Bridging Therapy and Lymphodepleting Chemotherapy

Bristol Myers Squibb™

Patient Journey Through the CAR T Cell Therapy Process

Patient selection → Patient consent & education → Patient screening → Leukapheresis and cell transport → CAR T manufacturing → **Bridging and lymphodepleting chemotherapy** → CAR T infusion & patient monitoring → Post hospital discharge monitoring → Long-term monitoring

1 Patient Identification

- Appropriate patients will be identified for treatment at qualified treatment sites or referring sites
- Company will be notified and leukapheresis and treatment dates will subsequently be scheduled

2 Leukapheresis

- Patient will undergo apheresis, which involves collection of white blood cells
- Collected apheresis product will be sent to the manufacturer for production

3 Manufacturing

The CAR T cell product is created at a manufacturing facility

4 Prep

- Patients may require bridging therapy to maintain disease control while the CAR T cell product is being manufactured
- Shortly prior to CAR T cell administration, the patient is prepared for treatment with lymphodepletion

5 Treat

- The CAR T cell product is delivered to the treatment site
- Product is administered

6 Monitor

- The patient is monitored closely for at least 4 weeks and side effects are promptly managed. Caregiver support is critical during this time
- Thereafter, the patient is periodically monitored long term

Reference: 1. Beaupierre A, et al. *Clin J Oncol Nurs*. 2019;23:27-34.

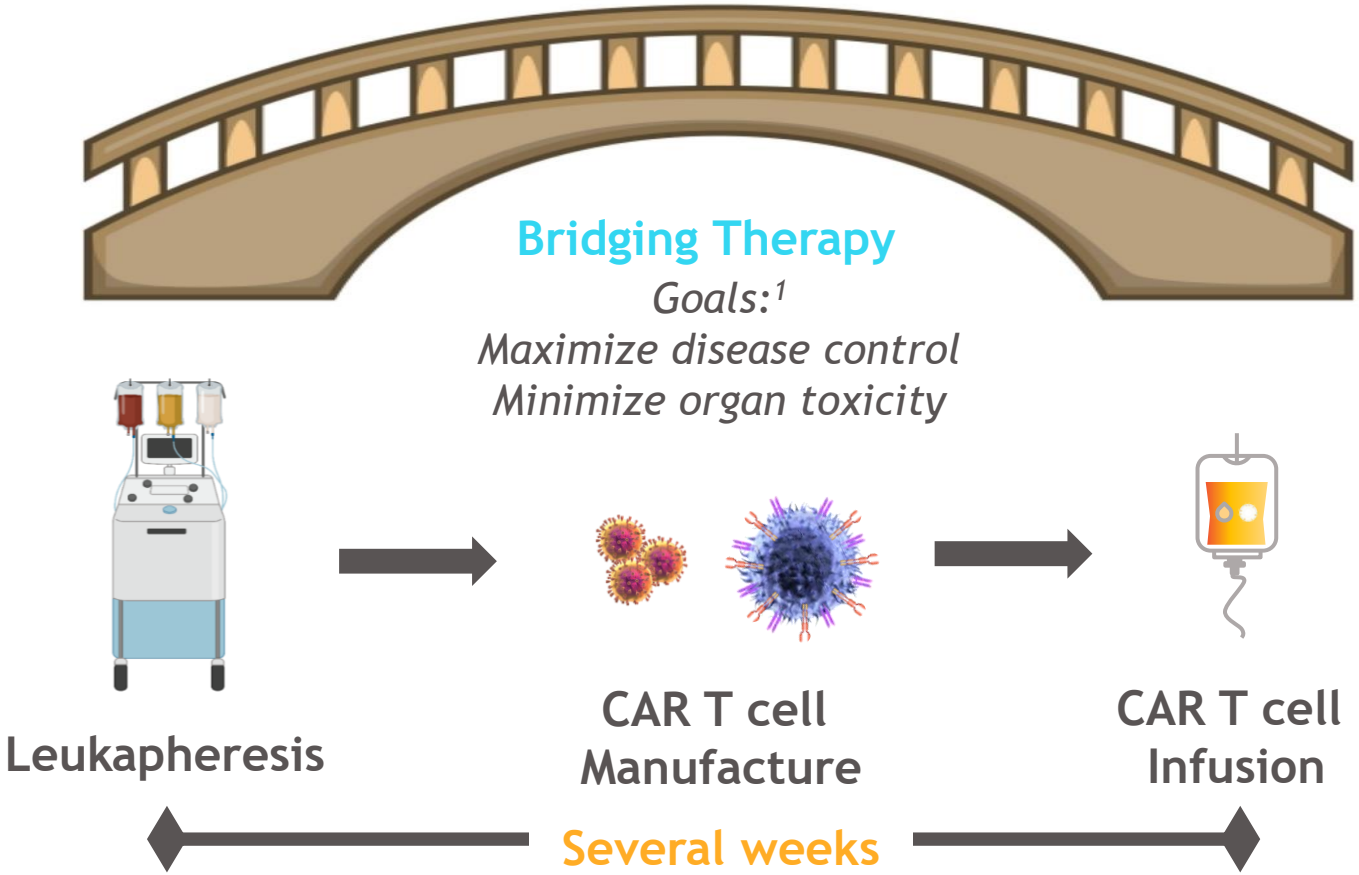
CAR T Academy: Bridging Therapy and Lymphodepleting Chemotherapy

