The success of the BiTE format triggered the search for intellectual property space among bispecific antibody formats of similar size and valence. A potentially competing format was recently developed by the biotechnology company MacroGenics Inc and termed DART (for Dual-Affinity Re-Targeting). The DART format is based on the diabody format that separates cognate variable domains of heavy and light chains of the 2 antigen binding specificities on 2 separate polypeptide chains. Whereas the 2 polypeptide chains associate noncovalently in the diabody format, the DART format provides additional stabilization through a C-terminal disulide bridge (see figure). DARTs can be produced in high quantity and quality and reveal exceptional stability in both formulation buffer and human serum. In this issue of Blood, Moore et al conduct a side-by-side comparison of the in vitro performance of CD19xCD3 DART and BiTE molecules that were based on the same parental mouse anti-human CD3 and mouse anti-human CD19 monoclonal antibodies as blinatumomab. In various redirected cytotoxicity assays with human B-cell lines and autologous human B cells, the bispecific antibody in the DART format consistently outperformed the BiTE format with respect to the maximal level of B-cell lysis, the concentration required for half-maximal B-cell lysis, and the induction of molecular markers of T-cell activation. Neither format induced the activation or proliferation of T cells in the absence of B cells. The comparison appears legitimate as the previously reported low picomolar concentrations of the BiTE format required for half-maximal target-cell lysis were confirmed. Compared with the BiTE format, the DART format revealed a moderately higher association rate constant for CD3, a moderately lower dissociation rate constant for CD19, and an ability to cross-link T cells and B cells more efficiently. The authors discuss that the more rigid configuration of the DART format with limited flexibility between the 2 antigen-binding specificities may explain these favorable features.

In addition to comparing CD19xCD3 DART and BiTE formats, Moore et al also generated and characterized a CD19xCD3 DART that engages the TCR complex through an invariant epitope displayed by the TCR rather than by CD3 (see figure). Notably, the CD19xCD3 DART revealed virtually identical in vitro activity as the CD19xCD3 DART and demonstrated in vivo activity based on a xenograft mouse model with human effector and target cells. While this finding along with the recently published CD32BxCD16 and CD32BxCD79B DARTs underlines the adaptability of this bispecific antibody platform, it also provides an alternate T-cell recruiting and activation mechanism that may have a different activity and toxicity profile than blinatumomab.

So do DARTs BiTE better? Although this study would have been more complete by including side-by-side comparisons of the stability of DART and BiTE in formulation buffer and human serum and the in vivo activity in xenograft mouse models, Moore et al make a strong case for clinical translation of the DART format in general and CD19xCD3 and CD19xCD79B DARTs in particular. Ultimately, only clinical trials can provide a comprehensive side-by-side comparison of DART, BiTE, and other bispecific antibody formats with identical antigen-binding specificities. Perhaps more importantly, the perceived clinical viability of bispecific antibody platforms developed by competing biotechnology companies has attracted resourceful pharmaceutical companies into the arena. This can be considered good news for cancer patients. Conflict-of-interest disclosure: The author declares no competing financial interest.

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The Children’s Oncology Group (and other international cooperative groups) has published guidelines for screening for MS in 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 Ouédin 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 pathophysiological 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 health care 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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Comment on Zhang et al, page 4569

Oxidative stress may cause ITP

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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 how platelets are targeted by the host’s immune system. Infection-related oxidative stress may induce disturbed immune response. Autoantibodies or immune complexes against platelets lead to early destruction of platelets by phagocytosis or by cytotoxic T cells in predisposed individuals. The immune disturbances of ITP and
The metabolic cost of childhood ALL
Paul C. Nathan and Stacey L. Urbach

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