



Reducing the red blood cell transfusion threshold from 8·0 g/dl to 7·0 g/dl in acute myeloid leukaemia patients undergoing induction chemotherapy reduces transfusion rates without adversely affecting patient outcome

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Vox Sanguinis

Background and Objectives Red blood cell (RBC) transfusions are needed by almost every acute myeloid leukaemia (AML) patient undergoing induction chemotherapy and constitute a cornerstone in supportive measures for cancer patients in general. Randomized controlled trials have shown non-inferiority or even superiority of restrictive transfusion guidelines over liberal transfusion guidelines in specific clinical situations outside of medical oncology. In this study, we analysed whether more restrictive RBC transfusion reduces blood use without affecting hard outcomes.

Materials and Methods A total of 352 AML patients diagnosed between 2007 and 2018 and undergoing intensive induction chemotherapy were included in this retrospective analysis. In the less restrictive transfusion group, patients received RBC transfusion for haemoglobin levels below 8 g/dl (2007–2014). In the restrictive transfusion group, patients received RBC transfusion for haemoglobin levels below 7 g/dl (2016–2018). Liberal transfusion triggers were never endorsed.

Results A total of 268 (76·1%) and 84 (23·9%) AML patients fell into the less restrictive and restrictive transfusion groups, respectively. The less restrictive transfusion group had 1 g/dl higher mean haemoglobin levels, received their first RBC transfusions earlier and needed 1·5 more units of RBC during the hospital stay of induction chemotherapy. Febrile episodes, C-reactive protein levels, admission to the intensive care unit, length of hospital stay as well as response and survival rates did not differ between the two cohorts.

Conclusion From our retrospective analysis, we conclude that a more restrictive transfusion trigger does not affect important outcomes of AML patients. The opportunity to test possible effects of the more severe anaemia in the restrictive transfusion group on quality of life was missed.

Key words: acute myeloid leukaemia, induction chemotherapy, RBC, transfusion.

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Introduction

Acute myeloid leukaemia (AML) is a haematological malignancy of the myeloid blood lineage. A curative therapy approach can only be achieved by intensive treatments such as induction chemotherapy and allogeneic stem cell transplantation (SCT) [1,2]. Due to disease- or therapy-related anaemia and thrombocytopenia, prophylactic or therapeutic administration of red blood cell (RBC) and platelet concentrates are needed in almost every leukaemia patient and constitute a cornerstone of supportive measures in cancer patients in general.

The benefits and risks of RBC transfusions have been investigated in different patient populations during the last 20 years. The golden threshold where potential risks of RBC transfusions are preferably low and benefits are very high is not yet determined and may depend on the clinical situation. Therefore definitions for *restrictive* and *liberal* transfusion triggers vary amongst different health systems, hospitals and clinicians. A rather restrictive transfusion trigger avoiding haemoglobin (Hb) levels below 8 g/dl has been shown to be non-inferior in patients undergoing orthopaedic hip surgery when compared to a liberal transfusion rule that aimed to maintain Hb levels at 10 g/dl or higher [3,4]. Similarly, the TRACS trial proved non-inferiority of restrictive RBC transfusion (to maintain a haematocrit $\geq 24\%$) compared with liberal RBC transfusion (to maintain a haematocrit $\geq 30\%$) in patients undergoing elective cardiac surgery [4]. Hebert *et al.* [5] published a milestone study in 1999 showing superior overall survival in a subgroup of a heterogeneous critically ill study population when treated with a restrictive (maintenance of Hb concentration at 7.0–9.0 g/dl) instead of a liberal transfusion strategy (maintenance of Hb concentration at 10.0–12.0 g/dl). Villanueva *et al.* [6] showed in 2013 that in patients with upper gastrointestinal bleeding it is safe and effective to not perform RBC transfusion until Hb level drops below 7 g/dl.

