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References

1. Kjeldsen-Kragh J, Killie MK, Tomter G, Golebiowska E, Randen I, Hauge R, et al. A screening and intervention program aimed to reduce mortality and serious morbidity associated with severe neonatal alloimmune thrombocytopenia. Blood 2007;110:833-9.
2. Killie MK, Husebekk A, Kjeldsen-Kragh J, Skogen B. A prospective study of maternal anti-HPA 1a antibody level as a potential predictor of alloimmune thrombocytopenia in the newborn. Haematologica 2008;93:870-7.
3. Rodey GE. Anti-idiotypic antibodies and regulation of immune responses. Transfusion 1992;32:361-76.
4. Shoenfeld Y. The idiotypic network in autoimmunity: antibodies that bind antibodies that bind antibodies. Nat Med 2004;10:17-8.
5. Semple JW, Kim M, Lazarus AH, Freedman J. Gammaglobulins prepared from sera of multiparous women bind anti-HLA antibodies and inhibit an established in vivo human alloimmune response. Blood 2002;100:1055-9.
6. Atlas E, Freedman J, Blanchette V, Kazatchkine MD, Semple JW. Downregulation of the anti-HLA alloimmune response by variable region-reactive (anti-idiotypic) antibodies in leukemic patients transfused with platelet concentrates. Blood 1993;81:538-42.

Slow responses to standard dose rituximab in immune thrombocytopenic purpura

We read with interest the article by Zaja *et al*. in which the results of a prospective multicenter Phase II study to assess the response rates of lower dose rituximab in adults with chronic immune thrombocytopenic purpura (ITP) were reported.[1] In this single arm study 28 ITP patients received rituximab (100 mg/m^2) weekly for four weeks. An overall response (platelet count >50×10^9/L) and complete response (platelet count >100×10^9/L) was achieved in 21/28 (75%) and 12/28 (43%) of patients, respectively. Interestingly the time to treatment response with lower dose rituximab was longer than in published studies with standard dose (375mg/m^2 weekly for four weeks).[2-4] The median time to a complete response was 44 days with a range of 7-90 days.

In a recent prospective Phase II study which assessed the efficacy of standard dose rituximab in chronic adult ITP patients, most patients who responded to rituximab did so early and none of the patients who failed to reach a platelet count of 50×10^9//L in two weeks achieved a good response at one year.[2]

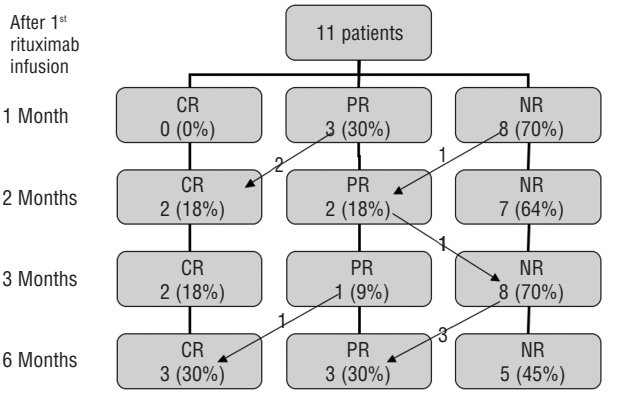

Figure 1. Response of chronic ITP patients over time, following first rituximab infusion. Complete response (CR), platelet count >100×10^9/L partial response (PR), platelet count 50-100×10^9/L. No response (NR). The arrows and overlying numbers represent patients changing response. Patients who required alternative treatment were classified as having no response.

In our center we have treated 11 patients (6 female and 5 male, mean age 50) with refractory chronic ITP with standard dose rituximab (375 mg/m^2 weekly for four weeks) with similar response rates (6 patients reached a platelet count of >50×10^9/L, including 3 >100×10^9/L at six months) but we have noted that delayed responses to standard dose rituximab also occur (Figure 1). The best responses were seen in 2 female patients, aged 32 and 26 years, with baseline platelet counts of 4 and 25×10^9/L. Their platelet counts at one month were 87 and 84×10^9/L and at six months were 521 and 230×10^9/L, respectively without any further treatment. In fact in our experience, at one month, no patient had platelets > 100×10^9/L (Figure 1). In a systemic review, complete responses usually occurred 3-8 weeks after the first infusion of rituximab.[5] However, our data show that delayed responses to standard dose rituximab can occur. These responses are unlikely to reflect spontaneous remission as this rarely occurs in adult chronic ITP.[6]

Splenectomy has been considered standard second-line therapy for ITP.[7] The response rate is about 65% but it is associated with a mortality of 0.2-1% and morbidity of 9.6-12.9% depending on the age of the patient and technique used.[8] There is accumulating evidence that rituximab can be a safe and effective way to defer splenectomy particularly in younger patients.[9] A lower dose rituximab regimen would result in considerable cost savings compared to a standard dose regimen and may be associated with less transfusion related reactions. While delayed responses may occur in the lower dose regimen they may also occur with standard dose rituximab. Since maximal response to both dosing regimens may be delayed, a decision regarding splenectomy should not be made until at least six months after rituximab therapy.

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Key Words: platelets, immune thrombocytopenic purpura, disorders of platelet function.

