From www.bloodjournal.org by guest on September 16, 2016. For personal use only.

(i) other risk factors for inhibitors, such as intensity of treatment,[4] may have confounded the study by Goudemand et al[1]; (ii) some plasma-derived products indeed confer a lower risk of inhibitors. Yet, it seems unlikely that von Willebrand factor is a major player in this.

Johanna G. van der Bom, Samantha C. Gouw, and H. Marijke van den Berg

Correspondence: Johanna G. van der Bom, Department of Clinical Epidemiology, Leiden University Medical Center and van Creveldkliniek/Department of Hematology, University Medical Center Utrecht, The Netherlands; e-mail: j.g.vanderbom@lumc.nl.

References

1. Goudemand J, Rothschild C, Demiguel V, et al. Influence of the type of factor VIII concentrate on the incidence of factor VIII inhibitors in previously untreated patients with severe hemophilia A. Blood. 2006;107:46-51.
2. Chalmers EA, Brown SA, Keeling D, et al. Early factor VIII exposure and subsequent inhibitor development in children with severe haemophilia A. Haemophilia. 2007;13:149-155.
3. Gouw SC, van der Bom JG, Auerswald G, Escuriola EC, Tedgard U, van den Berg HM. Recombinant versus plasma-derived factor VIII products and the development of inhibitors in previously untreated patients with severe hemophilia A: the CANAL cohort study. Blood. 2007;109:4693-4697.
4. Gouw SC, van der Bom JG, van den Berg HM. Treatment-related risk factors of inhibitor development in previously untreated patients with hemophilia A: the CANAL cohort study. Blood. 2007;109:4648-4654.

To the editor:

Lenalidomide therapy in a patient with POEMS syndrome

The immune modulatory drugs (IMiDs) are powerful drugs against malignant plasma cells.[1,2] They also reduce the production of proinflammatory and proangiogenic cytokines. The POEMS (polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, skin changes) syndrome is a paraneoplastic syndrome that is driven by such cytokines,[3] most notably vascular endothelial growth factor (VEGF).[4] There are anecdotal reports of benefit of thalidomide for patients with POEMS.[5] Enthusiasm for its use in a condition in which the dominant complaint is sensorimotor peripheral neuropathy is tempered by the high incidence of thalidomide-induced peripheral neuropathy with long-term use.[6]

A 40-year-old African-American man presented to the Mayo Clinic with a 4-year course of progressive peripheral neuropathy, weight-loss, fatigue, anasarca, hypertrichosis, hyperpigmentation, gynecomastia, and erectile dysfunction. One year into his symptoms, he was diagnosed with chronic inflammatory demyelinating neuropathy (CIDP). For this diagnosis, he was treated with corticosteroids, plasmapheresis, and finally azathioprine without significant benefit. He continued to deteriorate, and a

Table 1. Patient findings before and after lenalidomide therapy

Patient's parameters	Activities of daily living: Before lenalidomide†	Activities of daily living: After 9 cycles‡
Karnofsky score	40	70
Hypertrichosis	Present	Improved
Hyperpigmentation	Present	Improved
Edema	++++	Trace
Gynecomastia	Present	Improved
Neuropathy impairment score*	121	113
C-reactive protein, mg/dL	0.4	<0.3
Gamma globulin, g/L	31	20
IgG, g/L	31.6	17.8
Kappa, mg/L	145	42.6
Lambda, mg/L	177	82.4
K/L ratio	0.82	0.52
Monoclonal protein	IgG lambda by immunofixation	IgG lambda by immunofixation
Bone marrow plasma cells, %	5% (monoclonal lambda)	10% (polyclonal)
Cytogenetics	t(9;17)(q22;q25)	No abn by FISH or metaphase
VEGF, pg/mL	948	303
IL-6, pg/mL	140.1	6.6
Testosterone, total, ng/dL	276	424
Testosterone, bioavailable, ng/dL	17	36
Urine total protein, mg/24 h	427	158
Pulmonary function		
FVC, % predicted	75	81
FEV-1, % predicted	70	79
PImax, % predicted	47	75
PEmax, % predicted	25	49

Normal values: VEGF < 83 pg/mL; IL-6 < 5 pg/mL; total testosterone, 240–950 ng/dL; bioavailable testosterone, 61–213 ng/dL.

