blood

To the editor:

Rituximab reduces risk for relapse in patients with thrombotic thrombocytopenic purpura

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Recent systematic reviews assessing the role of rituximab in the management of patients with acquired thrombotic thrombocytopenic purpura (TTP)[1,2] identified 2 major observational studies describing relapse after rituximab treatment. One report described a significantly decreased frequency of relapse in 40 patients who, in addition to plasma exchange (PEX) and high-dose corticosteroids, were treated with rituximab within 3 days of diagnosis as compared with historical control patients who had not received rituximab.[3] The other report compared 22 patients who were treated with rituximab for an inadequate response after initial treatment with PEX and corticosteroids with historical control patients who had not received rituximab; the researchers reported no significant difference in relapse frequency related to rituximab treatment.[4] Both studies had important limitations.[1] Control patients were retrospectively selected from a time period preceding the patient group receiving rituximab. Some patients had a history of previous episodes of TTP. Not all patients had ADAMTS13 activity <10%. The frequency of corticosteroid use and other treatments for TTP was not controlled. A shorter duration of follow-up of rituximab-treated patients compared with control patients potentially biased the results to observe fewer relapses in the treatment group. We updated our previous systematic review[1] to February 23, 2016, and identified no additional comparable studies of rituximab treatment of TTP.

We report the experience of the Oklahoma TTP Registry with rituximab treatment of initial episodes of acquired TTP. The Registry is an inception cohort of all consecutive patients for whom the Oklahoma Blood Institute (OBI) is requested to provide PEX for patients with a clinical diagnosis of TTP.[5] Because the OBI is the sole provider of PEX for all hospitals in our region, the Registry includes all patients without selection or referral bias. All identified patients have been enrolled; no patients were excluded. The Registry is approved by the institutional review boards of the University of Oklahoma Health Sciences Center and each participating hospital.

Our report describes all 41 consecutive patients enrolled in the Registry with their first episode of acquired TTP in December 2003 through December 2014. The diagnosis of TTP was documented by ADAMTS13 activity <10%. Four (10%) of the 41 patients died with their initial episode: 2 were not treated with rituximab (1 died before PEX began and 1 died during her first PEX) and 2 were treated with rituximab (1 died of *Staphylococcus aureus* sepsis and 1 died after failure of multiple agents). Follow-up of 36 of the 37 surviving patients is complete through 2015; 1 patient who was not treated with rituximab relapsed at 6 months and then was lost to follow-up.

Sixteen (43%) of the 37 surviving patients were treated with rituximab for their initial episode. Fourteen were treated because they were unresponsive to PEX and corticosteroids or they had recurrent thrombocytopenia when PEX was stopped. One patient was treated with rituximab because she could not return for evaluations. One patient was treated with rituximab (once) and corticosteroids for a diagnosis of primary immune thrombocytopenia 5 days before TTP was diagnosed and PEX was begun; she then had 3 more weekly infusions. Fourteen of the 16 patients received 4 weekly infusions of 375 mg/m^2. Two patients received only 1 infusion: 1 because she developed bacteremia and 1 because of no insurance.

Comparison of the 16 rituximab-treated patients to the 21 patients not treated with rituximab demonstrated no significant differences in demographic features, initial clinical data, or the year of their initial episode (Table 1). The only significant differences were that rituximab-treated patients had more PEX treatments over a longer duration and received a greater total dose of corticosteroids, reflecting their inadequate response to initial treatment. Two of the 37 patients subsequently died (16 and 30 months) after TTP; neither had been treated with rituximab for the TTP initial episode and neither had relapsed. Both deaths were related to systemic lupus erythematosus that preceded TTP.

The frequency of relapse among the rituximab-treated patients was significantly less than that among patients not treated with rituximab ($P = .009$, Figure 1).[6] Two rituximab-treated patients relapsed at 2.5 and 9.9 years after the initial episode. Both patients had received 4 infusions of rituximab for their initial episode; they had ADAMTS13 activity <10% at the time of their relapse and were re-treated with rituximab. Nine patients not treated with rituximab relapsed at 0.4 to 5.9 years (median, 3.1 years) after their initial episode. Two of 6 patients who received rituximab for their initial relapses relapsed again after 3.0 and 8.6 years; they were again treated with rituximab. One of 3 patients who had not received rituximab for their initial relapses relapsed again after 10 months; she was then treated with rituximab. ADAMTS13 activity was <10% in 11 of 12 relapses (it was not measured in 1 patient). All 11 relapsing patients have survived.

