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IMMUNOBIOLOGY AND IMMUNOTHERAPY

*Comment on Konishi et al, page 1789*

# Multiple myeloma treatment: one bridge closer

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**In this issue of *Blood*, Konishi et al describe an antibody that stimulates T cells on one side while binding off-the-shelf monoclonal antibodies (mAbs) on the other.[1]**

Bispecific antibodies have injected new momentum into the cancer immunotherapy revolution. By recognizing a surface tumor-specific protein on one arm and stimulating an immune receptor on the other, bispecific antibodies effectively bridge the gap between immune cells and tumor cells. This is especially useful in cancers that elicit a poor immunologic response.

Bispecific antibodies that agonize the T-cell signaling receptor CD3 are particularly promising in hematologic malignancies that invade naturally T cell–rich environments. In multiple myeloma (MM), clonal malignant plasma cells accumulate in the bone marrow, leading to anemia, bone erosion, and end-organ damage from deposition of clonal immunoglobulins. Although MM remains incurable, multiple lines of treatment are now available to patients, significantly extending life expectancy in recent years. Nevertheless, with disease progression, relapses occur at an increased frequency, and treatment needs to be adapted swiftly and sequenced deftly. Two recent phase 2 trials reported striking results of bispecific antibodies stimulating CD3 and recognizing the MM protein BCMA (teclistamab[2]) or GPC5RD (talquetamab[3]). In both cases, deep and durable responses were observed in a population of patients with advanced MM, refractory to multiple lines of treatment. Thus, bispecific antibodies represent a promising new frontier in MM treatment.

The currently approved reagents as well as most of those in the pipeline target a single tumor antigen and stimulate a single cell type, mostly T cells. These limitations may expose patients to primary resistance if T cells are hyporesponsive at baseline or acquired resistance if the tumor downregulates the target antigen. Konishi and coauthors, therefore, sought to circumvent these limitations by designing a bridging bispecific T-cell engager (B-BiTE), a reagent coupling an antibody variable fragment specific for the Fc domain of human immunoglobulin G, and an antibody variable fragment that stimulates the CD3 signaling complex. When they incubated this reagent with human mAbs, therefore, they obtained a complex in which the original mAb confers antigen specificity and the B-BiTE activates T cells. Because the arsenal of anticancer drugs includes a growing number of mAbs, the B-BiTE can serve as a backbone to customize T-cell immunotherapy using off-the-shelf antibodies.

The authors demonstrated the efficacy and safety of B-BiTE with a number of in vitro an in vivo approaches. Initially, they generated B-BiTE complexes with the mAbs daratumumab and rituximab, which target CD38 and CD20, respectively. In vitro, in cocultures with target antigen-expressing cell lines, they observed activation of both T cells and, importantly, natural killer (NK) cells. Indeed, the B-BiTE design allows the coupled mAb to still stimulate NK cells through their Fc receptors. The degree of NK stimulation is an important difference between B-BiTE and conventional bispecific antibodies, which are often Fc-silent. Moreover, they showed that T-cell activation also promotes NK proliferation, resulting in a synergistic, powerful dual lymphoid activation.

The authors then showed efficacy of the B-BiTE approach by showing that patient T and NK cells responded to autologous myeloma cells in the presence of daratumumab/B-BiTE. Then they explored the therapeutic advantage conferred by B-BiTEs in mouse models of a $CD38^{low}$ tumor, as a model of resistance to daratumumab. Here, they showed that sequencing of 2 B-BiTEs complexes using mAbs approved for treatment of MM (daratumumab and elotuzomab, the latter targeting the tumor antigen SLAMF7) is superior to sequencing of the 2 uncoupled mAbs. These experiments were conducted in immune-deficient mice reconstituted with human peripheral blood mononuclear cell (PBMCs) and injected with tumor cells either subcutaneously or, more relevantly, intratibially.

Finally, the authors addressed the essential question of safety. In theory, it is possible that B-BiTEs will uncouple from therapeutic mAbs in vivo and form complexes with existing antibodies, resulting in potentially calamitous and unpredictable toxicity. After injection of human polyclonal immunoglobulin into immune-deficient mice, followed by administration of daratumumab/B-BiTE, the authors collected serum and used it to stimulate human PBMCs. No T-cell or NK-cell reactivity was observed, suggesting that no complex had formed that included an autoantibody specific for antigens expressed by PBMCs. Overall, this work highlights the following advantages of B-BiTEs: they provide 2 binding sites for a tumor antigen of interest, instead of just 1 like mAbs. They simultaneously stimulate T cells and NK cells and the interaction between the 2 cell types. By allowing the rapid generation of new complexes with different mAbs, they can

be used for timely treatment changes as soon as resistance develops.

