) is lacking. As a result, the impact of RBC transfusions on outcomes following HSCT is not well understood.

Methods We performed a multicenter (n=4) non-inferiority randomized controlled trial evaluating patients with a a hematologic malignancy requiring HCT. Patients were randomized to either a restrictive (Hemoglobin (Hb) threshold <70g/L) or liberal (Hb threshold <90g/L) RBC transfusion strategies between Day-0 and Day-100). Permutated randomization blocks of 2 and 4 were used. The non-inferiority margin corresponds to a 12% absolute difference between groups in FACT-BMT score relative to baseline. The Primary Outcome was health related quality of life (HRQOL) measured by FACT-BMT at Day 100. The following endpoints were collected: 1) HRQOL by FACT-BMT at Baseline, Day 7, 14, 28, 60 and 100), transplant related mortality, length of hospital stay, ICU admissions, incidence and grade of acute graft-versus-host disease, Bearman toxicity score, sinusoidal obstruction syndrome, serious infections, transfusion requirements, bleeding as per WHO Bleeding Scale and adverse transfusion reactions. Clinicaltrials.gov: NCT01237639

Findings A total of 300 patients underwent randomisation between 2011 and 2016. Post-HCT, mean pre-transfusion hemoglobin levels were 70.9g/L and 84.6g/L in the restrictive and liberal strategies ($p < 0.0001$). The number of RBC units transfused was lower in the restrictive-strategy than in the liberal-strategy [mean of 2.73(4.81) vs. 5.02(6.13), p=0.0004]. The restrictive-strategy had a marginally higher FACT-BMT score at day 100 [RR=1.02; 95%CI(0.96-1.07)]

which was statistically non-inferior ($p<0.0001$) compared to the liberal-strategy. There were no significant differences in any clinical outcomes between the two groups.

Interpretation In patients undergoing HCT, the use of a restrictive RBC transfusion strategy of 70g/L as compared to a threshold of 90g/L results in similar HRQOL and HCT outcomes with fewer transfusions.

Funding Canadian Institute of Health Research & Canadian Blood Services

INTRODUCTION

Red blood cell transfusions are an integral part of the supportive therapy in patients undergoing hematopoietic stem cell transplantation (HSCT) to manage chemotherapy associated anemia.[1-4] However, there is little evidence to determine the appropriate use of red cell transfusions or the effects of red cell transfusions on clinical outcomes in patient with hematologic malignancies, in general, or specifically in HSCT.[2,5]

While there are clear benefits of red cell transfusion in treating anemia, potential harm has been noted in a number of patient groups[6-8]. A large number of observational studies have demonstrated an association of red cell transfusion with worse clinical outcomes.[9,10] In the setting of HSCT, observational studies suggest that low pre-transplant hemoglobin levels and red cell transfusions are associated with poorer post-transplant outcomes.[11] Over the past 20 years, there has been increasing evidence demonstrating that a restrictive transfusion strategy as compared to a liberal strategy does not increase mortality or other serious morbidity in a variety of clinical settings[7] including critical care[12], septic shock[13], orthopedic surgery[14], gastrointestinal hemorrhage[15] and cardiac surgery.[16-18] However, there may be circumstances that a higher threshold could be beneficial.[19,20] Only 3 small randomised controlled trials[21-23] have evaluated red cell transfusions in patients with hematologic malignancies receiving chemotherapy despite the fact that these patients represent a significant proportion of all red cell transfusions.[24,25]

Unlike the clinical settings of critical care, surgery and gastrointestinal hemorrhage, patients with hematologic malignancy and patients undergoing HSCT typically experience a prolonged period of anemia and often need ongoing transfusion support.[26] One of goals of red cell transfusion is to promote and maintain quality of life through the primary illness - consistent with a patient-centred approach as championed by the Patient-Centered Outcomes Research

Institute. Evaluation of quality of life is particularly salient in patients with hypoproliferative anemia as a result of chemotherapy. Despite the unique challenge of balancing potential toxicities of transfusion with quality of life facing this group of patients[2,26], there have been no randomised studies to guide optimal red cell transfusion.[1,2]

Given the lack of evidence to guide practice, we designed a non-inferiority randomised controlled trial comparing the impact of a restrictive and a liberal red blood cell transfusion strategy on both health-related quality of life (HRQOL) and HSCT outcomes.

METHODS

Study design

Following approval from each participating center's local ethics committee, four Canadian adult HSCT centers underwent screening and randomization of participants between 28 Mar 2011 and 3 Feb 2016. Written consent was obtained from all participants. The trial is registered on clinicaltrials.gov (NCT01237639). The pilot study protocol is available online as an open access peer-reviewed publication.[26] There was no commercial involvement in any aspects of this study.

Participants

All patients older than 18 years of age undergoing autologous or allogeneic HSCT for any hematologic malignancy were eligible. We excluded patients who were: 1) Pregnant or lactating at the time of enrollment, 2) Already received red cell transfusion after HSCT but prior to enrollment, 3)Unable/unwilling to provide informed consent and 4) Patients receiving HSCT for non-malignancies.

Randomization and masking

We designed a non-inferiority randomised controlled trial evaluating a restrictive and liberal red blood cell transfusion strategy. Our non-inferiority margin of a 12% difference in HRQOL at 100 days post-transplant was based on data from our pilot RCT. A secure online electronic randomization was performed using a computer generated randomization sequence. Simple randomization in a 1:1 ratio was based on variable permutated blocks of 2 and 4 and was stratified by transplant center and by type of HSCT: autologous or allogeneic. Given the nature of the intervention, it was not possible to blind patients or caregivers to the study allocation. However, the baseline FACT-BMT was collected prior to randomization.

Procedures

Participants randomised to the liberal strategy received 2 units of red blood cells if the hemoglobin level fell below 90g/L, targeted to maintaining a level of 90-110g/L, while participants randomised to the restrictive strategy received 2 units of red blood cells if the hemoglobin level fell below70g/L, targeted to maintaining a level of 70-90g/L. The choice for the 2 red cell transfusion strategies was based data from previous published trials evaluating red cell transfusion thresholds, local expert opinion and a survey of practice patterns of Canadian HSCT centres.[26] Transfusion(s) of red cells outside the red cell transfusion strategy was permitted whenever the treating physician judged it to be clinically indicated, such as symptomatic anemia. Likewise, transfusions can be withheld for clinical reasons such as volume overload. The randomised transfusion strategy was initiated on the day of HSCT (Day 0) and was maintained until 100 days after transplant.

All red cells were supplied by the Canadian Blood Services. All red cell units were derived from whole blood collections collected in CPD anticoagulant, leukoreduced before storage and suspended in a saline–adenine–glucose–mannitol (SAGM) additive solution.[27]

The conditioning chemotherapy prior to HCST followed local standards and in general, is standardised for the underlying malignancy. The intensity of the chemotherapy are categorized according to the Center for International Blood and Marrow Transplant Research (CIBMTR).[28,29] All other post-HSCT and supportive care measures were provided as per local institution practices, policies and procedures.

