gastrointestinal symptoms to indicate progression of tissue damage. Serial evaluation of λ-FLC level showed an increase to 17.7 mg/dL by June 2008. She has thus relapsed with increased λ-FLC level and gastrointestinal amyloid deposits on a recent biopsy, but has refused a second ASCT. Serum FLC data indicate she remained in molecular remission for more than 18 months after her last bortezomib treatment.

ASCT provides a substantial median survival in select AL patients,[8] but an over 25% mortality rate if even one organ has significant AL damage.[8,9] Our data suggest treatments that improve end-organ damage should reduce transplant-related mortality, ultimately allowing a higher percentage of patients to undergo ASCT with improved outcomes.[10] Bortezomib can reliably decrease serum FLC levels.[11] In our 2 patients, we documented reversal of AL organ damage with what appears to be promising disease-free survival. Furthermore, Patient 1, who received a second transplant, has remained in remission for three years. This suggests that second transplants may result in improved outcomes by significantly decreasing the AL disease burden. Treatment with bortezomib-based therapy may result in hematologic and organ responses that would enable patients with end-organ damage who would have otherwise been precluded from transplantation to undergo ASCT.

Mark W. Brunvand[1] and Mitchell Bitter[2]

[1]Rocky Mt. Blood & Marrow Transplant Program, and [2]Unipath, Denver, CO, USA

Acknowledgments: the authors would like to thank Steve Hill and Jane Saunders of FireKite for editorial assistance in the preparation of this letter.

Correspondence: Mark W. Brunvand, Rocky Mountain Blood and Marrow Transplant Program, Denver, CO 80218, USA.
Phone: international +1.303.3884876. Fax: international +1.303.3362186.
E-mail: mbrunvand@mac.com

Citation: Brunvand MW, Bitter M. Amyloidosis relapsing after autologous stem cell transplantation treated with bortezomib: normalization of detectable serum-free light chains and reversal of tissue damage with improved suitability for transplant. Haematologica. 2010; 95:519-521. doi:10.3324/haematol.2009.013102

References

1. Comenzo RL. Current and emerging views and treatments of systemic immunoglobulin light-chain (Al) amyloidosis. Contrib Nephrol. 2007;153:195-210.
2. Wechalekar AD, Hawkins PN, Gillmore JD. Perspectives in treatment of AL amyloidosis. Br J Haematol. 2008;140(4):365-77.
3. Merlini G, Bellotti V. Molecular mechanisms of amyloidosis. N Engl J Med. 2003;349(6):583-96.
4. Sanchorawala V, Skinner M, Quillen K, Finn KT, Doros G, Seldin DC. Long-term outcome of patients with AL amyloidosis treated with high-dose melphalan and stem-cell transplantation. Blood. 2007;110(10):3561-3.
5. Gertz MA, Lacy MQ, Dispenzieri A. Myeloablative chemotherapy with stem cell rescue for the treatment of primary systemic amyloidosis: a status report. Bone Marrow Transplant. 2000; 25(5):465-70.
6. Gertz MA, Lacy MQ, Dispenzieri A, Hayman SR, Kumar S. Transplantation for amyloidosis. Curr Opin Oncol. 2007;19(2): 136-41.
7. Richardson PG, Mitsiades C, Schlossman R, Ghobrial I, Hideshima T, Munshi N, et al. Bortezomib in the front-line treatment of multiple myeloma. Expert Rev Anticancer Ther 2008; 8(7):1053-7.
8. Dispenzieri A, Kyle RA, Lacy MQ, Therneau TM, Larson DR, Plevak MF, et al. Superior survival in primary systemic amyloidosis patients undergoing peripheral blood stem cell transplantation: a case-control study. Blood. 2004;103(10):3960-3.
9. Moreau P, Leblond V, Bourquelot P, Facon T, Huynh A, Caillot D, et al. Prognostic factors for survival and response after high-dose therapy and autologous stem cell transplantation in systemic AL amyloidosis: a report on 21 patients. Br J Haematol. 1998;(4):766-9.
10. Lachmann HJ, Gallimore R, Gillmore JD, Carr-Smith HD, Bradwell AR, Pepys MB, et al. Outcome in systemic AL amyloidosis in relation to changes in concentration of circulating free immunoglobulin light chains following chemotherapy. Br J Haematol. 2003;122(1):78-84.
11. Wechalekar AD, Lachmann HJ, Offer M, Hawkins PN, Gillmore JD. Efficacy of bortezomib in systemic AL amyloidosis with relapsed/refractory clonal disease. Haematologica. 2008;93(2): 295-8.

