Bone Marrow Transplantation (2003) 31, 861–864

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CD34+ Numbers

Ideal or actual body weight to calculate CD34+ cell doses for autologous hematopoietic stem cell transplantation?

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Summary:

The number of CD34+ cells infused influences the speed of hematologic recovery post-transplant. There are limited data on whether ideal (IBW) or actual (ABW) body weight should be used to calculate CD34+ cell dose. We compared the correlation between recovery to 0.5×10^9/l neutrophils and the CD34+ cell dose based upon ABW as well as IBW in 87 patients autografted for cancer. ABW was $\geqslant$25% over IBW in 43% of patients. The median number of CD34+ cells administered was 3.6×10^6/kg ABW and 4.2×10^6/kg IBW. The time to neutrophil recovery was 8–15 days (median 10). There was a stronger inverse correlation between CD34+ cell dose/IBW and neutrophil recovery ($r^2 = 0.308$; $P < 0.0001$) than between CD34+ cell dose/ABW and neutrophil recovery ($r^2 = 0.267$; $P < 0.0001$). The median time to neutrophil recovery was comparable for those receiving $\geqslant 2 \times 10^6$/kg CD34+ cells/kg IBW as well as ABW (10 days) and those receiving $\geqslant 2 \times 10^6$/kg CD34+ cells/kg IBW but <2/kg ABW (10 days), but was significantly slower for those receiving $<2 \times 10^6$/kg CD34+ cells/kg IBW (12 days). These data show that the CD34+ cell dose based on IBW is a better predictor of neutrophil recovery after autotransplantation.
Bone Marrow Transplantation (2003) **31,** 861–864. doi:10.1038/sj.bmt.1703955
Keywords: autotransplantation; CD34+ cells; engraftment; myeloid recovery; weight

Historically, the progenitor cell content of the graft in patients undergoing autotransplantation has been measured in terms of the number of nucleated cells.[1] The preferred way of measuring this now is in terms of the number of CD34+ cells.[2–5] The progenitor cell dose, expressed as the number of cells per unit recipient body weight, is an important determinant of the speed of hematologic recovery.[1–5] However, it is not known whether ideal (IBW) or actual (ABW) body weight should be used for this calculation.

One study has suggested that the progenitor cell dose expressed by IBW is a better predictor of myeloid recovery after autotransplantation than ABW.[6] Other studies either make no mention of the parameter used or use ABW.[1–5] In reports of our previous work from the Royal Marsden Hospital, UK, we have always used ABW to determine cell dose for autograft and allograft recipients.[1,7–9] At Northwestern Hematopoietic Stem Cell Transplant Program, Chicago, IBW has been used to express progenitor cell collections.

This retrospective study was undertaken to determine the correlation between engraftment and CD34+ cell dose expressed on the basis of ABW as well as IBW in the same population of patients.

Patients and methods

In all, 87 adult patients with malignant diseases autografted in the Hematopoietic Stem Cell Transplant Program of the Division of Hematology/Oncology of the Northwestern University Feinberg School of Medicine and the Northwestern Memorial Hospital between February 1998 and March 2001, who had adequate ABW and IBW data available, were studied.

Stem cells were collected using the Fenwal CS 3000 Plus cell separator (Baxter, Deerfield, IL, USA) or the Cobe Spectra cell separator (Gambro BCT, Lakewood, CO, USA).[10,11] The target cell dose for collection and transplantation was 2×10^6 CD34+ cells/kg IBW. CD34+ cells were enumerated using standard techniques[12] on the peripheral blood prior to leukapheresis and on the apheresis product prior to processing and cryopreservation.

IBW (kg) was calculated by a standard formula using gender and height: 50 + {2.3 × (height in inches −60)} for males and 45.5 + {2.3 × (height in inches −60)} for females.[13]

The stem cell mobilization regimens were varied, and included filgrastim alone, combination of chemotherapy and filgrastim, or chemotherapy with filgrastim-GM-CSF. The conditioning regimens employed were standard, and included high-dose melphalan (plasma cell dyscrasias),

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Received 28 August 2002; accepted 21 November 2002

Table 1 Patient characteristics

n	87
Age (years)	49 (17–67)
Male	37 (43%)
Diagnosis	
Lymphoma	48
Breast cancer	18
Plasma cell dyscrasia	12
Acute myeloid leukemia	6
Other	3
ABW (kg)	81 (42–122)
IBW (kg)	64 (42–104)
ABW−IBW difference (%)	+19 (−21 to +89)
ABW ⩾25% over IBW	37 (43%)
CD34+ cell dose (10^6/kg)	
Based on IBW	4.2 (0.6–33.9)
Based on ABW	3.6 (0.7–30.0)
IBW−ABW CD34+ cell dose difference (10^6/kg)	+0.7 (−2.0 to +8.0)
Days to 0.5×10^9/l neutrophils	10 (8–15)

Figures represent medians and ranges

busulfan–etoposide (acute myeloid leukemia), busulfan–cyclophosphamide (lymphoma), carmustine–etoposide–cytarabine–melphalan (BEAM) (lymphoma, Hodgkin's disease), cyclophosphamide–carboplatin–etoposide with total–lymphoid irradiation (Hodgkin's disease), or cyclophosphamide–carboplatin–thiotepa (breast cancer). All patients received G-CSF post-transplant at the dose of 5–10 μg/kg subcutaneously daily from day +1 until the absolute neutrophil count (ANC) exceeded 0.5×10^9/l on 3 consecutive days. The first day with ANC of $\geqslant 0.5\times10^9$/l was considered the day of engraftment. Table 1 shows the patient characteristics.

