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LYMPHODEPLETION IN CELL THERAPY

Eduardo José de Alencar Paton[1]
Fernando Barroso Duarte[2]

1 ONCOBIO Health Services
2 Hospital Universitário Walter Cantideo/ Universidade Federal do Ceará/ Departamento de Cirurgia

Correspondence to: Fernando Barroso Duarte (nutriquimio@uol.com.br)

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ABSTRACT

Chimeric antigen receptor (CAR) T-cell therapy has become a factible therapy for hematologic neoplasms. Prior to infusion, strategies as lymphodepletion and bridge therapy are frequently performed to prolong the persistence of infused cells and increase the effectiveness of the treatment. The aim of this review is to investigate the use of Lymphodepletion and bridge therapy, protocols available, indications, advantages, negative effects, agent associated toxicity, applicability for specific onco-hematological diseases and how to optimize the procedure, guarantying security and efficacy of this approach.

Keywords: Lymphodepletion. Bridge Therapy. Cell Therapy.

OBJECTIVE

To describe the importance and applicability of Lymphodepletion and bridge therapy, specifying the indication and its types, considering the appropriate time for both.

INTRODUCTION

"Adoptive" cell therapy (ACT) is a therapeutic option already available for cancer patients. T cells genetically modified to express a chimeric antigen receptor (CAR) against CD-19 antigens have been approved by the US Food and Drug Administration (FDA) for the treatment of acute lymphoblastic leukemia and non-specific lymphoma. Hodgkin in 2017 and 2018[1,2]. Currently, TCA studies with tumor-infiltrating lymphocytes (TILs) are ongoing in patients with melanoma metastatic[3-6] and other solid tumors. Previous studies have shown that the success rate for obtaining adequate amounts of TILs and the adequate time for their preparation can be obstacles to large-scale use.

Studies performed over a decade ago in patients with metastatic melanoma showed that a conditioning regimen of lymphodepletion prior to adoptive cell transfers significantly improved the efficacy of treatment with expanded TILs "in vitro"[7]. A conditioning regimen of lymphocyte depletion likely acts through multiple mechanisms, including the elimination of consuming structures ("sinks") of homeostatic cytokines, such as interleukins 2 (IL-2), IL-7 and IL-15; the eradication of immunosuppressive agents such as regulatory T cells and myeloid-derived suppressor cells, the induction of costimulatory molecules and the inhibition of indoleamine 2,3-deoxygenase in tumor cells; promoting the expansion, function and persistence of transferred T cells[7-9]. These experiments resulted in the use of conditioning of lymphocyte depletion in clinical trials with treatment with CAR-T cells. Studies have shown the association between an increased serum level of IL-15 after lymphodepletion and better clinical response in the treatment of lymphomas with anti-CD19[10] CAR-T cells and an increased expansion

and persistence of anti-CD19 CAR-T cells and better outcomes. Clinical trials on lymphocyte-depleting conditioning regimens that combined fludarabine with cyclophosphamide compared to regimens without fludarabine in patients with non-Hodgkin lymphomas[11].

Lymphodepletion causes lymphopenia and affects subpopulations of T, B, and NK cells, having several positive effects:

- **Tumor burden reduction**

- Changes in tumor phenotype:
  - Decreased production of tumor cell metabolites: adenosine, kynurenines (indoleamine 2,3-deoxygenase and tryptophan 2,3-deoxygenase), prostaglandin E2, norepinephrine and epinephrine; metabolites that inactivate tumor-infiltrating immune cells and polarize them to anti-inflammatory phenotypes.

  Changes in the expression of costimulatory molecules.

- **Changes in the tumor microenvironment:**

  - Reduction of regulatory T cells and vascular endothelial cell damage making the environment more favorable for CAR-T cells.

- **Removal of cytokine "sinks":**

  - Greater availability of IL-2, IL-7 and IL-15, associated with optimized response to CAR-T cells.

- **Suppression of the host's immune system:**

  - Decreased immunogenicity and increased persistence of infused CAR-T cells.

  - The negative effects of lymphodepletion can be:

- **Pancytopenia and immunosuppression, increasing the risk of infections.**

- **Specific toxicities of cytotoxic agents:**

  - Fludarabine: fever and neurotoxicity.

  - Cyclophosphamide: hemorrhagic cystitis, pericarditis and neurotoxicity.

