2

Introduction

3

Objectives

- Understand the important role of CAR-T cell therapy in current treatment landscape
- Understand the basic biology of T cell therapy and manufacturing process
- Discuss current FDA approved indications for CAR-T cell therapy
- Understand risk factors and therapies for cytokine release syndrome (CRS)
- Understand barriers and limitations of CAR-T cell therapy, specifically in Hawaii

4

Question 1: What are the current FDA approved indications for CAR T cell therapy? (Select all that is correct)

A: Patients < 25 years of age with relapsed/refractory B-cell acute lymphoblastic leukemia

B: Adults with relapsed/refractory large B-cell lymphoma

C: Adults with relapsed/refractory mantle cell lymphoma

D: A and B

E: All of the above

5

Question 2: What is the only FDA approved treatment for cytokine release syndrome?

A: Anakinra (interleukin-1 receptor antagonist)

B: Dexamethasone

C: Tocilizumab (interleukin-6 receptor antagonist)

D: Etanercept (tumor necrosis factor inhibitor)

6

Question 3: What are the current limitations and barriers to CAR T cell therapy?

A: Non-response and disease relapse

B: Complex manufacturing process

C: Efficacy of CAR T cell therapy in non-hematologic solid tumors

D: Financial toxicity

E: All of the above

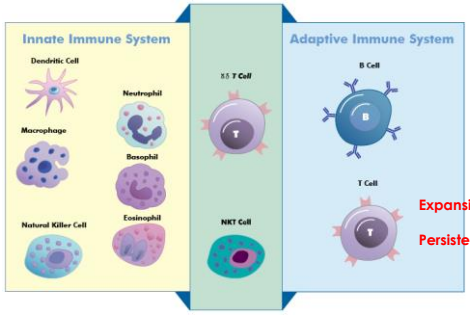
7

Immunotherapy as the new pillar of cancer therapy

Blinatumomab
Inotuzumab
CAR T cells

8

Quick immunology refresher

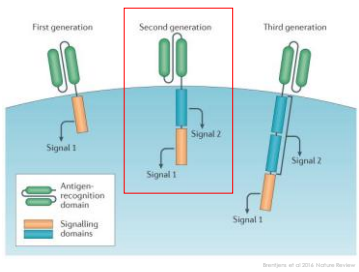


Expansion

Persistence

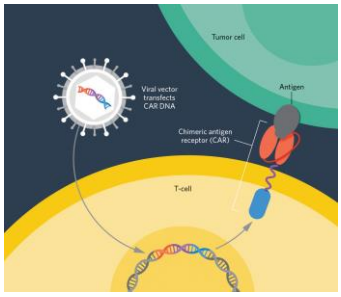
9

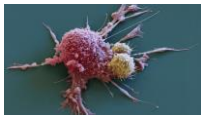
Current FDA approved CAR T products are 2nd generation CARs



10

CAR T cell therapy's mechanism of action is unique as it functions as a "living" drug





11

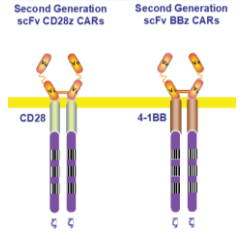
Current FDA approved CAR T products and indications

Product	Indications
tisagenlecleucel	• Children and young adults up to age 25 years of age with B-cell precursor acute lymphoblastic leukemia that is refractory or in second or later relapse • Adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy including diffuse large B-cell lymphoma (DLBCL) not otherwise specified, high grade B-cell lymphoma, and DLBCL arising from follicular lymphoma
axicabtagene ciloleucel	• Adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy, including DLBCL not otherwise specified, primary mediastinal large B-cell lymphoma, high grade B-cell lymphoma, and DLBCL arising from follicular lymphoma
brexucabtagene autoleucel	• Adult patients with relapsed/refractory mantle cell lymphoma

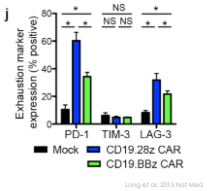
12

The difference between the 2 current FDA approved CAR T product is in the co-stimulatory domain

axicabtagene
brexucabtagene



tisagenlecleucel



13

The story of CAR T cell therapy began with a girl named Emily…

14

CAR T cell therapy as the success story for difficult to treat cancers

15

Encouraging results from clinical trials led to FDA approval of CAR T cell therapy