Statistical methods

While the original stem cell dose was based upon IBW, cell doses were calculated based on ABW for each patient for the purpose of this analysis.

The inverse curve fit technique was used to determine the correlation between the CD34+ cell doses (by IBW and ABW separately) and days to ANC recovery. Time to ANC recovery was compared for various CD34+ cell dose cutoff values (<2 *vs* $\geqslant 2$, <3 *vs* $\geqslant 3$, <4 *vs* $\geqslant 4$, and <5 *vs* $\geqslant 5$) separately for ABW and IBW. The Wilcoxon's rank-sum test was used to compare time to engraftment. Finally, patients were divided into three groups for engraftment comparison: (1) CD34+ cell dose $<2\times10^6$/kg IBW, (2) CD34+ cell dose $<2\times10^6$/kg ABW but $\geqslant 2\times10^6$/kg IBW, and (3) CD34+ cell dose $\geqslant 2\times10^6$/kg IBW as well as $\geqslant 2\times10^6$/kg ABW. The aim was to determine if the time to neutrophil recovery for Group 2 was similar to Group 1 or Group 3.

Results

ABW was less than IBW in 13 patients; in six by $\leqslant 10\%$ and in seven by $>10\%$. ABW and IBW were identical in one. In the remaining 73 patients, ABW was greater than IBW. Most patients ($n=82$; 94%) met the target CD34+ cell dose of 2×10^6/kg IBW. A lower proportion of patients ($n=73$; 84%) met the target CD34+ cell dose if the calculation was based upon ABW ($P=0.05$; Fisher's exact test). Neutrophil recovery occurred in all patients at a median of 10 days (range, 8–15 days).

Figures 1 and 2 show that the correlation between the CD34+ cell dose and time to ANC recovery was statistically significant. This correlation was stronger for IBW (higher r^2 value; Figure 1) than for ABW (Figure 2).

As Table 2 shows, for all cutoff level comparisons, the lower CD34+ cell dose was associated with slower engraftment. This difference was significant for all four cutoff level comparisons based on IBW, and was significant for two cutoff levels based on ABW, and was not significant for the other two. For each cutoff level comparison, the difference was more significant when based upon IBW (ie a lower P value) than ABW. Figure 3 shows time to 0.5×10^9/l ANC recovery in the three groups defined above. It is clear that Group 2 behaves like Group 3 rather than like Group 1. The time to engraftment for Groups 1 and 2 ($P=0.02$) and Groups 1 and 3 ($P<0.0001$) is significantly different, whereas it is comparable for Groups 2 and 3 ($P=0.12$). Table 3 shows the days to neutrophil recovery in terms of medians and ranges for the three groups.

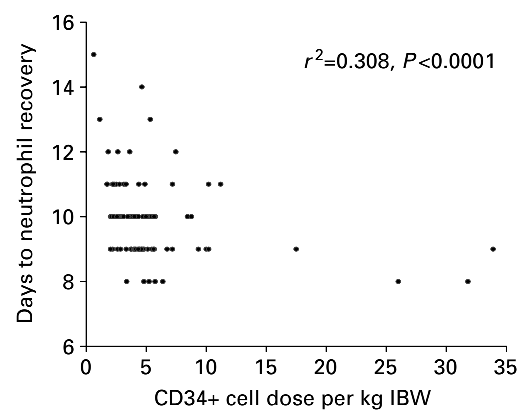

Figure 1 Correlation between CD34+ cell dose based on IBW and time to neutrophil recovery.

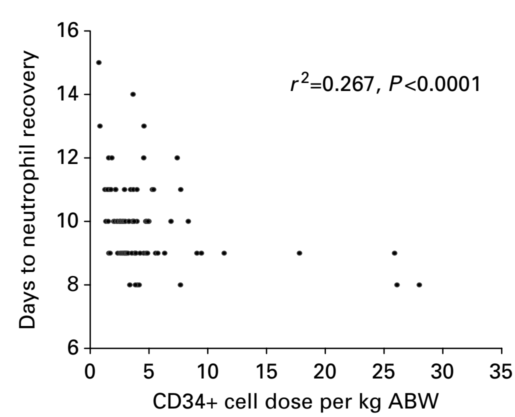

Figure 2 Correlation between CD34+ cell dose based on ABW and time to neutrophil recovery.