Outcomes

Health Related Quality of Life. The primary outcome measure was HRQOL measured by the FACT-BMT[30] scale at Day 100, as it is commonly used and validated measure in HSCT.[31] The FACT-BMT is a validated self-report questionnaire that utilizes a 5 point Likert scale in 5 domains. The FACT consists of 4 subscales that measure physical well-being, functional well-being, social/family well-being and emotional well-being. The BMT subscale of includes additional items specifically designed to test quality of life and symptoms specific to transplant patient and covers 5 domains that include physical, social and family, emotional and functional well-being. Scoring produces a range from 0-148, the higher the score, the better the quality of life. Further, we measured FACT-BMT at Baseline, Day 7, 14, 28, and 60. FACT-anemia[32] and EQ5D[33] were also measured at Baseline, Day 7, 14, 28, 60 and 100.

Clinical Outcomes. We included HSCT and Safety outcomes : 1) Transplant related mortality at Day 100, 2)Length of hospital stay, 3) ICU admissions, 4) Incidence and grade of acute graft

versus host disease, 5) Incidence of serious infections (grade 3 or higher), 6) Transfusion requirements, 7) Bleeding as per WHO Bleeding Scale, 8) Incidence of adverse transfusion reactions, 9) Bearman Toxicity Score at Day 28[34] and 10) Sinusoidal obstruction syndrome.[35] Adverse events were collected using the NCI Common Toxicity Index. Serious adverse events were defined and recorded in keeping with ICH standards.

Statistical analysis

Sample Size and Non-inferiority Margin. The choice of non-inferiority margin was based on expert opinion, investgator consensus, and preliminary data from a pilot study, in which we found the mean (SD) change in FACT-BMT from baseline to 100 days post-transplant to be 12% (20%). Under the Cohen guidelines, a 12% difference corresponds to a clinically significant moderate effect size (0.6)[36] and with further consultation with HSCT physicians at participating centres, we selected it as our non-inferiority margin. Assuming an actual difference of 6% (ie. that quality of life at 100 days would be 6% lower in the restricted group) and a standard deviation of 20%, and adjusting for 15% dropout, we calculated that a total sample size of 300 would provide 80% power to reject the hypothesis of inferiority.

Primary Analysis. FACT-BMT scores were summarized as mean(SD) at each measurement time. In order to represent percent change, the primary outcome was log-transformed and analyzed using a linear model with three coefficients for baseline FACT-BMT, transplant type (allogeneic vs. autologous), and treatment group. Upon exponentiation, the linear treatment provided an estimate of the ratio of the FACT-BMT scores for the restrictive to the liberal groups, after controlling for baseline FACT-BMT and the type of transplant, as well as a 95%

confidence interval. The treatment was judged to be statistically non-inferior if the confidence interval was entirely above 0.88 (a 12% reduction in mean FACT-BMT at 100 days).

Secondary Analyses. FACT-BMT scores at earlier time points were analyzed in the same way as the 100 day measurement. Baseline characteristics and secondary outcomes were summarized using mean(SD), median(IQR), or n(%), as appropriate. Transfusion outcomes were summarized by both mean(SD) and median(IQR) per patient. Between group differences in binary outcomes were summarized using relative risk with 95% confidence intervals and tested using Chi-square or Fisher's tests, as appropriate. Continuous outcomes were tested with t-tests and summarized as mean differences with 95% confidence intervals. Time-to-event outcomes were summarized with median(IQR) and tested using log-rank tests. All tests were conducted at the 0.05 level of significance.

Role of funding source

The funders, Canadian Institute of Health Research and Canadian Blood Services, had no role in study design, data collection, data analysis, data interpretation, or writing of the report. All listed authors vouch for the adherence to the study protocol, the integrity, completeness, transparency and accuracy of the data presented. The authors affirm no important aspects of the study have been omitted. Further, the listed authors made substantial contributions to the drafts, final manuscript and made the decision to submit the final manuscript for publication. The corresponding author had full access to all the data in the study and had fnal responsibility for the decision to submit for publication. Finally, the results of this study was presented at the American Society of Hematology Meeting on 2016.[37]

RESULTS

We approached n=534 potential participants between between 28 Mar 2011 and 3 Feb 2016. Of these, n=234 were excluded as they did not meet eligibility criteria (n=15), were co-enrolled on a conflicting study (n=4), declined participation due to geographic reasons (n=26), too unwell or overwhelmed (n=20), refused (n=71) and for other reasons not disclosed by the potential participants (n=98). A total of n=300 participants underwent randomization and 1 was excluded after randomization for ineligibility (autologous HSCT for multiple sclerosis). A total of n=149 and n=150 participants in the restrictive and liberal strategy arms, respectively, were included in the intention to treat analyses- Figure 1. The baseline patient and disease characteristics were similar in the two randomised groups - Table 1, with a preponderance of males.

The mean FACT-BMT (95%CI) score at baseline was 108.0 (104.7-111.3) in the restrictive group and 103.2 (100.0-106.5) in the liberal group. By 100 days post-transplant, the mean scores had risen to 112.8 (109.3-116.3) in the restrictive group and 107.5 (103.8-111.1) in the liberal group. The ratio of adjusted mean scores at 100 days post-transplant (95%CI) was 1.02 (0.96-1.07). This means that, after adjusting for baseline FACT-BMT and for type of transplant (autologous vs allogeneic), the restrictive group had a marginally higher expected FACT-BMT than the liberal group. The lower end of the confidence interval corresponds to a 4% reduction in expected FACT-BMT. Given that our non-inferiority margin was 0.88 (a 12% reduction), the restrictive transfusion strategy was statistically non-inferior to the liberal strategy ($p<0.0001$) – Table 2. Pre-specified subgroup analyses in the autologous and allogeneic transplant groups found the restrictive strategy to be statistically non-inferior in both groups - Figure 2. While the original model included the possibility of an interaction between the transfusion strategy and the type of transplant, that interaction was not statistically significant

(p=0.79) and hence the interaction term was dropped from the model. Further, the restrictive strategy was also statistically non-inferior in older patients (>60 years) and when limiting the analysis to patients who were transfused - Figure 2.

