Lymphodepleting Conditioning Regimens

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Lymphodepleting conditioning regimens are essential for the success of CAR-T cell treatment. Their importance in the proliferation and persistence of CAR-T cells has become clearer in the recent years. The suggested mechanisms are described in Table 25.1 and include the effects on immune cells and cytokines, creating an environment for optimal functioning and increasing the peak of expansion of the infused CAR-T cells (Neelapu 2019).

The addition of fludarabine to cyclophosphamide has been important in increasing the efficacy of CAR-T cell treatment and is currently the most commonly used combination (Turtle et al. 2016). In the applied conditioning regimens, the dosing of fludarabine is relatively consistent, with the use of 25–30 mg/m², given on 3 sequential days, but the dosing of cyclophosphamide differs in days and intensity. A “higher intensity” cyclophosphamide dosing regimen seems to be preferred (Hirayama et al. 2019). However, even with the best lymphodepletion regimen, some patients fail to develop a favourable cytokine profile, suggesting that the host biological response to lymphodepletion chemotherapy is important (Hirayama et al. 2019). Most conditioning regimens can be given on an outpatient basis.

In Hodgkin lymphoma treated with anti-CD30 CAR-T cells, bendamustine has been used as conditioning regimen, but in this disease, the addition of fludarabine to the regimen has also been shown to increase antitumour responses. Whether an even more intensive regimen is needed in solid tumours is currently unknown.

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Table 25.1 Adapted from Neelapu (2019)

Effects of a conditioning regimen	
Lymphodepletion	Lowers total NK, B, and T cells
Fewer anti-CAR-T cell immune responses	Reduces anti-transgene immune reactions
Eradication of immune suppressor cells	Tregs and MDSCs
Modulation of tumour suppressive effects	Lowers IDO expression, increases levels of costimulatory molecules
Elimination of homeostatic cytokine sink	Increases IL-2, IL-7, IL-15, and MCP-1 expression levels
Increased expansion, function, and persistence of CAR-T cells	Better and durable tumour responses

Tregs regulatory T cells, *MDSCs* myeloid-derived suppressor cells, *IDO* indoleamine deoxygenase, *MCP-1* monocyte chemoattractant protein-1

The timing of the conditioning regimen is typically within a week before the planned infusion, with a minimum of 2 resting days to avoid a negative impact of chemotherapy on the infused cells. If, after the start of the conditioning regimen, the patient cannot receive CAR-T cells, most protocols allow a waiting time of 2–4 weeks before a new conditioning regimen must be started. In other protocols, conditioning regimens are not given if the absolute lymphocyte count is below 200 cells/ μ L.

The negative effects of conditioning regimens include pancytopenia and prolonged immune suppression and add to the enhanced risk of (viral) infections seen after CAR-T cell treatment. In addition, fludarabine can induce fever, neurotoxicity, cyclophosphamide haemorrhagic cystitis, and pericarditis, and both drugs may increase the risk of secondary malignancies.

Key Points

- An effective lymphodepleting regimen increases the proliferation and persistence of CAR-T cells.
- Fludarabine seems essential and is typically used with cyclophosphamide.

References

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