Oxidative stress may cause ITP

Paul Imbach  UNIVERSITY CHILDREN’S HOSPITAL BASEL

ITP has served as a model for autoimmune disorders with disturbances of the innate and adaptive immunity where targeted treatment with immunomodulation has proven effective. In this issue of Blood, Zhang et al report that these immune disturbances are triggered by oxidative stress. In addition, the molecular-based results indicate the possibility of distinguishing the transient, self-limited form of ITP from chronic, long-term ITP.

Confronted with a patient with newly diagnosed ITP, the physician cannot determine if the patient has a transient, self-limited disorder or long-term, chronic ITP. In children ITP is often present after an infection or vaccination. In adults, ITP is associated with heliobacter pylory, hepatitis C virus, HIV, and other viral infections, although the mechanism is not clear. It is unknown; published studies have either relied on patient self-report without confirmation of relevant laboratory results or have evaluated the prevalence in restricted cohorts of survivors, making their conclusions susceptible to bias.

Among the components of MS, obesity is a particular concern in ALL survivors. Patients treated with cranial radiation therapy are at increased risk for being overweight after therapy, in part because of radiation-induced growth hormone insufficiency and leptin insensitivity. However, even survivors treated without radiation (who represent the majority of children with ALL treated in the current era) may be at risk for obesity as a consequence of their cancer therapy. Corticosteroids can cause increased energy intake during therapy, and may lead to physical inactivity secondary to myopathy, osteonecrosis, and reduced bone mineral density. Vincristine-induced peripheral neuropathy may further limit activity. In addition, unhealthy lifestyle behaviors such as poor diet and increased sedentary time may develop during treatment protocols that can last for 3 years or more.

While much work remains to be done to understand the pathophysiology of metabolic derangements in children treated for ALL, it is clear that these abnormalities place survivors at increased risk for cardiovascular disease and stroke. In fact, the Childhood Cancer Survivor Study has demonstrated that ALL survivors are 4.2 times more likely than the general population to die of cardiac disease, and 6.4 times as likely to suffer a late-occurring stroke. Consequently, all survivors of ALL, but particularly those exposed to cranial radiation therapy, HSCT, or total body irradiation, require regular follow-up care that is adapted to address the metabolic and cardiovascular risks that arise from their prior therapy.

The Children’s Oncology Group (and other international cooperative groups) has published guidelines for screening for MS in survivors (www.survivorshipguidelines.org). The challenge is to ensure that these guidelines reach their intended target.

A study of health care utilization in 8522 North American childhood cancer survivors revealed that less than 15% of survivors continue to receive follow-up care at a cancer center once they become adults. Most are seen by a primary care clinician in their community. Survivors’ risks of developing late effects of therapy rise steadily over time without plateauing, in lock-step with a decreasing proportion seeking care at a cancer center.

Primary care clinicians are often unaware of the specific risks faced by survivors and without this knowledge may not screen for MS in young survivors, particularly in the absence of obesity. Despite a higher prevalence of obesity in ALL survivors, many develop 1 or more cardiovascular risk factors without actually being obese. In the French cohort described by Oudin et al, only 14.5% had an elevated waist circumference, while 25.3% were hypertensive and 31.8% had low HDL cholesterol. Appropriate early screening will facilitate intervention with lifestyle counseling focused on increasing physical activity, improving diet, and curbing risky behaviors such as cigarette smoking. When necessary, hypertension, dyslipidemia, and impaired glucose tolerance can be treated pharmacologically, but intervention at this late stage is not enough. Pediatric oncologists must find ways to interrupt the path between leukemia treatment and the cascade of behavioral and pathophysiologic consequences that lead to MS. Treatment modifications such as the elimination of cranial radiation from most ALL regimens will modify the risk, and multidimensional programs targeting lifestyle during ALL therapy are being evaluated in ongoing clinical trials.

As healthcare practitioners who care for children during and in the wake of cancer therapy, our mission is to ensure that the excellent cure rate of childhood ALL translates into lives unburdened by the cost of that cure.

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of other autoimmune disorders have been indirectly documented by therapeutic immunomodulatory intervention such as intravenous human immunoglobulin concentrate, which targets the whole immune response, monoclonal anti-CD20 antibodies, by cyclosporine A, or by nonspecific immunosuppressants on an empiric basis.

Zhang and colleagues report here on gene-expression and molecular-oxidative stress results as causative factors for chronic ITP in children. With transcriptome cDNA microarray analysis of peripheral blood, the authors could show differences of clustering profiles among patients with transient, self-limited ITP and chronic, long-term ITP and control individuals. Overexpression of the gene vanin-1 (VNN1)—an oxidative stress sensor—was associated with chronic ITP only (see figure). VNN1 is characterized by its role in oxidative stress response, characterized by its role in oxidative stress response, and it mediates production of inflammatory cytokines by antagonizing peroxisome proliferator-activated receptor γ (PPARγ). VNN1 is the only gene that was detected in chronic ITP. Exposure of human blood mononuclear cells to oxidative stress inducers (LPS, sodium arsenite) up-regulates VNN1. Quantitative real-time PCR measurement of VNN1 expression confirmed the oxidative stress events in peripheral blood cells. In addition, the ratio of reduced to oxidized glutathione—a parameter of the cellular redox state—was significantly down-modulated in children with chronic ITP in comparison to healthy controls.

In the present study by Zhang et al, the numbers of the patient/control groups are small, but ongoing oxygen stress is a significant factor in patients with chronic ITP. Chronic ITP is an autoimmune disorder where isolated low–platelet counts indicate the immune pathogenesis. In chronic ITP, clinical bleedings occur in some patients with very low platelet counts. Many other autoimmune disorders such as Guillain Barre syndrome, Kawasaki syndrome, lupus erythematosus, dermatomyositis, and dermatologic blistering disease have similar pathogeneses and respond to similar therapeutic interventions.

To gel or not to gel

Dennis K. Galanakis  STONY BROOK UNIVERSITY SCHOOL OF MEDICINE

In this issue of Blood, Chernysh et al examine the pregelation phase of fibrin polymerization, and by demonstrating heterogeneous polymeric structures that progressively coalesce into scaffolds provide novel insights into this process with potential implications on circulating soluble fibrin.

initiated by thrombin cleavage of the 2 FpAs (see figure panel A), fibrin polymerization is mainly mediated by the 2 “A” knobs in the central region (E) that bind to complementary “a” pockets constitutively present on each outer (D) region of another molecule. The resulting, staggered 2–molecule-thick structure (see figure panel B) elongates by sequential binding of additional monomers to form the protofibril. Prototibrils

REFERENCES

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