The impact of different transfusion triggers on cancer patients has not been sufficiently studied in randomized controlled trials. We know that anaemia in cancer patients is associated with a shorter survival in almost all cancer types studied [7–10] and that the prevalence of anaemia is almost twice as high in haematological patients as in patients with solid tumours [11]. We also know that anaemia significantly impairs quality of life [12,13]. Pilot studies have been performed to confirm feasibility of large randomized controlled trials that are now ongoing comparing restrictive and liberal transfusion strategies in haematological patients [14–16]. Results from these trials are awaited eagerly. In fact, an abstract of the TRIST trial (transfusion of red cells in haematopoietic stem cell transplantation) has been presented at the

annual meeting of the American Society of Hematology (ASH) in 2019 and its publication is expected soon. In this study, a liberal RBC transfusion strategy (Hb threshold 9 g/dl) was compared with a restrictive RBC transfusion strategy (Hb threshold 7 g/dl) in 300 patients undergoing allogeneic or autologous SCT. Health-related quality of life scales, mortality, length of hospital stay, admission to the intensive care unit (ICU), infections and bleeding were collected as end-points. The results showed non-inferiority for RBC transfusion with a 7 g/dl Hb threshold.

Anaemia accompanying cancer chemotherapy is very distinct from trauma, surgical or medical haemorrhagic patients such as were studied in the above-referenced studies. Patients with liver diseases and oesophageal varices bleeding are obviously at risk for renewed haemorrhage when portal pressure is high, particularly when it is acutely elevated by blood transfusions; similar observations may apply in neurosurgical patients with cerebral oedema. A subset of surgical patients, especially cardiac bypass surgery patients, may benefit from better rheological properties of relative haemodilution; the same likely applies to trauma patients. In leukaemia patients, anaemia represents the slow, linear drop of Hb caused by the natural death of RBCs in the absence of erythropoiesis due to chemotherapy-induced myelosuppression. These patients develop anaemia rather insidiously, and Hb will continue to fall until haematopoiesis resumes. Thus, RBC transfusions do not tide patients over somewhat acute but short-lived dips in Hb levels as in patients with acute blood loss but otherwise intact haematopoiesis. Instead, RBC transfusions maintain a certain Hb level. Intuitively, if a lower level can be accepted, inevitably less blood should be required. Mathematically, on average, accepting levels of 1 g/dl less Hb will save 1–1.5 units of blood (approximately the equivalent of 50–75 g of Hb). We here applied in successive cohorts transfusion triggers of first 8 g/dl, then 7 g/dl and sought to determine the following: (1) is adoption of stricter thresholds reflected by patient blood counts, (2) do stricter thresholds reduce the utilization of blood and (3) is blood sparing achieved without affecting hard outcome end-points such as length of hospital stay, severe intercurrent illnesses and survival.

Materials and methods

Study design and treatment protocols

In this single-centre study, we retrospectively included all patients with AML (excluding acute promyelocytic leukaemia) who underwent intensive induction chemotherapy between 2007 and 2018. Until August of 2015, AML patients undergoing intensive induction chemotherapy

received 2 units of RBC concentrates if matutinal Hb levels dropped below 8 g/dl (hereinafter referred to as the *less restrictive* transfusion group). To be more in line with the German Medical Association's guidelines for therapy with blood components in September 2015, the institutional transfusion guideline was changed and AML patients received 2 units of RBC concentrates if matutinal Hb levels dropped below 7 g/dl (hereinafter referred to as the *restrictive* transfusion group) [17]. Blood testing (haematology, liver and kidney function, coagulation and inflammation markers) was performed every other day routinely. In case of anaemia-related symptoms, RBC transfusion at a higher threshold was allowed in both cohorts if deemed indicated by the clinician in charge. Platelet concentrates were given if platelet count dropped below 10 000/ μ l or at a higher threshold if the patient presented with haemorrhage [18]. For platelet transfusions pooled buffy coat platelets from four buffy coats were used with a median platelet content of 2.9×10^{11} /unit. Packed red cell units consisted of leukocyte- and plasma-depleted RBCs in PAGGS-M with an Hb content of ≥ 40 g.

