The clonal hydra: neoantigen-specific T-cell response in germ cell tumors

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Germ cell tumors (GCT) occur in men aged 15-35 years and are the most prevalent malignancies within this demographic. Over the past decade, introduction of platinum-based therapeutics have proven to effectively treat GCT and improve outcomes.[1] GCT, while predominantly occurring in the testes, can be found to originate in the mediastinum, accounting for 10% of all mediastinal neoplasms.[2] Mediastinal GCT pose a unique challenge to clinicians due to their propensity for the development of other malignancies. One in every 17 patients with a mediastinal GCT will develop a hematologic malignancy.[3,4] Apart from hematologic malignancies, sarcomas and carcinomas can develop in patients with mediastinal GCT. Despite the success of platinum-based regimens in testicular GCT, primary mediastinal GCT have proven to be resistant to platinum-based agents, necessitating alternative treatment strategies.[5] Interestingly, it has been shown that GCT and hematologic malignancies arising in the same individual share the presence of isochromosome 12p [i(12p)].[6,7] Using whole exome sequencing, Taylor and colleagues definitively showed that these malignancies arise from a progenitor that can differentiate into GCT, sarcomas, or hematologic malignancies.[8] Despite the improved understanding of their origin, the outcomes for mediastinal GCT with secondary somatic tumors is around 6 months, making discovery of novel treatments for these patients imperative.

Genoud *et al.* report results of a case study consisting of a 22-year-old male with a mediastinal PLAP-positive mixed GCT with $CD61^+$ large cells.[9] The patient's bone marrow was infiltrated with $CD34^-$, $CD61^+$, and $CD43^+$ cells with multilobulated nucleus and eosinophilic cytoplasm showing polyploidy, +der(3), and i(12p) on cytogenic analysis. Following a diagnosis of synchronous acute myeloid leukemia (AML) and primary mixed GCT, the patient was initially treated with three cycles of cytarabine, mitoxantrone, etoposide, and cisplatin. Intrathecal therapy consisting of methotrexate, cytarabine, and methylprednisone was administered during the second cycle. Moreover, two additional cycles of etoposide and cisplatin were given. The patient achieved complete leukemic remission and metabolic activity of the mediastinal mass was shown to have decreased. Following conditioning, the patient underwent an allogeneic hematopoietic stem cell transplant (HSCT) from a mismatched unrelated donor with $CD34^+$ harvested donor cells. Six months after HSCT, the patient was found to have 60% increased mass of residual and metabolic activity with biopsy showing a fusiform sarcoma with angiomatous differentiation. Ten months after HSCT, the patient was given two donor lymphocyte infusions ($5x10^5$ and $6x10^6$ $CD3^+$ cells/kg). Ultimately, complete donor chimerism was obtained and persistent complete hematologic remission was achieved such that no neoplastic disease was found even 10 years after HSCT. Somatic mutations from the three tumors were used in order to identify mutation-specific neoantigens by filtering through the following criteria: major histocompatibility complex binding affinity, strong binding affinity compared to normal proteins, and protein expression in cancer. Identification of 84 common neoepitopes that played a role in recognition of mutation-specific proteins revealed the sarcoma-specific neo-peptide $IL36G_{16\text{-}24}$YPSMCKPIT, which elicited a positive response when tested in interferon-γ ELISPOT assays with the patient's peripheral blood mononuclear cells. Furthermore, the neoantigen response to $IL36G_{16\text{-}24}$YPSMCKPIT was, remarkably, detected in the patient's peripheral blood mononuclear cells 7 years post-HSCT. Tumor exon sequencing revealed 48 somatic mutations detected in the GCT, 17 in the leukemia, and 331 in the sarcoma with phylogenic reconstruction revealing 13 shared events between the three malignancies confirming a common clonal origin. A *TP53* driver splice site mutation, chromosome 17 splice site mutation involving CDK12, and five loss of heterozygosity events including PTEN loss of