Patients treated with rituximab for their initial TTP episode had significantly fewer relapses than patients not treated with rituximab, even though their initial episodes were complicated by inadequate response to initial treatment with PEX and corticosteroids. Compared with the previous reports,[3,4] our 2 groups of patients were concurrent. Only patients with their first episode of TTP were included. All patients had ADAMTS13 activity <10% at the time of their initial episodes. The patients' demographics, initial clinical data, and the durations of follow-up were not different. The greater total dose of corticosteroids given to rituximab-treated patients may have confounded our interpretation that rituximab was associated with the decreased frequency of relapses. Other limitations of our data are that there was no standard treatment protocol and only selected patients received rituximab. Although these patients were treated in 9 different Oklahoma City hospitals, 1 of the authors (J.N.G.) saw each of these 37 patients and participated in treatment decisions.

Table 1. Comparison of 16 patients who were treated with rituximab for their initial episode of TTP with 21 patients who were not treated with rituximab, 2003-2014

	Rituximab	No rituximab	*P**
Characteristics			
Patients, n	16	21	—
Median age, y (range)	41 (20-79)	38 (18-69)	.17
Race, n (% black)	7 (44)	8 (38)	.75
Gender, n (% female)	12 (75)	15 (71)	1.00
Initial episode in 2009-2014, n (%)	10 (63)	11 (52)	.74
Initial clinical data			
Median hematocrit, % (range)	22 (8-26)	21 (13-33)	.42
Median platelets, $\mu L \times 10^3$ (range)	8 (5-29)	13 (4-63)	.32
Median creatinine, mg/dL (range)	1.5 (0.8-6.5)	1.2 (0.8-4.4)	.12
Median LDH, U/L (range)	1 206 (664-3 319)	1479 (343-3519)	.73
No. of severe neurologic abnormalities (%)	8 (50)	11 (52)	1.00
Treatment of initial episode			
Median no. of PEX treatments (range)	16 (5-79)	8 (5-24)	<.01
Median days from first to last PEX (range)	21 (5-76)	8 (5-43)	<.01
Corticosteroid, n (%)	16 (100)	21 (100)	—
High-dose corticosteroid, n (%)	6 (38)	3 (14)	.14
Median corticosteroid total dose, mg (range)	3 975 (1 000-14 070)	2135 (300-8870)	.03
Cyclophosphamide, n (%)	2 (13)	0	.18
Vincristine, n (%)	1 (6)	0	.43

Comparison of the patients who did or did not receive rituximab for an initial episode of TTP, 2003-2014. This patient cohort was selected to begin with the first patient who was treated with rituximab for her refractory initial TTP episode in December 2003. LDH values were adjusted for an upper limit of normal of 200 U/L. Major neurologic abnormalities were primarily transient focal abnormalities; seizures, stroke, and coma also occurred. The median time when rituximab was started was day 11 (day 1 is the day of the first PEX). One patient was treated with corticosteroids and 1 rituximab infusion for an initial diagnosis of primary immune thrombocytopenia 5 d before TTP was diagnosed and PEX was started; she required only 5 PEX sessions; she completed the course of 4 weekly rituximab infusions. High-dose corticosteroid was methylprednisolone, 1000 mg/d for 3 d. The total dose of corticosteroid was calculated in prednisone equivalents for the duration of the hospital treatment of TTP. Posthospital tapering doses of prednisone were not available.

LDH, lactate dehydrogenase.

*Median values were compared by the Wilcoxon 2-sample test with *t* approximation. Fisher's exact test was used for comparing proportions. Dashes represent data for which statistical comparisons were not appropriate.

These data do not provide the strength of evidence of a randomized, controlled trial. However, because TTP is a rare disorder, it is unlikely that the effectiveness of rituximab will be studied in a randomized, controlled trial. The National Heart, Lung, and Blood Institute Transfusion Medicine/Hemostasis Clinical Trials Network initiated a randomized, placebo-controlled trial to evaluate the efficacy of rituximab for initial treatment of patients with TTP in 2009[7]; the trial was stopped for futility after enrollment of only 3 patients in the first year. The recently reported phase 2 trial of caplacizumab for TTP[8] also emphasizes the difficulty of conducting a randomized, controlled trial for patients with acquired TTP: 56 sites in 13 countries required 40 months to enroll 75 patients.

