Algorithms to predict CD34+ cell collection with the new generation of cell separator machines

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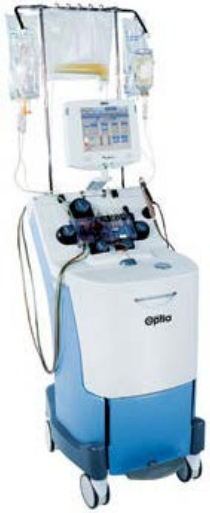


Predicting CD34+ cell dose from peripheral CD34+ cell count during PBSC collection

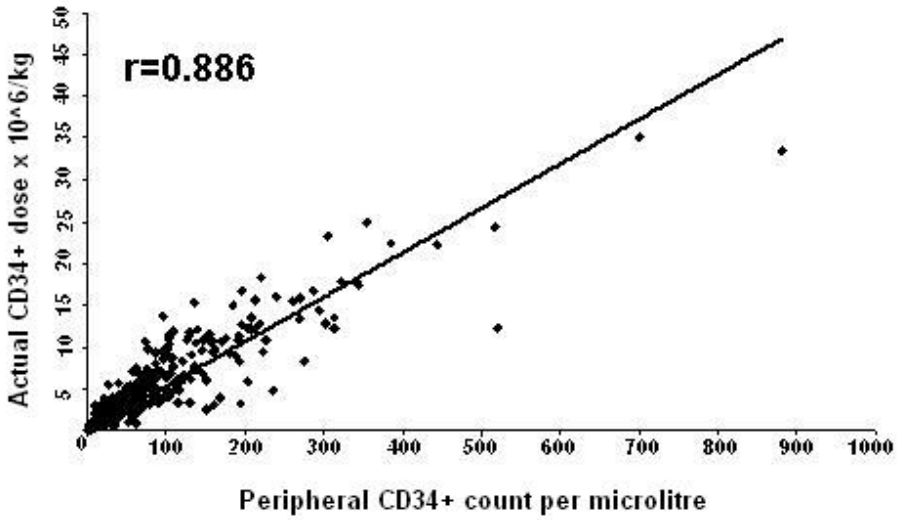
- Most centres in Europe have introduced routine peripheral CD34+ count monitoring over the past 20 years, to assist timing of autologous PBSC collection, and as a predictor of likely mobilisation success (or a warning of likely mobilisation failure) in allogeneic PBSC collection
- Guiding initiation of apheresis on the basis of a "trigger" peripheral CD34+ count, rather than just total WCC, has been reported to result in significant cost savings[1], particularly after chemotherapy-based mobilisation
- This approach also prevents patients from undergoing "worthless" autologous PBSC collections yielding very poor CD34+ doses
- However, peripheral CD34+ counts have other uses apart from just being apheresis "triggers" – in particular, they can be used to predict likely CD34+ yield in the apheresis product

1. Meehan KR, Hill JM, Patchett L, Webber SM, Wu J, Ely P, Szczepiorkowski ZM. (2006) Implementation of peripheral blood CD34 analyses to initiate leukapheresis: marked reduction in resource utilization. *Transfusion* **46**:523–529.

Prediction of CD34+ yield based on peripheral CD34+ count: “Collect ratio” method

- Numerous studies have shown a strong linear correlation between peripheral blood CD34+ count immediately pre-apheresis and CD34+ cell yield in the product
- The correlation is good enough to be used for dose prediction, simply by plotting peripheral CD34+ counts against CD34+ yield (dose) in the product for a number of individual collection procedures and deriving a trendline by linear regression
- The gradient of the trendline may then be used to predict likely CD34+ yield at the beginning of a collection, based on pre-apheresis CD34+ count
- Predicted CD34+ yield = (peripheral CD34+ count x gradient of trendline)
- If peripheral CD34+ count units are per microlitre, and CD34+ yield units are x 10^6/kg, then gradient will be around 0.07 to 0.1 for most cell separator platforms
- Has sometimes been called “rule of tens” i.e. predicted CD34+ yield x 10^6/kg is *about* tenfold less than periph CD34+ count

Example of a correlation graph using “Collect Ratio” method (CAU Glasgow data)



Correlation between peripheral CD34+ count and CD34+ cell yield in apheresis product, from 440 consecutive PBSC collections performed on Cobe Spectra at Clinical Apheresis Unit, Glasgow. From: Douglas K, “Experience with apheresis procedures after plerixafor mobilisation”, in: Fruehauf , Zeller & Calandra (Eds.), “Novel developments in stem cell mobilization: focus on CXCR4”, Springer, 2011

Limitations of the “Collect Ratio” method

- Although simple, the “Collect Ratio” method has one obvious limitation: it does not take account of the volume of the patient’s blood actually processed by the cell separator machine
- It will predict the same cell dose for a 5-hour procedure as for a 3-hour procedure (at the same blood flow rate and the same pre-apheresis peripheral CD34+ count)
- As anyone working in apheresis knows, this is not usually the case

Does extending the run time of an apheresis procedure yield proportionately more CD34+ cells?

