Teaming up for CAR-T cell therapy

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The recent advances in immunotherapy using genetically modified T cells have been successful in broadening public awareness of this approach. Chimeric antigen receptor (CAR)-T cells show great promise in the treatment of even very advanced malignant diseases. So far, B-cell antigens in particular, such as CD19, CD22 or BCMA, have represented highly useful targets for this approach.[1] CD19 CAR-T cells have shown complete response rates of up to 90% in acute B-lymphoblastic leukemia[2-4] and in up to 50% of aggressive B-cell non-Hodgkin lymphoma,[5,6] in the relapsed/refractory setting, which has led to the approval of CD19-CAR-T cells for these entities. BCMA-CAR-T cells for multiple myeloma show similar intriguing results for the treatment of relapsed/refractory myeloma and are under intense clinical development.[7]

CAR-T cells are genetically modified autologous T cells from the respective patient, which are harvested by an unstimulated leukapheresis. Lenti- or retroviral vectors are used to introduce a construct combining an antibody fragment to recognize the tumor antigen with the T-cell receptor signaling domain CD3-zeta to activate the modified T-cell (first generation) and with addition of one (second-generation) or two (third-generation) co-stimulatory domains, usually CD28 or 4-1BB, to further enhance T-cell activation. Following *in vitro* expansion, these cells are re-transfused into the patient after lymphodepleting chemotherapy with cyclophosphamide and fludarabine to enhance homeostatic expansion of modified T cells.[8,9]

However, this important treatment advance comes at a price: a) potential side effects; b) production of CAR-T cells for some selected patients can be a lengthy process with no guarantee of success; and c) the costs of the procedure. Also, long-term clinical responses are lower than hoped for and further improvements are needed.

CAR-T cells can induce severe life-threatening side effects, such as cytokine-release syndrome (CRS) or neurotoxicity (NT). The major symptoms of CRS are fever, hypotension, hypoxia and organ toxicity, which may result in organ failure. The main risk factors for grade III-IV events are high tumor load, co-morbidities and short CRS latency (<72 h following infusion). NT, also called CRES (CAR-T-cell related encephalopathy syndrome) or ICANS (Immune Effector Cells Associated Neurotoxicity Syndrome), has a broad spectrum of clinical symptoms including global encephalopathy, epilepsy and increased intracranial pressure which may occur in a bi-phasic course up to four weeks after infusion. Treatment includes supportive care, the anti-IL6-antibody tocilizumab, and steroids.[10-13]

Other problems are represented by the long production time, which makes it challenging to bridge refractory patients until CAR-T cell transfusion can be performed. This may be overcome by localized production of the cell product, instead of the current centralized production. Another potential alternative is using off-the-shelf allogeneic CAR-T cells. The current very high costs may be reduced by efforts for self-production by academic centers instead of obtaining a commercial industry product. Other challenges are resistance mechanisms, such as antigen escape, which may be overcome by using two CAR-T for different antigens, for example CD19 and CD22. Moreover, resistance to CAR-T over time may occur by upregulation of PD-1. Additional treatment with checkpoint inhibitors can potentially solve this problem. The biggest challenge is perhaps the development of CAR-T strategies for malignancies other than B-cell neoplasms, with the problem of defining a suitable antigen, or for solid cancers with an immunosuppressive microenvironment.[14]

Patients who experience adverse events have to undergo frequent treatment in an intensive care unit (ICU). Therefore, treatment with CAR-T cells must involve a team of specialized physicians including hematologists, intensive care physicians and neurologists. While the specialized hematologist should be responsible for identifying suitable patients to receive CAR-T cell therapy, current guidelines, in accordance with those issued by regulatory agencies, recommend that the medical center where the procedure is to be performed should have extensive experience in cell therapies and allogeneic transplantation with sufficient numbers of allogeneic transplantations per year. The reason for this is that allotransplant specialists will have the greatest experience in the treatment of the potential severe CAR-T cell-induced side effects.[15,16]

In the article by Moreau *et al.* in this edition of Haematologica, European Myeloma Network (EMN) experts discuss the future use of CAR-T cell therapies in multiple myeloma patients (by multiple myeloma experts, rather than an allogeneic team) as highly relevant and warranted.[17] The recommendation for specialist care by allogeneic-transplant specialists in CAR-T-cell therapies is, therefore, debated by Moreau *et al.* for myeloma patients, one reason being that centers with leading expertise in myeloma treatment including autologous stem cell transplantation may not necessarily have a unit for allogeneic transplantation. Therefore, this poses the dilemma of who is eventually responsible for CAR-T cell therapies in hematology/oncology patients: the disease specialist or the expert in allogeneic transplantation? There are several reasons to believe that the disease specialist should lead treatment: first, an accurate indication is extremely important; second, the greater the experi-

ence in CAR-T cell treatment, the earlier any side effects will be recognized and appropriately treated, therefore, becoming less severe; third, it is likely that side effects are less severe in different upcoming entities such as multiple myeloma making the allogeneic transplant expert less important. However, currently the most beneficial approach would be the joint effort of both, i.e. of myeloma and CAR-T-cell specialists, the latter often coming from allogeneic teams like ours (or being combined in an allogeneic and myeloma expert in one person), which is already pursued in many centers worldwide.[18]

In summary, while it may be good thinking to start with the best available team including the allogeneic transplant expert, once the treatment procedure becomes established, the specialized hematologist will presumably take over the leading role in guiding and performing the application of CAR-T cells, including the treatment of any potentially evolving complications.

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