COMMENTARY

Readiness for Innovation and Pioneer Spirit

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Almost 10 years ago, the first cases of patients with aggressive lymphoma successfully treated with chimeric antigen receptor (CAR) T cells were presented at major hematology meetings and led to a burst of excitement amongst hemato-oncologists and hope for cure in patients.

Approximately five years ago, CAR T cells became available in the clinic, both in clinical trials and as commercial products. As a result, and together with other innovative drugs that have emerged, patients with formerly lethal disease stages can live significantly longer and some can even be cured.

During the past five years we have learned many lessons, on patient selection, risk and treatment of "new" side effects, such as cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS), holding and bridging therapy strategies, optimal patient preparation before CAR T cells and much more, while other questions remain to be answered. CAR T cells have moved to earlier lines of treatment and can be offered to a broader range of disease subtypes.

Recently, the Erlangen group around Andreas Mackensen and Georg Schett presented the first cases of patients with systemic lupus erythematosus, successfully treated with CAR T cells, followed by some other autoimmune diseases (AID). Young patients with multiorgan involvement recovered from their detrimental diseases and are now healthy, happy and going to university or work. The Erlangen team recently published the first follow-up (up to three years post CAR T-cell treatment) of their first 14 patients: all clinical responders; in contrast to patients with large tumors barely any side effects; in all treated patients disappearance of autoantibodies and normalization of other lab abnormalities; none of them required any further immunosuppressive treatment for relapsed autoimmunity. And to make things even better: early reemergence of a naïve B-cell compartment without evidence of reemergence of autoreactive B-cell clones.

Other centers in Europe, the United States and China followed the example of Erlangen. Today, approximately 50 patients with AID have been treated with CAR T cells, including patients with neurological disorders, such as myasthenia gravis and multiple sclerosis, but also rare diseases, such as stiff person syndrome. Within the community of cell therapists, rheumatologists and neurologists, movies of patients who can stand up and walk again

(stiff person syndrome and autoimmune encephalitis) or chop wood in their garden (myasthenia gravis) are shared. It feels a bit like in the early days of CAR T cells for lymphoma.

What implication does this have for hemato-oncologists?

Cell therapy becomes an interdisciplinary entity – no longer reserved to serve malignant hematology. Treatment teams will comprise disease specialists (from different fields) AND cell therapists – working hand in hand, educating not only patients but also each other.

This is incredibly exciting – but also raises the question of whether we have enough resources for all patients that would benefit from cell therapy. Enough beds in cell therapy units? Enough specialized nursing staff and cell therapy physicians? Enough manufacturing capacity for CAR T-cell production? And finally, enough financial resources?

We need to talk about these things and discuss potential solutions. The time of clear separation of departments, competences and "Schrebergarten-Denken" are definitely over and, where still enforced, inhibit progress. The era of interdisciplinarity with discussions on same eye levels has begun! As a trained hemato-oncologist, I am happy to learn so many new facts and hypotheses on immune function and dysfunction from my partners in neurology and rheumatology every day!

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Conflict of interest

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