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- This has been a surprisingly controversial issue
- The answer hinges on whether a mobilised patient recruits significant numbers of fresh CD34+ cells into their bloodstream in the course of the procedure
- If the answer is “no”, then extending run time will lead to rapidly diminishing returns, as the machine will have “caught” all the available cells
- (Like running round a room with a set number of butterflies, gradually catching them all with a net)
- However, if the answer is “yes”, then extending run time should yield proportionately more cells
- Imagine this as butterflies continuously trafficking in and out of the “room” of the bloodstream through an open window
- On the other side of the window is the “room” of the bone marrow, which is absolutely crammed with butterflies
- However many are “caught” from the bloodstream, there are always going to be plenty more to catch!

CD34+ cell Collection Efficiency – How to calculate it

- Collection Efficiency (CE for short) of any individual PBSC collection procedure = “Cells Collected” / “Cells Processed”
- This may be calculated using a formula along the lines of: “Actual Absolute CD34+ cell dose obtained” / (“Volume of blood actually processed” x “CD34+ cell concentration in the patient’s blood on the day of collection”)

A TECHNICAL NOTE FOR THOSE WHO ARE INTERESTED: More specifically, this simple method of calculating Collection Efficiency has been called ‘CE2 collection efficiency’, as opposed to ‘CE1 collection efficiency’, commonly used for machine validation, which uses an average of pre- and post-run peripheral blood CD34+ counts

Why CE is useful for CD34+ yield prediction

A very simple rearrangement of the formula used to calculate Collection Efficiency allows calculation of predicted CD34+ cell dose from a 'benchmark' CE, rather than calculation of individual procedure Collection Efficiency from an actual CD34+ cell yield

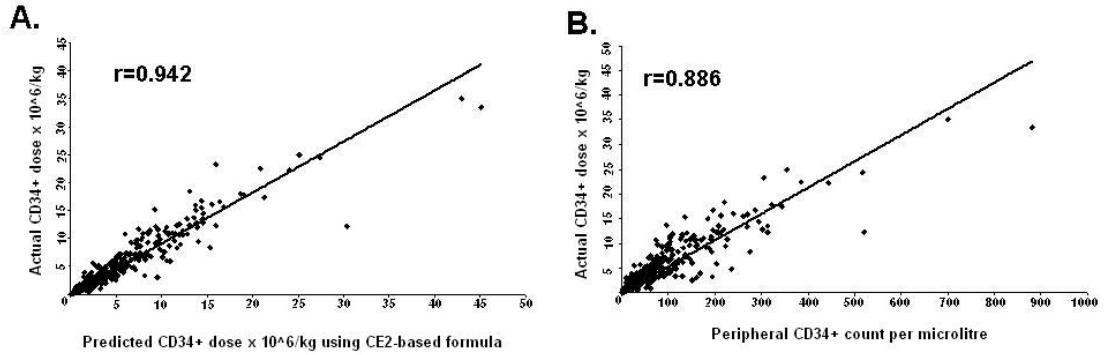
- CE = "Actual Absolute CD34+ cell yield obtained" / ("Volume of blood actually processed" x "CD34+ cell concentration in the patient's blood")
- This rearranges to:
- PREDICTED Absolute CD34+ yield = "Benchmark" CE* x "Volume of blood planned to be processed" x "CD34+ cell concentration in the patient's blood"
- To get CD34+ yield in more familiar units, both sides of this equation can be divided by the patient's weight in kg
- This gives the following:
- Predicted CD34+ yield x 10^6/kg = (Benchmark CE x Volume of blood to be processed x peripheral CD34+ count per µl) / Patient's weight in kg x metric conversion factor

* "Benchmark" CE2 Collection Efficiency is easily determined as the median CE of a large number of individual PBSC collection procedures performed on the same cell separator platform, ideally at the same centre

Does it work?

