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Is there a *threshold dose* of CD34-positive cells for posttransplant bone marrow recovery?

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Summary

Using diverse data we show CD34-positive cells are not an accurate estimator of numbers of haematopoietic stem cells in humans. We also show in the context of umbilical cord transplants for leukaemia there is likely no threshold of CD34-positive cells needed to restore bone marrow function after high-dose pretransplant therapy. Lastly, we show that, when CD34-positive cells are used as a surrogate marker for human haematopoietic stem cells, the dose should be expressed as numbers *per* blood volume and not body weight. These conclusions, if validated, may have important clinical implications.

Keywords

CD34-positive cells, threshold dose, transplant, graft dosage.

Introduction

It is widely believed that the recovery of bone marrow function after haematopoietic cell transplantation arises from pluripotent haematopoietic stem cells (HSCs). It is also generally assumed that the contents of CD34-positive cells in a graft are an accurate proxy for numbers of HSCs, that the dose of CD34-positive cells should be quantified by body weight and that there is a *threshold dose* of CD34-positive cells required for successful bone marrow recovery post-transplant. We argue that several or all of these beliefs are wrong. We consider biological plausibility and clinical data from persons receiving umbilical cord blood cells transplants and advanced statistical analyses of this dataset. Our conclusions have important implications for transplant practices.

Biology

HSCs and CD34-positive cells are not the same

There is no accurate way to identify human haematopoietic *stem* cells (HSCs) [1-3]. Although many people assume human HSCs to be CD34-positive but this is conjecture lacking a human HSC assay [4-6]. Quiescent HSCs in mice are CD34-negative acquiring CD34 expression only after they begin dividing and, thus, are no longer stem cells [7]. Some data suggest an ever-changing phenotype of human HSCs [1, 2].

Most CD34-positive cells in blood, bone marrow and umbilical cord blood cell grafts in humans are not HSCs [4]. Data from transplanting human haematopoietic cells into immune-deficient mice suggest that 10E-6 to 10E-7 CD34-

positive mononuclear cells might be HSCs, a frequency which could be relatively higher in human umbilical cord blood grafts and lower in bone marrow grafts, and still lower in quiescent and *mobilised* blood cell grafts [8].

Since almost all CD34-positive cells in a graft are not HSCs the estimated contents of HSCs based on numbers of CD34-positive cells must be imprecise. If we assume that the ratio of HSCs to CD34-postive cells is 1 to 5000 in umbilical cord blood, a graft containing 40×10E+5 CD34-positive cells could have variation of +10 percent in numbers of HSCs due to Poisson noise.

Posttransplant bone marrow recovery is not only from HSCs

Another complexity is that we lack knowledge of which haematopoietic cell(s) underly posttransplant recovery of bone marrow function. Data in mice indicate that a number of different cells in a graft including many which are not HSCs contribute to short- and long-term bone marrow recovery [9-11]. Data obtained in humans are largely consistent with animal data [12-14]. Even within the phenotypically most primitive HSCs, the pool of individual *stem cells* can have very different self-renewal potentials and different contribution to bone marrow recovery [15-21]. Namely, not all HSCs contribute equally to sustained multi-lineage haematopoiesis and most of them show biased differentiation towards specific haematopoietic lineages.

Clinical considerations

We are left with an insoluble challenge. First, we don't know which cells in a graft are responsible for short- and long-term posttransplant bone marrow recovery. This is especially true after autotransplants and after allotransplants with less intensive pre-transplant conditioning. Second, without this knowledge, we obviously lack an accurate assay for whether a graft will restore short- and long-term post-transplant bone marrow function.

Clinicians need to address 2 questions: (1) how to derive a measure for haematopoietic potential of a graft using the number of CD34-positive cells despite the caveats we discuss above; and (2) whether there is a *threshold dose* needed for successful posttransplant bone marrow recovery.

Although numbers of CD34-positive cells in a graft and ability to restore posttransplant bone marrow function are dissimilar for reasons we discuss, as long as the two maintain a relatively predictable ratio, the dose of CD34-positive cells might still be a useful surrogate. This raises the question of how the numbers of CD34-positive cells may be converted to a dose. Presently, CD34-positive cell dose is quantified on body weight [22, 23]. Why this is so is unclear: In the graft we are dealing with some cells with substantial proliferative potential, not like a medical drug that is stoichiometrically metabolised by the liver or excreted by the kidneys. Mammals come in various sizes: from a mouse (20 g) to humans (70 kg), and to elephants (7500 kg). A human gaining 20 kg does not suddenly have more cells (just bigger fat cells) and his or her blood volume certainly would not suddenly increase by 30 percent, since blood volume correlates better with lean body mass than with body weight, body mass index or body surface area across both sexes at all Tanner stages [24]. Such a person, obviously, does not need 30 percent more CD34-positive cells to recover posttransplant bone marrow function [25, 26].

