inside blood commentary

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CLINICAL TRIALS AND OBSERVATIONS

Comment on Kong et al, page 1097

TPO for ITP in pregnancy

James B. Bussel and Eun-Ju Lee WEILL CORNELL MEDICINE

In this issue of *Blood*, Kong et al describe a novel approach to immune thrombocytopenia (ITP) in pregnancy.[1]

In 1990, 3 studies summarized in Bussel et al[2] all showed a low incidence of severe fetal thrombocytopenia (10% to 15%) and a very low incidence of intracranial hemorrhage (0.5% to 1%) in infants of mothers with ITP. These findings, combined with the difficulty with fetal blood[3] and scalp sampling,[4] altered the consensus recommendations on vaginal delivery instead of cesarean section for routine deliveries. The challenge remained of preventing maternal bleeding and allowing epidural anesthesia. Because platelet counts typically fall during the third trimester, the 80 000 to 100 000 $\times 10^9$/L count required for an epidural, more than enough for safe delivery, often is a difficult platelet threshold to achieve.

Generally accepted treatments of ITP in pregnancy are IV immunoglobulin (IVIG) and steroids. IVIG has a substantial but all-too-temporary platelet effect. It is primarily useful for scheduled, elective delivery or in an emergency if steroids are ineffective. Steroids (prednisone) have little fetal toxicity because of placental 21β hydroxylase. In view of the low required platelet counts during pregnancy (only 20 000 $\times 10^9$/L), starting with 10 to 20 mg daily of prednisone is often a good approach; higher doses are often needed later in gestation and may not be sufficient.[5] A recent study suggested that these 2 main treatments are less effective for ITP in pregnant than in nonpregnant women.[6]

Second-line treatments are rarely invoked. Rituximab has been accidentally used (not knowing the mother was pregnant), when other treatments had failed, and when the mother herself requires treatment. Fetal toxicity seems low, although clinical and laboratory follow-up has not been comprehensive. Anti-D immunoglobulin is used at 28 weeks (and at delivery) in thousands of rhesus factor–negative pregnancies per year; however, the ITP dose is 10 times as high as for prophylaxis and could result in maternal or fetal hemolysis. Treatment with azathioprine during pregnancy to prevent rejection of a transplanted kidney seems safe for the fetus; however, azathioprin is not very effective in maternal ITP, and onset of its effect requires weeks.

The study by Kong et al treated 31 pregnant women with ITP, almost all during their first pregnancy. The women were selected because they had failed to respond to corticosteroids and/or IVIG. Twenty-three responded, with 10 women achieving a platelet count >100 000 $\times 10^9$/L and another 13 peaking in the 30 000 to 100 000 $\times 10^9$/L range. Patients received 300 U/kg of recombinant human thrombopoietin (TPO) for 14 days and were then dosed according to their response. Recombinant human TPO is licensed in China for ITP.

Having another effective, safe agent to use would be useful in pregnant women with ITP. The 2 thrombopoietic agents available worldwide, eltrombopag[7] and romiplostim,[8] would both be expected to cross the placenta and have been avoided during pregnancy due to concerns of the effects on fetal bone marrow. An unanswered question is whether the thrombopoietic agent described in this study would cross the placenta or appear in breast milk. The authors suggest that the modification of the TPO-like molecule makes this unlikely. The neonatal safety and median 53-week follow-up for growth and development is encouraging, as is the not-increased TPO level in cord blood. There are too few patients to use the low rate of neonatal thrombocytopenia to suggest that the TPO agent affected the fetal count. Although small case reports suggest maternal efficacy of TPO agonists in very refractory ITP cases in pregnancy,[9] rigorous studies are needed of romiplostim and eltrombopag to see if the findings of Kong et al can be replicated with the 2 more widely available agents. This treatment could greatly facilitate management of ITP in pregnant women if it is confirmed to be both safe and effective.