The FACT-BMT scores at Days 7, 14, 28 and 60 are tabulated in Table 2. At all these time points, the restrictive strategy was found to be greater than and statistically non-inferior to the liberal strategy. Similarly, the FACT-Anemia scores were greater in the restrictive transfusion group at all time points, both overall and for the autologous and allogeneic sub-groups – Table 3 There were no statistically significant differences between the restrictive and liberal strategy groups in any of the secondary clinical outcomes - Table 4. There were 2 and 4 deaths in the restrictive and liberal transfusion strategies, respectively. Slightly more patients in the restrictive group were admitted into the ICU (n=9) compared with the liberal group (n=6). The number of hospital re-admissions did not differ significantly between the restricted (n=22) and liberal group (n=25). Pre-specified subgroup analyses in autologous and allogeneic hematopoietic stem cell population also did not demonstrate any statistically significant differences in any of the secondary clinical outcomes – Table 5 and 6.

Table 7 presents describes the average transfusion experiences in each arm, demonstrating that the restrictive strategy led to substantially fewer transfusions being performed. Over the course of the study, patients in the restrictive arm received a mean (SD) of 2.73 (4.81) units of red blood cells and 1.57 (2.96) transfusion episodes each. The mean duration of storage of transfused red cells was 18.46 (7.27) and 19.95 (7.52), p=0.001 in the restrictive and liberal strategy respectively. In contrast, patients in the liberal arm received 5.02 (6.13) units and 2.71 (3.33) transfusions each. There was also a marked difference in the number of patients who were transfused: 80 patients in the restrictive arm and 129 in the liberal arm received at least

one – Table 8. There was little difference between the groups in the amount of platelets transfused – Table 7.

Most transfusions were administered according to protocol but some were administered when hemoglobin levels were above the target thresholds – Table 8. By day 3, patients in the restrictive group had statistically significant lower median hemoglobin level. This continued for most of the study period but ceased to be statistically significant by week 13 – Figure 3.

There were 7 (2.34%) and 5 (1.67%) red cell transfusion reactions associated with the restrictive and liberal transfusion strategies respectively. The events include 8 febrile non-hemolytic reactions, 3 transfusion associated cardiac overloads and 2 urticarial reactions.

DISCUSSION

We demonstrated that a restrictive red cell transfusions strategy of 70g/L was not inferior to a liberal red cell transfusion strategy of 90g/L with respect to heath related quality of life as measured by the FACT-BMT at 100 days post-transplant. Interestingly, after adjusting for baseline scores, we observed higher FACT-BMT scores at all study time-points in the participants assigned to the restrictive strategy as compared to the liberal strategy, although this difference was neither statistically nor clinically significant. There were also no differences in HRQOL as measured by the EQ-5D (data not shown) or symptom specific (FACT-anemia) HRQOL scores between the restrictive and liberal red cell transfusion groups.

We also observed no significant differences between the restrictive and liberal red cell transfusion strategies in any of our secondary outcomes related to mortality or transplant related morbidity including: transplant related mortality, incidence of sinusoidal obstruction syndrome and acute graft versus host disease amongst allogeneic transplant recipients, Bearman toxicity

scores, bleeding rates, hospital length of stay, ICU admissions and hospital re-admissions. These results complement and are consistent with the published literature demonstrating that a restrictive red cell transfusion threshold is equivalent to a liberal transfusions threshold.[7]

Importantly, the proportion of patients in our study who did not require any red cell transfusions increased from 14% to 46.31% by utilizing a restrictive red cell transfusion strategy within 100 days of HSCT, which represents an important cost-saving. In a previous retrospective study conducted at our centre, we identified higher pre-transplant hemoglobin, autologous transplant for myeloma and early stage disease were associated with avoidance of red cell transfusions with an overall rate of 10% not requiring red cell transfusions.[38]

Our study represents the first large randomised controlled trial evaluating a restrictive transfusion threshold in cancer patients receiving chemotherapy. Previously only 3 small randomised controlled trials[21-23] representing 156 patients have evaluated the effect of different red cell transfusion thresholds on outcomes and only one study[21] specifically evaluated a restrictive transfusion threshold of 90g/L in adult patients. Our results for patients with hematologic malignancies undergoing HSCT add to the published literature demonstrating that a restrictive red cell transfusion threshold is equivalent to a liberal transfusions threshold.[7] Patients undergoing HSCT represent a different population from the previous large studies evaluating a restrictive red cell transfusion strategies as they require red cell transfusion support for a prolonged period due to the impaired red cell production post myeloablative chemotherapy. Importantly, these patients were treated as both inpatients and subsequently as outpatients for 100 days with no significant clinical issues, comparable HRQOL despite differences in hemoglobin values.

The previous large randomised controlled trials evaluating a restrictive transfusion strategy included patients with an acute self-limited anemia (major surgery, trauma or GI blood loss) or non-ambulatory patients (critical care), all of which were in the acute illness context. Interestingly, there have been several meta-analyses that suggest the a liberal transfusion strategy could be beneficial in the perioperative setting [18-20] and in older adults.[39] Although the results are intriguingly, the population reviewed is again limited to the acute settings of surgery, trauma, GI loss and critical care. Interestingly in our subgroup analysis, older patients did not benefit from a liberal transfusion strategy, further bolstering our assertion that data from other acute settings may not be applicable to the oncology and HSCT population.

The goal of red cell transfusion is multi-faceted, aiming to improve delivery of oxygen to tissues safely, and ultimately to reduce mortality, morbidity and improve patient quality of life.[2,26] From previous large randomised controlled studies, we have not seen a difference in mortality or major morbidity with a restrictive transfusion strategy. Thus, HRQOL is increasingly considered a cornerstone of transfusion research where it has been argued that patient perceived wellness and experiences are most important.[2,26,40] Historic studies have focused on mortality and morbidity outcomes with little to no attention to quality of life.[7] Indeed, only two other randomised studies in transfusion medicine assessed functional outcomes and this was only at a single time-point.[7]

To our knowledge, this is the first large randomised controlled trial in HSCT patients or hematology/oncology setting to assess red cell transfusion thresholds in this high utilization population using patient-centered outcome as our primary endpoint. Moreover, we made use of multiple measures of HRQOL across multiple time-points to better capture the patient experience while paying attention to potential transplant related toxicities. Importantly, we believe that the

results of our study is generalizable to the general oncology setting given the less intensive chemotherapy received in general oncology.