Standard induction chemotherapy was the so-called 7 + 3-regime; cytarabine 100 mg/m² given intravenously (IV) continuously for 7 days is combined with daunorubicin 60 mg/m² given as a 30-min IV infusion on days 3, 4 and 5 [19]. Patients under the age of 60 received a second induction therapy with 7 + 3 if early blast clearance was achieved in d15 bone marrow blood evaluation or with *HAM protocol* (cytarabine 3000 mg/m² was administered by 3-h IV infusion every 12 h on day 1 through 3 and mitoxantrone 10 mg/m² by 30-min IV infusion on days 3,4 and 5) if blast clearance was not achieved on d15 bone marrow blood evaluation [20]. Patients above the age of 60 received only a second induction chemotherapy with HAM (with reduced cytarabine dose of 1000 mg/m²), if the first induction therapy cycle was not sufficient to achieve bone marrow blast clearance on d15 [21]. In case of a complete remission (CR) after induction chemotherapy with 7 + 3 alone or with 7 + 3 and HAM, patients went on to receive a consolidation treatment with either high-dose cytarabine or with an allogeneic SCT. All patients received routinely antimicrobial prophylaxis with levofloxacin and posaconazole daily as suggested by current guidelines [22,23]. A day with fever was defined if body temperature was measured $\geq 38.3^{\circ}\text{C}$ once or $\geq 38.0^{\circ}\text{C}$ on two consecutive days [24]. If fever or a significant increase of C-reactive protein (CRP) (doubling of CRP level and absolute value above 5 mg/dl, norm <0.5 mg/dl) was found, antibiotic prophylaxis was replaced by intravenous broad-spectrum antibiotics.

The study was performed in accordance with the 2013 Helsinki declaration. Patients provided informed written consent to retrospective data extraction from patient

charts and patient data were provided after approval by the local Ethics Committee (approval number SHN-04-2018). The ethics committee waived the requirement for informed consent from the legally authorized representative for deceased patients. In addition, the majority of patients were also enrolled in the AML registry of the Study Alliance Leukaemia (approval number EK 98032010). After ethics approval, data from all AML patients receiving intensive induction chemotherapy at the University Hospital Frankfurt were retrieved from the clinical cancer registry of the University Cancer Center (UCT) Frankfurt and complemented by data directly from the patients archived medical records. Data analysis was performed on anonymized data.

Statistical analysis

This study was designed as a retrospective cohort study. Patients were followed till death or last contact. Dates of treatment start and finish with induction chemotherapy were assessed separately. Continuous variables are shown as means \pm standard deviation, and categorical variables are reported as frequencies and percentages. All continuous variables were tested for normality and were analysed by using the Student's *t*-test or the Wilcoxon–Mann–Whitney test accordingly. Chi-squared test was used for binary variables. Predictors of survival were determined using a univariate Cox regression hazard model. Death was recorded as an event. Statistical analysis was performed with SPSS (version 22.0, IBM, Armonk, NY, USA).

Results

A total of 384 patients diagnosed with AML between 2007 and 2018 that underwent intensive induction therapy were included in this retrospective analysis. Transfusion strategy was adapted in September 2015. To avoid potential bias during the time of adapting the new transfusion guideline, 32 AML patients diagnosed in 2015 were excluded to guarantee two clearly separated study populations. Hereafter, 352 AML patients fell either into the less restrictive transfusion group (2007–2014, $n = 268$) or into the restrictive transfusion group (2016–2018, $n = 84$).

Baseline characteristics

Median age was 59 years (range 18–82) in the less restrictive and 58 years (range 20–79) in the restrictive transfusion group ($P = 0.891$). At time of diagnosis, there was no significant difference between both cohorts with respect to sex, lactate dehydrogenase (LDH), platelet count, Hb level, or WHO classification [25]. AML risk groups according to the European Leukaemia Net (ELN)

recommendations from 2010 were equally distributed between the two cohorts (Table 1) [26].

Transfusion-related analysis

During the hospital stay of induction chemotherapy, AML patients treated according to the less restrictive transfusion guideline received in median 1.5 more units of RBC concentrates than AML patients treated according to the restrictive transfusion guideline (12 (0–55) vs. 10.5 (0–41), $P = 0.046$). AML patients in the less restrictive transfusion group received their first RBC transfusion 2 days (0–77) after admission to hospital compared with 5 days (0–24) after admission in the restrictive transfusion group ($P = 0.002$). The less restrictive transfusion group had a median Hb level of 9.3 g/dl (7.6–11.3) during the hospital stay of induction chemotherapy compared with 8.25 g/dl (6.8–11.8) in the restrictive transfusion group ($P < 0.001$), that is reduction of transfusion triggers by 1 g/dl showed the proportional effect on Hb levels. Mean adherence to transfusion guideline was 50.8% in the less restrictive transfusion group and 65% in the restrictive transfusion group ($P = 0.001$). A median of 10 platelet concentrates was transfused in the less restrictive transfusion group compared with eight platelet concentrates in restrictive transfusion group (10 vs. 8, $P = 0.259$) with median platelet counts of 28 000/ μ l and 31 000/ μ l, respectively ($P = 0.223$) (Table 2).

