bortezomib. It is not immediately apparent which of these is better than conventional treatment. This uncertainty together with the large number of drugs to test will likely sound the death knell for the conventional phase 3 trial, especially when utilizing conventional hazard ratios. Phase 3 trials are ill-suited for a disease as heterogeneous as AML. Both in Europe and recently in US cooperative groups, smaller comparative trials have been explored, under the assumption that the worst false-negative results when a drug is not studied at all.\(^1\) In this way, as in the introduction of qualitatively distinct drugs such as lenalidomide, clinical research in AML is truly in ferment.

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

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Comment on Wang et al, page 1888

**Fitness without exhaustion**

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Next-generation adoptive leukemia immunotherapy will likely be based on injection of T cells targeted to specific antigens (Ag). This approach is currently limited by our inability to generate sufficient numbers of Ag-specific T cells that can survive and proliferate in vivo. In this issue of Blood, Wang and colleagues demonstrate that central memory T cells can generate ex vivo Ag-specific T cells that thrive well after in vivo transfer.¹

Cure of hematologic malignancies after standard allogeneic hematopoietic cell transplantation (AHCT) is due mainly to the so-called graft–versus-leukemia (GVL) effect, that is, eradication of host neoplastic cells by donor T cells. The allogeneic GVL effect represents, by far, the most successful form of cancer immunotherapy in humans. It is initiated by T cells mostly found in the naive compartment, which recognize minor histocompatibility Ags (MiHAs) and also perhaps leukemia-associated Ags.²,³

GVL induction has practically not evolved over the last 2 decades. Accordingly, despite its great paradigmatic and clinical relevance, the allogeneic GVL effect remains a quite rudimentary form of leukemia immunotherapy. It still involves injection of unselected donor lymphocytes that have not been primed against their target Ags. This current approach is fraught with 2 major limitations. First, injection of polyclonal allogeneic T cells lacks specificity and is therefore highly toxic: these T cells react against several host MiHAs, resulting in graft–versus-host disease (GVHD) in 60% of recipients. Second, naive unprimed T cells induce only an attenuated form of GVL reaction because, in contrast to pre-activated T cells, they can become tolerant after encounter with tumor cells. Experimental mouse models have revealed that far superior results could be achieved by adoptive immunotherapy with preactivated Ag-specific T cells: primed T cells targeted to a single MiHA have cured leukemia and melanoma without causing any toxicity to the host.⁴,⁵ The outcome depended on 2 T-cell effector mechanisms: direct killing of neoplastic cells by granule exocytosis and inhibition of angiogenesis by interferon-γ.⁶,⁷

If leukemia immunotherapy with activated Ag-specific T cells holds such great promises, what is the problem with its application in humans? The mean frequency of Ag-specific T cells in the preimmune human T-cell repertoire is approximately 10⁻⁸ and at least 10⁻⁹ to 10⁻¹⁰ Ag-specific T cells are presumably required for successful treatment.⁸,⁹ Therefore, procurement of sufficient numbers of T cells for immunotherapy requires massive expansion of the few Ag-specific T cells present in a donor’s peripheral blood. Proof-of-principle studies in mice resorted to a trick that cannot be used in humans: expansion of Ag-specific T cells was performed in vivo by immunizing the donor against the target Ag.⁸ Because donor immunization would raise major ethical issues in humans, we are left with one possibility: to proceed with ex vivo expansion of Ag-specific T cells. That would be theoretically feasible if we knew how to generate self-renewing memory T cells. While such memory T cells having stem cell–like self-renewal potential exist in vivo,¹⁰-¹³ we ignore how to generate them ex vivo. Current methods for ex vivo expansion of Ag-specific T cells yield poorly functional exhausted T cells that rapidly disappear after in vivo transfer. Nonetheless, we know that naturally occurring memory stem cells reside in the pool of central memory T cells (T<sub>CM</sub>). Using an instructive mouse model, Wang et al found that after massive ex vivo expansion, the progeny of human T<sub>CM</sub> established a persistent reservoir of functional T cells in vivo.¹ Accordingly, they now propose a novel strategy for generating therapeutically relevant numbers of Ag-specific T cells: introduction of genes encoding tumor-specific receptors into T<sub>CM</sub> followed by ex vivo expansion and adoptive transfer. It is of course difficult to predict the merit of that approach, but further studies along those lines will be instructive and are eagerly awaited.

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CD9 phones home with a TEM of its own

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