Is there a required threshold dose for CD34-positive cells?

We suggest it is biologically implausible there is a *threshold dose* of CD34-positive cells for successful post-transplant bone marrow recovery. If there is a *threshold dose* for CD34-positive cells, the hazard function for recovery of bone marrow function is expected to be zero until the dose, however, quantified, exceeds the threshold. Conversely, if there is no threshold dose, the hazard function would continuously increase provided the dose is not zero (Fig. 1A). Previous research that interrogated the relationship between CD34-positive cell dose and posttransplant bone marrow recovery uniformly analysed dose by discretizing it into multiple classes with contradictory results [27-35]. This approach could not uncover the shape of the dose-response curve for CD34-positive cell dose *versus* haematopoietic function recovery and, therefore, is not suitable for answering the question whether there is a *threshold dose* of CD34-positive cells [36].

Consensus guidelines suggest a threshold dose of CD34-positive cell dose ranging from ≥1.5×10E+5/kg for umbilical cord blood cell grafts to ≥5×10E+6/kg for mobilized peripheral blood cell grafts [23, 37]. Applying this recommendation, only 4 percent of the US cord blood inventory is suitable for single-unit transplants to adults [38]. Theoretically, however, even one HSC is capable of restoring post-transplant bone marrow function given sufficient time and provided we can keep the recipient alive for this interval [8, 26]. Data in mice indicate that some HSC clones are highly efficient in restoring long-term bone marrow function [39]. Moreover, we reported recovery of bone marrow function in a person exposed to acute extremely high-dose and dose-rate total body radiation doses without a transplant [40]. Because radiation killing of cells is stochastic it is impossible any dose of ionising radiations could kill every HSC without killing the person. These data indicate the concept of so-called *myelo-ablative* pretransplant conditioning regimens to be a misnomer.

Clinical data

To help resolve these controversies we interrogated data from 619 consecutive subjects with acute leukaemia receiving a single-unit umbilical cord blood cell transplant 2015-2020. Mean age was 13.6 (0.7-62.3) years. Most had acute leukemia. The absolute dose of CD34-positive cells was 72.15×10+5 (Range, 3.85-502×10E+5/kg) with median dose of 1.90×10+5/kg (Range, 0.17-10.90×10E+5/kg). Median CD34+ cell dose was 1.9 0×10E+5/L recipient blood volume (Range, 0.02-2.40)×10E+5/L. We choose umbilical cord blood cell transplants because an insufficient CD34-positive cell dose is often referred as the reason to exclude potential adult recipients and because umbilical cord blood is likely to have the highest fraction of HSCs amongst different CD34-positive cell populations [8].

We considered 3 expression modes of CD34-positive cell dose: (1) absolute numbers of CD34-positive cells (Abs

CD34-positive); (2) numbers of CD34-positive cells *per* kg of recipient body weight (CD34-positive/BW); and (3) numbers of CD34-positive cells *per* estimated liter recipient blood volume (CD34-postive/BV) [24].

Our focus was on granulocyte recovery since the analyses of RBCs and platelet recovery are confounded by pre- and posttransplant transfusions and because granulocytes are the most short-lived cells. Analyses of survival and other transplant endpoints are tangential to our primary concern because of confounders such as infections and graft-versus-host disease [26]. We used a Bayesian Cox regression model with restricted cubic splines. We found the hazard function for granulocyte recovery was erratic when CD34-positive

