A model for erythropoiesis in transplanted patients with stable chimerism

We propose to model erythropoiesis with a simple two-compartment model:

a) The first compartment contains early progenitor cells that have not differentiated to the erythroid lineage.

b) The second compartment contains the late progenitors in the erythroid lineage along with mature erythroid cells.

A successful transplant results in chimerism, with both recipient and donor cells persisting in stable equilibrium. We shall model this state of affairs by assuming that there are two copies of each of these compartments: one copy for the recipient and another copy for the donor's cells. Altogether there are then four compartments, with P_H and P_D representing the populations of recipient and donor cells in the early progenitor compartments; and M_H and M_D representing the populations of recipient and donor cells in the late progenitor/mature erythroid compartments.

Recipient and donor cells differ principally in the fact that the recipient's cells are homozygous in an abnormal hemoglobin beta gene, while the donor's cells are (generally) heterozygous in this gene. It is reasonable to assume that the kinetics of recipient and donor cells is identical in any cell not expressing the hemoglobin beta gene. Therefore, both early progenitor recipient and donor cells share the same rate of self-renewal, λ, and rate of differentiation. In the simplest model both self-renewal and differentiation are first order processes, therefore dynamics in the early progenitor compartments will be described by following first order differential equations:

$$\begin{aligned} \frac{dP_R}{dt} &= \lambda P_R - \delta P_R \\ \frac{dP_D}{dt} &= \lambda P_D - \delta P_D \end{aligned} \qquad \text{[S-1]}$$

In steady state the stem cell number is stable, i.e. $\delta = \lambda$.

In contrast to the early progenitors, the late erythroid progenitors and mature erythroid cells express the hemoglobin beta gene and therefore we would expect the dynamics of recipient and donor cells to differ. Early progenitor cells differentiate to the late progenitor compartments stem cells at the rate δ, which is identical for both recipient and donor cells as neither express the hemoglobin beta gene. The consumption of recipient and donor erythrocytes occurs at different rates, α_R and α_D.

$$\begin{aligned} \frac{dM_R}{dt} &= \delta P_R - \alpha_R M_R \\ \frac{dM_D}{dt} &= \delta P_D - \alpha_D M_D \end{aligned} \qquad \text{[S-2]}$$

We note that our model implicitly models both ineffective erythropoiesis in the late progenitor cells as well as shortened erythrocyte life times. The kinetic factors α encapsulate depletion of late progenitor cells through ineffective erythropoiesis as well as the reduced erythrocyte lifetime through hemolysis.

In steady state

$$M_R = \frac{\delta P_R}{\alpha_R}$$
$$M_D = \frac{\delta P_D}{\alpha_D} \qquad \text{[S-3]}$$

The fraction of donor erythrocytes, $f_M = M_D / \left(M_D + M_R\right)$ is therefore related to the fraction of donor progenitor cells as follows:

$$f_M = \frac{\alpha P_D}{\alpha_R P_D + \alpha_D P_D} = \frac{\alpha_R f_P}{\alpha_R + \alpha_D \left(1 - f_P\right)} \qquad \text{[S-4]}$$

where $f_P = P_D / \left(P_D + P_R\right)$ is the fraction of early progenitors.

It is readily shown that the average erythrocyte survival times, t_{mean}, are inversely related to α, i.e.

$$t_{mean} = \frac{1}{\alpha} \qquad \text{[S-5]}$$

Parenthetically we note that, to the extent that ineffective erythropoiesis does play a role, it does act to further reduce the effective lifetime of cells in late progenitor / mature erythrocyte compartment. Substituting the relation between α and t_{mean}, we find

$$f_M = \frac{f_P t^D_{mean}}{f_P t^D_{mean} + \left(1 - f_P\right) t^R_{mean}} \qquad \text{[S-6]}$$

Finally, we note that donor erythrocytes generally contain a fraction F^D_{HbA} of HbA in their hemoglobin with the remainder $\left(1 - F^D_{HbA}\right)$ as HbS. Then altogether the fraction of HbS in the chimeric recipient is given by

$$F_{HbS} = \left(1 - F^D_{HbA}\right) f_M + (1 - f_M) = 1 - F^D_{HbA} f_M \qquad \text{[S-7]}$$

or substituting equation S-6 into S-7, we find

$$F_{HbS} = 1 - F_{HbS}^{D} \frac{f_P t_{mean}^{D}}{f_P t_{mean}^{D} + (1 - f_P) t_{mean}^{R}} \qquad \text{[S-8]}$$

Estimating average HbSS erythrocyte lifetime and sickle cell trait HbA fraction via non-linear regression

We compiled post-transplant laboratory data available for 67 patients at 100 days, 6 months, 12 months, 18 months, 24 months, 30 months, 36 months, 48 months and 60 months after transplant. At day 100 cell line counts in most patients were still undergoing rapid changes and many patients required intermittent transfusions by Day 100. Therefore we presumed that hematopoiesis had not yet achieved steady state by day 100 and censored those data from our fits. Patients #4, #14, #36, #48, #49, #54, #65 and #66 were excluded from the data due to the fact that they received transfusions for primary graft failure. Patients #26 and #51 died before achieving steady state in hematopoiesis. Patients #13, #17, #20 and #27 took longer to engraft and continued to require transfusions: therefore data from patient #13 were censored to the 2 year point; data from patient #17 were censored to the 1 year point; data from patient #20 were censored out to 6 months; and data from patient #27 were censored out to 6 months. Myeloid chimerism and HbS fraction data from the remaining patients were fit via non-linear regression analysis to formula S-8 on a patient by patient basis using the R package nlstools[1]. We computed an erythrocyte lifetime of 6.22 days (95% confidence interval 1.22 to 29.21 days).

Supplemental References

1. Florent Baty, Christian Ritz, Sandrine Charles, Martin Brutsche, Jean-Pierre Flandrois, Marie-Laure Delignette-Muller (2015). A Toolbox for Nonlinear Regression in R: The Package nlstools. *Journal of Statistical Software*, **66**(5), 1-21

Table S1: Baseline Characteristics

Patient ID	Age at HSCT	Gender	Donor Type	Donor HbS	CD34 dose (x 10^6/kg)	CD3 dose (x10^8/kg)	Baseline Complications
1	27	Male	HLA-matched	40%	7.56	2.27	Recurrent painful crises
2	31	Female	Haplo	36%	13.0	8.07	Moyamoya syndrome
3	24	Male	Haplo	39%	13.4	2.59	End stage renal disease Cardiomyopathy Recurrent painful crises