  - Increased risk of secondary neoplasms.

A broad spectrum of conditioning regimens are used to improve response rates to adoptive cell therapies, but no more consistent approach has been documented. Comparative studies between different regimens are scarce and with a small number of patients recruited, making it difficult to conclude which are the best agents and dosages, given that both response rates and toxicity seem to be dependent on the disease and its stage of each patient. and each specific cellular product.

Pre-immunotherapy CAR-T-cell lymphodepletion in hematologic malignancies: The use of pre-CAR-T-cell therapy lymphocyte depletion conditioning regimens is almost unanimous. Despite this, comparative studies between regimens are very limited, making it difficult to conclude which is the best approach between different treatments. The table 1 below summarizes some of these studies:

Other early-stage studies seek to optimize pretreatment lymphodepletion with CAR-T cells in patients with B-cell malignancies. The table 2 lists some of these studies:

Pretreatment Lymphodepletion of Solid Tumors with CAR T Cells: Although CAR-T cells were initially evaluated in the context of solid tumor treatment, the results were poor; with the emergence of the importance of lymphodepletion, new studies, although limited, were carried out and are presented in the table 3:

- **Pre-infusion CAR-T cell bridging therapy**

In the process between leukopheresis, processing and infusion of CAR-T cells, disease progression can occur. Clinical management during this period is a challenge. Intervention strategies are known as bridging therapy and are usually performed with high doses of chemotherapy, immunochemotherapy and/or radiotherapy.

Clinical studies on the impact of bridging therapy and how it should be performed are scarce. Luft et al., retrospectively reviewed 75 cases of patients with relapsed/refractory large B-cell lymphoma who received CAR-T therapy. Of these, 52 received bridging therapy (BT) and 23 did not (NBT). BT included high-dose corticosteroids (HD, n=10), chemotherapy-based regimen (CT, n=28) and radiotherapy (RT, n=14). CT included cytotoxic chemotherapy, immunotherapy and targeted therapy. There was no significant difference in overall response rate, overall survival, and progression-free survival between groups and subgroups of BT[39].

The development of cytokine release was similar in the groups, but there was a tendency towards an increase in the average level of neurotoxicity syndrome associated with immune effector cells in the

group submitted to BT. The development of cytopenias on day +180 after CAR-T therapy was significantly higher in the BT (50%) vs NBT (13.3%) group and was statistically significant (p = 0.038). Subgroup analysis also showed significantly greater cytopenias at day +180 in the CT (58.3%) and RT (57.1%) subgroups (p = 0.04).

Recently, Liebers et al.[40] analyzed 105 patients with relapsed/refractory large B-cell lymphoma (LGCB) who received the monoclonal antibody polatuzumab vedotin with bendamustine and rituximab (pola-BR) as salvage therapy (n=54) or bridging therapy (n=51) for CAR-T infusion (n=41) or for allogeneic bone marrow transplantation (n=10). Overall survival (OS) at six months was 49.6% and 77.9% for the rescue and bridging therapy groups, respectively.

Kuhnl et al. presented the profile of 250 patients with high-grade relapsed/refractory (LGCB) from the CAR-T program in England, where 174 patients were selected for therapy with (axicabtagene ciloleucel (axi-cel) and 76 for use of tisagenlecleucel (tisagen). Regarding the severity of the disease, 79% of the cases were in an advanced stage, 31% had bulky disease and 66% had extranodal involvement. In relation to previous treatment, (39%) of the patients had received 3 or more lines of treatment previous studies, 33 patients were previously submitted to auto HSCT, and 5 to allo HSCT; 77% of patients had stable or progressive disease as a better response to the last line of treatment[41].

In a retrospective study of patients with relapsed/refractory B-cell acute lymphoblastic leukemia undergoing CAR T-cell (tisagenlecleucel) infusion after cyclophosphamide/fludarabine lymphodepleting chemotherapy Fabricio et al. 2022 estimated the fludarabine exposure as area under the curve (AUC; mg × h/L) using a validated population pharmacokinetic (PK) model. The optimal fludarabine exposure was found to be ≥ 13.8 mg × h/L and was associated with reduced disease relapse and a clinically relevant composite end point of relapse or loss of B-cell aplasia. No increase in toxicity was noted in the analysis, but according to the authors, this is an important consideration for prospective studies. Fludarabine exposure before CD19- specific CAR T-cell therapy (tisagenlecleucel) in pedaytric and young adult patients with R/R B-ALL was associated with lower relapse probability. Similar analysis with other CAR T-cell products that use fludarabine-based lymphodepleting chemotherapy will be useful to identify the optimal fludarabine exposure for individual products[42].

