identified for these problems, which are likely to be heterogeneous in origin, but manifest through common pathophysiologic processes; specifically, disturbance of the hemostatic system and inadequate placentation. For example, in preeclampsia we have known for almost half a century that there is coagulation activation, thrombin generation, microvascular fibrin deposition, endothelial dysfunction, disturbed trophoblast invasion of the maternal circulation, and placental infarction.[2] Indeed this knowledge led to antiplatelet therapy with low-dose aspirin being introduced in the 1980s with a modest effect (~ 15%) in preventing preeclampsia and FGR.[3] However, these conditions remain major challenges affecting approximately 10% of pregnancies, with major contributions to both maternal and perinatal morbidity and mortality.

In antiphospholipid syndrome similar hemostatic changes and placental infarcts are seen. This is manifest clinically not only by the late pregnancy problems of preeclampsia, FGR, and abruption, but also by recurrent miscarriage. The latter problem is responsive to antithrombotic intervention with low-dose aspirin and heparin.[3] Further, women with acquired or heritable thrombophilia are more likely to develop preeclampsia and FGR, although the risk may be overestimated from retrospective case-control and cohort studies as prospective investigations have not confirmed these findings.[3] Nonetheless, a logical conclusion from these data was that antithrombotic interventions may prevent late pregnancy complications. The increasing awareness of the association between thrombophilia and late pregnancy complications, and the lack of alternative treatment, led obstetricians to use low molecular weight heparins (LMWHs), which are safe in pregnancy,[3,4] for prevention and treatment of these conditions. This practice, driven by the lack of effective therapy, was based on extrapolation, with the hope and anticipation that subsequent supportive evidence would emerge. Trials were therefore urgently required to test the hypothesis that such treatment was actually effective.

Martinelli et al report the first large, well-designed, multicenter, prospective, randomized trial to examine Heparin in pregnant women with Adverse Pregnancy outcome to improve the rate of successful PregnancY (the HAPPY trial).[1] They compared event recurrence in 135 women, after screening 250, considered at increased risk because of previous late pregnancy complications. The women were randomized to treatment with a LMWH (nadroparin) in addition to medical surveillance, or to medical surveillance alone. The difficulty in conducting these trials should not be underestimated given the demand from women for an active intervention, the frustration felt by obstetricians because of the lack of an effective therapy, and the now widespread nonevidenced-based use of LMWH for pregnancy complications. Despite the commendable perseverance of the researchers, after 3 years only 50% of the planned study participants had been recruited and the trial was stopped by reason of futility. Overall, 21% of participants randomized to active treatment developed a combined end point compared with 18% of controls. This is a nonsignificant event risk difference of 2.2 (95% CI: −11.6 to 16.0). The distribution of the single components of the composite end point (preeclampsia, eclampsia, HELLP [Hemolysis Elevated Liver enzymes and Low Platelets] syndrome, FGR, intrauterine fetal death, and abruption) was also similar. There were no serious adverse events associated with LMWH.

These data show that nadroparin has no impact in preventing these conditions (see figure). This is in agreement with other reports including a systematic review of several heterogeneous studies of LMWH for women with late pregnancy complications,[5] and is also consistent with 2 recent large, randomized trials that showed no benefit from LMWH and low-dose aspirin in women with recurrent pregnancy loss.[6,7] The results of these large, methodologically sound trials may differ from smaller, methodologically limited or pilot studies,[3,8] thus emphasizing the critical importance of an adequate evidence base to avoid the premature adoption of potential new interventions into clinical practice. Such interventions might still prove effective in specific subgroups, such as those with thrombophilia, but this cannot be assumed and specific trials are required, some of which are under way.

In the meantime we should learn the lesson of premature acceptance of hypothetically beneficial treatment into routine clinical practice. This is important, not only to reduce cost in already challenged health care services, but also to protect our patients from unnecessary risk, and specifically to protect women suffering such devastating pregnancy complications from iatrogenic false hope.

