Check for updates

integrin complexed with the drug that caused the thrombocytopenia. They called these changes in the integrin mimetic-induced binding sites, or MIBs. Cross-reactivity existed with the antibodies of some patients (13 of 43 patients). The cross-reacting antibodies bound $\alpha_{IIb}\beta_3$ when platelets were pretreated with any one RGD mimetic drug or RGD peptide. These MIBS were located in the head region of $\alpha_{IIb}\beta_3$, near the RGD recognition site, probably on the β-propeller domain of α_{IIb} or the βA domain of β_3 (see figure). There appeared to be 3 eptifibatide-dependent and 3 tirofiban-dependent antibody binding sites, each with an individual footprint. MIBS in this report were identified by cross-blocking studies using monoclonal antibodies with known epitopes. More precise epitope mapping, particularly identification of α_{IIb} or β_3 sequences that mediate antibody binding, may have to await further in-depth investigations using site-directed mutagenesis or structural studies such as x-ray crystallography or nuclear magnetic resonance.

The findings of Bougie et al provide important insights into the mechanism whereby patient antibodies bind integrin $\alpha_{IIb}\beta_3$ and the results have significant clinical implications. Before this study it was assumed that eptifibatide- and tirofiban-dependent antibodies do not cross-react as the 2 drugs have different chemical structures. However, Bougie and colleagues found that the 2 drug-dependent antibodies did cross-react in approximately 30% of patients.[1] Their findings suggest that it might not be safe to administer tirofiban to a patient with eptifibatide-induced thrombocytopenia and vice versa. One approach is to assess antibody cross-reactivity before administration of an alternative RGD mimetic as some clinical laboratories may be able to detect eptifibatide- and tirofiban-dependent antibodies[4] and assess antibody cross-reactivity using flow cytometry. However, the clinical usefulness of such laboratory investigations will have to await confirmation by future studies.

Understanding the pathogenesis of drug-induced thrombocytopenia may lead to development of safer RDG mimetic inhibitor drugs. Recently, Zhu et al described an RDG mimetic inhibitor (designated RUC-1) that blocks fibrinogen binding to activated $\alpha_{IIb}\beta_3$ but does not induce conformational changes in the integrin nor emergence of LIBS and presumably MIBS.[9] Consequently, RUC-1 and RUC-1–like drugs are unlikely to be antigenic and may not cause immune thrombocytopenia. Currently, if a patient with RGD mimetic-induced thrombocytopenia has a serious or potentially fatal bleed, there is no treatment to rapidly increase the patient's platelet count. Identification of α_{IIb} or β_3 sequences that mediate antibody binding by more precise epitope mapping studies may allow development of effective drugs such as inhibitory small molecules, peptides, or antibody fragments that block antibody binding to platelets and promote platelet recovery. Such novel drugs could be very helpful in this clinical setting.

Conflict-of-interest disclosure: The author declares no competing financial interests. ■

REFERENCES

1. Bougie DW, Rasmussen M, Zhu J, Aster RH. Antibodies causing thrombocytopenia in patients treated with RGD-mimetic platelet inhibitors recognize ligand-specific conformers of alphaIIb/beta3 integrin. *Blood*. 2012; 119(26):6317-6325.
2. Reese JA, Li X, Hauben M, et al. Identifying drugs that cause acute thrombocytopenia: an analysis using 3 distinct methods. *Blood*. 2010;116(12):2127-2133.
3. Aster RH, Curtis BR, McFarland JG, Bougie DW. Drug-induced immune thrombocytopenia: pathogenesis, diagnosis and management. *J Thromb Haemost*. 2009; 7(6):911-918.
4. Aster RH, Curtis BR, Bougie DW, et al. Thrombocytopenia associated with the use of GPIIb/IIIa inhibitors: position paper of the ISTH working group on thrombocytopenia and GPIIb/IIIa inhibitors. *J Thromb Haemost*. 2006; 4(3):678-679.
5. Bougie DW, Wilker PR, Wuitschick ED, et al. Acute thrombocytopenia after treatment with tirofiban or eptifibatide is associated with antibodies specific for ligand-occupied GPIIb/IIIa. *Blood*. 2002;100(6):2071-2076.
6. Frelinger AL III, Du XP, Plow EF, Ginsberg MH. Monoclonal antibodies to ligand-occupied conformers of integrin alpha IIb beta3 (glycoprotein IIb/IIIa) alter receptor affinity, specificity, and function. *J Biol Chem*. 1991; 266(26):17106-17111.
7. Asvadi P, Ahmadi Z, Chong BH. Drug-induced thrombocytopenia: localization of the binding site of GPIX-specific quinine dependent antibodies. *Blood*. 2003; 102(5):1670-1677.
8. Chong BH, Isaacs A. Heparin-induced thrombocytopenia: What clinicians need to know. *Thromb Haemost*. 2009; 101(2):279-283.
9. Zhu J, Negri A, Provasi D, Filizola M, Coller BS, Springer TA. Closed headpiece of integrin alpha IIb beta3 and its complex with an alpha IIb beta3-specific antagonist that does not induce opening. *Blood*. 2010;116(23):5050-5059.