- **CTL019**
  - Phase 1/2a single arm, single center open label studies conducted at CHOP/UPenn
  - 4-1BB signaling endodomain
  - 30 patients with r/r CD19+ B-ALL were treated
  - ORR = 90% 1 month post infusion
  - 63% of patients continued to have remission with a median follow-up of 7 months
- **ELIANA**
  - FDA approval of tisagenlecleucal was based on this Phase 2 multicenter trial
  - 79 patients received CAR T product (61% had previously undergone allogeneic stem cell transplant)
  - ORR = 82% at 3 months post infusion
  - RFS = 66% at 12 months, 62% at 24 months
  - OS = 76% at 12 months, 66% at 24 months

16

CAR T cell therapy has also been encouraging in patients with r/r DLBCL

- **JULIET**
  - Phase 2, multicenter, international trial
  - 4-1BB signaling endodomain
  - 115 adult patients with r/r DLBCL were treated
  - ORR = 54% (40% CR, 13% PR)
  - RFS = 66% at 6 months, 64% at 12 and 18 months
  - Median OS = 11.1 months

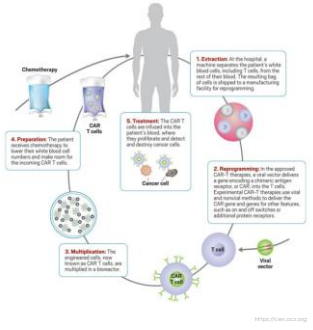
17

Encouraging results from clinical trials led to FDA approval of CAR T cell therapy- adults w/ refractory NHL

- **ZUMA-1**
  - Phase 2, multicenter
  - CD28 signaling endodomain
  - 101 adult patients with refractory **DLBCL, PMBCL, transformed FL**
  - ORR = 82%, CR = 54%
  - 42% of patients continued to have response with median follow up of 15.4 months
  - OS = 52% at 18 months
- **ZUMA-2**
  - Phase 2, multicenter
  - 68 adult patients with refractory **mantle cell lymphoma**
  - ORR = 85%, CR = 59%
  - 57% in remission at 12 months
  - PFS = 61% at 12 months
  - OS = 83% at 12 months

18

CAR T cell therapy is a process, not a drug



19

The most common treatment-related toxicities is cytokine release syndrome

- CRS is a constellation of inflammatory symptoms resulting from cytokine elevations associated with T cell expansion, proliferation, immune system activation, and tumor cell elimination
- Can be applied to any T-cell activating/engaging therapy
- Symptoms comes in a range of mild to life-threatening

- High disease burden (in acute lymphoblastic leukemia) is a risk factor for severe CRS

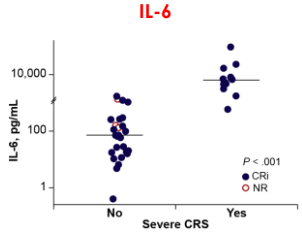
20

Different CAR constructs leads to different toxicity profile- CRS

Study	Product	N=	Median time of CRS onset (days)	CRS All grades	Severe CRS	Reference
ELIANA (peds r/r ALL)	CD19/CD3ζ /4-1BB	65	3	77%	21%	Maude et al, NEJM 2018
JULIET (adult NHL)	CD19/CD3ζ /4-1BB	111	3	58%	22%	Schuster et al, NEJM 2019
ZUMA-1 (adult NHL)	CD19/CD3ζ /CD28	101	2	93%	13%	Neelapu et al, NEJM 2017
ZUMA-2 (adult mantle cell lymphoma)	CD19/CD3ζ /CD28	68	2	91%	15%	Wang et al, NEJM 2020

25

IL-6 was found to be more elevated in patients with severe CRS



Maude et al 2014 NEJM

26

Tocilizumab is the only FDA approved medication for CAR T cell induced CRS

- Tocilizumab specifically blocks IL-6 receptors
- Received FDA approval for CAR T associated CRS in patients >2 years of age in 2017
- Does not appear to suppress T cell function and/or induce T cell apoptosis

27

CRS management generally recommends tocilizumab to be given with moderate or severe CRS

Cytokine Release Syndrome Treatment Algorithm

CRS is managed clinically according to the following algorithm:[1]