Successful eradication of acquired factor-VIII-inhibitor using single low-dose rituximab

It was with great interest that we read the recent recommendations regarding the treatment of acquired hemophilia A published in Haematologica[1] and followed the subsequent discussion.[2,3] The described treatment algorithm for this disease, which occurs at an incidence of 1.5/million/year,[4] stresses the importance of early eradication of the acquired fVIII-inhibitor. Using prednisolone alone or in combination with cyclophosphamide, this approach will be successful in 30-50% of affected individuals.[5] As Huth-Kühne pointed out, the CD20-antibody rituximab may be an attractive alternative in non-responders or patients with contraindications to steroids.[6] However, concerns have been raised because of rituximab side-effects including associations with progressive multifocal leukencephalopathy (PML).[7] Furthermore, as Mannucci *et al.*[2] emphasized, the use of this drug is hampered by its substantial costs. Restricting the administered dose to the lowest effective level, seems to be a reasonable strategy to minimize potential risks and costs of rituximab treatment.

We report a 66-year old male AHA-patient successfully treated with single low-dose rituximab. The patient presented with multiple hematomas and severe anemia after recovering from a respiratory infection. Prolonged activated partial-thromboplastin-time (aPTT) in combination with undetectable fVIII-activity due to an fVIII-inhibitor was observed. There was no clinical history of any prior hemorrhages nor a family history of bleeding. Clinical and imaging examinations could not reveal any pathological findings suggesting an idiopathic cause of AHA. Prednisolone (1 mg/kg) was started immediately

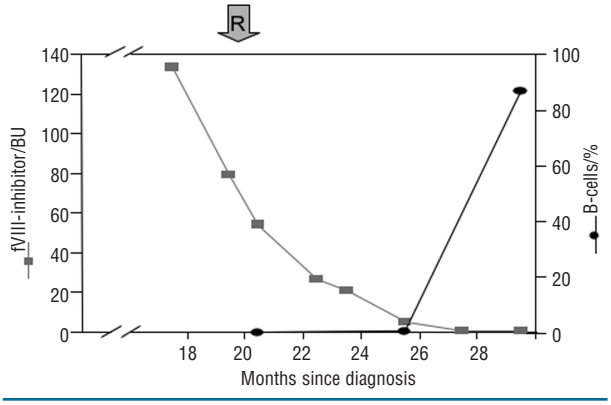

Figure 1. Clinical course overview. Time since diagnosis in months (x-axis). fVIII-inhibitor titer in Bethesda Units (BU) (left y-axis). B-cell proportion (%) (right y-axis). R: time of rituximab application.

and 2 units of packed red blood cells had to be administered. Afterwards, bleeding ceased, correlating with an increase in fVIII-activity to 28%. Steroids were completely tapered over the next weeks and the patient was lost to follow-up. However, during the following year the patient experienced recurrent episodes of minor bleeding.

Seventeen months after the first onset of AHA, he again presented at our institution for follow-up. He reported no spontaneous bleeding episodes; however, fVIII-activity was 15% translating into an fVIII-inhibitor of 133 BU (Bethesda Units). Two months later, severe limb-bleeding requiring surgical treatment occurred after a minor accident. FVIII-inhibitor could still be detected at high levels (79 BU). Because of impaired wound-healing, steroids were deemed contraindicated. Therefore, given our experience with patients with auto-immune diseases other than AHA,[8] inhibitor-eradication treatment was started with a single flat dose of 100 mg rituximab. Treatment was well tolerated and three weeks later complete B-cell depletion could be demonstrated (Figure 1). There was no reoccurrence of significant bleeding and even an accident was tolerated without complications. At last presentation, nearly ten months after rituximab treatment, the patient had only a low residual fVIII-inhibitor activity, in spite of a normal B-cell count. FVIII-levels stabilized at a level of 15 to 20% and aPTT was never again found to be prolonged after rituximab treatment.