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REFERENCES

1. Martinelli I, Ruggenenti P, Cetin I, et al. Heparin in pregnant women with previous placenta-mediated pregnancy complications: a prospective, randomized, multicenter, controlled clinical trial. *Blood*. 2012;119(14):3269-3275.
2. Greer IA. Thrombosis in pregnancy: maternal and fetal issues. *Lancet*. 1999;353(9160):1258-1265.
3. Bates SM, Greer IA, Middeldorp S, Veenstra DL, Prabulos AM, Vandvik PO. VTE, thrombophilia, antithrombotic therapy, and pregnancy: antithrombotic therapy and prevention of thrombosis (9th Ed): American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest*. 2012;141(2 suppl):e691S-e736S.
4. Greer IA, Nelson-Piercy C. Low-molecular-weight heparins for thromboprophylaxis and treatment of venous thromboembolism in pregnancy: a systematic review of safety and efficacy. *Blood*. 2005;106(2):401-407.
5. Dodd JM, McLeod A, Windrim RC, Kingdom J. Antithrombotic therapy for improving maternal or infant health outcomes in women considered at risk of placental dysfunction. *Cochrane Database Syst Rev*. 2010;CD006780.DOI: 10.1002/14651858. CD006780.pub2.
6. Clark P, Walzer ID, Langhome P, et al. SPIN (Scottish Pregnancy Intervention) study: a multicenter, randomized controlled trial of low-molecular-weight heparin and low dose aspirin in women with recurrent miscarriage. *Blood*. 2010;115(21):4162-4167.
7. Kaandorp SP, Goddijn M, van der Post JAM, et al. Aspirin plus heparin or aspirin alone in women with recurrent miscarriage. *N Engl J Med*. 2010;362(17):1586-1596.
8. Rey E, Garneau P, David M, et al. Dalteparin for the prevention of recurrence of placental mediated complication of pregnancy in women without thrombophilia: a pilot randomized controlled trial. *J Thromb Haemost*. 2009; 7(1):58-64.

● ● ● LYMPHOID NEOPLASIA

Comment on Xi et al, page 3330

BRAF mutation: supporting diversity in HCL

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In this issue of *Blood*, Xi and colleagues report on v-raf murine sarcoma viral oncogene homolog B1 (BRAF) mutations in hairy cell leukemia (HCL) subsets, demonstrating that BRAF V600E mutations are absent in variant HCL forms and in a subset of classic HCL (HCLc).[1]

Specifically, the authors found non-mutated wild-type BRAF in all cases of variant HCL, in all HCL cases expressing IGHV4-34, and surprisingly also in 21% of HCLc, disturbing the uniform picture of BRAF mutations in HCL.[2] In this series, BRAF mutations, which previously were described to be present in all cases of HCLc,[2] were detected in only 79% of HCLc. Xi et al propose that this genetic diversity supports the classification of variant and IGHV4-34$^+$ HCL cases as distinct disease subgroups with a pathogenesis different from HCLc, in terms of clinical presentation, immunophenotypic differences, and inferior responses to standard therapy.

BRAF is a member of the serine–threonine kinase RAF family, and participates in the mitogen-activated protein kinase (MAPK) signaling cascade downstream of RAS signaling proteins, transmitting survival and proliferation signals from cell surface receptors to the nucleus. BRAF mutations initially were discovered as oncogenic events in solid tumors, most notably in melanoma.[3] The mutated BRAF protein containing an amino acid switch at position 600 (V600E) results in the activation of BRAF kinase activity, causing constitutive downstream signaling and cell growth.

The recent initial report about BRAF mutations in HCL, based on whole-exome sequencing of HCL cells, caused great interest and excitement,[2] given that such a long-sought recurrent genetic lesion in HCL had not previously been identified. The high frequency of V600E BRAF mutations in HCLc and lack of such mutations in other B-cell malignancies indicates that this mutation represents a disease-defining mutation in HCL. The initial report about BRAF mutations in HCL based on 48 HCL samples has been extended and corroborated in larger cohorts of patients from different institutions, using allele-specific PCR assays.[4-6]

The findings by Xi et al overall confirm the importance and high prevalence of BRAF mutations in HCLc.[1] It is tempting to speculate that lack of BRAF mutations in a significant proportion of immunophenotype-defined HCLc cases (n = 11) could be related to the higher prevalence of HCLc patients who were on treatment or unresponsive to standard therapy in this series,[1] but as discussed by Xi et al, such HCLc cases with wild-type BRAF clinically do not appear to behave differently compared with BRAF-mutated cases.