CRS Severity	Management
Prodromal syndrome: Low-grade fever, fatigue, anorexia	Observe in person; exclude infection; administer antibiotics per local guidelines if neutropenic; provide symptomatic support.
CRS requiring mild intervention (one or more of the following): • High fever • Hypoxia • Mild hypotension	Administer antipyretics, oxygen, intravenous fluids and/or low-dose vasopressors as needed.
CRS requiring moderate to aggressive intervention (one or more of the following): • Hemodynamic instability despite intravenous fluids and vasopressor support • Worsening respiratory distress, including pulmonary infiltrates, increasing oxygen requirement including high-flow oxygen and/or need for mechanical ventilation • Rapid clinical deterioration	• Administer high-dose or multiple vasopressors, oxygen, mechanical ventilation, and/or other supportive care as needed • Administer tocilizumab ◦ Patient weight less than 30 kg: 12 mg/kg intravenously over 1 hour ◦ Patient weight greater than or equal to 30 kg: 8 mg/kg intravenously over 1 hour (maximum dose 800 mg) Repeat tocilizumab as needed at a minimum interval of 8 hours if there is no clinical improvement. If no response to second dose of tocilizumab, consider a third dose of tocilizumab or pursue alternative measures for treatment of CRS. Limit to a maximum total of 4 tocilizumab doses. • If no clinical improvement within 12 to 18 hours of the first tocilizumab dose, or worsening at any time, administer methylprednisolone 2 mg/kg as an initial dose, then 2 mg/kg per day until vasopressors and high-flow oxygen are no longer needed, then taper

http://hcp.novartis.com

28

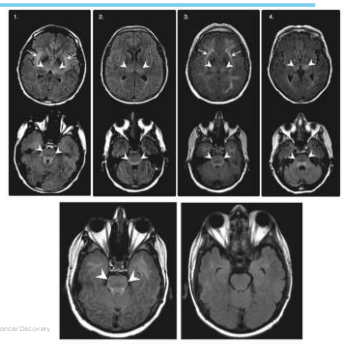
Many challenges remain in optimal CRS management

- Unfortunately, not all patients with severe CRS respond to tocilizumab
  - Ongoing investigations for alternative therapies: siltuximab, dasatinib etc
- Optimal timing of tocilizumab is a subject of ongoing clinical trials
  - Prophylactic treatment strategy is being explored

29

Neurotoxicity is another common toxicity seen after CAR T cell therapy

- ICANS = immune effector cell therapy associated neurotoxicity syndrome
- Symptoms: global encephalopathy i.e. aphasia, confusion, hallucination, tremor, agitation
- MRI changes seen in some, but not all patients with severe neurotoxicity
- Complete reversal of MRI changes upon symptoms resolution

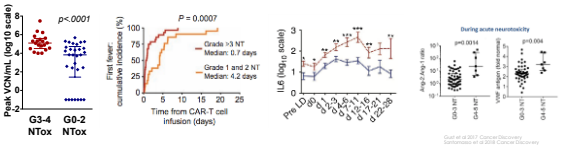


Gust et al 2017 Cancer Discovery

30

Neurotoxicity is another common toxicity seen after CAR T cell therapy

- Severe neurotoxicity correlated with peak CAR expansion, earlier onset of fever, elevated serum cytokines, and endothelial activation



Gust et al 2017 Cancer Discovery
Contassiotis et al 2018 Cancer Discovery

- Onset of ICANS is during CRS or shorty after resolution
- Pathophysiology is unclear

31

Different CAR constructs leads to different toxicity profile- ICANS

Study	Product	N=	ICANS	Severe ICANS	Deaths from Cerebral edema (n=)	Reference
ELIANA (peds r/r ALL)	CD19/CD3ζ /4-1BB	65	40%	13%	0	Maude et al, NEJM 2018
JULIET (adult NHL)	CD19/CD3ζ /4-1BB	111	21%	12%	0	Schuster et al, NEJM 2019
ZUMA-1 (adult NHL)	CD19/CD3ζ /CD28	101	64%	28%	2	Neelapu et al, NEJM 2017
ZUMA-2 (adult mantle cell lymphoma)	CD19/CD3ζ /CD28	68	63%	31%	0	Wang et al, NEJM 2020

Tocilizumab is NOT effective in ICANS, focused more on supportive care

32

Current challenges and barriers to CAR T cell therapy

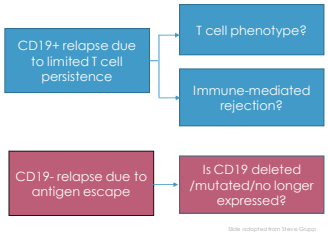
34

Unfortunately, not all patients who receive CAR T cell therapy are cured

- CAR products with 41-BB costimulatory domain, 10-20% of patients fail to enter remission, and 30-50% of patients who achieve remission will have antigen positive or negative relapse
- ELIANA trial
  - 38% patients relapsed within 24 months
  - 14 of 19 (74%) had evidence of CD19 negative relapse

35

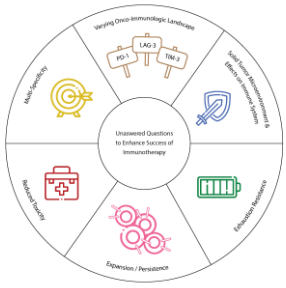
Mechanisms of post CAR T cell therapy relapse is complicated and multi-faceted



Slide adapted from Steve Grupp

36

Other engineering strategies to enhance adoptive T cell therapy



37

CAR T cell therapy is expensive!