FISH indicates fluorescent in situ hybridization; AFO, ankle foot orthotic; FVC, forced vital capacity; FEV-1, forced expiratory volume of 1 second; PEmax, maximal exploratory pressure; PImax, maximum inspiratory pressure; and ++++, high level of edema.

*The lower the number, the better the function.

†Barely able to roll over in bed; unable to bathe, dress, or transfer himself; transportation restricted to wheelchair.

‡Capable of all ADLs except pulling on support hose; walks with AFOs and walker with ease.

From www.bloodjournal.org by guest on September 16, 2016. For personal use only.

diagnosis of POEMS was made based on the following findings: *p*eripheral neuropathy, *o*rganomegaly (lymphadenopathy and mild splenomegaly), *e*ndocrinopathy (primary gonadal insufficiency, elevated prolactin, and gynecomastia), *m*onoclonal protein (IgG lambda), *s*kin changes (hyperpigmentation, hypertrichosis), anasarca, diffuse sclerotic bone lesions, abnormal pulmonary function tests, plasma IL-6 of 140 pg/mL, and plasma VEGF 948 pg/mL. Bone marrow had 5% monoclonal lambda plasma cells. On metaphase cytogenetics, t(9;17)(q22; q25) was seen in 2 of 32 cells.

Given his poor performance status, early high-dose chemotherapy with peripheral blood stem cell transplantation was not an option.[7] He was started on lenalidomide 15 mg per day for 21 days of a 28-day cycle with once-weekly dexamethasone (40 mg). The dose of lenalidomide was gradually increased to the standard 25-mg dose. In total, he received 9 cycles of treatment over a course of 9 months.

By his third cycle of therapy, he was able to perform more ADLs and use a walker with more ease. After 4 cycles, he was depending on his walker rather than wheelchair, and by 6 months, he had only trace ankle edema. By 10 months (6 weeks after his last cycle), his functional status, VEGF and IL-6 levels, skin changes, and anasarca had improved substantially. Modest improvements were also seen in his pulmonary function tests, polyclonal hypergammaglobulinemia, and testosterone levels. The most salient findings are shown in Table 1. The treatment plan is to consolidate his response with high-dose peripheral stem cell transplantation.

Like the observation made by Badros et al using anti-VEGF antibodies to treat patients with POEMS,[8] the use of lenalidomide supports the principle that POEMS is a cytokine-mediated syndrome. The 3 cases of bevacizumab use in patients with POEMS would suggest that anti-VEGF antibodies alone are likely not sufficient[9] since anti-VEGF antibodies do little against the clonal plasma cells. The 2 responses seen with bevacizumab were in patients receiving concomitant alkylator.[8,9] Lenalidomide has the advantage of being both immune modulatory and cytotoxic to malignant plasma cells. This observation opens a new treatment option for patients with POEMS syndrome.

Angela Dispenzieri, Christopher J. Klein, and Michelle L. Mauermann

Conflict-of-interest disclosure: A.D. receives research dollars from Celgene. The other authors declare no competing financial interests.

Correspondence: Angela Dispenzieri, Associate Professor of Medicine, Mayo Clinic, 200 First St SW, Rochester, MN 55905; e-mail: dispenzieri.angela@mayo.edu