01 Bridging Therapy

02 Lymphodepletion

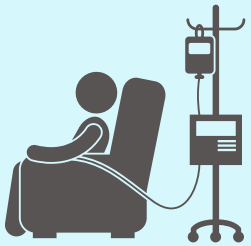
Bridging Therapy May Help Control Disease Until CAR T Cells Are Ready for Infusion

- Following leukapheresis, it can take several weeks before the CAR T cell product can be manufactured and delivered to the patient[1,2]
- Because most patients undergoing CAR T cell therapy have active disease, some will require bridging therapy during this period[1]



References: 1. McGuirk J, et al. *Cytotherapy*. 2017;19:1015-1024. **2.** Perica K, et al. *Biol Blood Marrow Transplant*. 2018;24:1135-1141. // *Bridge icon attribution: round PNG Designed By Ylivdesign from https://pngtree.com/*

Coordination and Delivery of Bridging Therapy



Regimens are highly variable and depend on:[1]

- Specific malignancy
- Disease burden
- Patient age
- Comorbidities
- Prior response to therapy

- Bridging therapy is carefully planned and selected with the aim to avoid patient harm or delay CAR T cell infusion[1]
- Patients are closely monitored for infections and other toxicities[2]
- Typically coordinated by and delivered at the referring institution or the treating center[1,2]
- Close communication between treating institutions and CAR T cell manufacturing sites is important for adjusting bridging therapy delivery (eg, if there are delays in CAR T cell manufacturing)[1]

References: 1. McGuirk J, et al. *Cytotherapy*. 2017;19:1015-1024. **2.** Beaupierre A, et al. *Clin J Oncol Nurs*. 2019;23:27-34.

Possible Bridging Therapy Options

Bridging therapy options vary based on different factors (eg, diagnosis)

Examples of Bridging Therapy

- Chemotherapy (oral or IV), including alkylating agents and proteasome inhibitors[1,2]
- Immunomodulatory agents[2]
- Radiation therapy[1]
  - For symptomatic or large masses
- Monoclonal antibodies[2]
- Antibody-drug conjugates[3]
- Corticosteroids, including high-dose steroids[1,2]
- Lower-intensity regimens (as appropriate for certain patients)[1]

Targeted agents and/or novel agents may also be utilized, provided they yield a rapid reduction in tumor burden and will not produce lasting effects that may adversely influence CAR T cell therapy[1]

IV, intravenous.

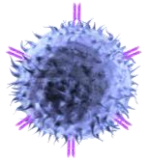
References: 1. Beaupierre A, et al. *Clin J Oncol Nurs*. 2019;23:27-34. **2.** Raje N, et al. *N Engl J Med*. 2019;380:1726-1737. **3.** Hashmi H, et al. *Hematol Oncol Stem Cell Ther*. 2021;S1658-3876(21)00062-5.