Clinical findings and outcome

There was no difference between the two cohorts with respect to the length of the hospital stay for induction chemotherapy (48 d vs. 47.5 d, $P = 0.843$). Days with

fever were equally distributed between both groups (5 vs. 5.5, $P = 0.908$), and median CRP level was 4.33 mg/dl (0.2–34.32) in the less restrictive transfusion group and 3.87 mg/dl (0.27–22.16) in the restrictive transfusion group ($P = 0.628$). A total of 49 (18.3%) AML patients of the less restrictive and 16 (19.1%) of the restrictive transfusion group required transfer to the ICU ($P = 0.875$). The CR rate was 61.9% in both cohorts ($P = 0.854$). A total of 138 AML patients (51.5%) in the less restrictive transfusion group went on to receive allogeneic SCT as consolidation therapy compared to 53 patients (63.1%) in the restrictive transfusion group ($P = 0.079$) (Table 3).

To analyse restrictive RBC transfusion as a prognostic parameter in AML patients undergoing intensive induction chemotherapy, a multivariate Cox regression model with forward stepwise likelihood ratio was performed. The nominal dichotome variables female sex, age below 60 years, non-adverse risk AML, CR after induction chemotherapy, allogeneic SCT as consolidation therapy and less restrictive RBC transfusion were included in this model. As shown in Table 4, age below 60 years, non-adverse risk AML, CR after induction chemotherapy and allogeneic SCT as consolidation therapy were independently associated with OS. Restrictive RBC transfusion was not significantly associated with survival. The noticeable but statistically not significant trend towards improved survival in the restrictive transfusion group (HR: 0.681 and P -value 0.076) is due to bias caused by the study design with sequential comparisons and will be further commented on in the discussion section of the manuscript.

Table 1 Baseline characteristics

| Characteristic | All | Less restrictive transfusion | Restrictive transfusion | P -Value |
|--|----------------|------------------------------|-------------------------|------------|
| Number of patients (n , %) | 352 (100) | 268 (76.1) | 84 (23.9) | |
| Median age (median, range) | 59 (18–82) | 59 (18–82) | 58 (20–79) | 0.891 |
| Male sex (n , %) | 181 (51.4) | 137 (51.1) | 44 (52.4) | 0.901 |
| AML with recurrent genetic abnormalities (n , %) | 145 (41.2) | 113 (42.2) | 32 (38.1) | 0.495 |
| AML with myelodysplasia-related changes (n , %) | 79 (22.4) | 55 (20.5) | 24 (28.6) | 0.495 |
| Therapy-related myeloid neoplasms (n , %) | 5 (1.4) | 4 (1.5) | 1 (1.2) | 0.495 |
| AML not otherwise specified (n , %) | 123 (34.9) | 96 (35.8) | 27 (32.1) | 0.495 |
| Thrombocytes/ nl^a (median, range) | 54 (5–780) | 52 (5–590) | 67 (6–780) | 0.083 |
| Haemoglobin g/dl ^a (median, range) | 9.1 (4.5–16.5) | 9.2 (4.5–16.5) | 9.05 (4.5–14.5) | 0.196 |
| Lactate dehydrogenase U/l ^a (median, range) | 406 (110–6223) | 403 (110–6223) | 438 (136–2893) | 0.790 |
| Favourable ELN risk group | 72 (20.5) | 53 (19.8) | 19 (22.6) | 0.451 |
| Intermediate-I ELN risk group | 137 (38.9) | 101 (37.7) | 36 (42.9) | 0.451 |
| Intermediate-II ELN risk group | 81 (23) | 67 (25) | 14 (16.7) | 0.451 |
| Adverse ELN risk group | 60 (17.1) | 46 (17.2) | 14 (16.7) | 0.451 |

All P -values reported are two-sided.

Statistical significance was defined as $P \leq 0.05$.

^aOn the day of admission to hospital.