References

1. Richardson PG, Schlossman RL, Weller E, et al. Immunomodulatory drug CC-5013 overcomes drug resistance and is well tolerated in patients with relapsed multiple myeloma. Blood. 2002;100:3063-3067.
2. Rajkumar SV, Hayman SR, Lacy MQ, et al. Combination therapy with lenalidomide plus dexamethasone (Rev/Dex) for newly diagnosed myeloma. Blood. 2005;106:4050-4053.
3. Gherardi RK, Belec L, Soubrier M, et al. Overproduction of proinflammatory cytokines imbalanced by their antagonists in POEMS syndrome. Blood. 1996; 87:1458-1465.
4. Watanabe O, Maruyama I, Arimura K, et al. Overproduction of vascular endothelial growth factor/vascular permeability factor is causative in Crow-Fukase (POEMS) syndrome. Muscle Nerve. 1998;21:1390-1397.
5. Kim SY, Lee SA, Ryoo HM, Lee KH, Hyun MS, Bae SH. Thalidomide for POEMS syndrome. Ann Hematol. 2006;85:545-546.
6. Tosi P, Zamagni E, Cellini C, et al. Neurological toxicity of long-term (>1 yr) thalidomide therapy in patients with multiple myeloma. Eur J Haematol. 2005; 74:212-216.
7. Dispenzieri A, Moreno-Aspitia A, Suarez GA, et al. Peripheral blood stem cell transplantation in 16 patients with POEMS syndrome, and a review of the literature. Blood. 2004;104:3400-3407.
8. Badros A, Porter N, Zimrin A. Bevacizumab therapy for POEMS syndrome. Blood. 2005;106:1135.
9. Straume O, Bergheim J, Ernst P. Bevacizumab therapy for POEMS syndrome. Blood. 2006;107:4972–4973, author reply 4973-4974.

To the editor:

Influence of host irradiation on long-term engraftment by CD34-deficient hematopoietic stem cells

Hematopoietic stem cell (HSC) transplantation and evaluation of long-term repopulation (LTR) is the gold standard for assessing HSC function. Although myeloablative irradiation is typically used in animal models to enhance host engraftment,[1] a frequently overlooked concern is that this severely damages bone marrow (BM) architecture and may therefore mask defects in HSC trafficking.[2] To illustrate this concept, we evaluated the importance of a commonly used HSC marker, the antiadhesin CD34, in engraftment of irradiated and nonirradiated recipients.

W/W^v mice were used as recipients since a lack of the functional stem cell factor (SCF) receptor, c-kit, renders them highly receptive to donor engraftment in the absence of lethal irradiation.[3,4] A 1:1 ratio of *wt* and *cd34*$^{-/-}$ embryonic day 15 (E15) fetal liver cells (FTLs) was transplanted into lethally or sublethally irradiated W/W^v recipients, and donor engraftment was assessed, as outlined in Figure 1A. Strikingly, we found that while *cd34*$^{-/-}$ and *wt* HSCs exhibited similar abilities to reconstitute W/W^v mice pretreated with high-dose irradiation (Figure 1B), *cd34*$^{-/-}$ cells performed very poorly (5-fold less engraftment) in sublethally irradiated recipients (Figure 1C).

To confirm that these results were not a W/W^v-related artifact, we also injected *wt* or *cd34*$^{-/-}$ (CD45.2) cells into nonirradiated *wt* (CD45.1) recipients and assessed the frequency of donor-derived cells in peripheral blood 12 weeks after transplantation. Since donor cells have no advantage over endogenous cells in this system, reconstitution levels were predictably low but, as with W/W^v experiments, *wt* cells were considerably more effective at LTR than *cd34*$^{-/-}$ cells (Figure 1D). Taken together, our results demonstrate that in 2 independent systems, although *cd34*$^{-/-}$ and *wt* cells show similar abilities to engraft lethally irradiated mice, *cd34*$^{-/-}$ cells are profoundly impaired in engraftment of nonirradiated or sublethally irradiated recipients.

What then is the function of CD34 in BM engraftment? Previous studies suggest that sialomucins, like CD34, tend to block cell adhesion through their bulky, negatively charged extracellular domains.[5] For example, CD34-null mast cells aggregate in vitro, while ectopic expression decreases cell adhesion.[6] Likewise, overexpression of the CD34 relative, podocalyxin, also serves to decrease cell adhesion.[7,8] Thus, CD34 expression on migrating hematopoietic cells and most

From www.bloodjournal.org by guest on September 16, 2016. For personal use only.