The need and intensity of bridging therapy must be evaluated in each case in a specific way and depends on factors such as the aggressiveness of the disease, response to previous treatments, related toxicity, among others. However, studies have shown promising results with bridge therapy for the use of CAR-T treatment in diseases such as lymphomas and ALL. New prospective studies are needed to better assess the role of different BT strategies in the use of CAR-T cells.

CONCLUSION

-Lymphodepletion improves the expansion, persistence and migration of CAR-T cells, enhancing their antitumor effect and available homeostatic cytokines, depleting inhibitory molecules and cell populations. Beneficial actions on the microbiome have also been reported.

- The scarcity of comparative studies between different lymphodepletion regimens does not allow a consensus on the best approach to obtain it.

- It is related to a number of toxicities, including varying degrees of cytopenias and even, in more severe cases, the cytokine release syndrome.

- Higher intensity and inclusion of Fludarabine in their protocols are associated with greater efficacy but also more toxicity.

- The addition of intermedayte doses of Fludarabine to conditioning regimens is increasingly used to improve the expansion and persistence of infused cells, in addition to reducing the immunogenicity of transgenic products.

- A number of alternatives to lymphodepletion are under development, including the addition of stimulatory cytokines to the infused cells.

- Regarding Bridge Therapy, it can be essential, in cases where the disease activity does not allow waiting the necessary time for the production of CAR-T cells.

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TABLE 1: Comparative studies of lymphocyte depletion conditioning regimens for Hematologic malignancies

Study	Neoplasm	Cell's	Lymphodepletion	Results
MMSKCC12	LLC R/R	CD-28 2ª g CAR T	CY (1,5 ou 3 g/m2) X No LD	- Increased persistence of CAR-T cells. - Better effectiveness
Geyer et al.13	LLC R/R	CD-28 2ª g CAR T	FLU/CY X CY	FLU/CY: - Higher lymphocyte nadir - Higher peak cell expansion. circulating CAR-T
Curran et al.14	LLA-B R/R	CD-28 2ª g CAR T	CY 3 g/m2 X CY 1,5 g/m2	CY 3 g/m2: - Higher CR rates - Greater depletion of lymphocytes and greater peak of CAR-T cell expansion.
UPENN15	Neoplasias of células B	4-1BB- 2ª g CAR (CTL-019)	FLU/CY X Pentostatin/CY X Bendamustina	No differences
ELIANA16	LLA-B R/R	Tisagenlecleucel (CTL-019)	FLU 30 mg/m2 x 4 days e CY 500 mg/m2 x 2 days	66% SFR in 18 m
JULIET17	LNHDGCB R/R	Tisagenlecleucel (CTL-019)	FLU 25 mg/m2 x 3 days e CY 250 mg/m2 x 3 days X Bendamustina 90 mg/m2 x 2 days X No LD	FLU/CY: - Higher overall response rate18
NCI19	Neoplasias of células B	CD19 específico CD28 2ª g CAR	FLU 25 mg/m2 x 5 days e CY 60 mg/Kg x 2 days X FLU 30 mg/m2 x 3 days e CY 300 – 500 mg/m2	Higher neurotoxicity in the group with higher doses of CY
ZUMA-120	Primary LNHDGCB and LNH of mediastinum R/R	CD19 específico CD28 2ª g CAR axicabtagene ciloleucel (Axi-cel)	FLU 30 mg/m2 e CY 500 mg/m2 x 3 days	40% RC in 14,5 m
Wang et al.21	CML R/R	KTE-X19 brexucabtagene autoleucel	FLU 30 mg/m2 e CY 500 mg/m2 x 3 days	61% SLR in 12 m
FHCRC22	ALL B R/R	4-1BB-based 2ª g CAR céls. CD4+ e CD8+ of memória purificadas - lisocabtagene maraleucel (liso-cel)	CY (3 differents doses) X FLU 25 mg/m2 x 3 or 5 days e CY 60 mg/Kg x 1 day	FLU/CY: - Increase in the area under the CAR-T cells curve. - Better evolution
FHCRC23	LNH-B R/R	lisocabtagene maraleucel (liso-cel)	CY (3 differents doses) X FLU 25 mg/m2 x 3 ou 5 days e CY 60 mg/Kg x 1 day	FLU/CY: - Higher overall response rate and CR - Higher rates of CAR-T cell expansion and persistence.