CAR T Academy: Bridging Therapy and Lymphodepleting Chemotherapy

01 Bridging Therapy

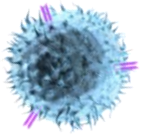
02 Lymphodepletion

Key Immune Cells and Molecular Components Affected By Lymphodepleting Chemotherapy



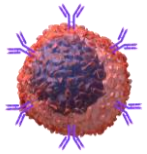
Cytotoxic T cell

- A type of lymphocyte that has antigen-specific surface receptors
- Functions involve killing infected/abnormal cells by inducing apoptosis



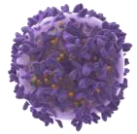
Regulatory T cell

- A type of lymphocyte that has antigen-specific surface receptors
- Functions involve suppressing immune responses through secretion of immunosuppressive cytokines or cell-to-cell contact



B cell

- A type of lymphocyte that has antigen-specific surface receptors
- Functions include presenting antigens to T cells and developing into plasma cells that produce antibodies



Natural killer cell

- A type of lymphocyte that lacks antigen-specific surface receptors
- Functions involve killing infected/abnormal cells by inducing apoptosis
- Important for tumor surveillance

Cytokines

- Polypeptides secreted by immune and other cells
- Serve as signaling molecules to influence the magnitude of inflammatory and immune responses
- Act sequentially, synergistically, or antagonistically

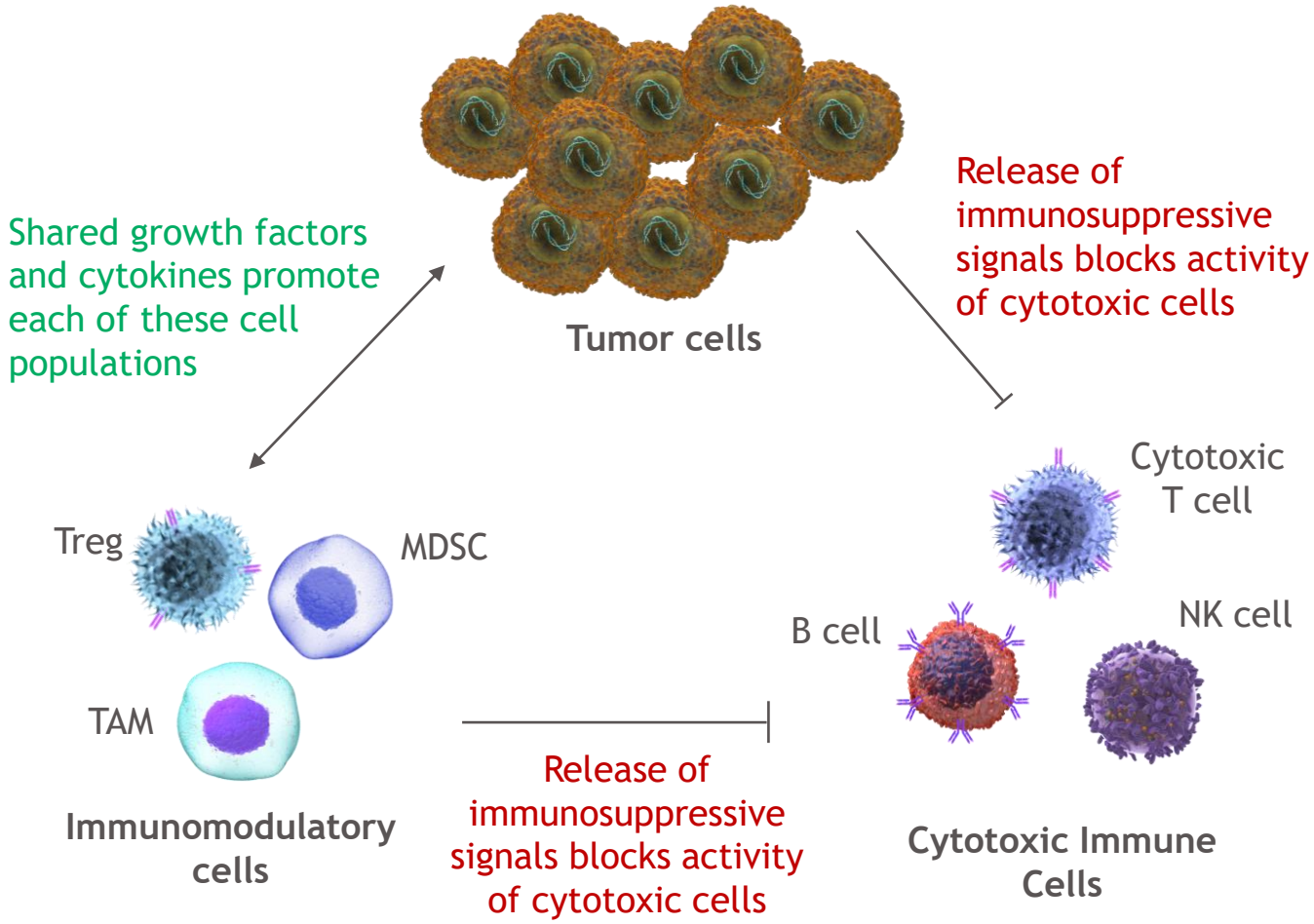
Reference: Delves PJ. *Merck Manual Professional Version*. Last updated Dec 2018.

