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 disulfide bridge (see figure). DART's can be produced in high quantity and quality and reveal disulfide bridge (see figure). DART's can be produced in high quantity and quality and reveal disulfide bridge (see figure). DART's can be produced in high quantity and quality and reveal disulfide bridge (see figure). DART's can be produced in high quantity and quality and reveal disulfide bridge (see figure). DART's can be produced in high quantity and quality and reveal disulfide bridge (see figure). DART's can be produced in high quantity and quality and reveal disulfide bridge (see figure).

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 CD19xCDTCR 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 commercial 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.

REFERENCES

CLINICAL TRIALS

Comment on Oudin et al, page 4442

The metabolic cost of childhood ALL

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In this issue of Blood, Oudin and colleagues report an increased prevalence of the metabolic syndrome (MS) in a cohort of adult survivors of childhood leukemia. The coupling of a growing population of maturing childhood leukemia survivors with a syndrome that predisposes to cardiovascular disease, diabetes, and premature mortality is a call to arms for those clinicians who provide long-term care to survivors of childhood cancer.

Survival of acute lymphoblastic leukemia (ALL), the most prevalent childhood malignancy, now exceeds 80%. Consequently, there are more than 50,000 survivors of childhood ALL alive in the United States, and the ranks continue to swell. Although ALL survivors are generally at lower risk of developing long-term sequelae of therapy compared with survivors of other cancer diagnoses (notably Hodgkin lymphoma, brain tumors, and sarcomas), this group has a particular predisposition for metabolic derangements. Several studies have demonstrated an increased prevalence of MS and its components (central obesity, hypertension, impaired glucose metabolism, and dyslipidemia) in this population. Patients treated with cranial radiation and hematopoietic stem cell transplantation (HSCT) appear to be particularly vulnerable: in the Oudin study, 18.6% of survivors treated with the combination of HSCT and total body irradiation met the criteria for MS. The true prevalence of MS in ALL survivors is...
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 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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REFERENCES

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 helicobacter pylori, 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. (Auto)-antibodies 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
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