In the future, it will be essential to continue exploring the possibility of in vivo coupling of B-BiTEs with circulating antibodies. This is particularly relevant for patients with autoimmune disease, as well as those with autoantibodies of unknown clinical significance. Moreover, all patients with MM present with elevated amounts of mAbs; although the antigen specificity of these paraproteins remains poorly understood, it has been proposed that chronic antigen stimulation causes monoclonal gammopathy of undetermined significance,[4] the premalignant, precursor stage of MM. The possibility that these antibodies react to chronic viruses[5] or self-antigens[6] should be considered when evaluating the safety of this treatment. Finally, the authors did not observe regulatory T-cell (Treg) activation, despite the ability of Tregs to be activated by CD3. This finding deserves further exploration, especially as preliminary results suggest that Tregs may limit the activity of the bispecific antibody teclistamab in MM.[7] These concerns notwithstanding, further developments of this therapeutic strategy could provide clinicians with an arsenal of flexible options for T-cell (and NK-cell) redirecting therapy and could benefit the care of patients with MM.

*Conflict-of-interest disclosure: The author declares no competing financial interest.* ■

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**LYMPHOID NEOPLASIA**

*Comment on Kim et al, page 1806*

# Unraveling *KMT2A*-rearranged ALL

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**In this issue of *Blood*, Kim et al[1] from the Group for Research on Adult Acute Lymphoblastic Leukemia (GRAALL) take us one giant leap forward in our understanding of adult *KMT2A*-rearranged (*KMT2A*-r) B-cell precursor acute lymphoblastic leukemia (B-ALL). For the first time, they demonstrate the ability to risk stratify young adults within this high-risk group and identify patients with *KMT2A*-r B-ALL with outstanding outcomes when treated with intensive, pediatric-inspired chemotherapy, even *without* allogeneic hematopoietic stem cell transplant (HSCT).**

We have come a long way since 1948 when Sidney Farber announced transient responses in 5 children treated with the folic acid antagonist aminopterin.[2] What has followed is 75 years of worldwide, pediatrician-led collaboration to improve outcomes in ALL. We are fortunate that now >90% of children diagnosed with ALL in resourced settings are cured with modern, risk-adapted chemotherapy.[3] Younger adults treated with intensive, pediatric-style asparaginase-based chemotherapy are also now frequently cured, almost (although not quite) as often as children.[4] The use of HSCT is typically reserved for high-risk patients (by various definitions) or those not achieving an optimal early response.[5]

Still, *KMT2A*-r ALL remains a feared subtype of ALL with historically dismal outcomes in infants,[6] as well as adults.[7] Indeed, relapsed *KMT2A*-r ALL is a dreaded occurrence given infrequent and fleeting responses to available immunotherapy (blinatumomab, inotuzumab ozogamicin, and chimeric antigen receptor T cells) and risk of lineage switch. Thus, most adult groups recommend HSCT in first complete remission (CR1) for eligible patients based on the presumption of consistently adverse disease biology. Until now, there have been no data to help a clinician further risk stratify a patient or support a non-HSCT approach.

In this context, the GRAALL investigators studied 141 adult patients with *KMT2A*-r ALL (median age, 41 years; range, 18-59 years; 12.9% of overall GRAALL cohort) treated on 3 successive GRAALL trials of intensive pediatric-inspired chemotherapy (GRAALL-2003, GRAALL-2005, and GRAALL-2014) with the goal of identifying factors associated with clinical outcomes. The *KMT2A*-r patients in the GRAALL cohort were, as expected, characterized by high-risk clinical features (older age and higher white blood cell count) but almost universally achieved CR1 with a single induction with a 5-year cumulative incidence of relapse (CIR) of 40.7% and a 5-year overall survival (OS) of 53.3%. The authors then demonstrated that patients with *KMT2A*-r ALL could be risk stratified using genetic profiling and measurable residual disease (MRD) assessment.

Regarding genetics, like infant *KMT2A*-r ALL, there was a low rate of additional mutations, with the most frequent being subclonal mutations in *RAS* and receptor