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COMMENTARY

# Anti-PD-1 therapy can possibly reverse CAR T cells exhaustion in DLBCL

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Commentary on: Gazeau et al. Safety and efficacy of nivolumab in patients who failed to achieve a complete remission after CD19-directed CAR T-cell therapy in diffuse large B cell lymphoma. Br J Haematol 2023;202:434-436.

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In this issue, Gazeau et al. report on their experience with nivolumab in an attempt to rescue 11 patients that did not achieve a complete remission 30 days after axicabtagene ciloleucel for an R/R DLBCL. With other works detailed in the commentary, it suggests a potential therapeutic benefit of the reversion of CAR T cell exhaustion with anti-PD-1 therapy. Ongoing clinical trials will help to determine the best candidates and modalities for such salvage.

Exhaustion describes a condition in which T cells are unable to perform any function. It has been characterized by chronic infections and cancers.[1] Various features within the tumour microenvironment led to dysfunction of T infiltrating lymphocytes, such as antigen persistence, nutrient deprivation and/or *PDCD1* demethylation.[2] This gene codes for the protein PD-1, whose expression is the most known feature of exhaustion. Targeting PD-1 with nivolumab or pembrolizumab led to impressive clinical success in the context of various metastatic tumours and Hodgkin lymphoma.[3] Even though single-agent anti-PD1 showed low and transient antitumor activity in R/R DLBCL,[4] with the exception of patients with HIV-related lymphoma, that may benefit of a long-term disease control.[5]

About 60 per cent of patients treated with axicabtagene ciloleucel for a relapsing or refractory diffuse large B cell lymphoma (R/R DLBCL) do not achieve a persistent response.[6] Massive research effort has been undertaken to dissect CAR T cell failure. Among other causes, absence/low expansion, functionality or persistence of those engineered T cells had been related to exhaustion features. These characteristics have been described among harvested T cells, CAR T cells from the final product and/or circulating CAR T cells, themselves linked to tumour burden, tumour microenvironment and/or systemic inflammation.[7]

In this issue, Gazeau et al. report on their experience with nivolumab in that context. With that drug, they have been trying to rescue 11 patients that did not achieve a complete remission 30 days after axicabtagene ciloleucel for a R/R DLBCL. They treated patients in 3 different situations. The "primary refractory" group included patients who showed stable or progressive disease at initial evaluation, the "booster" group included patients who achieved a partial response and were belief to require additional therapy, and the "salvage" group included patients who progressed after achieving a partial response and therefore required salvage therapy. Nivolumab was administrated every 2 weeks, and efficacy was evaluated by PET/CT after four injections. Regarding safety, four mild respiratory tract infections were reported, and no CRS/ICANS was observed. Four patients achieved a complete response after 2 months of treatment, two patients were in the situation of partial response at D30 and two others were experiencing relapsing disease after a partial response. A second expansion of circulating CAR T cells was observed, after a single injection of nivolumab, which argues on reversion of CAR T cell exhaustion: $C_{max}$ was 0.035 G/L, lower that the initial expansion but following a long period when the CAR T cells were undetectable. Moreover, the secretion of pro-inflammatory cytokines is probably reflecting the functionality of those CAR T cells.

Another group recently reported three patients with early progression or relapse, after being treated with 4-1BB

costimulated CD19 CAR T cells, who responded to pembrolizumab.[8] Ten out of the 12 patients treated in this study experienced a second expansion of circulating CAR T cell. Interestingly, pretreatment biopsy from seven out of nine patients had positive PD1 ligand expression (PD-L1). Other groups described that PD-L1 expression by DLBCL tumour cells is associated with activated B cell genotype, as well as poor outcomes.[9] Taken together, those clinical data suggest a potential therapeutic benefit of the reversion of CAR T cell exhaustion with anti-PD-1 therapy. Ongoing clinical trials will help to determine the best candidates and modalities for such salvage.

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