There are limitations to our trial. First, the study was non-blinded potentially introducing bias, but unfortunately blinding to patients and health-care professionals to hemoglobin levels is not practically feasible in this population. Second, the FACT-BMT scale may not fully capture the consequences of a patient's experience(s) of anemia and red cell transfusion(s). Nonetheless, it remains a widely used, validated scale with face validity. It is commonly assumed that the symptoms of resultant anemia is the pathway that impacts HRQOL with respect to red cell transfusion support. However, the experience of (non) transfusions and the relative importance of anemia within the larger context of the HSCT trajectory is unclear, and the reliance on HRQOL measures that only capture symptoms of anemia may be too narrow. To our knowledge that there is no succinct and comprehensive HRQOL measure that describes the experiences of a patient receiving red cell transfusions in larger HSCT context. We suggest that the FACT-BMT best embraces the experience of red cell transfusion thresholds, beyond symptoms that are associated with anemia within the larger context of HSCT.[31] Of note, we also did not see any differences on the FACT-anemia, which is a symptom specific HRQOL scale. Third, with the Choosing Wisely initiatives, many clinicians have moved towards transfusion of 1 unit, as opposed to 2 units at a time. Observational studies suggest that this strategy is safe and results in decreased red cell utilization.[41,42] However, such studies have not evaluated the impact of a single unit transfusion strategy in the context of HRQOL. Fourth, despite randomisation the duration of storage of transfused red cells was statistically different between the 2 arms of the study. However, we would argue that a 1 day difference in red cell storage is not clinically significant. Moreover, there have been a number of randomised trials that have mitigated this concern.[43] Further, we

have previously demonstrated that duration of storage of transfused red cells did not negatively affect HSCT and cancer patient outcomes.[44,45] Additionally, some clinicians worry that that thrombocytopenic individuals may be an increased risk of bleeding – they might benefit from a higher red cell transfusion threshold. This is unlikely to be the case in our trial - patients received prophylactic platelet tranfusions if their platelet count was $<10 \times 10^9$/L. Given that our HRQOL and clinical outcomes are the similar in both groups, this would imply that the rates of bleeding between the 2 groups in those with profound thrombocytopenia are similar. Moreover, in a pilot study randomising patients to a red cell transfusion threshold of either 80g/L or 120g/L in patients with either acute leukemia or undergoing autologous HSCT, there was no difference in bleeding.[22] Fifth and from a health care utilisation perspective, we did not document the number of outpatient visits between the 2 arms of the study. However, it is unlikely there is a difference in health care utilisation given that both clinical and HRQOLoutcomes are similar between the 2 arms of the study.

The selection of a non-inferiority margin is often inherently arbitrary. We felt that a 12% difference in FACT-BMT score was a reasonable choice for a minimal clinically important difference. Futher, the confidence interval on our final adjusted ratio between expected mean scores was (0.96-1.07); thus, our trial demonstrates non-inferiority for any non-inferiority margin greater than 4%. We expect that most will accept a 4% difference in HRQOL as not clinically important. Finally, despite the randomization, the restrictive and liberal arms were imbalanced in their baseline FACT-BMT scores. The mean score in the restrictive arm was almost 5% higher than in the liberal group. This difference is small, less than a quarter of the standard deviation in baseline scores, but was maintained at every time point where FACT-BMT was measured. Our analysis was designed to look at relative differences after adjusting for

baseline. The relative change from baseline in each group was almost identical at every time point, which reinforces our conclusion that the restrictive strategy was not associated with lower HRQOL.

In summary, patients undergoing HSCT for hematologic malignancies who receive a red cell transfusion threshold of 70g/L as compared with a threshold of 90/L have similar HRQOL and transplant related outcomes while receiving fewer transfusions. Our results support a strategy of not performing transfusion until the hemoglobin concentration falls below 70g/L in patients undergoing HSCT for hematologic malignancies. This restrictive strategy is effective, safe and potentially associated with cost savings and a reduction in transfusion-related adverse events.

Table 1: Baseline Characteristics

Characteristics	**Restrictive Strategy (N= 149)**	**Liberal Strategy (N=150)**
Age (years)		
Median	57.47	56.04
Interquartile range (IQR)	(48.94, 62.66)	(48.27, 62.24)
Sex male (%)	97 (65.10)	94 (62.67)
Diagnosis (%)		
Acute Leukemia	38 (25.50)	36 (24.00)
Chronic Leukemia	10 (6.71)	9 (6.00)
Myeloproliferative Disorder	4 (2.68)	3 (2.00)
Lymphoma	46 (30.87)	50 (33.33)
Myeloma	36 (24.16)	42 (28.00)
Others	15 (10.07)	10 (6.67)
Type of HSCT (%)		
Autologous	74 (49.66)	75 (50.00)
Allogeneic	75 (50.34)	75 (50.00)
Allogeneic HSCT – Donor		
Matched Related Donor	35 (46.67%)	36 (48.00%)
Matched Unrelated Donor	40 (53.33%)	39 (52.00%)
Conditioning for Allogeneic HSCT		
Myeloablative	49 (66.21%)	49 (65.33%)
Reduced Intensity	25 (33.78%)	26 (34.67%)
Karnofsky performance Status		
Median (IQR)	90 (80, 90)	90 (80, 90)
HCT-Comorbidity Index		
Median (IQR)	0 (0, 2)	1 (0,2)

HSCT: Haematopoietic Stem Cell Transplant

Table 2: Primary Outcome – FACT-BMT scores

Characteristics	Restrictive Strategy	Liberal Strategy	Point estimate and 95%CI on % difference	P Value (NI test)
FACT-BMT - mean (95 % CI)				
Full Cohort	**N=149**	**N=150**		
Total score at baseline	108 (104.7, 111.3)	103.2 (100.0, 106.5)		
Total score at 7 days post-HSCT	93.9 (90.5, 97.3)	88.5 (85.6, 91.5)	2.68 (-1.25, 6.77)	< 0.0001
Total score at 14 days post-HSCT	98.6 (95.3, 101.9)	95.2 (91.9, 98.6)	1.11 (-3.10, 5.49)	< 0.0001
Total score at 28 days post-HSCT	101.9 (98.6, 105.1)	97.2 (93.7, 100.6)	2.05 (-2.40, 6.69)	< 0.0001
Total score at 60 days post-HSCT	107.4 (104.0, 110.8)	102.6 (99.1, 106.0)	1.89 (-2.23, 6.19)	< 0.0001
Total score at 100 days post-HSCT	112.8 (109.3, 116.3)	107.5 (103.8, 111.1)	2.28 (-1.93, 6.68)	< 0.0001
Allogeneic HSCT subgroup	**N=75**	**N=75**		
Total score at baseline	107.8 (102.8, 112.8)	105.8 (101.6, 109.9		
Total score at 7 days post-HSCT	98.0 (92.6, 103.4)	95.3 (91.2, 99.4)	0.71 (-4.50, 6.21)	< 0.0001
Total score at 14 days post-HSCT	98.0 (93.1, 102.9)	97.8 (92.5, 103.1)	0.92 (-5.08, 7.30)	< 0.0001
Total score at 28 days post-HSCT	98.4 (93.2, 103.6)	97.5 (92.3, 102.7)	0.84 (-5.29, 7.37)	< 0.0001
Total score at 60 days post-HSCT	100.6 (95.6, 105.5)	98.6 (93.6, 103.5)	1.24 (-4.21, 7.00)	< 0.0001
Total score at 100 days post-HSCT	106.7 (101.4, 112.0)	102.8 (97.6, 108.0)	2.59 (-3.11, 8.62)	< 0.0001
Autologous HSCT subgroup	**N=74**	**N=75**		
Total score at baseline	108.2 (103.9, 112.6)	100.8 (95.9, 105.7)	-	-
Total score at 7 days post-HSCT	90.0 (86.0, 94.0)	81.7 (78.1, 85.3)	5.13 (-0.19, 10.73)	< 0.0001
Total score at 14 days post-HSCT	99.0 (94.5, 103.6)	92.9 (88.7, 97.0)	1.28 (-4.49, 7.39)	< 0.0001
Total score at 28 days post-HSCT	105.1 (101.1, 109.1)	96.8 (92.0, 101.6)	3.02 (-3.14, 9.58)	< 0.0001
Total score at 60 days post-HSCT	113.8 (109.7, 118.0)	106.4 (101.7, 111.0)	2.14 (-3.22, 7.80)	< 0.0001
Total score at 100 days post-HSCT	118.2 (113.8, 122.5)	111.9 (106.9, 117.0)	1.38 (-4.00, 7.06)	< 0.0001