PLAT-0224	LLA-B R/R CYA	lisocabtagene maraleucel (liso-cel)	CY (2 – 4 g/m2) X FLU 30 mg/m2 x 4 days e CY 500 mg/m2 x 2 days.	FLU/CY: - Largest CAR-T cell peaks and the area under the curve
TRANSCEND25	LNH-B R/R	lisocabtagene maraleucel (liso-cel)	FLU 30 mg/m2 e CY 300 mg/m2 x 3 days	53% RC in 18,8 m
CARTITUDE-126	MM R/R	Céls. BAR-T anti-BCMA 2ª g CD28/CD3ζ	FLU 30 mg/m2 e CY 300 mg/m2 x 3 days	77% SLP in 12 m
Ramos27	LH R/R	Céls CAR-T anti CD-30 CD28ζ 2ª g	FLU 30 mg/m2 x 3 days, CY 500 mg/m2 x 3 days, bendamustina 90 mg/m2 x 2 days ou FLU 30 mg/m2 x 3 days e bendamustina 70 mg/m2 x 3 days	36% SLP in 12 m
CALM28 e PALL29	LLA-B R/R	UCART19/ALLO-501	FLU 90 mg/m2, CY 1500 mg/m2, Alemtuzumab 1 mg/Kg (máx. 40 mg) – (CALM) FLU 150 mg/m2, CY 120 mg/Kg, Alemtuzumab 1 mg/Kg (máx. 40 mg)	Phase I Allogeneic CAR-T cells

TABLE 2: Strategies to optimize lymphodepletion with CAR-T cells in patients with B-cell malignancies

Method	Study	Objective
Add a inhibitor of "checkpoint"	ALEXANDER (AUTO-330)	Increase activity and persistence of CAR-T
Add of Rituximab	ZUMA-14 (axi-cel)31	Increase the anti-lymphoma effect and persistence of CAR-T
Add of monoclonal antibody anti-CD52	ALPHA (Allo-501)32	Increase the anti-lymphoma effect and persistence of CAR-T
Add radioimunotherapy with antibody anti CD45 conjugated to I31	Ludwig33	Increase the specificity of lymphodepletion.

TABLE3: Recent studies of Lymphodepletion in different Neoplasms

Study	Neoplasm	Cell's	Lymphodepletion	Results
Christie Cancer Centre34	Neoplasias that expressed Carcioembryogenic Antigen (CEA)	1ª g CAR-T directed to Carcioembryogenic Antigen (CEA) + systemic IL-2	FLU 25 mg/m2 x 5 days X FLU 25 mg/m2 x 5 days e CY 60 mg/Kg x 2 days	FLU/CY: - Longer duration of lymphopenia - 3 in 4 patients reached stable disease - Pulmonary toxicity peak-associated to CAR-T
Baylor35	Rhabdomyosarcoma that expressed HER2	CAR-T cells with CD-28 against HER2	FLU/CY	CC after reinfusion of CAR-T post relapse
Heczey36	Neuroblastoma R/R that expressed Disialoganglioside (GD2)	CAR-T cells of 3ª generation against GD2	FLU 30 mg/m2 x 2 days, CY 500 mg/m2 x 3 days +/- inhibitor of PD-1	- Increase in homeostatic cytokines - Increased persistence of CAR-T - Limited efficacy even in the anti-PD-1 group
Adaptimmune37,38	Synovial Sarcoma	CAR-T cells against NY-ESO-1 peptide	CY 1800 mg/m2 x 2 days X FLU 30 mg/m2 x 4 days e CY 600 mg/m2 x 2 days X FLU 30 mg/m2 x 4 days e CY 1800 mg/m2 x 2 days	- Better results in the group with more intensive conditioning - FLU/CY: increase of circulating homeostatic cytokines, grafting and persistence of CAR-T - Grade 4 adverse effects in all patients