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REFERENCES

1. Kong Z, Qin P, Xiao S, et al. A novel recombinant human thrombopoietin therapy for the management of immune thrombocytopenia in pregnancy. *Blood*. 2017;130(9):1097-1103.

2. Bussel JB, Druzin ML, Cines DB, Samuels P. Thrombocytopenia in pregnancy. *Lancet*. 1991;337(8735):251.

3. Paidas MJ, Berkowitz RL, Lynch L, et al. Alloimmune thrombocytopenia: fetal and neonatal losses related to cordocentesis. *Am J Obstet Gynecol*. 1995;172(2 Pt 1):475-479.

4. Adams DM, Bussel JB, Druzin ML. Accurate intrapartum estimation of fetal platelet count by fetal scalp samples smear. *Am J Perinatol*. 1994;11(1):42-45.

5. Gernsheimer T, James AH, Stasi R, How I treat thrombocytopenia in pregnancy. *Blood*. 2013;121(1):38-47.

6. Sun D, Shehata N, Ye XY, et al. Corticosteroids compared with intravenous immunoglobulin for the treatment of immune thrombocytopenia in pregnancy. *Blood*. 2016;128(10):1329-1335.

7. Bussel JB, Cheng G, Saleh MN, et al. Eltrombopag for the treatment of chronic idiopathic thrombocytopenic purpura. *N Engl J Med*. 2007;357(22):2237-2247.

8. Bussel JB, Kuter DJ, George JN, et al. AMG 531, a thrombopoiesis-stimulating protein, for chronic ITP. *N Engl J Med*. 2006;355(16):1672-1681.

9. Decroocq J, Marcellin L, Le Ray C, Willems L. Rescue therapy with romiplostim for refractory primary immune thrombocytopenia during pregnancy. *Obstet Gynecol*. 2014;124(2 Pt 2 suppl 1): 481-483.