CI: Confidence Interval; HSCT: Haematopoietic Stem Cell Transplant; NI: Non-Inferiority

Table 3: Heath Related Quality of of Life Outcome: FACT-Anemia Scores

Characteristics	Restrictive Strategy	Liberal Strategy	Restrictive as % of Liberal	P Value
FACT-Anemia - mean (95 % CI)				
Full Cohort	**(N=51)**	**(N=53)**		
Total score at baseline	136.0 (128.8, 143.3)	128.0 (121.1, 134.9)		
Total score at 7 days post-HSCT	118.2 (110.3, 126.2)	103.6 (96.4, 110.7)	110.3 (101.4, 119.9)	0.02
Total score at 14 days post-HSCT	120.1 (112.2, 128.0)	108.6 (100.8, 116.4)	107.7 (99.5, 116.5)	0.07
Total score at 28 days post-HSCT	122.7 (114.3, 131.0)	118.6 (110.3, 127.0)	102.9 (94.0, 112.6)	0.54
Total score at 60 days post-HSCT	134.9 (127.2, 142.6)	126.5 (117.9, 135.0)	108.6 (100.5, 117.3)	0.04
Total score at 100 days post-HSCT	142.3 (133.3, 151.3)	134.8 (126.3, 143.2)	106.0 (97.8, 114.9)	0.16
Allogeneic HSCT subgroup	**(N=29)**	**(N=29)**		
Total score at baseline	132.7 (121.7, 143.7)	129.9 (120.0, 139.8)		
Total score at 7 days post-HSCT	119.6 (107.5, 131.7)	109.7 (99.8, 119.5)	105.9 (94.9, 118.1)	0.31
Total score at 14 days post-HSCT	117.6 (106.8, 128.5)	109.4 (98.0, 120.7)	110.5 (99.2, 123.1)	0.07
Total score at 28 days post-HSCT	120.8 (108.7, 132.9)	111.6 (99.8, 123.5)	110.3 (97.7, 124.4)	0.11
Total score at 60 days post-HSCT	127.6 (117.6, 137.6)	116.0 (104.7, 127.2)	111.3 (100.4, 123.3)	0.04
Total score at 100 days post-HSCT	133.6 (120.9, 146.3)	125.8 (113.5, 138.1)	104.10 (93.6, 115.9)	0.46
Autologous HSCT subgroup	**(N=22)**	**(N=24)**		
Total score at baseline	140.6 (131.7, 149.5)	125.8 (115.7, 135.8)		
Total score at 7 days post-HSCT	116.5 (106.0, 127.1)	96.1 (85.8, 106.5)	114.9 (101.3, 130.2)	0.03
Total score at 14 days post-HSCT	123.2 (110.9, 135.6)	107.8 (96.1, 119.5)	104.5(93.5, 117.9)	0.41
Total score at 28 days post-HSCT	125.1 (112.9, 137.3)	126.2 (114.3, 138.1)	96.0 (83.8, 109.9)	0.55
Total score at 60 days post-HSCT	143.6 (131.9, 155.3)	137.0 (124.8, 149.2)	105.9 (94.4, 118.9)	0.33
Total score at 100 days post-HSCT	152.3 (139.9, 164.6)	143.8 (132.5, 155.0)	107.9 (95.7, 121.8)	0.22

CI: Confidence Interval; HSCT: Haematopoietic Stem Cell Transplant

Table 4: Clinical Outcomes – Full Cohort

Characteristics	Restrictive Strategy (N=149)	Liberal Strategy (N=150)	RR (95% CI)	P Value
Transplant Related Mortality at 100 days	2 (1.34)	4 (2.67)	0.50 (0.09, 2.71)	0.42
Incidence of Sinusoidal Obstruction Syndrome	4 (5.71)	4 (5.56)	1.03 (0.27, 3.95)	0.97
Acute Graft versus host Disease	20 (31.75)	27 (39.71)	0.80 (0.50, 1.27)	0.35
Bearman Toxcity Score at Day 28				
Median (IQR)	2 (1, 3)	2 (1, 4)		
Mean (SD)	2.53 (2.21)	2.79 (2.29)	-0.25 (-0.75, 0.26)	0.34
WHO Bleeding Scores (%)				
Day 14	G0: 96 (68.09) G1: 20 (14.18) G2: 24 (17.02) G3: 1 (0.71) G4: 0 (0)	G0: 85 (59.86) G1: 22 (15.49) G2: 34 (23.94) G3: 1 (0.70) G4: 0 (0)		0.44
Day 28	G0: 127 (89.44) G1: 8 (5.63) G2: 7 (4.93) G3: 0 (0.00) G4: 0 (0)	G0: 126 (88.73) G1: 7 (4.93) G2: 7 (4.93) G3: 2 (1.41) G4: 0 (0)		0.74
Day 100	G0: 120 (93.02) G1: 6 (4.65) G2: 2 (1.55) G3: 1 (0.78) G4: 0 (0)	G0: 126 (96.18) G1: 2 (1.53) G2: 2 (1.53) G3: 1 (0.76) G4: 0 (0)		0.55
Number of Grade ≥ 4 Infections				
Day 14	1 (0.70)	4 (2.84)	0.25 (0.03, 2.18)	0.21
Day 28	3 (2.11)	0 (0)	-	-
Day 100	1 (0.73)	1 (0.70)	1.04 (0.07, 16.41)	0.98
Length of Hospitalization (Days)				
Median (95 % CI)	23 (20, 25)	23 (20, 25)		
Mean (SD)	23.95 (16.25)	24.48 (15.84)		0.43
Number of patients ≥1 ICU admission	9 (6.04)	6 (4.00)	1.51 (0.52, 4.41)	0.45
Length of Stay of ICU admission (days)				
Median (IQR)	5 (3,7)	13 (3, 23)		
Mean (SD)	9.22 (11.54)	13.57 (11.56)	0.59	0.49
Hospital Re-admissions- *Mean (SD)*	22 (15.17)	25 (17.01)	0.80 (0.44, 1.48)	0.48