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References

1. Zaja F, Battista ML, Pirrotta MT, Palmieri S, Montagna M, Vianelli N, et al. Lower dose rituximab is active in adults patients with idiopathic thrombocytopenic purpura. Haematologica 2008;93:930-3.
2. Godeau B, Porcher R, Fain O, Lefrère F, Fenaux P, Cheze S, et al. Rituximab efficacy and safety in adult splenectomy candidates with chronic immune thrombocytopenic purpura: results of a prospective multicenter phase 2 study. Blood 2008;112:999-1004.
3. Stasi R, Pagano A, Stipa E, Amadori S. Rituximab chimeric anti-CD20 monoclonal antibody treatment for adults with chronic idiopathic thrombocytopenic purpura. Blood 2001;98:952-7.
4. Zaja F, Vianelli N, Battista M, Sperotto A, Patriarca F, Tomadini V, et al. Earlier administration of Rituximab allows higher rate of long-lasting response in adult patients with autoimmune thrombocytopenia. Exp Hematol 2006;34:571-2.
5. Arnold DM, Dentali F, Crowther MA, Meyer RM, Cook RJ, Sigouin C, et al. Systematic review: efficacy and safety of rituximab for adults with idiopathic thrombocytopenic purpura. Ann Intern Med 2007;146:25-33.
6. Stasi R, Stipa E, Masi M, Cecconi M, Scimò MT, Oliva F, et al. Long-term observation of 208 adults with chronic idiopathic thrombocytopenic purpura. Am J Med 1995;98:436-42.
7. Provan D, Newlan A, Norfolk D, Bolton-Maggs B, Lilleyman J, Greer I, et al. Guidelines for the investigation and management of idiopathic thrombocytopenic purpura in adults, children and in pregnancy. Br J Haematol 2003;120:574-96.
8. Kojouri K, Vesely SK, Terrell DR, George JN. Splenectomy for adult patients with idiopathic thrombocytopenic purpura: a systematic review to assess long-term platelet count responses, prediction of response, and surgical complications. Blood 2004;104:2623-34.
9. Garvey B. Rituximab in the treatment of autoimmune haematological disorders. Br J Haematol 2008;141:149-69.

Slow responses to standard dose rituximab in immune thrombocytopenic purpura. Author reply

We read the letter of Kelly *et al.*,[1] who report the results of their experience with standard dose rituximab (SD, *i.e.* 375 mg/m^2 weekly for four weeks) in patients with chronic immune thrombocytopenic purpura (ITP). Overall data are confirmatory to that previously reported by other authors: 6 out of 11 patients achieved a partial response (PR, platelet count > 50×10^9/L) and 3 a complete response (CR, > 100×10^9/L). The authors highlight that the time to CR was longer than expected (two months in 2 patients and six months in one), suggesting that a longer time of observation after rituximab therapy (at least six months) might be necessary before the decision regarding splenectomy.

Data from the literature indicate that in adult patients with ITP the response to SD rituximab develops more frequently early and often already within the fourth administration. Table 1 summarizes the results of some studies where data regarding the kinetic of response are available. In our previous study,[2] the median time to achieve PR and CR were 7 and 14 days respectively and only 3% and 10% of patients experienced PR and CR beyond the second and fourth month from the beginning of treatment.

In the reports of Stasi *et al.*[3] and Giagounidis *et al.*[4] all PRs and CRs were achieved within the first month of therapy. The paper of Cooper *et al.*,[5] on the contrary, showed 3 different timings of CR, suggesting that a significant proportion of patients may achieve CR much later (33% between month +4 and +6). Finally, in his systematic review, Arnold *et al.*[7] indicated a median time to response of 5.5 weeks from the first dose of rituximab in 123 valued patients with a range of 2-18 weeks. Different behavior can be seen with the use of low-dose rituximab (LD, *i.e.* 100 mg total dose weekly for four weeks), a very promising new therapeutic schedule for ITP.[6,8]

In our experience LD rituximab led to short and mid-term response rates similar to SD but with slower timing of response, with a median time to PR and CR of 31 and 44 days respectively[6] (Table 1). Taken together these data indicate that in ITP the time to response to rituximab may be different according to clinical, biological and therapeutic variables.

We agree that, when possible, a period of at least six months of observation from rituximab therapy may be necessary before undergoing splenectomy since at present we still don't have enough indicators predictive of brief and mid-term response.

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References

1. Kelly K, Gleeson M, Murphy PT. Slow response to standard dose rituximab in immune thrombocytopenic purpura. Haematologica 2009;94:443-4.
2. Zaja F, Vianelli N, Battista M, Sperotto A, Patriarca F, Tomadini V, et al. Earlier administration of Rituximab allows higher rate of long lasting reponse in adult patients with autoimmune thrombocytopenia. Exp Hematol 2006;34:571-2.
3. Stasi R, Pagano A, Stipa E, Amadori S. Rituximab chimeric anti-CD20 monoclonal antibody treatment for adults with chronic idiopathic thrombocytopenic purpura. Blood 2001;98:952-7.
4. Giagounidis AA, Anhuf J, Schneider P, Germing U, Söhngen D, Quabeck K, et al. Treatment of relapsed idiopathic thrombocytopenic purpura with the anti-CD20 monoclonal antibody rituximab: a pilot study. Eur J Haematol 2002;69:95-100.
5. Cooper N, Stasi R, Cunningham-Rundles S, Feuerstein MA, Leonard JP, Amadori S, et al. The efficacy and safety of B-cell depletion with anti-CD20 monoclonal antibody in adults with chronic immune