Table 2 Transfusion-related analysis

| Characteristic | Less restrictive transfusion | Restrictive transfusion | P-Value |
|--|------------------------------|-------------------------|---------|
| Number of patients | 268 | 84 | |
| Transfused RBC concentrates (median, range) | 12 (0–55) | 10.5 (0–41) | 0.047 |
| Transfused platelet concentrates (median, range) | 10 (0–108) | 8 (2–73) | 0.259 |
| Adherence to RBC transfusion guideline % (mean, SD) | 50.8 (32.3) | 65.0 (34.4) | 0.001 |
| Haemoglobin g/dl (median, range) | 9.3 (7.6–11.3) | 8.25 (6.8–11.8) | <0.001 |
| Thrombocytes $\times 10^3/\mu\text{l}$ (median, range) | 28 (7–200.5) | 31 (7–794) | 0.223 |
| Days from admission to 1st RBC transfusion (median, range) | 2 (0–77) | 5 (0–24) | 0.002 |

All *P*-values reported are two-sided.

Statistical significance was defined as $P \leq 0.05$.

Discussion

In this study, we compared the impact of a less restrictive transfusion guideline (transfusion if Hb < 8 g/dl) practised from 2007 to 2015 to a more restrictive transfusion guideline (transfusion if Hb < 7 g/dl) that was implemented in September 2015 in AML patients undergoing intensive induction chemotherapy at the University Hospital Frankfurt. Of note, the transfusion trigger guideline did not apply specifically to AML patients during induction therapy, but to all in-patients with haematological malignancies. The AML patients were singled out for this analysis due to their high homogeneity and the over time unchanged induction chemotherapy, which causes a predictable protracted aplasia. Reducing the red blood cell transfusion threshold from 8.0 g/dl to 7.0 g/dl in acute myeloid leukaemia patients undergoing induction chemotherapy reduced the use of RBC concentrates rates without adversely affecting patient outcome.

In the last 20 years, multiple studies have suggested advantages of restrictive transfusion guidelines in certain patient populations [3–6]. The definitions of what constitutes liberal vs. restrictive transfusion vary greatly and far exceed long-standing recommendations for rational blood use. Causes of blood loss and risks of more

generous RBC transfusion vary greatly with respect to the treated patient population, which was insufficiently considered. Thus careful individual assessment should guide transfusion practice [27]. However, more restrictive transfusion guidelines have been adapted for haematological patients in the past decade, although studies for this specific patient cohort were missing. It is unclear what constitutes optimal blood use for this exceptional patient cohort. Potential risks of under-transfusion (inability of patients to self-mobilize, tissue hypoxemia, impaired wound healing, falls due to arterial hypotension, cardiac stress, heart failure and myocardial infarcts due to attempts of physiological adaptation to anaemia, fatigue, etc.) and over-transfusion (arterial hypertension, cardiac overload (TACO), acute transfusion reactions, TRALI, costs, etc.) must be carefully balanced and likely the occasional patient becoming a victim of the one or the other will go overlooked in cohort analyses such as these with grave competing risks.

Change of the transfusion trigger from 8 to 7 g/dl Hb resulted in a mean reduction of the AML patients Hb level of precisely these 1 g/dl. This reduced blood use by 1.5 units and delayed the first transfusion by three days, which is the time it takes for an aplastic patient without haemorrhage to lose 1 Hb point. In this respect, reduced

Table 3 Clinical findings

| Characteristic | Less restrictive transfusion | Restrictive transfusion | P-Value |
|--|------------------------------|-------------------------|---------|
| Number of patients (<i>n</i> , %) | 268 (76.1) | 84 (23.9) | |
| Length of hospital stay (median, range) | 48 (7–128) | 47.5 (15–127) | 0.843 |
| Days with fever (median, range) | 5 (0–31) | 5.5 (0–30) | 0.908 |
| C-reactive protein (median, range) | 4.33 (0.2–34.32) | 3.87 (0.27–22.16) | 0.628 |
| Patients admitted to the intensive care unit (<i>n</i> , %) | 49 (18.3) | 16 (19.1) | 0.875 |
| Complete remission after induction chemotherapy (<i>n</i> , %) | 166 (61.9) | 52 (61.9) | 0.854 |
| Stem cell transplantation as consolidation therapy (<i>n</i> , %) | 138 (51.5) | 53 (63.1) | 0.079 |

All *P*-values reported are two-sided.