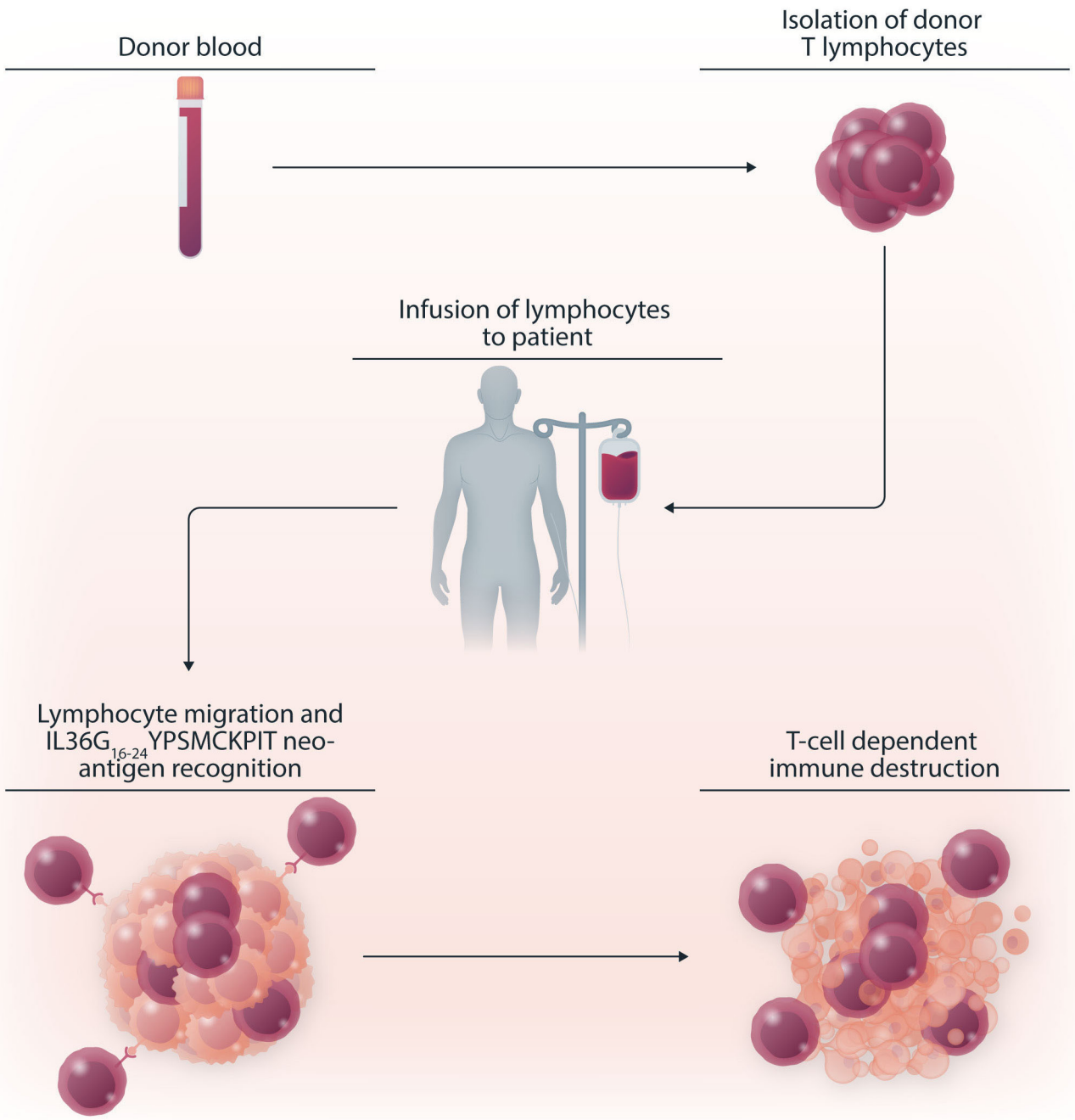

Figure 1. How donor T-lymphocyte infusion can lead to neoantigen-specific response in mediastinal germ cell tumors.

heterozygosity were all seen amongst the GCT, hematologic malignancy, and sarcoma. Like the multi-headed hydra monster from Greek mythology, mediastinal GCT with secondary somatic tumors tend to come back stronger when the heads are chopped off. However, the key to killing the hydra, and possibly to overcoming this often fatal malignancy, is to strike a blow to the common part (the body, or in this case, shared neoantigen).

Despite Genoud *et al.* successfully demonstrating the potential of donor T-lymphocyte infusions in this case study, there are some limitations to the present findings. Firstly, the study's reliance on a single patient and lack of a comparative group limits its ability to establish broad conclusions or generalize findings to a larger population. Currently, high-dose chemotherapy and autologous SCT have been used to treat relapsed GCT.[10] However, such a treatment regimen has been shown to have patients recurrently relapsing with hematologic disease, all of which have demonstrated common mutations.[8] The findings in this study argue for the role of allogeneic SCT and also open the doors to further exploration of novel treatments. For example, with the identification of the sarcoma-specific neo-peptide $IL36G_{16-24}$YPSMCKPIT, there is potential for the development of chimeric antigen receptor (CAR) T-cell therapy which may prove to have efficacy against development of malignancies in patients with GCT. Additionally, a concern with usage of donor lymphocyte infusions is that patients are at high risk for developing graft-*versus*-host disease, which has further potential to evolve into chronic disease. Development of alternative therapies that can elicit a neoantigen-specific T-cell response, such as CAR T-cell therapy, which have predominantly acute adverse events, may provide clinicians and patients with better alternatives with regards to therapeutic options.

In conclusion, the study by Genoud *et al.* provides hope of successful treatment options for patients with mediastinal GCT refractory to general therapy by using neoantigen-specific T-cell response following a donor lym-

phocyte infusion post allogeneic HSCT. The authors have demonstrated a favorable outcome in a patient 10 years after HSCT which if shown in a larger number of patients, could ultimately help patients with achieving persistent and complete remission from mediastinal GCT and secondary somatic malignancies.

Disclosures

No conflicts of interest to disclose.

Contributions

SM and JT conceived, wrote and edited the manuscript.

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