Although our data documented decreased frequency of relapse when rituximab was added to initial treatment with PEX and corticosteroids, we have not yet begun to use rituximab as initial treatment of all patients with TTP. Excluding the 2 patients who died with systemic lupus erythematosus, 10 (53%) of the remaining 19 patients whose initial episode responded promptly and completely without rituximab have not relapsed, with a median follow-up of 5.7 years (range, 2.5-9.2 years). Because we believe that patients who relapse are at greater risk

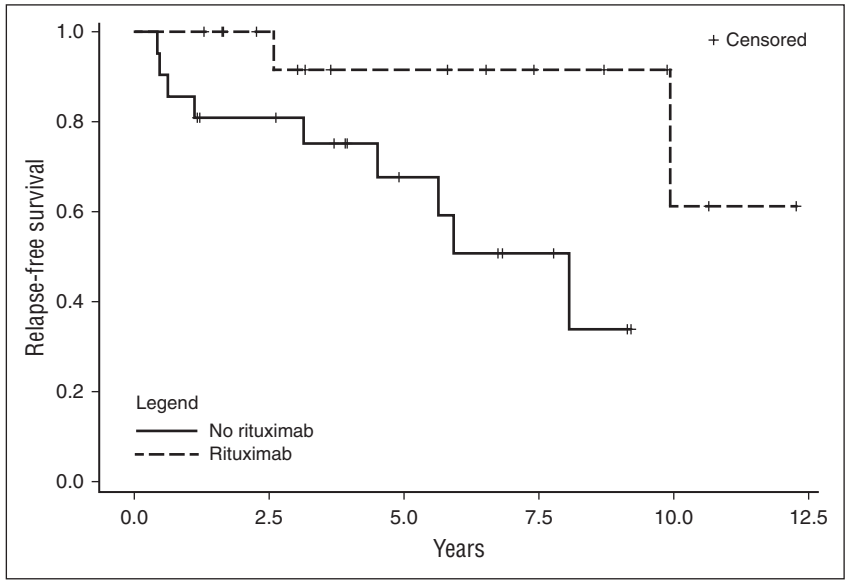

Figure 1. Kaplan-Meier analysis of the time to relapse for 16 patients treated with rituximab and 21 patients not treated with rituximab for their initial episode of TTP. Two patients relapsed after rituximab treatment at 2.5 and 9.9 years. Nine patients who did not receive rituximab relapsed at 0.4 to 5.9 years (median, 3.1 years). Censored patients who had not relapsed at the time of their last follow-up are indicated by hash marks. Two patients not treated with rituximab and who had not relapsed died at 16 and 30 months; their deaths were related to preexisting systemic lupus erythematosus. Hash marks do not discriminate between 2 patients treated with rituximab who had the same duration of follow-up (1.5 years) and 2 patients not treated with rituximab who had the same duration of follow-up (3.8 years). The difference was significantly different ($P = .009$, calculated to account for the 2 competing events of death).[6]

for subsequent relapses, we usually treat patients who have relapsed episodes of TTP with rituximab. The values and preferences of patients and physicians are essential for these treatment decisions.

There is an Inside *Blood* Commentary on this article in this issue.

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To the editor:

CSF3R mutations have a high degree of overlap with CEBPA mutations in pediatric AML

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Childhood cancers represent distinct clinical entities, often with unique genomic alterations and therapeutic responses that differ from cancers arising in adults. Pediatric acute myeloid leukemia (AML) comprises ~25% of childhood leukemias.[1] In contrast to acute lymphoblastic leukemia, which has a 90% survival rate, outcomes for pediatric AML patients remain poor, with an ~50% relapse rate despite intensive regimens.[1] Our limited understanding of the genetic alterations in pediatric AML has hindered development of targeted therapeutic strategies. Given that AML is primarily an adult disease, until recently, our understanding of pediatric AML had been informed by data generated in adults. Yet, some newly discovered mutations in adult AML are rare or entirely lacking in pediatric AML, thus validating critical differences in the pathogenesis. The Therapeutically Applicable Research to Generate Effective Treatments (TARGET) initiative (https://ocg.cancer.gov/programs/target), a collaboration between the Children's Oncology Group (COG) and the National Institutes of Health National Cancer Institute, has addressed this issue by large-scale genomic analysis of pediatric AML. For the first time, "pediatric-specific" genomic lesions are being defined that may alter the therapeutic options in childhood AML.

Through the TARGET initiative, comprehensive genomic analysis was performed on 186 cases of pediatric AML, 95 with matched relapse and all with matched remission samples in the discovery phase. Samples were marrow or peripheral blood. Research was approved by the appropriate review board and conducted in accordance with the Declaration of Helsinki. The analysis included whole genome (WGS) and exome sequencing from which a custom capture panel of ~200 genes of interest was generated. A total of 787 samples were then deep sequenced using this custom capture panel, including samples from the discovery cohort. All sequencing files were deposited to the Database of Genotypes and Phenotypes under TARGET AML substudy ID phs000465 (http://www.ncbi.nlm.nih.gov/projects/gap/cgi-bin/study.cgi?study_id=phs000465.v10.p3). Through these efforts, we have identified oncogenic colony-stimulating factor 3 receptor (CSF3R) mutations in pediatric AML.

CSF3R, also known as granulocyte colony-stimulating factor (G-CSF) receptor is a major driver of neutrophil proliferation and