Statistical significance was defined as $P \leq 0.05$.

Table 4 Univariate and multivariate analysis associated with survival in AML patients

| Parameter | HR | 95% CI | P value | HR | 95 % CI | P value |
|--|---------------------|-------------|---------|-----------------------|-------------|---------|
| | Univariate analysis | | | Multivariate analysis | | |
| Female sex | 0.774 | 0.571–1.048 | 0.098 | | | |
| Age < 60 | 0.377 | 0.274–0.518 | <0.001 | 0.560 | 0.397–0.791 | 0.001 |
| Non-adverse risk AML | 0.581 | 0.404–0.835 | 0.003 | 0.551 | 0.381–0.795 | 0.001 |
| Complete remission after induction chemotherapy | 0.379 | 0.279–0.515 | <0.001 | 0.341 | 0.248–0.497 | <0.001 |
| Stem cell transplantation as consolidation therapy | 0.353 | 0.258–0.482 | <0.001 | 0.351 | 0.248–0.496 | <0.001 |
| Restrictive red blood cell transfusion | 0.681 | 0.446–1.041 | 0.076 | | | |

CI, indicates confidence interval; HR, hazard ratio.

All *P*-values reported are two-sided. Statistical significance was defined as $P \leq 0.05$.

transfusion triggers completely met expectations. The 12.5% reduction of RBC transfusion is in accordance to a feasibility study by DeZern *et al.* in 2016. Here, 90 acute leukaemia patients admitted to hospital for intensive treatment were 2:1 assigned to a restrictive (<7 g/dl) or a less restrictive (<8 g/dl) transfusion trigger to determine feasibility of a larger clinical trial. The restrictive transfusion guideline led to an approximate 20% reduction of RBC transfusions [14].

Due to the retrospective nature of our study, we cannot comment on whether the reduced number of RBC transfusion and the consequently lower Hb levels impaired quality of life by worsening anaemia and fatigue symptoms or inability to be mobilized. However, as elaborated before, Hb levels were not exclusively respected as a transfusion trigger by the treating physicians; clinical indications for transfusions could always over-ride the numeric threshold. In other words, symptoms related to anaemia will result in earlier transfusion than dictated by Hb levels. Thus, higher prevalence of unacceptable anaemia symptoms could be detected as decreased adherence to pre-defined transfusion rules. However, this was not observed. On the contrary, in our study, adherence to the restrictive transfusion rule was higher than adhesion to the less restrictive transfusion rule. Therefore, one can postulate that the presence of anaemia-related symptoms was not markedly more frequent in the restrictive transfusion cohort compared with the less restrictive transfusion cohort. This interpretation is in accordance with the more formal study of DeZern *et al.* Here, restrictively transfused patients did not experience higher fatigue scores; however, the analysed study population was very small ($n = 89$) [14]. Larger prospective randomized trials with formalized analyses for more sensitive patient-relevant outcomes are needed to draw definitive conclusions regarding the impact of different transfusion guidelines on quality of life.

At first, it was surprising to us that the restrictive transfusion guideline was more constantly followed than

the less restrictive transfusion guideline (66.6% vs. 50%, $P = 0.001$). We posit that this observation could be due to bias resulting from the different time of periods in which our cohorts were treated for AML. Being a non-issue for decades, within the past decade, restrictive transfusion guidelines have become clinical practice especially in critical care and gastroenterology patients [5,6]. Hence, clinicians feel probably more comfortable taking care of patients with low Hb levels of <8 g/dl. For example, adherence to transfusion guideline in our clinic increased over time from 33.3% in 2008 and 2009 to 83.3% in 2014 although the transfusion guidelines stayed the same during that time, supporting our hypothesis that administration of RBC transfusion became increasingly restrictive over time regardless of the given transfusion guideline.

