EDITORIAL

Chimera's curse: myeloid clonal evolution after CD19-directed chimeric antigen receptor T-cell therapy

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"And her mother bare Chimera, in rage and flame, a creature mingled of diverse parts."

- Ovid, Metamorphoses (Book IX)

Ancient Greek myths of Chimera described a monstrous, fire-breathing, hybrid creature typically depicted as a lion's body with a goat's head erupting from its back, and a snake's head sprouting from its tail (Figure 1). The stories, though diversely interpreted, have been used to invoke lessons pertaining to the consequences of unnatural construction and the pursuit of wild dreams.

In this issue of *Haematologica*, Sillito and colleagues from University College London contribute a collection of novel cases which enhance our understanding of an important yet incompletely understood clinical concern: clonal myeloid disorders arising in patients with non-Hodgkin lymphoma (NHL) treated with CD19-directed chimeric antigen receptor (CAR) T-cell therapies.[1] Given that the entry of CAR T cells into the therapeutic toolbox for advanced lymphomas has enabled durable remissions and potential cures for many patients, justifiable attention is now being paid to issues concerning survivorship, including the development of late complications. As the authors correctly pointed out in their article, real-world evidence published subsequently to pivotal NHL CAR T-cell studies has identified therapy-related myeloid neoplasms (tMN) as adverse events after CAR T-cell therapy for NHL. When compared to autologous stem cell transplant, after which high rates (12-24%) of tMN are observed at a longer time to onset (4-5 years),[2] initial studies of tMN after CAR T-cell therapy for NHL have demonstrated shorter latency (3-10 months)[3] and an incidence in the range of 3-6%.

The study by Sillito *et al*. uncovered a 2.48% incidence of tMN with a median onset of 11.2 months after CAR T-cell therapy for NHL. By studying a cohort of ten tMN cases and 30 matched controls, the authors employed univariable analysis to identify a history of prior autologous transplant, high baseline CAR-HEMATOTOX score, and number of prior lines of therapy as being significantly associated with the subsequent development of tMN. The breakdown of myeloid malignancy diagnoses after CAR T-cell therapy included two cases of acute myeloid leukemia and eight cases of myelodysplastic syndrome.

Tissue specimens taken prior to the CAR T-cell therapy were available from seven of the ten patients in the study cohort, and included lymph node and pleural fluid samples, in addition to bone marrow biopsy material. Pathogenic variants in genes such as *TP53*, *TET2*, *ASXL1* and *PPM1D* detected prior to CAR T-cell therapy were noted to have persisted or expanded at tMN diagnosis in the majority of reported cases. It should be noted that next-generation sequencing surveys from non-marrow compartments could represent lymphoid clonal hematopoiesis of indeterminate potential, but the inclusion of these data does allow for a more holistic appreciation of mutational evolution to study tMN manifestations. Longitudinal next-generation

Figure 1. Chimera.

sequencing within these seven patients, benchmarked to absolute neutrophil count, allowed for the construction of mutational roadmaps depicting clonal evolution towards tMN. A median overall survival of 8.1 months was observed after the diagnosis of tMN, with all deaths attributed to tMN. Based on observations that higher peak lymphocyte counts, a known surrogate for CAR T-cell expansion, were significantly associated with tMN risk, the authors postulate that CAR T-cell-induced inflammation may promote evolution of clonal myeloid populations present prior to CAR T-cell therapy. The data also demonstrated a trend (P=0.053) towards higher cytokine release syndrome grade during treatment and eventual tMN development. Although larger studies will be necessary to confirm a possible link between inflammatory toxicities and tMN risk, a recent analysis of 539 NHL patients performed across four French centers identified a relationship between higher neurotoxicity grade during CAR T-cell therapy and eventual tMN development by utilizing both univariate and propensity score matching analyses.[4] Notably, this analysis did not uncover a relationship between CAR-HEMATOTOX score and future tMN diagnosis. Another recently published study from the Mayo Clinic found an association between CAR-HEMATOTOX score and tMN, and this effect was augmented when incorporating age into the statistical modeling.[5]

Recognizing that an increasing number of lines of therapy conferred higher risk of development of tMN following CAR T-cell therapy in the study by Sillito and colleagues, it would be useful for larger datasets to focus on tMN incidence when stratified by number of prior treatment lines. As astutely pointed out by the authors, ascertaining whether CD19-directed CAR T-cell therapy independently drives tMN risk or whether the risk is conferred by prior multiple genotoxic therapies,[6] suggesting a dose-dependent relationship, will help to inform therapy sequencing and potentially support a preference for CAR T-cell therapy in earlier lines of therapy. Given the dismal prognosis of tMN once evident, it may also be advantageous to leverage next-generation sequencing applications both before and after CAR T-cell therapy to recognize and track clonal myeloid processes. Such an endeavor might not only lead to an enhanced understanding of the behavior of clonal hematopoiesis or clonal cytopenias in the setting of CAR T-cell therapy but may further detail trajectories of clinical tMN development and aid in the informed consent process when CAR T-cell therapy is being considered.

Disclosures

GWR reports participating in advisory boards for Kite/Gilead and Autolus.

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