● ● ● CLINICAL TRIALS

Comment on Lokhorst et al, page 6219

Death of frontline allo-SCT in myeloma

Philippe Moreau UNIVERSITY HOSPITAL NANTES

In this issue of *Blood*, Lokhorst et al report the results of a donor versus no-donor comparison trial, which unambiguously establishes that reduced intensity conditioning allogeneic stem cell transplantation (RIC allo-SCT) should not be offered as part of frontline therapy in multiple myeloma (MM).[1]

At the end of the 1990s, 2 prospective trials compared autologous stem cell transplantation (auto-SCT) with myeloablative allo-SCT in MM.[2,3] In both of these, extremely high rates of transplant-related mortality (TRM) were observed in the allogeneic arms, ranging from 30% despite partial T-cell depletion in the study conducted by the HOVON group,[2] up to 53% in the United States Intergroup trial (S9321), in which T-cell depletion was not carried out.[3] As a result, myeloablative allo-SCT was abandoned and the procedure is not recommended as part of frontline therapy in patients with symptomatic de novo MM.[4]

Although the introduction of RIC regimens has resulted in a decrease in the high incidence of TRM associated with myeloablative conditioning, an intense debate is currently ongoing regarding the question of whether patients should be subjected to the substantial morbidity, especially graft-versus-host disease (GVHD), and the risk of mortality associated with RIC allo-SCT as part of first-line therapy compared with the relatively safe procedure of auto-SCT.[5-11] Lokhorst et al performed a donor versus no-donor analysis of patients included in the phase 3 HOVON-50 MM trial.[1] After a single auto-SCT, eligible patients were randomized according to the availability of an HLA-identical sibling to receive either maintenance therapy consisting of thalidomide or α-interferon or RIC allo-SCT after low-dose 2 Gy total body irradiation. Importantly, the trial included a large number of patients, and the median follow-up, which exceeds 6 years, is long enough to draw reliable conclusions. The complete response, the overall survival (OS), and progression-free

Downloaded from http://ashpublications.net/blood/article-pdf/119/26/6178/1497624/zh802612006178.pdf by guest on 08 June 2024

survival (PFS) rates were not significantly different between the donor and no-donor groups. As expected, the cumulative incidence of nonrelapse mortality was significantly higher, while the incidence of relapse was significantly decreased in the RIC allo-SCT group. The PFS of patients who actually received RIC allo-SCT was significantly prolonged compared with the patients who continued maintenance, but this difference did not translate into a survival benefit.

These results differ from those previously reported by the Italian[5,6] and the European Blood and Marrow Transplantation (EBMT) groups[7] regarding the comparison of tandem auto-SCT with a sequential application of single auto-SCT followed by RIC allo-SCT. In both of these trials PFS and OS were improved for patients with a sibling donor. Interestingly, in all 3 studies, the Lokhorst trial as well as the Italian and EBMT studies, which used the same conditioning regimen before RIC allo-SCT, the PFS and OS of patients who had a donor and underwent the auto-SCT/RIC allo-SCT procedure appeared similar. The absence of a difference between the donor and the no-donor groups in the Lokhorst study, which is the major finding of this trial, is related to a much better outcome of the no-donor group compared with the EBMT and the Italian series. The HOVON study was the last of the 3 trials to be initiated, and was conducted when lenalidomide and/or bortezomib could be routinely given at the time of relapse in the no-donor group of patients. The results of the HOVON trial are in line with those of a recent donor versus no-donor comparison reported by the Blood and Marrow Transplant Clinical Trials Network (BMT-CTN) group, in which after a shorter follow-up no difference was seen in outcome between patients in the tandem auto-SCT arm and those undergoing auto-SCT followed by RIC allo-SCT.[11] Overall, 6 donor versus no-donor studies are now available, 2 supporting[5-7] and 4 opposing[1,8-11] the sequential approach of auto-SCT followed by RIC allo-SCT.

The impact of the HOVON study is substantial, because it is the only one to be performed at a time of widespread use of novel agents at relapse. The systematic use of combinations of novel agents upfront as induction therapy before auto-SCT, as well as their incorporation into the consolidation and/or maintenance settings after auto-SCT, which can be considered an optimal strategy in the 2010s, will further improve the results of procedures not including RIC allo-SCT. Moreover, recent attempts aimed at bettering outcomes with RIC allo-SCT, such as the use of maintenance treatment with low-dose lenalidomide in the HOVON-76 study, failed because of the rapid induction of acute GVHD.[12] It can be anticipated that the gap between the results achieved with auto-SCT versus those obtained with RIC allo-SCT, also taking into account toxicity, will widen in the future to the detriment of the allogeneic procedure.

