blood® commentary

CLINICAL TRIALS AND OBSERVATIONS

Comment on Wang et al, page 17

Welcome to the CART cocktail reception

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In this issue of *Blood*, Wang et al[1] report that treatment of relapsed/refractory (r/r) acute lymphoblastic leukemia (ALL) patients with a cocktail of both CART19- and CART22-cells prevents the antigen escape of CD19$^-$ CD22$^+$ blasts.

Many of us have struggled along our professional careers with the very high mortality associated with refractory hematologic malignancies, even after allogeneic stem cell transplantation. In patients with advanced disease, the immune attack driven by the donor's lymphocytes seems to be both not potent enough to eradicate malignant cells and nonspecific, causing serious and long-lasting damage to normal tissues in the form of graft-versus-host disease. The story of Emily Whitehead, a girl with refractory ALL treated successfully 7.5 years ago at the University of Pennsylvania, showed that chimeric antigen receptor (CAR) T cells targeting CD19 (CART19 cells) had a very impressive antileukemic potency and specificity. This result was confirmed in a series of patients with r/r ALL in whom CART19 cells achieved remission rates >80% and a 1-year disease-free survival ranging from 35% to 50%.[2-7] It is nowadays well established that a single infusion of autologous CART19 cells is enough to achieve these excellent results with manageable toxicity in most patients. Of note, CART cell-associated side effects, mainly cytokine release syndrome and immune effector cell-associated neurotoxicity syndrome, remain a source of concern even though they are generally reversible and cause very little long-term sequelae.

In ALL, relapse remains the Achilles heel of CART19-cell therapy. Thus, a significant proportion of patients with r/r ALL, ranging from 30% to 60%,[2-7] relapse after obtaining a complete remission with CART19. There are 2 plausible mechanisms for this phenomenon. One is early loss of CART19 cells, which is usually associated with CD19$^+$ relapses. The second is probably caused by a strong and persistent pressure of CART19 cells on the CD19$^+$ lymphoblasts, leading to the natural selection of CD19$^-$ tumor cells and subsequent relapse. These CD19$^-$ tumor cells generally express CD22 on their surface, and these patients may still go into remission after receiving CART22 cells,[8] but unfortunately, a significant proportion of them eventually experiences a relapse with CD22$^-$ or CD22-low lymphoblasts.

Wang et al herein report on the clinical outcome of patients with r/r ALL and non–Hodgkin lymphoma sequentially treated with a "cocktail" of both CART19 and CART22 cells. With this strategy, the authors aimed to avoid, especially for patients with r/r ALL, the antigen escape of CD19$^-$ CD22$^+$ blasts. They succeeded in their goal, because virtually no CD19$^-$ relapses were observed. Unfortunately, however, the cumulative incidence of disease relapse with blasts expressing both CD19 and CD22 antigens was as high as 47%. Thus, CART cells targeting both antigens were effective in avoiding the antigen escape of CD19$^-$ blasts, but CART cell persistence or functionality seemed to be not good enough to avoid CD19$^+$ and CD22$^+$ relapses, which happened in 47% of patients with ALL. Consequently, additional measures are apparently needed when dual (or multi) specific CART targeting is used to prevent antigen escape, including an scFv with a higher affinity for the target antigen, bivalent CARTs (a CAR with 2 target-binding domains, some of which are already being tested in clinical trials),[9] target antigen modulation, a different combination of costimulatory molecules, or the promotion of specific T-cell subpopulations.[10] Well-designed clinical trials will certainly be needed to elucidate the best option for this high-risk patient population.

Conflict-of-interest disclosure: The authors declare no competing financial interests. ■