ICU: Intensive Care Unit; IQR: Interquartile Range; RR: Relative Risk; SD: Standard Deviation; WHO: World Health Organisation

Table 5: Clinical Outcomes - Allogeneic HCT Subgroup

Characteristics	Restrictive Strategy (N=75)	Liberal Strategy (N=75)	RR (95% CI)	P Value
Transplant Related Mortality at 100 days	2 (2.67)	4 (5.33)	0.50 (0.09, 2.65)	0.41
Sinusoidal Obstruction Syndrome	4 (5.71)	4 (5.56)	1.03 (0.27, 3.95)	0.97
Acute Graft versus host Disease	20 (31.75)	27 (39.71)	0.80 (0.50, 1.27)	0.35
Bearman Toxcity Score at Day 28				
Median (IQR)	2 (1, 4)	3 (2, 4)		
Mean (SD)	3.00 (2.69)	3.31 (2.68)	-0.31 (-1.02, 0.41)	0.40
WHO Bleeding Scores				
Day 14	G0: 37 (54.41) G1: 14 (20.59) G2: 16 (23.53) G3: 1 (1.47) G4: 0 (0)	G0: 3(52.86) G1: 11 (15.71) G2: 21 (30.00) G3: 1 (01.43) G4: 0 (0)		0.81
Day 28	G0: 58 (84.06) G1: 6 (8.70) G2: 5 (7.25) G3: 0 (0.00) G4: 0 (0)	G0: 55 (79.71) G1: 6 (8.70) G2: 6 (8.70) G3: 2 (2.90) G4: 0 (0)		0.69
Day 100	G0: 53 (85.48) G1: 6 (9.68) G2: 2 (3.23) G3: 1 (1.61) G4: 0 (0)	G0: 60 (92.31) G1: 2 (3.08) G2: 2 (3.08) G3: 1 (1.54) G4: 0 (0)		0.52
Number of Grade ≥ 4 Infections				
Day 14	0 (0)	2 (2.90)	-	0
Day 28	3 (4.35)	0 (0)	-	-
Day 100	1 (1.59)	1 (1.49)	1.06 (0.07, 16.64)	0.97
Length of Hospitalization (Days)				
Median (95 % CI)	28 (25, 29)	28 (27, 31)		
Mean (SD)	28.03 (20.35)	29.22 (18.32)		0.21
Number of pts with ≥ 1 ICU admission	6 (8.00)	4 (5.33)	1.50 (0.44, 5.10)	0.52
Length of Stay of ICU admission (days)			1.40	0.72
Median (IQR)	6 (5, 20)	6 (3, 13)		
Mean (SD)	12.67 (12.97)	9.00(9.19)		
Hospital Re-admissions - *Mean (SD)*	17 (23.94)	17 (23.61)	1.01 (0.56, 1.82)	0.96

ICU: Intensive Care Unit; IQR: Interquartile Range; RR: Relative Risk; SD: Standard Deviation; WHO: World Health Organisation

Table 6: Clinical Outcomes - Autologous HCT Subgroup

Characteristics	Restrictive Strategy (N=74)	Liberal Strategy (N=75)	RR (95% CI)	P Value
Transplant Related Mortality at 100 days	0 (0)	0 (0)	-	
Bearman Toxcity Score at Day 28				
Median (IQR)	2 (1, 3)	2 (1, 3)		
Mean (SD)	2.09 (1.53)	2.28 (1.69)	-0.19 (-0.89,0.52)	0.61
WHO Bleeding Scores				
Day 14	G0: 59 (80.82) G1: 6 (8.22) G2: 8 (10.96) G3: 0 (0) G4: 0 (0)	G0: 48 (66.67) G1: 11 (15.28) G2: 13 (18.06) G3: 0 (0) G4: 0 (0)		0.16
Day 28	G0: 69 (94.52) G1: 2 (2.74) G2: 2 (2.74) G3: 0 (0) G4: 0 (0)	G0: 71 (97.26) G1: 1 (1.37) G2: 1 (1.37) G3: 0 (0) G4: 0 (0)		0.71
Day 100	G0: 67 (100) G1: 0 (0) G2: 0 (0) G3: 0 (0) G4: 0 (0)	G0: 66 (100) G1: 0 (0) G2: 0 (0) G3: 0 (0) G4: 0 (0)		
Number of Grade ≥ 4 Infections				
Day 14	1 (1.37)	2 (2.78)	0.49 (0.05, 5.32)	0.56
Day 28	0 (0)	0 (0)	-	-
Day 100	0 (0)	0 (0)	-	-
Length of Hospitalization (Days)				
Median (95 % CI)	18 (17, 20)	18 (17, 19)		
Mean (SD)	19.05 (6.45)	19.17 (10.26)		0.77
Number of patients ≥1 ICU admission	3 (4.05)	2 (2.67)	1.52 (0.26, 8.84)	0.64
Length of Stay of ICU admission (days)			0	0.14
Median (min, max)	1 (1, 5)	25 (18, 32)		
Mean (SD)	2.33 (2.31)	25 (9.90)		-
Hospital Re-admissions - *Mean (SD)*	5 (6.76)	8 (10.67)	0.63 (0.22, 1.85)	0.40

ICU: Intensive Care Unit; IQR: Interquartile Range; RR: Relative Risk; SD: Standard Deviation; WHO: World Health Organisation

Table 7: Transfusion Utilization

Characteristics	Restrictive Strategy (N=149)	Liberal Strategy (N=150)	P value
Red Cell transfusions - UNITS			
Median (IQR)	2 (0, 2)	4 (2, 6)	
Mean (SD)	2.73 (4.81)	5.02 (6.13)	p=0.0004
Red Cell transfusions - EPISODES	234	407	
Median (IQR)	1 (0, 2)	2 (1, 3)	
Mean (SD)	1.57 (2.96)	2.71 (3.33)	p=0.002
Duration of storage of transfused Red Cells			
Median (IQR)	17 (13, 23)	20 (15, 25)	
Mean (SD)	18.46 (7.27)	19.95 (7.52)	p=0.001
Platelet transfusions - EPISODES			
Median (IQR)	2 (1, 3)	2 (1, 4)	
Mean (SD)	3.84 (8.24)	3.61 (4.87)	p=0.77
Platelet transfusions - UNITS			
Median (IQR)	2 (1, 3)	2 (1, 4)	
Mean (SD)	4.11 (9.73)	3.75 (5.44)	p=0.69
Pre-transfusion Hemoglobin (g/L)			
Median (IQR)	69 (67, 75)	86 (83, 88)	
Mean (SD)	70.90 (7.44)	84.61 (6.38)	p< 0.0001
Difference of the mean pre-transfusion Hemoglobin (g/L) mean (SD)	13.71 (6.77)		
Threshold allocation minus pre-transfusion Hemoblobin (g/L) mean (SD)	-0.90 (7.44)	5.39 (6.38)	