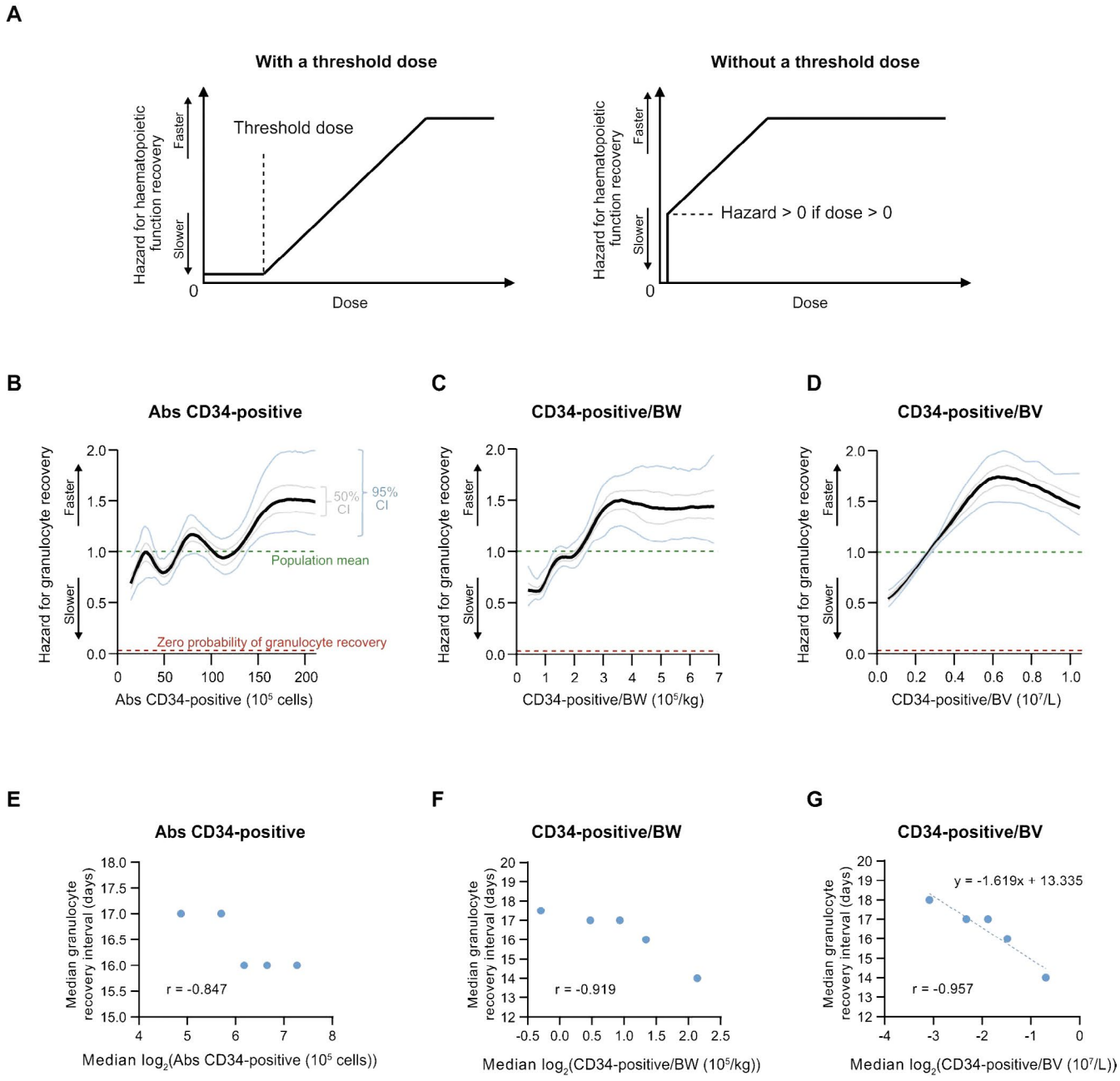

Figure 1. Theoretical scenarios for hazard functions and estimated dose response curves of CD34-positive cells after UBC transplant

A – Hazard functions for haematopoietic function recovery under two contrasting scenarios: with or without a threshold dose.

B, C, D – Hazard functions of Abs CD34-positive (B), CD34-positive/BW (C) and CD34-positive/BV (D) for granulocyte recovery in the Anhui umbilical cord blood cell transplant data [41]. Hazard is calculated with respect to the population mean. "Hazard = 0.5" means that the instantaneous recovery rate (from day 1 posttransplant to infinity) is half-magnitude compared to the population mean. "Hazard = 0" means zero probability of granulocyte recovery.

E, F, G – Relationship between CD34-positive cell dose and interval to granulocyte recovery interval: Abs CD34-positive (E), CD34-positive/BW (F) and CD34-positive/BV (G) in the Anhui umbilical cord blood cell transplant data [41]. All the patients are divided into 5 quintiles according to the panel's respective measure of CD34-positive cell dose. Each dot summarizes one quintile, with its x and y coordinates representing the median CD34-positive cell dose and the median interval to granulocyte recovery, respectively, of the quintile.

cell dose was quantified as Abs CD34-postive (Fig. 1B). In contrast, the hazard function of CD34-positive cell dose *per* kilogram body weight reached a plateau at ≈1.5 once CD34-postive/BW was >3×10E+5/kg and there was no threshold value below which the hazard function abruptly dropped to zero (Fig. 1C). The hazard function of CD34-positive cell dose *per* L of blood volume reached plateau values at >1.5 when CD34-positive/BV was >0.5×10E+7/L and the hazard remained ≈0.5 even when CD34-positive/BV dropped to 0.05×10E+7/L, the 2.5th-percentile value in the study cohort (Fig. 1D).