- One-time injection of tisagenlecleucel for ALL: $475,000
- One-time injection of tisagenlecleucel/axicabtagene for NHL: $373,000
- All hospital cost > $1 million
- Few issues of getting insurance reimbursement in pediatric cancers
- Medicare reimbursement process is improving

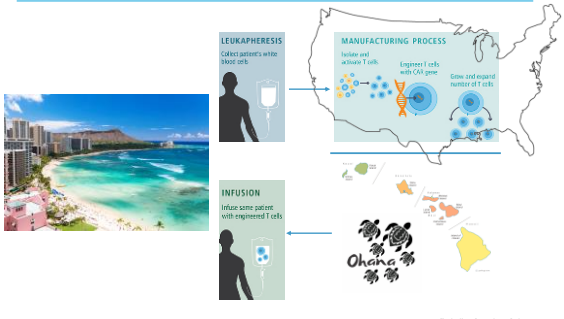
38

For Hawaii, access to CAR T cell therapy remains as the largest barrier

- 114 institutions in the U.S. that are eligible to administer tisagenlecleucal
- Limited by complex manufacturing process, expertise in managing unique toxicities
- In Hawaii, we are working with many experts from all disciplines to move this process forward

39

Proposed model of how we can offer CAR T cell therapy in Hawaii to our patients



Illustrations from diana-farber.org

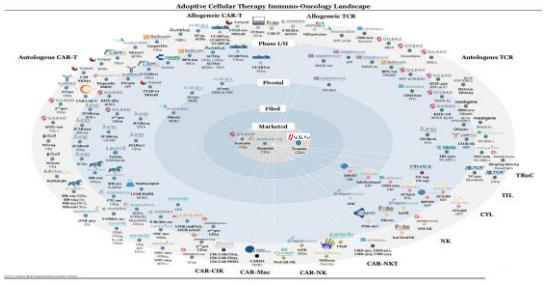
40

It takes a TEAM to move mountains!

Slide adapted from Claire White, BSN, RN, CPHON

41

It's an exciting world out there!



Slide courtesy of Steve Gruppo

42

Question 1: What are the current FDA approved indications for CAR T cell therapy? (Select all that is correct)

A: Patients < 25 years of age with relapsed/refractory B-cell acute lymphoblastic leukemia

B: Adults with relapsed/refractory large B-cell lymphoma

C: Adults with relapsed/refractory mantle cell lymphoma

D: A and B

E: All of the above

43

Question 1: What are the current FDA approved indications for CAR T cell therapy? (Select all that is correct)

A: Patients < 25 years of age with relapsed/refractory B-cell acute lymphoblastic leukemia

B: Adults with relapsed/refractory large B-cell lymphoma

C: Adults with relapsed/refractory mantle cell lymphoma

D: A and B

E: All of the above

44

Question 2: What is the only FDA approved treatment for cytokine release syndrome?

A: Anakinra (interleukin-1 receptor antagonist)

B: Dexamethasone

C: Tocilizumab (interleukin-6 receptor antagonist)

D: Etanercept (tumor necrosis factor inhibitor)

45

Question 2: What is the only FDA approved treatment for cytokine release syndrome?

A: Anakinra (interleukin-1 receptor antagonist)

B: Dexamethasone

C: Tocilizumab (interleukin-6 receptor antagonist)

D: Etanercept (tumor necrosis factor inhibitor)

46

Question 3: What are the current limitations and barriers to CAR T cell therapy?

A: Non-response and disease relapse

B: Complex manufacturing process

C: Efficacy of CAR T cell therapy in non-hematologic solid tumors

D: Financial toxicity

E: All of the above

47

Question 3: What are the current limitations and barriers to CAR T cell therapy?

A: Non-response and disease relapse

B: Complex manufacturing process

C: Efficacy of CAR T cell therapy in non-hematologic solid tumors

D: Financial toxicity

E: All of the above

48

49