Table 2 Engraftment time by IBW and ABW for various CD34+ cell dose cutoff levels

CD34+ cell dose (10^6/kg)	*Basis*	*n*	*% (n=87)*	*Days to 0.5×10^9/l neutrophils*		*P*
				Median	*Range*	
<2	IBW	5	6	12	11–15	<0.0001
⩾2		82	94	10	8–14	
<2	ABW	14	16	11	9–15	0.0002
⩾2		73	84	10	8–14	
<3	IBW	21	24	11	9–15	0.001
⩾3		66	76	10	8–14	
<3	ABW	34	39	10	9–15	0.02
⩾3		53	61	9	8–14	
<4	IBW	38	44	10	8–15	0.01
⩾4		49	56	9	8–14	
<4	ABW	56	64	10	8–15	0.08
⩾4		31	36	9	8–13	
<5	IBW	59	68	10	8–15	0.04
⩾5		28	32	9	8–13	
<5	ABW	70	80	10	8–15	0.09
⩾5		17	20	9	8–12	

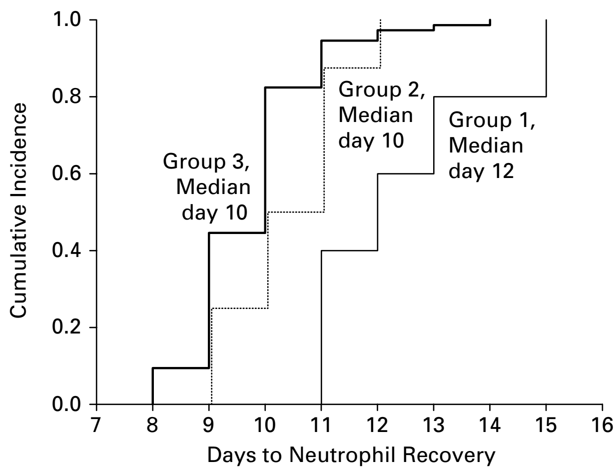

Figure 3 Days to neutrophil recovery by the number of CD34+ cells infused. The thick line shows Group 3 (⩾2×10^6/kg IBW and ⩾2×10^6/kg ABW), the dashed line shows Group 2 (<2×10^6/kg ABW but ⩾2×10^6/kg IBW), and the thin line shows Group 1 (<2×10^6/kg IBW). The differences between Groups 1 and 2 and Groups 1 and 3 are significant, whereas there is no significant difference between Groups 2 and 3 (Table 3).

Table 3 Time to engraftment for three groups based upon CD34+ cell doses

Group	*CD34+ cell dose*	*Days to engraftment*		*P*
		Median	*Range*	
1 (*n*=5)	<2/IBW	12	11–15	<0.0001 (*vs* Group 3)
2 (*n*=8)	<2/ABW, ⩾2/IBW	10	9–12	0.02 (*vs* Group 1)
3 (*n*=74)	⩾2/IBW and ABW	10	8–14	0.12 (*vs* Group 2)

Discussion

Our data show that there is a better correlation between CD34+ cell dose based upon IBW and neutrophil engraftment compared with the cell dose based upon ABW and engraftment (Figures 1 and 2), CD34+ cell dose thresholds based upon IBW provide better discrimination between more rapid and less rapid engraftment (Table 2), and patients receiving a 'low' CD34+ cell dose based on ABW (<2×10^6/kg) experience prompt neutrophil engraftment as long as the dose is adequate based on IBW (⩾2×10^6/kg) (Table 3, Figure 3).

Is this observation of any practical significance? Obviously, it is of no consequence in patients in whom an excellent quantity of stem cells is collected rapidly. However, in patients who require a number of aphereses to reach a predefined target and in whom ABW exceeds IBW by a significant margin, measuring CD34+ cells based upon IBW would help decrease the number of apheresis procedures while ensuring that enough cells were available for prompt engraftment.

Similarly, if a substantial quantity of stem cells is available for an autotransplant, a calculation based upon IBW may permit the infusion of an adequate quantity of stem cells while retaining a reasonable number of stem cells for potential future use such as another transplant procedure.

This relatively simple but clinically important issue has been addressed only once before.[6] In an informal survey, the authors found that nine of 10 transplant centers relied on ABW to calculate cell doses. They also found the nucleated and CFU-GM dose based upon IBW to be a better predictor of neutrophil recovery than ABW. The study had only 34 patients who had CD34+ cell counts available, and thus could not find a significant difference in r^2 between IBW and ABW – which we did (Figures 1 and 2). However, our findings using CD34+ cell numbers, currently the preferred way of estimating progenitor cells, support their findings with nucleated cells and CFU-GM.

Based on these observations, we suggest that IBW should be adopted as the standard for measurement in clinical practice as well as reporting data.

Acknowledgements

This work was supported in part by the Auxiliary Board of the Northwestern Memorial Hospital.

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