Immunosuppression Results in Imbalances in Cell Activity

Tumor cells acquire the ability to escape detection and killing by cytotoxic immune cells by:

- Production of signals that downregulate anti-tumor immune responses[1]
- Downregulation of signals that activate anti-tumor immune responses[1]
- Recruitment of immunomodulatory cells (eg, MDSCs, Tregs, TAMs) that suppress anti-tumor immune responses[1,2]

These various mechanisms may contribute to the typically poor response of aggressive tumors and late-stage cancers to immunotherapies[1]

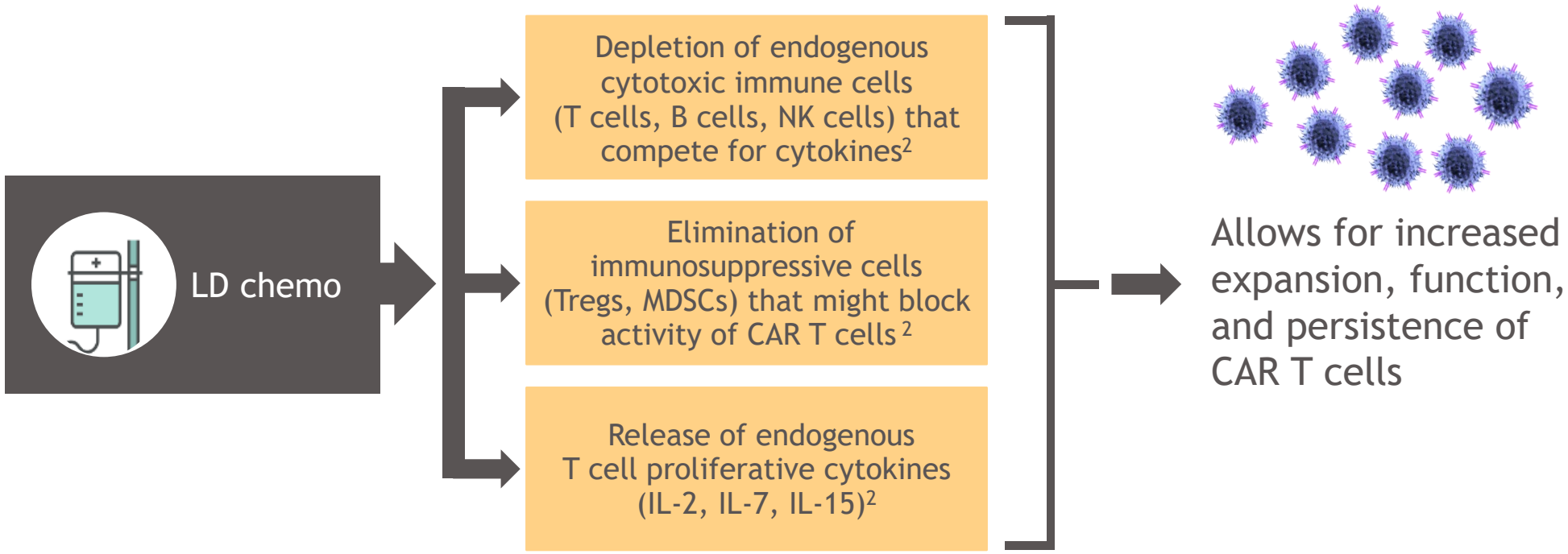


MDSCs, myeloid-derived suppressor cells; NK, natural killer; TAM, tumor-associated macrophage; Treg, regulatory T cell.