IQR: Interquartile Range; RR: Relative Risk; SD: Standard Deviation

Table 8: Red Cell Transfusion Adherence

Characteristics	**Restrictive Strategy (N=149)**	**Liberal Strategy (N=150)**
Number of recorded Red cell transfusion episodes	234	407
Number of recorded Hemoglobin values	4648	5025
Number of non-adherences to assigned threshold *(Number of non-adherences to recorded hemoglobin values)*	98 (2.11%)	248 (4.94%)
Number of transfusions received above assigned threshold	80 (1.72%)	13 (0.26%)
Number of transfusions NOT given when assigned threshold reached	18 (0.39%)	235 (4.68%)
Number of patients who had ≥1 non-adherence to assigned trigger. *(Number of non-adherence patients to total patients)*	44 (29.53%)	75 (50%)
Number of patients receiving transfusions above assigned threshold	35 (23.49%)	11 (7.33%)
Number of patients NOT receiving transfusions when assigned threshold reached	14 (9.40%)	72 (48%)
Patients who never received a Red cell transfusion	69 (46.31%)	21 (14%)
Autologous HCT (% of all autologous HCT)	42 (56.76%)	12 (16 %)
Allogeneic HCT (% of all allogeneic HCT)	27 (36%)	9 (12%)

HCT: Hematopoietic Stem Cell Transplantation

Figure 1: CONSORT Statement Flow Diagram

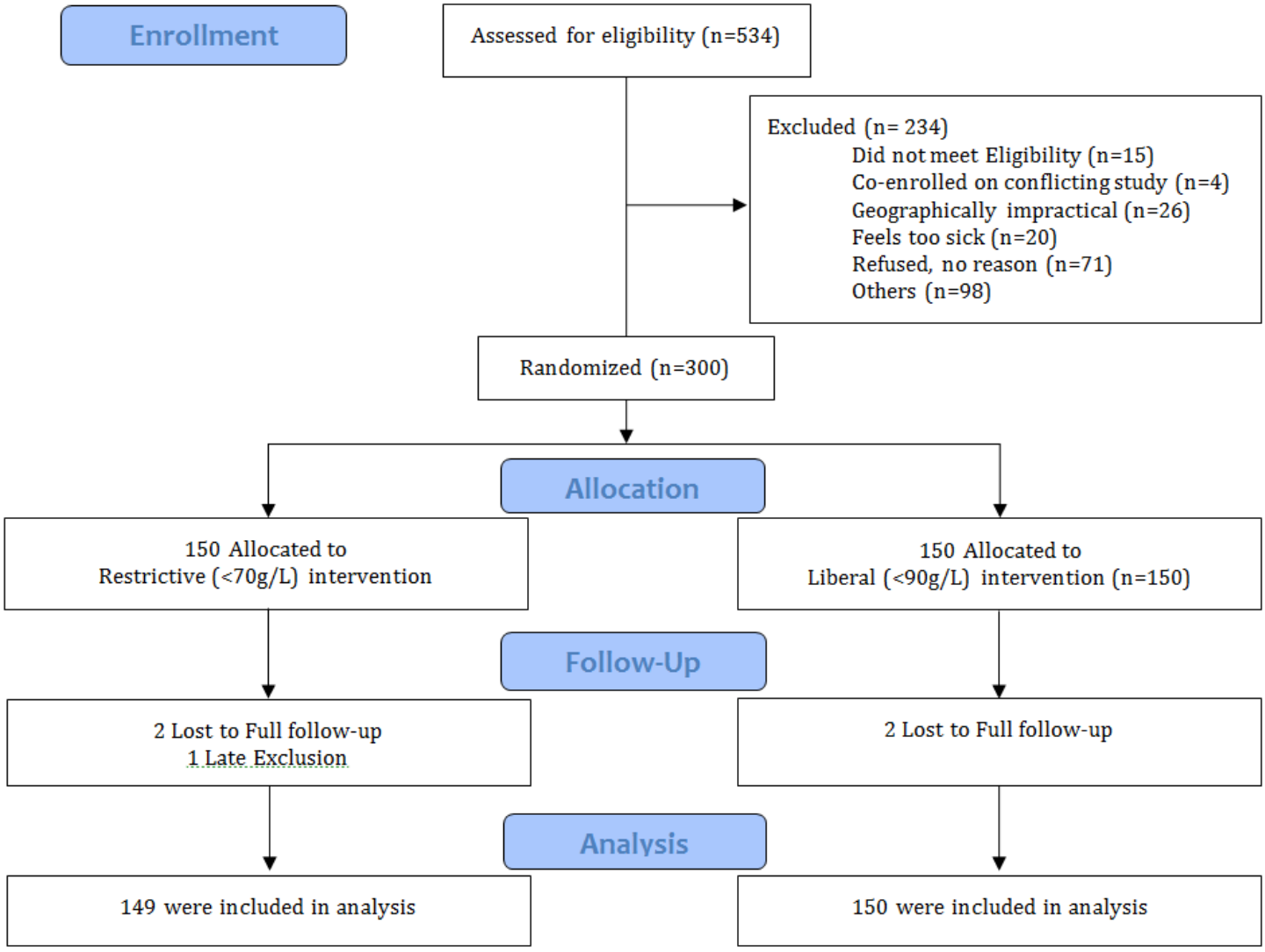
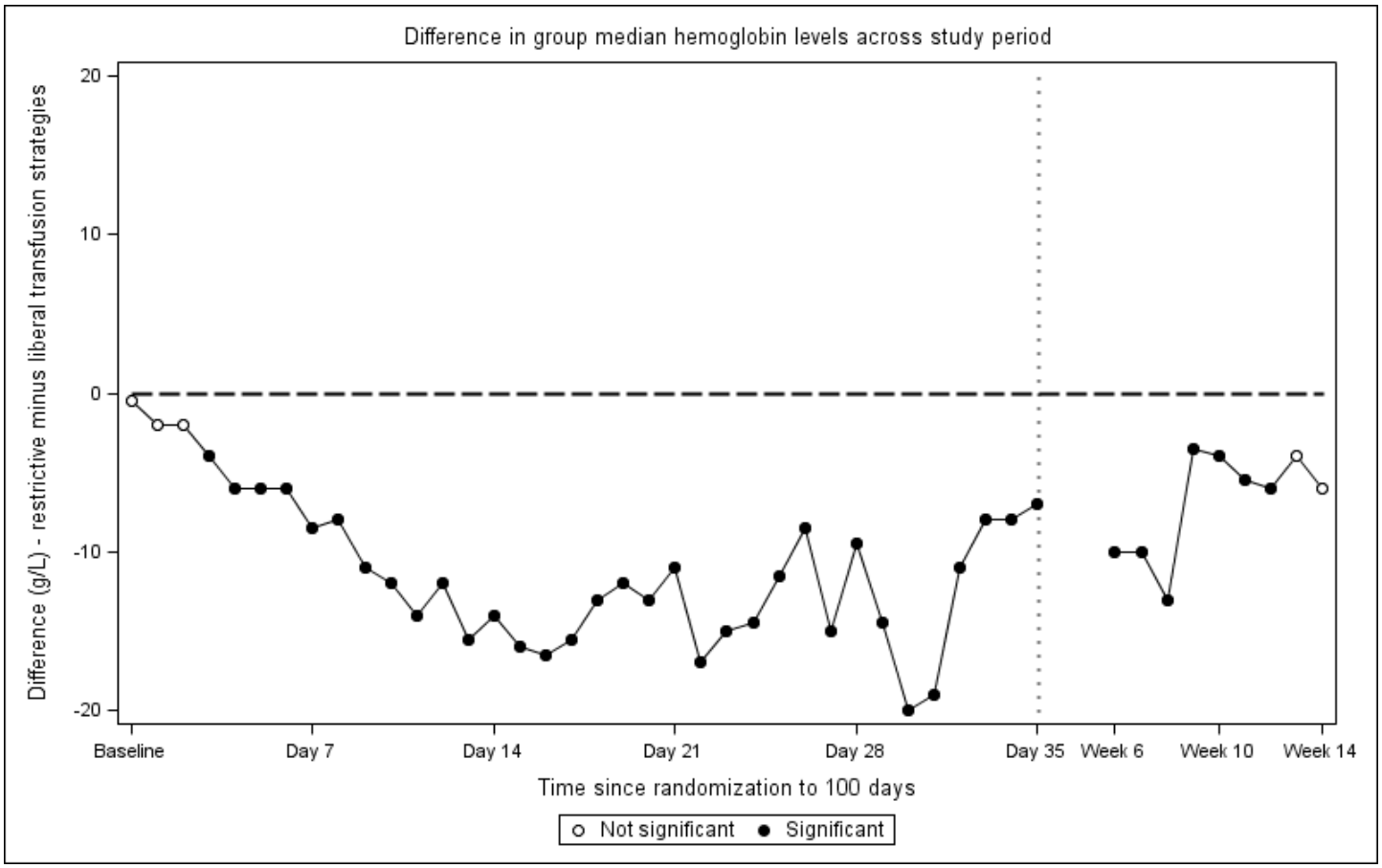
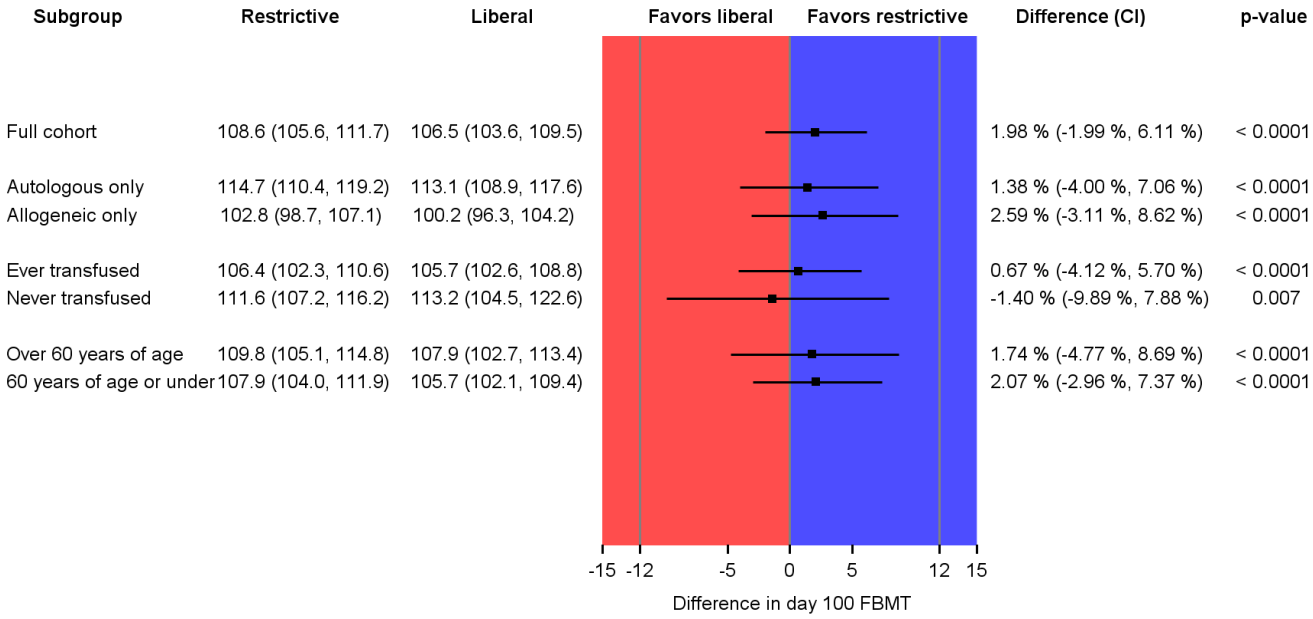


Figure 2: Difference in group median hemoglobin levels at baseline and up to day 100.