In their important report and analysis, Lokhorst et al note that the study was not powered to address the significant issue of the outcome of poor-risk patients, such as those harboring the 17p deletion. This subgroup, which constitutes 7% to 10% of all patients, might be the only one to derive a benefit from an allogeneic effect, which, however, will have to be proven in clinical trials.

In conclusion, front-line myeloablative allo-SCT in MM died 10 years ago, and the latest results from the HOVON-50 study further corroborate that RIC allo-SCT should not be recommended as part of front-line therapy in patients with symptomatic MM.

Conflict-of-interest disclosure: The author declares no competing financial interests. ■

REFERENCES

1. Lokhorst HM, van der Holt B, Cornelissen JJ, et al. Donor versus no-donor comparison of newly diagnosed myeloma patients included in the HOVON-50 multiple myeloma study. *Blood*. 2012;119(26):6219-6225.

2. Lokhorst HM, Segeren CM, Verdonck LF, et al. Partially T-cell-depleted allogeneic stem-cell transplantation for first-line treatment of multiple myeloma: A prospective evaluation of patients treated in the phase III study HOVON 24 MM. *J Clin Oncol*. 2003;21(9):1728-1733.

3. Barlogie B, Kyle RA, Anderson KC, et al. Standard chemotherapy compared with high-dose chemoradiotherapy for multiple myeloma: final results of phase 3 US Intergroup Trial S9321. *J Clin Oncol*. 2006;24(6):929-936.

4. Lokhorst H, Einsele H, Vesole D, et al. International Myeloma Working Group consensus statement regarding the current status of allogeneic stem-cell transplantation for multiple myeloma. *J Clin Oncol*. 2010;28(29):4521-4530.

5. Bruno B, Rotta M, Patriarca F, et al. A comparison of allografting with autografting for newly diagnosed myeloma. *N Engl J Med*. 2007;356(11):1110-1120.

6. Giaccone L, Storer B, Patriarca F, et al. Long-term follow-up of a comparison of nonmyeloablative allografting with autografting for newly diagnosed myeloma. *Blood*. 2011;117(24):6721-6727.

7. Björkstrand B, Iacobelli S, Hegenbart U, et al. Tandem autologous/reduced-intensity conditioning allogeneic stem-cell transplantation versus autologous transplantation in myeloma: long-term follow-up. *J Clin Oncol*. 2011;29(22):3016-3022.

8. Garban F, Attal M, Michallet M, et al. Prospective comparison of autologous stem cell transplantation followed by dose-reduced allograft (IFM99-03 trial) with tandem autologous stem cell transplantation (IFM99-04 trial) in high-risk de novo multiple myeloma. *Blood*. 2006;107(9):3474-3480.

9. Moreau P, Garban F, Attal M, et al. Long-term follow-up results of IFM99-03 and IFM99-04 trials comparing nonmyeloablative allotransplantation with autologous transplantation in high-risk de novo multiple myeloma. *Blood*. 2008;112(9):3914-3915.

10. Rosiñol L, Pérez-Simón JA, Sureda A, et al. A prospective PETHEMA study of tandem autologous transplantation versus autograft followed by reduced-intensity conditioning allogeneic transplantation in newly diagnosed multiple myeloma. *Blood*. 2008;112(9):3591-3593.

11. Krishnan A, Pasquini B, Logan B, et al. Autologous haemopoietic stem-cell transplantation followed by allogeneic or autologous haemopoietic stem-cell transplantation in patients with multiple myeloma (BMT CTN 0102): a phase 3 biological assignment trial. *Lancet Oncol*. 2011;12(13):1195-1203.

12. Kneppers E, van der Holt B, Kersten MJ, et al. Lenalidomide maintenance after non-myeloablative allogeneic stem cell transplantation in multiple myeloma is not feasible. Results of the HOVON 76 trial. *Blood*. 2011;118(9):2413-2419.

● ● ● IMMUNOBIOLOGY

Comment on Granados et al, page e181

All roads lead to "ome": defining the DRiPome

Jonathan W. Yewdell and Michael F. Princiotta NIAID; SUNY UPSTATE MEDICAL UNIVERSITY

In this issue of *Blood*, Granados et al explore the relationship between the cellular transcriptome and immunopeptidome,[1,2] the repertoire of peptides presented by MHC class I molecules for immunosurveillance.

Class I molecules are encoded by 3 highly polymorphic genes, HLA-A, -B, and -C, in humans, so individuals typically express 6 distinct class I molecules on their cell surface that function to regulate the effector functions of $CD8^+$ T cells and natural killer (NK) cells.

Downloaded from http://ashpublications.net/blood/article-pdf/119/26/6178/1497624/zh802612006178.pdf by guest on 08 June 2024