Low Hb levels may increase risk of bleeding by influencing coagulation as well as platelet adhesion and aggregation [28–30]. Therefore, we were interested in evaluating whether the statistically significantly lower Hb levels led to more transfusion of platelets concentrates in the restrictively transfused AML patients. Although the quantitatively modest difference in Hb levels was expected to not be associated with marked platelet dysfunction, the clinical relevance of the question merited such analyses. As we are showing, the number of platelet concentrates transfused during the hospital stay of induction chemotherapy was not significantly different between the restrictive and the less restrictive transfusion group. That observation is in accordance with a pilot-randomized study by Webert *et al.* [16]. Here, 60 acute leukaemia patients admitted to hospital for intensive treatment were included with bleeding being a primary end-point. Restrictive RBC transfusion neither increased the number of platelet transfusions nor of bleeding events even though a significantly higher Hb cut-off at 12 g/dl was used for the liberal transfusion group.

Studies from the past century suggested that RBC transfusion could accelerate haematopoietic recovery in children with leukaemia [31,32]. There is also evidence

that RBC transfusion attenuates chemotherapy-induced myelosuppression in adults [33]. Although these studies used hypertransfusion with RBC concentrates aiming Hb levels of 16 g/dl and higher, we wanted to analyse whether different RBC transfusion rates had impact on CR rates or time to discharge from hospital (both depending on haematopoietic recovery). In accordance with the current literature, different transfusion guidelines had no impact on CR rates or the length of hospital stay [14,34].

Bacterial infections are the most common cause for treatment-related mortality in AML patients and in patients with chemotherapy-induced neutropenia in general [22]. This is the first study to systematically analyse the impact of different transfusion guidelines on clinically relevant infectious parameters in a large uniformly treated AML cohort. In our analysis, the less restrictive transfusion group did not suffer from more days with fever, higher CRP levels or increased requirement of ICU treatment. There is no evidence that RBC transfusion increases infectious complications in AML patients undergoing intensive induction chemotherapy.

In our univariate and multivariate analyses, age below 60 years, non-adverse risk AML, CR after induction chemotherapy and allogeneic SCT as consolidation therapy were significantly associated with OS. Restrictive RBC transfusion was not significantly associated with a survival disadvantage; however, the HR was 0.681 and the *P*-value 0.076. This trend towards improved survival of the restrictive transfusion cohort represents changes in AML consolidation treatment practice and not changes in transfusion practice. Here, access to allogeneic transplantation as the only consolidation treatment, that can induce long-term remissions and cures in adverse-risk AML, is worth mentioning. Age restrictions for allogeneic SCT have been loosened, and the advent of post-transplant cyclophosphamide has improved the probability of timely identification of a suitable stem cell donor. We show that in the restrictive transfusion group more patients received allogeneic SCT as consolidation therapy than in the less restrictive transfusion group (63.1 vs. 51.5%, *P* = 0.079) explaining the trend towards improved OS rates in the restrictive transfusion group. The retrospective nature of this study and its sequential study design limits conclusions that can be made regarding

outcome, even though baseline characteristics were equally distributed (representing the nature of AML which, of course, has not changed) and local guidelines for AML induction treatment and supportive measures (such as anti-infective prophylaxis and management of febrile neutropenia) remained the same over time.

From a health economic aspect, it is worth mentioning that costs for blood transfusions are comparably low in Europe and especially in Germany, since blood manufacturers are not-for-profit. The costs associated with transfusion of a unit of RBCs were estimated for Austria at \$522.45 by Shander *et al.* in 2010 [35]. The approximate savings per AML patient undergoing induction chemotherapy thus amounts to roughly \$780 plus adjustment for inflation.

In summary, we found consistently with the current literature no direct or indirect evidence that reducing transfusion triggers from 8 to 7 g/dl affects the clinical course of AML patients undergoing intensive induction chemotherapy with respect to infectious parameters, length of hospital stay, remission rates, platelet transfusion frequency or mortality rates. Unfortunately, we cannot offer substantial information about one key factor of RBC transfusion as a supportive measure, that is its impact on quality of life. Trials that hopefully offer analysis about advantages and disadvantages of different transfusion guidelines are ongoing and urgently needed. The only completed randomized trial – the TRIST trial – is still to be published. Their results presented at the annual meeting of the American Society of Hematology are in line with our observations. However, the study population differs from ours as we did not include patients undergoing SCT and the difference of transfused RBC concentrates in the TRIST trial did not reach statistical significance. Proven advantages of restrictive transfusion triggers in other non-haematological patient populations do not justify an inconsiderate adaption of restrictive transfusion guidelines for AML or haematological patients in general.

Conflict of interests

The authors declare no conflict of interests.

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