Abstract

Gene therapy research remained stagnant for many years due to serious side effects. However, clinical gene therapy has been revived in Western countries, because a number of successful clinical trials have been reported recently, including hematopoietic stem cell gene therapy and AAV-vector gene therapy mainly for hereditary disorders. Regarding cancer gene therapy, there has been increasing focus on gene-modified T cell therapy, which is divided into CAR (chimeric antigen receptor)-T and TCR (T cell receptor)-T cell therapy. These technologies have different characteristics and are used depending on the type of target molecules. CARs are hybrid proteins consisting of an extracelluar single chain fragment of variable region (scFv) fused to intracellular lymphocyte signaling domains CD28 or 4-1BB, coupled with CD3ζ to mediate T cell activation. Recent clinical trials of CD19-targeted CAR-T cell therapy have achieved a great success in the treatment of relapsed/refractory B cell malignancies, including ALL, CLL, and non-Hodgkin lymphoma (NHL).

In Japan, we have started clinical study of CD19-CAR-T cell therapy for NHL at Jichi Medical University Hospital, in collaboration with Memorial Sloan Kettering Cancer Center and Takara Bio Inc. Multi-institutional clinical trials of CD19-CAR-T cell therapy for ALL are also being conducted. As for the unique side effects of CAR-T cell therapy, there are cytokine release syndrome (CRS) and neurological toxicities (including cerebral edema). Depletion of normal B cells is called “on-target, off-tumor reaction” and causes immunoglobulin deficiency in the late phase.

On August 30, 2017, the U.S. FDA (Food and Drug Administration) approved tisagenlecleucel (KYMRIAH®, CD19-CAR-T cell therapy; Novartis Pharmaceuticals Corp.) for the treatment of pediatric and young adult patients with relapsed/refractory B-ALL. The FDA also approved tocilizumab (ACTEMRA®, an interleukin-6 receptor antagonist; Genentech Inc.) for the treatment of CRS. In the near future, CAR-T cell therapy will be expanded to treat the other hematological malignancies and solid tumors. As for solid tumors, the other strategies will be needed to get efficacy in combination with CAR-T. Applications of gene-editing technologies are also exciting topics. Allo (universal) CAR-T cells can be produced by knockout of TCR gene, and PD-1 gene knockout will enhance the efficacy of CAR-T cell therapy by local immune checkpoint blockade. Gene-modified T cell therapy is now becoming one of the major treatments to conquer intractable cancer.