Legend: Plot of differences (restrictive minus liberal) between treatment group median hemoglobin values from baseline to day 100. Daily differences are given from baseline to day 35. From day 36 to day 91, differences between weekly medians are given (weeks 6 – 13). The calculation for week 14 includes days 99 and 100. All plotted differences were tested using Wilcoxon Mann-Whitney tests at $\alpha = 0.05$; filled circles indicate a difference was significant, and unfilled circles indicate a difference was not significant.

Figure 3: Primary Outcome subgroup analyses – FACT-BMT score at 100 days



Legend: Results from the models used in non-inferiority analyses are displayed here for the full cohort and subgroups. The adjusted means (95 % CI) for day 100 FACT-BMT are given for the restrictive and liberal groups in the second and third columns from left. The percentage difference (95 % CI) in restrictive relative to liberal score is given in the second column from the right, and the p-value for the non-inferiority test is given in the right-hand column. The percentage differences and their 95 % CIs are plotted along with vertical reference lines drawn at - / + 12 %.

Acknowledgments

This study was supported by grants from Canadian Institute of Health Research and the Canadian Blood Services.

The listed authors have no relevant conflict of interest to declare.

We thank the patients and clinical staff from hospitals (The Ottawa Hospital, London Health Sciences Centre, Saskatchewan Cancer Centre and Hamilton Health Sciences Centre) for their altruism, time, efforts and participation.

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