The clinical course of our patient demonstrates that complete B-cell depletion can be achieved with low-dose rituximab in AHA. We are aware that given the persistently low fVIII-level, our patient does not meet the strict criteria for inhibitor eradication proposed by Huth-Kühne. On the other hand, we have to acknowledge that he experienced no further bleeding and had inhibitor-titers near the detection limit. We, therefore, believe that future clinical trials should incorporate this low-dose regimen rather than the classical lymphoma-dose (e.g. 375 mg/m^2) in the treatment of acquired hemophilia A.

Martin Wermke,[1] Malte von Bonin,[1] Siegmund Gehrisch,[2] Gabriele Siegert,[2] Gerhard Ehninger,[1] and Uwe Platzbecker[1]

[1]Universitätsklinikum Carl-Gustav-Carus, Medizinische Klinik I, Fetscherstraße 74, 01307 Dresden, Germany;

[2]Universitätsklinikum Carl-Gustav-Carus, Institut für Klinische Chemie und Laboratoriumsmedizin, Fetscherstraße 74, 01307 Dresden, Germany

Key words: hemophilia A, partial-thromboplastin-time (aPTT), cyclophosphamide.

Correspondence: Uwe Platzbecker, Universitätsklinikum Carl-Gustav-Carus, Medizinische Klinik I, Fetscherstraße 740 1307 Dresden, Germany. Phone: international +49.351.4582583. Fax: international +49.351.4584373. E-mail: uwe.platzbecker@uniklinikum-dresden.de

Citation: Wermke M, von Bonin M, Gehrisch S, Siegert G, Ehninger G, and Platzbecker U. Successful eradication of acquired factor-VIII-inhibitor using single low-dose rituximab. Haematologica 2010;95:521-522. doi:10.3324/haematol.2009.017749

References

1. Huth-Kuhne A, Baudo F, Collins P, Ingerslev J, Kessler CM, Levesque H, et al. International recommendations on the diagnosis and treatment of patients with acquired hemophilia A. Haematologica. 2009;94(4):566-75.
2. Mannucci PM, Peyvandi F. Autoimmune hemophilia at rescue. Haematologica. 2009;94(4):459-61.
3. Huth-Kuhne A. Cautions and caveats to the treatment of acquired hemophilia A. Haematologica. 2009;94(8):1181-2.
4. Collins PW, Hirsch S, Baglin TP, Dolan G, Hanley J, Makris M, et al. Acquired hemophilia A in the United Kingdom: a 2-year national surveillance study by the United Kingdom Haemophilia Centre Doctors' Organisation. Blood. 2007;109(5):1870-7.
5. Green D, Rademaker AW, Briet E. A prospective, randomized trial of prednisone and cyclophosphamide in the treatment of patients with factor-VII autoantibodies. Thrombosis and Haemostas. 1993;70(5):753-7.
6. Franchini M. Rituximab in the treatment of adult acquired hemophilia A: A systematic review. Crit Rev Oncol Hematology. 2007;63(1):47-52.
7. Carson KR, Evens AM, Richey EA, Habermann TM, Focosi D, Seymour JF, et al. Progressive multifocal leukoencephalopathy after rituximab therapy in HIV-negative patients: a report of 57 cases from the Research on Adverse Drug Events and Reports project. Blood. 2009;113(20):4834-40.
8. Von Bonin M, Oelschlagel U, Radke J, Stewart M, Ehninger G, Bornhauser M, et al. Treatment of chronic steroid-refractory graft-versus-host disease with low-dose rituximab. Transplantation. 2008;86(6):875-9.