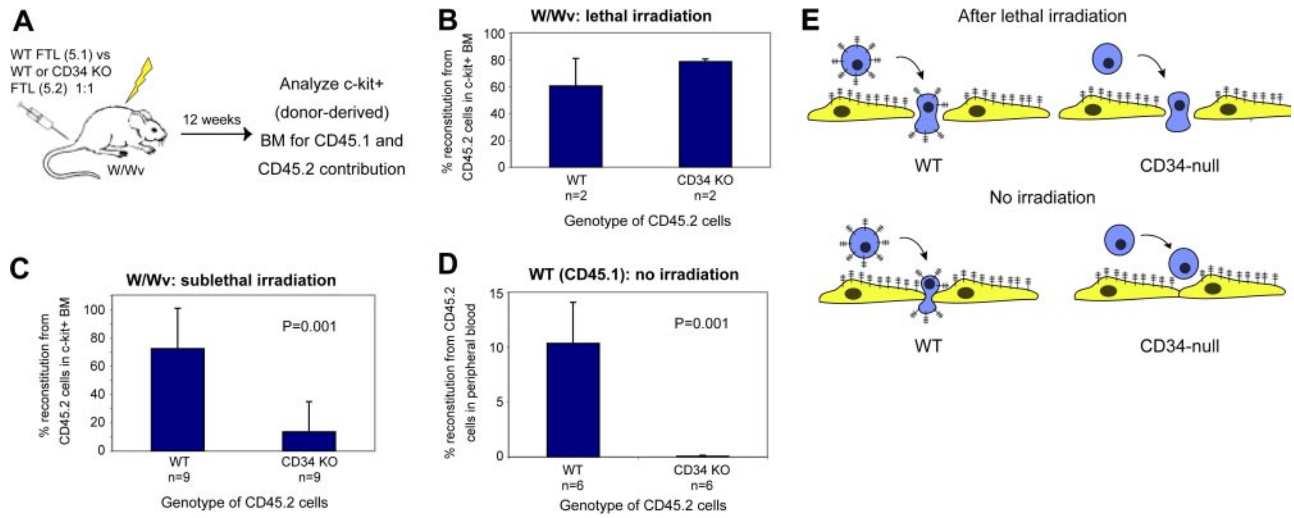

Figure 1. CD34 is required for engraftment of nonlethally irradiated recipients. (A) Schematic of experimental design. 5×10^6 E15 FTLs of each genotype were injected into irradiated W/W^v recipients. *wt* cells (bearing the CD45.1 allotypic marker) were injected competitively with *cd34*$^{-/-}$ or *wt* (control) cells (CD45.2), and donor-derived (c-kit$^+$) BM cells were analyzed for relative contributions 12 weeks after transplantation. (B) CD34 was not required for reconstitution of W/W^v mice pretreated with high-dose irradiation. Error bars represent SD. (C) *cd34*$^{-/-}$ cells were at a significant disadvantage in sublethally irradiated W/W^v recipients (combined data from 2 experiments; $P = .001$). Error bars represent SD. (D) *cd34*$^{-/-}$ cells did not contribute to long-term engraftment of nonirradiated *wt* recipients ($P = .001$). 10^7 CD45.2 (*wt or cd34*$^{-/-}$) cells were injected into nonirradiated *wt* (CD45.1) recipients, and donor-derived cells in peripheral blood were quantitated 12 weeks after transplantation based on CD45.2 expression. Error bars represent SD. (E) Proposed model demonstrating the effect of irradiation on the BM microenvironment and its effect on reconstitution by *wt* or *cd34*$^{-/-}$ cells. Lethal irradiation creates gaps between vascular endothelial cells, which allow extravasation of cells regardless of CD34 expression. In nonirradiated recipients, the vasculature remains intact, and the antiadhesiveness of CD34 enables transmigration. This is blocked in the absence of CD34.

vascular endothelial cells would normally prevent inappropriate adhesion and enhance mobility.

We therefore propose that our results reflect an impaired ability of the more adhesive *cd34*$^{-/-}$ cells to cross intact endothelial barriers en route to BM stem cell niches (Figure 1E). Conversely, irradiation-induced vascular permeability facilitates migration of *cd34*$^{-/-}$ HSCs into subvascular spaces, thereby explaining their favorable competition with *wt* cells for engraftment in preconditioned recipients. These data serve to highlight the importance of evaluating the ability of mutant and wild-type HSCs to engraft both irradiated and nonirradiated recipients, particularly when a mutation may influence the mobility or trafficking of stem cells.

Approval for these studies was obtained from the University of British Columbia Animal Care Committee.

Julie S. Nielsen and Kelly M. McNagny

Conflict-of-interest disclosure: The authors declare no competing financial interests.

