17 Developments in Other Haematological Malignancies: Other Lymphoid Malignancies

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Peripheral T cell lymphomas comprise a heterogeneous group of rare diseases, representing 10–15% of all non-Hodgkin lymphomas (NHLs). Upfront treatment for peripheral T cell lymphoma (pTNHL) includes CHOP-like (cyclophosphamide, adriamycin, vincristine, prednisone) multiagent chemotherapy with or without etoposide, followed by stem cell transplantation as consolidation in responsive fit patients. This approach induces durable long-term remission in approximately 40% of cases; early refractoriness during induction occurs in approximately 25% of patients, with the remaining patients typically relapsing within 24 months. With the exception of patients with anaplastic large cell lymphomas who are eligible to receive brentuximab vedotin, there is no standard of care in the relapse setting. In patients not eligible to receive high-dose chemotherapy followed by allogeneic stem cell transplantation, the prognosis is dismal.

CAR-T cells have shown impressive results in relapsed/refractory B-cell lymphoma and are currently under investigation in T cell lymphomas.

Target Antigens

The choice of the appropriate antigen constitutes the main challenge in targeting T cell malignancies using CAR-T cells. Many target antigens are expressed by both physiological T cells and engineered CAR-T cells (Tables 17.1 and 17.2).

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Table 17.1 Pan-T cell antigens

CD5	Expression in T cells, thymocytes, B-1 cells, and T cell malignancies: 90% T-ALL/Ly 85% PTCL-nos 96% AITL 26–32% ALCL 36% NK-T 85% ATLL 91% CTCL
CD7	Expression in T cells, thymocytes, NK cells, and T cell malignancies: 95% T-ALL/Ly 50% PTCL-nos 57% AITL 32–54% ALCL 79% NK-T 25% ATLL 18% CTCL

Table 17.2 Antigens with restricted expression

CD30	Expression in activated T and B cells and in T cell malignancies: 17% T-ALL/Ly 16% PTCL-nos 32–50% AITL 93% ALCL 64% NK-T 39% ATLL 18% CTCL
TRBC1	Expression in T cells and in T cell malignancies: 7–11% T-ALL/Ly 27% PTCL-nos 34% AITL 25% ALCL

Therefore, this shared antigen expression can potentially result in the following issues:

- A fratricide effect on CAR-T cells.
- Ablation of physiological donor T cells after CAR-T cell infusion, leading to deep and/or long-lasting immune deficiency and T cell aplasia.

CAR-T Development in T Cell Malignancies

Some experimentally engineered CAR-T cell products targeting CD5, CD7, CD30, and TRBC1 (T cell receptor beta chain 1) have been tested (Table 17.3).

Table 17.3 CAR-T cells targeting T lymphocyte antigens

CAR-T cells targeting CD5	*Mamonkin* et al. (Blood 2015), preclinical experience: – CD5 CAR-T cells eliminate malignant T-ALL/Ly lines in vitro and inhibit disease progression in xenograft mouse models – Second-generation CD5 CAR with a CD28 costimulatory domain: With the loss of CD5 expression on the surface of T cells, CD5 CAR-T cells become resistant to fratricide *Hill* et al. (Blood 2019), phase I dose escalation study, MAGENTA trial: – 9 patients enrolled (4 T-ALL, 5 T-NHL) – CD5 CAR-T cells are safe and can induce clinical responses (3 patients in complete response) in heavily pretreated relapsed/refractory T-ALL and T-NHL, without inducing T cell aplasia
CAR-T cells targeting CD7	*Gomes-Silva* et al. (Blood 2017), preclinical models of T cell malignancies: – Fulminant fratricide precluding expansion of CAR-T cells – Abrogation of CD7 expression from the cell surface shows potential activity A phase I study (CRIMSON trial) has been designed at Baylor College of Medicine but is not yet recruiting
CAR-T cells targeting TRBC1	*Maciocia* et al. (Nat Med 2017), preclinical studies: – CAR-T cells targeting TRBC1 are able to specifically eliminate malignant T cell lines expressing TRBC1 – TRBC1 CAR-T cells cannot target normal TRBC2-positive T cells A phase I/II study (AUTO4) coordinated by the University College of London is a single-arm trial evaluating the safety and clinical activity of a CAR-T cell targeting TRBC1 in patients with relapsed/refractory TRBC1-positive T cell lymphomas
CAR-T cells targeting CD30	*Dotti* et al. (Immunol Rev. 2014), preclinical studies: – CAR-T cells targeting CD30 generate tumour-specific T cells in patients with Hodgkin and anaplastic T cell lymphomas – Tumour recognition by CD30 CAR-T cells is MHC-unrestricted – CAR-T cells targeting CD30 potentially overcome tumour escape Several small clinical trials are being reported; some studies are ongoing and recruiting: – Two CAR-T constructs are under investigation, one CAR-T cell with the antigen-binding domain of the anti-CD30 and ant-CD28 costimulatory domain and another CAR-T cell targeting CD30 and 4-1BB as a costimulatory domain – In the *Ramos* et al. phase I study, 9 patients with relapsed/refractory Hodgkin and EBV-negative, CD30-positive ALCL have been treated; results are promising, with 1 patient in complete remission and 3 in stable disease, without relevant toxicities – *Wang* et al. enrolled 18 patients (17 Hodgkin, one ALCL); seven patients achieved a partial response and six achieved stable disease, with limited acute toxicities but an increased risk of infections – *Grover* et al. enrolled 24 patients (Hodgkin, ALCL, EATL, and Sezary syndrome) in a phase Ib/II study with anti-CD30 CAR-T cells, which demonstrated early clinical effects and good tolerability and safety – A phase I study is ongoing at the National Cancer Institute to assess safety and feasibility in advanced CD30-positive ALCL and PTCL-NOS

Key Points

- Target antigens are expressed by normal T cells, malignant T cells, and engineered CAR-T cells.
- Therefore, the major concern for targeting T cell malignancies with CAR-T cells is a fratricide effect.
- A second major issue is the ablation of normal T cells after CAR-T cell infusion, potentially causing severe and/or long-lasting immune deficiency and T cell aplasia.
- Currently, the most promising constructs are CAR-T cells targeting CD30.
- Phase I and II studies are ongoing in T cell malignancies and Hodgkin lymphoma, thus far demonstrating feasibility, tolerability, and potential for clinical efficacy.

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