- CE-based dose prediction is therefore a relatively simple concept
- However, it makes one crucial assumption, which is that the CD34+ cell concentration in the patient's bloodstream remains relatively constant at the starting level (i.e. the immediate pre-apheresis CD34+ cell count per µl) throughout the procedure
- In other words it assumes significant recruitment of CD34+ cells from bone marrow to bloodstream during apheresis
- …. So, does it work?

Yes.

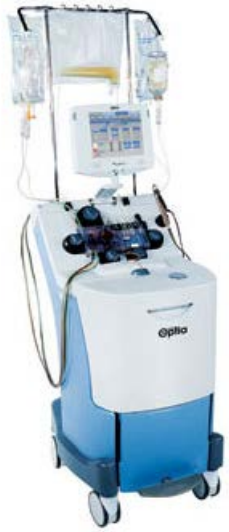


- Several studies have now demonstrated CE-based prediction of CD34+ yield to be superior to the simpler "Collect Ratio" method on several different cell separator platforms, including Cobe Spectra[1,2,3], Fresenius Com.Tec[1,3] and Spectra Optia[4]

- This implies that there must indeed be significant ongoing recruitment of fresh CD34+ cells from bone marrow to bloodstream in the course of PBSC collection

1. Pierelli L, Maresca M, Piccirillo N et al. (2006) Accurate prediction of autologous stem cell apheresis yields using a double variable-dependent method assures systematic efficiency control of continuous flow procedures. Vox Sanguinis 2006; 91:126–134 2. Douglas K. (2012) Experience with apheresis procedures after plerixafor mobilisation. How much blood to process? Dose prediction on the basis of peripheral CD341 counts. In: Fruehauf S, Zeller WJ, Calandra G, editors. Novel Developments in Stem Cell Mobilization. Focus on CXCR4. New York: Springer. 2012. p137-138 3. Hosing C, Saliba RM, Hamerschlak N, Kutner JM et al. (2014) Peripheral blood stem cell yield calculated using preapheresis absolute CD34+ cell count, peripheral blood volume processed and donor bodyweight accurately predicts actual yield at multiple centres. Transfusion. 2014 Apr;54(4):1081-7 4. Cousins AF, Sinclair JE, Alcorn MJ, Green RHA & Douglas KW. (2015) HPC-A Dose Prediction on the Optia Cell Separator based on a benchmark CE2 collection efficiency: promoting clinical efficiency, minimizing toxicity, and allowing quality control. J Clin Aph 30(6):321-328

Spectra Optia: Some background



Spectra Optia cell separator platform for plasma exchange, red cell exchange, leucodepletion and HPC-A collection

•The COBE Spectra cell separator, initially developed in the 1980s, remained the world market leader for therapeutic apheresis platforms throughout the 1990s and early 2000s

•Terumo BCT (formerly Caridian, formerly Gambro) were keen to introduce recent technological improvements into the Spectra platform

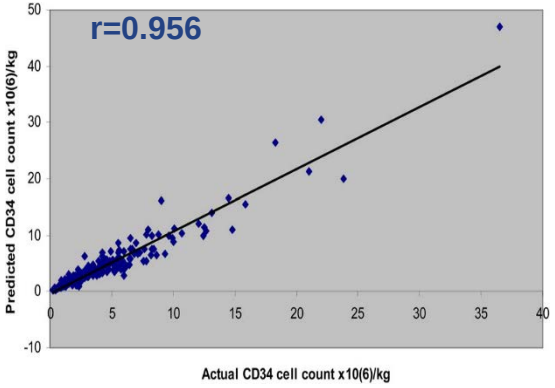
•The new cell separator platform, “Spectra Optia”, was developed by Caridian as a long-term replacement for Cobe Spectra. It has a number of potential advantages over the older Spectra, including:

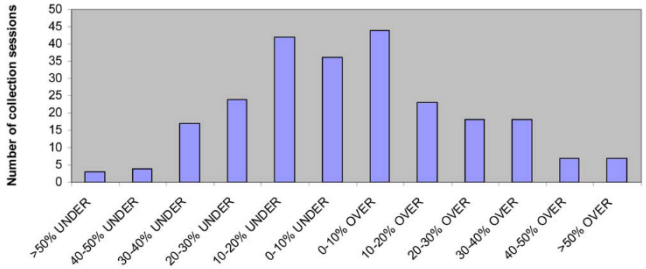
- Smaller, lighter machine
- Automated interface monitoring
- Graphical, touch-screen user interface

•It is based on partly on the old Spectra, but also partly on the existing Trima system for donor platelet apheresis, which is also a well-established and widely used system worldwide

•Spectra Optia obtained CE Marking (European regulatory approval) for PBSC collection in January 2008