We wish to thank Dr Tak Mak for cd34$^{-/-}$ *mice; Helen Merkens, Shierley Chelliah, and Lori Zbytnuik for expert technical assistance; and Robbi McDonald for help with statistical analysis. This work was supported by Canadian Institutes for Health Research (CIHR) grant no. MOP-64278. K.M.M. is a CIHR and Michael Smith Foundation for Health Research (MSFHR) scholar.*

Correspondence: Kelly M. McNagny, The Biomedical Research Centre, 2222 Health Sciences Mall, Vancouver, BC, V6T 1Z3 Canada; e-mail: kelly@brc.ubc.ca.

References

1. Tomita Y, Sachs DH, Sykes M. Myelosuppressive conditioning is required to achieve engraftment of pluripotent stem cells contained in moderate doses of syngeneic bone marrow. Blood. 1994;83:939-948.
2. Mazo IB, Quackenbush EJ, Lowe JB, von Andrian UH. Total body irradiation causes profound changes in endothelial traffic molecules for hematopoietic progenitor cell recruitment to bone marrow. Blood. 2002;99:4182-4191.
3. Geissler EN, Ryan MA, Housman DE. The dominant-white spotting (W) locus of the mouse encodes the c-kit proto-oncogene. Cell. 1988;55:185-192.
4. Migliaccio AR, Carta C, Migliaccio G. In vivo expansion of purified hematopoietic stem cells transplanted in nonablated W/Wv mice. Exp Hematol. 1999;27:1655-1666.
5. Hilkens J, Ligtenberg MJ, Vos HL, Litvinov SV. Cell membrane-associated mucins and their adhesion-modulating property. Trends Biochem Sci. 1992;17:359-363.
6. Drew E, Merzaban JS, Seo W, Ziltener HJ, McNagny KM. CD34 and CD43 inhibit mast cell adhesion and are required for optimal mast cell reconstitution. Immunity. 2005;22:43-57.
7. Takeda T, Go WY, Orlando RA, Farquhar MG. Expression of podocalyxin inhibits cell-cell adhesion and modifies junctional properties in Madin-Darby canine kidney cells. Mol Biol Cell. 2000;11:3219-3232.
8. Somasiri A, Nielsen JS, Makretsov N, et al. Overexpression of the anti-adhesin podocalyxin is an independent predictor of breast cancer progression. Cancer Res. 2004;64:5068-5073.

To the editor:

Analysis of *JAK3*, *JAK2*, and *C-MPL* mutations in transient myeloproliferative disorder and myeloid leukemia of Down syndrome blasts in children with Down syndrome

Children with Down syndrome are predisposed to 2 linked clonal myeloid disorders: transient myeloproliferative disorder (TMD[1]) and myeloid leukemia of Down syndrome (ML-DS). In addition to trisomy 21, somatic mutations in *GATA1* are required events for TMD and ML-DS (reviewed in Gurbuxani et al[2] and Hitzler and Zipursky[3]). Because only 20% to 30% of TMD cases progress to ML-DS, additional (epi)genetic events are likely to be important for the progression of TMD to ML-DS.[4]

From www.bloodjournal.org by guest on September 16, 2016. For personal use only.

2007 110: 1075-1076
doi:10.1182/blood-2007-03-082354

Lenalidomide therapy in a patient with POEMS syndrome

Angela Dispenzieri, Christopher J. Klein and Michelle L. Mauermann

Updated information and services can be found at:
http://www.bloodjournal.org/content/110/3/1075.full.html

Articles on similar topics can be found in the following Blood collections

Information about reproducing this article in parts or in its entirety may be found online at:
http://www.bloodjournal.org/site/misc/rights.xhtml#repub_requests

Information about ordering reprints may be found online at:
http://www.bloodjournal.org/site/misc/rights.xhtml#reprints

Information about subscriptions and ASH membership may be found online at:
http://www.bloodjournal.org/site/subscriptions/index.xhtml

Blood (print ISSN 0006-4971, online ISSN 1528-0020), is published weekly by the American Society of Hematology, 2021 L St, NW, Suite 900, Washington DC 20036.
Copyright 2011 by The American Society of Hematology; all rights reserved.