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LYMPHOID NEOPLASIA

Comment on Narita et al, page 1114

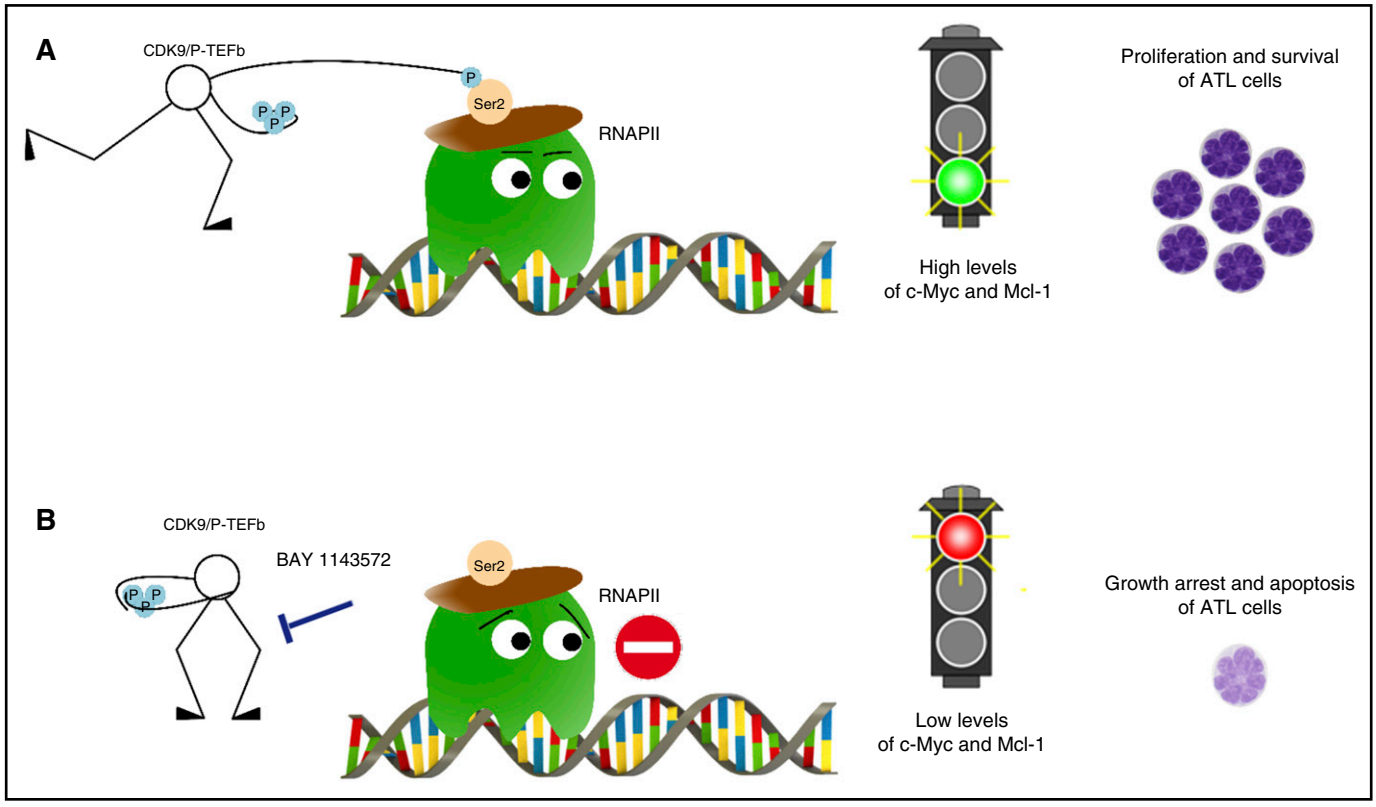
CDK9 inhibition for ATL therapy

Ali Bazarbachi AMERICAN UNIVERSITY OF BEIRUT

In this issue of *Blood*, Narita et al demonstrate that inhibition of cyclin-dependent kinase 9 (CDK9) signaling with the novel agent BAY 1143572 abrogates proliferation and induces apoptosis of adult T-cell leukemia/lymphoma (ATL) cells in cell lines, patient samples, and in xenografts in NOG mice.[1] This makes CDK9 a potentially promising therapeutic target in ATL, a deadly disease.

ATL is an aggressive proliferation of mature activated T cells transformed by human T-cell lymphotropic virus type-1 (HTLV-1) infection.[2] Despite more than 35 years of intensive research, prognosis for patients with ATL remains dismal, with most patients dying within 1 year.[3] This poor prognosis is the result of the intrinsic chemotherapy resistance of ATL cells and severe immune deficiency. The antiviral combination of zidovudine and interferon-α prolongs survival of patients with chronic and smoldering ATL subtypes and of a fraction of acute ATL patients whose cells contain wild-type P53.[4] Allogeneic stem cell transplantation results in prolonged survival of approximately one-third of patients, but unfortunately, only a small percentage of ATL patients can receive a transplant.[5] New promising agents include arsenic trioxide, lenalidomide, and mogamulizumab.[3] Nevertheless, there is an unmet need for improved therapy for most ATL patients, stressing the need for novel targeted therapies.

CDK9 is a subunit of the positive transcription elongation factor b (P-TEFb) complex.[6] It regulates the elongation step during gene transcription by phosphorylating the C-terminal domain of RNA polymerase II. Deregulation of CDK9/P-TEFb signaling has been found to play an important role in the development and/or maintenance of the malignant cell phenotype,[7,8] making CDK9 an



Inhibition of CDK9 signaling with the novel agent BAY 1143572 abrogates proliferation and induces apoptosis of ATL cells. (A) CDK9 phosphorylates RNA polymerase II (RNAPII) at serine 2 resulting in high levels of c-Myc and Mcl-1 and leading to proliferation and survival of ATL cells. (B) BAY 1143572 specifically inhibited CDK9-mediated phosphorylation at serine 2 of RNAPII resulting in decreased levels of c-Myc and Mcl-1, thus leading to growth arrest and apoptosis of ATL cells.