Next, we divided the subjects into 5 quintiles according to CD34-posive cell dose, and, for each quintile, median log2 of CD34-positive cell dose has been calculated *versus* time interval to granulocyte recovery. Quintile median log2(-dose) and quintile median recovery interval correlated better when dose was quantified *per* blood volume (r = –0.98 (CD34-positive/BV) *versus* –0.65 (Abs CD34-positive) and –0.92 (CD34-postive/BW); Fig. 1E, F, G). Analysis of the linear regression coefficients of quintile median recovery interval *versus* quintile log2(CD34-positive/BV) suggests that the CD34-positive cell population in the blood doubled every 1.6 days (Fig. 1G).

Discussion

We reviewed biological considerations and experimental data indicating cells responsible for posttransplant bone marrow recovery in humans cannot be accurately quantified. We also argue why numbers or dose of CD34-positive cells in a graft cannot be an accurate estimate of cells responsible for posttransplant bone marrow recovery. Nevertheless, given that many studies claiming a correlation between numbers of CD34-positive cells and posttransplant recovery of bone marrow function, we used new statistical methods to interrogate a large dataset of umbilical cord blood cell transplants to prove the non-linear CD34-positive cell dose effect and see if there is a threshold dose needed for posttransplant recovery of bone marrow function. More specifically, we used roughness penalty minimization and Markov chain Monte Carlo to estimate the CIs of smooth curves [42, 43]. We also found the best correlate with posttransplant granulocyte recovery was numbers of CD34-positive cells *per* blood volume, not *per* body weight.

We also found no *threshold dose* of CD34-positive cells for successful posttransplant granulocyte recovery. This observation has important clinical implications which may make more people eligible to receive haematopoietic cell transplant, especially an umbilical cord blood cell transplant, and may obviate the perceived need for repeated leukaphereses.

Our conclusions have limitations. 1st, our conclusions may not apply to other graft types. 2nd, our analyses of the clinical dataset were retrospective and possibly biased. 3rd, although we tested a range of CD34-positive cell doses none was <0.02×10E+7/L or <0.17×10E+5/kg.

In our Point-of-View we challenge current thinking and practices regarding whether CD34-positive cell dose in a graft should be used as a proxy for predicting short- and long-term posttransplant bone marrow recovery and, if there is no alternative, how CD34-positive cell dose should be quantified. Conclusions need further validation since they are potentially practice-changing.

Data Availability

Available upon reasonable request from Prof. Chen.

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Conflict of Interest

RPG is a consultant to Antengene Biotech LLC, Ascentage Pharma Group and NexImmune Inc.; Medical Director, FFF Enterprises Inc.; Board of Directors: Russian Foundation for Cancer Research Support; and Scientific Advisory Boards, Nanexa AB and StemRad Ltd.

Ethics

The study was approved by the Academic Committee (IIT2021042) of the Institute of Hematology, Chinese Academy of Medical Sciences (IHCAMS) and the Ethics Review Committees of IHCAMS and FAHUSTC (QT-JC2022026-EC-1 and 2022-RE-070). Subjects gave written informed consent consistent with the precepts of the Helsinki Declaration.

Author Contributions

The authors conceived the study, reviewed the typescript, take responsibility for the content and agreed to submit for publication.

Note

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Поиск пороговой дозы CD34-позитивных клеток, необходимой для восстановления гемопоэза после трансплантации

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Резюме

На основании различных данных мы демонстрируем, что CD34-позитивные клетки не являются точным предиктором количества гемопоэтических стволовых клеток у человека. На примере трансплантации клеток пуповинной крови при лейкозах мы также показываем, что, по-видимому, не существует пороговых значений для CD34-позитивных клеток необходимых для восстановления функций костного мозга после высокодозной претрансплантационной терапии. Наконец мы демонстрируем, что при использовании CD34-позитивных клеток в качестве суррогатного маркера гемопоэтических стволовых клеток человека, их доза должна выражаться количеством клеток на объем крови, а не на массу тела. Эти выводы, в случае их валидации, могут иметь важные клинические последствия.

Ключевые слова

CD34-позитивные клетки, пороговая доза, трансплантация, доза трансплантата.