References: 1. Wang Y, et al. *Cancer Drug Resist*. 2019;2:1-20. **2.** Sterner RC, Sterner RM. *Blood Cancer J*. 2021;11(4):69.

Purpose of Lymphodepleting Chemotherapy (LD Chemo)

Primary aim: prepare the patient for CAR T cell infusion by depleting endogenous immune cells; not used to control disease[1]

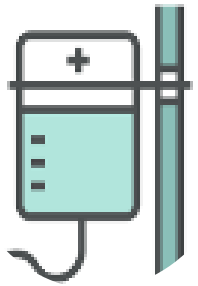


IL, interleukin; MDSCs, myeloid-derived suppressor cells; NK, natural killer; Tregs, regulatory T cells

References: 1. Beaupierre A, et al. *Clin J Oncol Nurs*. 2019;23:27-34. **2.** Neelapu SS. *Blood*. 2019;133:1799-1800.

Multiple LD Chemo Regimens Have Been Used in CAR T Cell Trials

- Cyclophosphamide[1]
- Fludarabine + cyclophosphamide[1]
- Pentostatin + cyclophosphamide[1]
- Bendamustine-based regimens[1]
- Disease-specific regimens[1]



Fludarabine + cyclophosphamide is a commonly used regimen[1,2]

LD, lymphodepletion.

References: 1. Brudno JN, Kochenderfer JN. *Blood Rev*. 2019;34:45-55. **2.** Perica K, et al. *Biol Blood Marrow Transplant*. 2018;24:1135-1141.

Fludarabine Is an Important Lymphodepletion Component But May Cause Toxicity

With the goal of reducing adverse events, clinicians should consider fludarabine dose-reduction for patients with increased sensitivity to fludarabine (eg, heavy pretreatment, renal insufficiency) and remain vigilant for myelosuppression, infections, and possible late-onset neurotoxicity in these individuals

Reference: Lowe KL, et al. *Gene Therapy*. 2018;25:176-191.

Delivery of Lymphodepleting Chemo

- Patients are treated with LD chemo several days before CAR T cells are infused[1]
- Coordinated by the treating facility, and can be delivered in the inpatient or outpatient setting[2]
- Active infection must be excluded or under control prior to the start of LD chemo[3]

Patients should have a caregiver that meets certain expectations[2]

Expectations for Caregivers During LD Chemo[2]

- Be at least 18 years old
- Be able to drive
- Stay with the patient 24 hours/day in the outpatient setting
- Live with the patient at a place within close proximity of the treating facility
- Transport patient to/from appointments
- Actively engage with the medical team
- Manage and administer the patient's medications
- Practice good home precautions
- Contact the medical team with any questions or regarding any symptoms or adverse events

References: 1. Perica K, et al. *Biol Blood Marrow Transplant*. 2018;24:1135-1141. **2.** Beaupierre A, et al. *Clin J Oncol Nurs*. 2019;23:27-34. **3.** Yakoub-Agha I, et al. *Haematologica*. 2020;105(2):297-316.

Summary

Bridging therapy

- Some patients may receive bridging therapy while CAR T cell therapy is being manufactured
- The purpose is to maximize disease control and minimize organ toxicity until CAR T cell therapy can be delivered
- The specific regimens used depends on the specific disease diagnosis, disease burden, patient age, comorbidities, and prior response to therapy
- Treatment is carefully planned and selected so as not to cause patient harm or delay CAR T cell infusion

LD chemo

- Patients typically receive LD chemo several days prior to CAR T cell infusion
- The purpose is to prepare the patient for CAR T cell infusion by depleting endogenous T cells—not to control disease
- This treatment elicits several effects that help increase the expansion, function, and persistence of CAR T cells
- Fludarabine + cyclophosphamide is a commonly used regimen

Thank you for completing this module of CAR T Academy

We hope you found it informative and educational

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