CE-based prediction of CD34+ yield works well for PBSC collection procedures on Optia





- In a study of 417 consecutive PBSC collection procedures on Optia in Glasgow, Collection Efficiency-based prediction of CD34+ yield significantly out-performed the simpler “Collect Ratio” method: see Cousins AF et al. (2015) J Clin Aph 30(6):321-328
- Our apheresis nursing team now use a CE-based formula for prediction of CD34+ yield for Optia PBSC collections on a day-to-day basis

The actual Optia formula

Predicted CD34+ yield (x 10^6/kg) =

$$\frac{\text{5.5 x periph CD34+ count (per µl) x predicted Whole Blood Processed (mls)}}{\text{Patient weight (kg) x 10 000}}$$

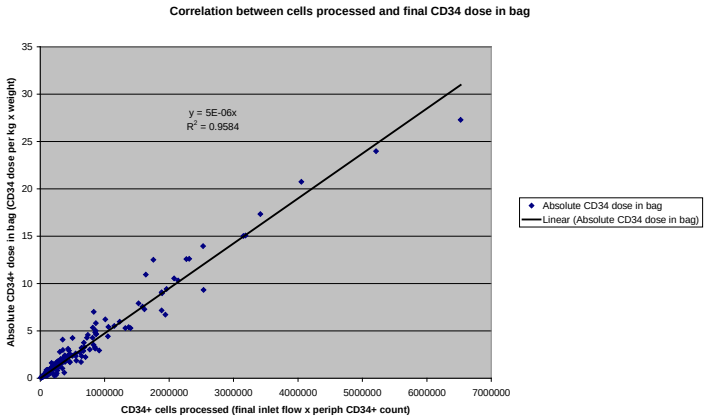
- See Cousins AF et al. (2015) J Clin Aph 30(6):321-328 for full discussion
- 5.5 comes from our benchmark CE figure of 55% for Optia PBSC procedures
- Predicted Whole Blood Processed is available at the start of an apheresis procedure from Optia's "predicted end-run results" screen
- The 10 000 is a metric conversion factor

Use of CE-based prediction of CD34+ yield to tailor the procedure to the patient

- Mrs H. has myeloma. She weighs 74 kg and has estimated Total Blood Volume of 3880 mls
- Following mobilisation, her peripheral CD34+ count on Apheresis Day 1 is 74 per µl
- Target CD34+ yield is 6 x 10^6/kg (to allow potential delayed 2nd transplant)
- Most cell separator platforms default to process 2 blood volumes, but this can easily be changed by the operator
- A “default” procedure processing 2 blood volumes (7760 mls) is predicted to yield a CD34+ dose of 4.27 x 10^6/kg, necessitating a 2nd apheresis day
- The apheresis nurse calculates that by processing 3.3 blood volumes (12800 mls), the predicted CD34+ yield will be 7.04 x 10^6/kg
- **This should allow the target yield to be achieved in a single apheresis, with a comfortable safety margin**

Other uses of routine CE calculation:

Quality Assurance for HPC-A collection

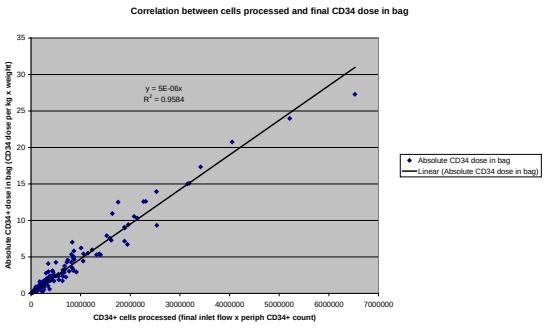


Routine calculation of CE for individual collection procedures has a number of other potential uses:

- Ongoing process qualification of PBSC collection: does CE remain constant over time at our centre?
- Performance comparison between different cell separator machines – do our seven Optia machines have similar median CEs?
- Validation of new machines: does the new machine demonstrate a similar median CE as the unit's established benchmark?

Other uses of routine CE calculation:

Quality Assurance for HPC-A collection



- Another potential use of a “benchmark” CE is that it can become part of the Product Specification for a HPC-A collection
- In other words, it is possible to set a minimum acceptable limit for CE in an individual collection procedure
- Individual procedures falling below this predetermined limit (e.g. CE ≤ 25%) can be logged and investigated for Quality Assurance purposes
- We have been doing this routinely in Glasgow over the past decade for PBSC procedures initially on Cobe Spectra, and now for Optia procedures too

Thank you


Optia