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LYMPHOID NEOPLASIA

Comment on Li et al, page 41

Chemotherapy at the wheel of ALL relapse

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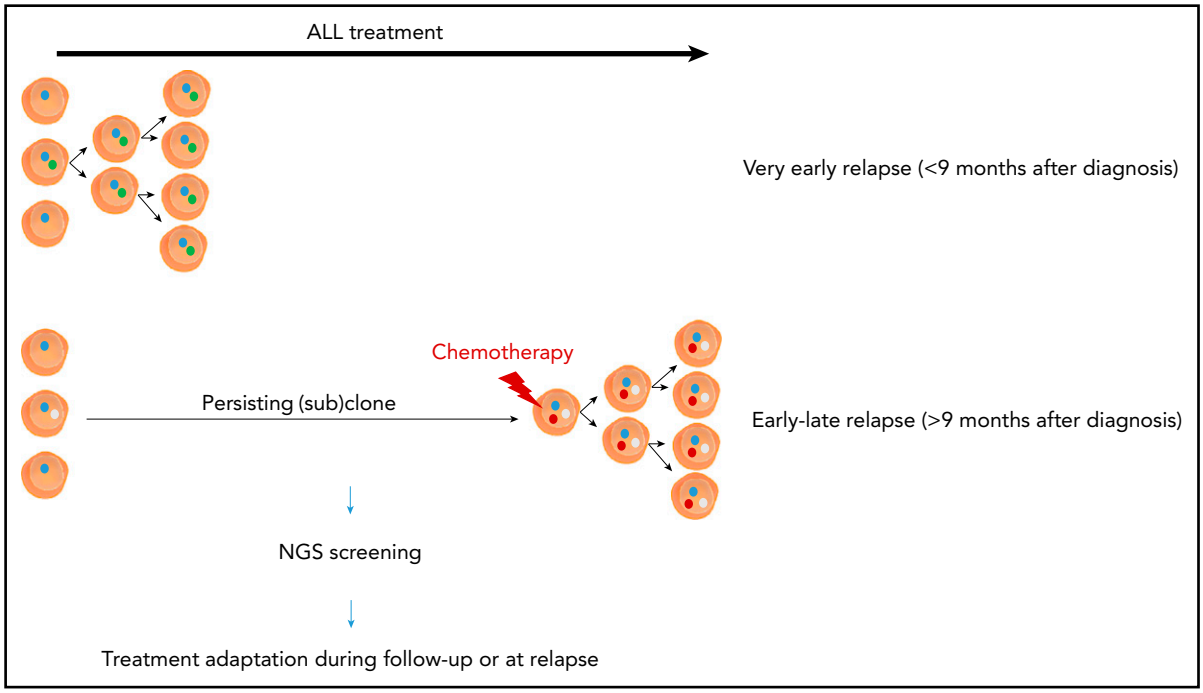
In this issue of *Blood*, Li et al[1] present an extensive in-depth genetic characterization of diagnostic, relapse, and remission samples from a cohort of 103 pediatric patients with acute lymphoblastic leukemia (ALL) treated according to the Shanghai Children's Medical Center ALL-2005 frontline protocol. Together with data obtained from 208 serial bone marrow samples collected during ALL therapy, their work suggests that relapse in a fraction of childhood ALL patients is driven by chemotherapy-induced mutations, which impact therapy response.

Since the early days of cancer treatment with chemotherapy in the 1960s, the cure rate of childhood ALL has dramatically improved.[2] Indeed, overall survival rates for pediatric ALL patients are currently well above 90% with contemporary treatment protocols that use minimal residual disease (MRD) measurements to guide treatment intensity.[2] Nevertheless, disease relapse is still a major clinical problem, and the biology of relapsed disease as well as the molecular mechanisms that drive therapy resistance remain poorly understood.[2]

By means of whole-genome sequencing, Li et al identified a set of 12 mutations that were significantly enriched or exclusively present at relapse in a large and uniformly treated cohort of pediatric ALL. Of note, this patient population only included 16 diagnosis-remission-relapse trios from T-cell ALL (T-ALL) patients, with a bias toward tumor material obtained from *TAL1*, *TAL2*, *LMO2*, or *LMO3* rearranged T-ALLs. Therefore, some of the results obtained in this study might not be readily transferable toward all genetic subtypes of T-ALL.[3]

Most of the relapse-associated genetic defects found in this work have previously been identified in relapsed ALL (*TP53*, *NR3C1*, *NR3C2*, *CREBBP*, *WHSC1*, *NT5C2*, *PRPS1*, *PRPS2*, *MSH2*, *MSH6*, and *PMS2*)[4,5] and are thought to affect chemotherapy responses to key components of ALL therapy, such as steroids or thiopurines.[6] However, in this study, Li et al also discovered that mutations and focal deletions in the folate metabolism gene *FPGS* exclusively occur in relapsed ALL and cause increased resistance to methotrexate,



Schematic overview of the differences between very early and early-late relapse in pediatric ALL. NGS, next-generation sequencing.