Other potential developments of BRAF mutations in HCL are novel diagnostic possibilities and options for therapeutic targeting of BRAF, using BRAF inhibitors. Based on the data by Xi et al, BRAF mutational analysis can help distinguishing HCLc from HCL variant and IGHV4-34$^+$ cases on the molecular level, and therefore such analyses are likely to become part of the diagnostic armamentarium in HCL. The therapeutic potential of targeting BRAF mutations in HCL is more difficult to predict. In vitro responsiveness of BRAF-mutated HCL to the BRAF inhibitor PLX-4720[2] supports further development of BRAF inhibitors in HCL patients.

Despite the current excitement about BRAF in HCL, we need to keep in mind that the importance of BRAF mutations for HCL pathogenesis and disease progression remains ill-defined. The mere presence of V600E BRAF mutations does not indicate that this genetic lesion is critical for the disease process or that BRAF inhibitors will follow the successful path of BCR-ABL kinase inhibitors. The phase 3 experience with the BRAF inhibitor vemurafenib (PLX4032) in previously untreated melanoma demonstrates that this kinase inhibitor improves overall and progression-free survival in patients with BRAF V600E mutation compared with dacarbazine.[7] However, such BRAF inhibitor–induced remissions are typically short-lived because of development of resistance. This resistance to BRAF inhibitors is because of the ability of melanoma cells to flexibly switch their signaling programs among different RAF isoforms,[8] underscoring the complexity and oftentimes redundancy of cell signaling, and the ability of cancer cells to adapt and bypass certain signaling modules that are pharmacologically blocked. In-depth analyses into the function of BRAF in HCL, and clinical trials with BRAF inhibitors such as vemurafenib in HCL will help to better define the role of V600E BRAF mutations in HCL and will strengthen our understanding of the molecular pathogenesis of HCL.

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REFERENCES

1. Xi L, Arons E, Navarro W, et al. Both variant and IGHV4-34–expressing hairy cell leukemia lack the BRAF V600E mutation. *Blood*. 2012;119(14):3330-3332.
2. Tiacci E, Trifonov V, Schiavoni G, et al. BRAF mutations in hairy-cell leukemia. *N Engl J Med*. 2011;364(24):2305-2315.
3. Davies H, Bignell GR, Cox C, et al. Mutations of the BRAF gene in human cancer. *Nature*. 2002;417(6892):949-954.
4. Tiacci E, Schiavoni G, Forconi F, et al. Simple genetic diagnosis of hairy cell leukemia by sensitive detection of the BRAF-V600E mutation. *Blood*. 2012;119(1):192-195.
5. Arcaini L, Zibellini S, Boveri E, et al. The BRAF V600E mutation in hairy cell leukemia and other mature B-cell neoplasms. *Blood*. 2012;119(1):188-191.
6. Blombery P, Wong SQ, Hewitt CA, et al. Detection of BRAF mutations in patients with hairy cell leukemia and related lymphoproliferative disorders [published online ahead of print December 1, 2011]. *Haematologica*. doi: 10.3324/haematol.2011.05487.
7. Chapman PB, Hauschild A, Robert C, et al. Improved survival with vemurafenib in melanoma with BRAF V600E mutation. *N Engl J Med*. 2011;364(26):2507-2516.
8. Villanueva J, Vultur A, Lee JT, et al. Acquired resistance to BRAF inhibitors mediated by a RAF kinase switch in melanoma can be overcome by cotargeting MEK and IGF-1R/PI3K. *Cancer Cell*. 2010;18(6):683-695.

● ● ● PLATELETS & THROMBOPOIESIS

Comment on Léon et al, page 3333

Does "more" necessarily mean "better"?

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In this issue of *Blood*, Léon and colleagues describe the effects of romiplostim, a thrombopoietin (Tpo) mimetic peptide, in the mouse model of inherited platelet dysfunction because of mutation of the myosin 9 gene.[1]

The diagnosis of immune thrombocytopenia (ITP) may sometimes conceal more rare cases of inherited disorders of the platelet function, particularly in patients found to be resistant to steroids or splenectomy. On the whole, these last include a crowded list of dysfunctions, involving platelet surface constituents or intracellular components.[2] Because two Tpo receptor agonists, eltrombopag and romiplostin, have been approved for chronic ITP adult patients unresponsive to glucocorticoids, intravenous immunoglobulin, or splenectomy,[3] their potential use also in inherited thrombocytopenia is attractive.