


Natural Line of Defense: Update on Immunotherapy in Hematologic Malignancies

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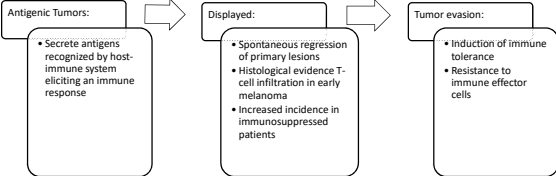
Conflict of Interest

- I have no professional/financial disclosures to report

Objectives

- Review the principles of immunotherapy in the treatment of hematologic malignancies
- Discuss chimeric antigen receptor (CAR) T-cell targets and current treatment strategies integrating recent data on patterns of response and mechanisms of resistance
- Summarize novel immunotherapy approaches in development for treatment of hematologic malignancies
- Evaluate common toxicities of immunotherapy and highlight the pharmacists' role for ensuring safe immunotherapy treatment

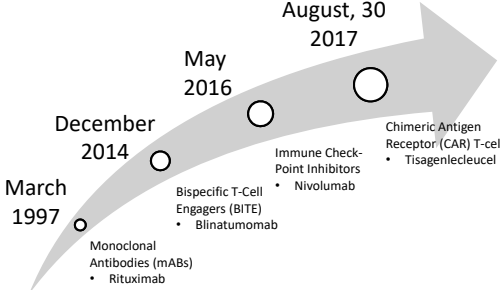
Immunogenicity of Cancer



- Immunotherapy has eradicated hematologic malignancies with allogeneic hematopoietic cell transplant (allo HCT)
 - Use of alloreactive T-cells to control recipient malignancy
 - Also target non malignant cells and cause graft versus host disease (GVHD)
 - Limitations to extending allo HCT to wider ranges of hematologic conditions

Guerry D et al. J Invest Dermatol. 1999 Mar;100(3):342S-345S.
 Weisick LA et al. Annu Rev Immunol. 2007;25:139-170.

Immunotherapy Agents



- March 1997**: Monoclonal Antibodies (mABs)
 - Rituximab
- December 2014**: Bispecific T-Cell Engagers (BiTE)
 - Blinatumomab
- May 2016**: Immune Check-Point Inhibitors
 - Nivolumab
- August, 30 2017**: Chimeric Antigen Receptor (CAR) T-cells
 - Tisagenlecleucel

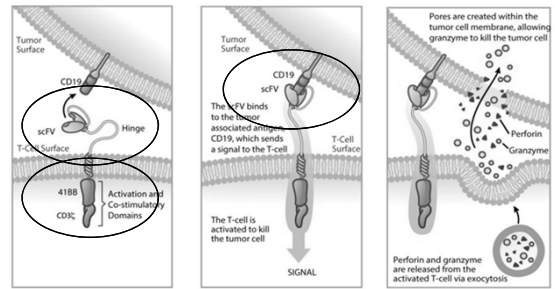
Chimeric Antigen Receptor (CAR) T-cells

CAR T-Cell

- First CAR T-Cell discovered in 1989
- Autologous T-lymphocytes genetically modified to combine the advantage of:
 - Human leukocyte antigen (HLA)- independent antigen recognition
 - Cytotoxic ability of T-cells

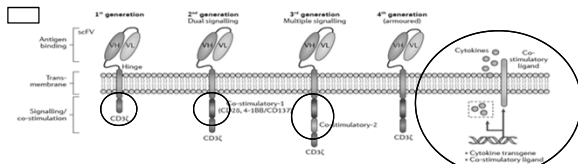
Namuduri M et al. Expert Rev Hematol. 2016 Jun;9(6):511-3. <https://am.ascopub.org/immunotherapy-approaches-expanding-hematologic-malignancies>

CAR T-cells in Action



<http://blogs.shu.edu/cancer/files/2015/11/CD19-CAR.jpg>

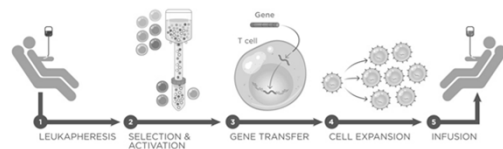
CAR T-cell Development



- 1st Generation: Single-chain variable fragment of an antibody specific for tumor antigen linked to the intracellular signaling domain of the TCR
 - Lacked significant antitumor activity most likely due to inadequate t-cell persistence
- 2nd/3rd Generation: added 1 (CD28/4-1BB) or 2 (CD28/4-1BB /OX40) co-stimulatory domains
 - Most display significant clinical activity
- 4th Generation: "armored CAR" combine a second-generation CAR with the addition of various genes, including cytokine and co-stimulatory ligands, to enhance the tumoricidal effect
 - Early in clinical testing

Batlevi CL et al. Nat Rev Clin Oncol. 2016 Jan;13(1):25-40. <https://www.nature.com/articles/nrclinonc.2015.2271>
 Tili B et al. Blood. 2008;112:2262-2271.
 Wang J et al. Hum Gene Ther. 2007; 18:712-725.
 Program H et al. Cancer J. 2014; 20: 127-133.

Car T-Cell Generation & Administration



1. Leukoapheresis of patients peripheral blood mononuclear cells (PBMCs)
2. T cells are activated and selected by incubation with anti-CD3 and anti-CD28 paramagnetic beads
3. Activated T-cells transduced with retro/lentiviral vectors carrying the CAR construct
4. Cells expanded 1,000 fold over a 1-2 week period
5. CAR T-cells infused into patient over 1-2 day period

Batlevi CL et al. Nat Rev Clin Oncol. 2016 Jan;13(1):25-40. <https://www.jmtherapeutics.com/our-science/scientific-platform/Car-T-Cell-Process>

CD 19 Antigen

- Attractive target due to:
 - Presence in the vast-majority of b-cells
 - 95% of NHL
 - Expressed throughout b-cell development
 - Wider range of b-cells to target than with CD20
 - Immature progenitor cells may be cause of relapse in mature b-cell malignancies
 - Depletion restricted to lymphoid system
 - B-cell aplasia not necessary life-threatening
- Most investigations conducted in CD19 positive hematologic malignancies such as:
 - B-cell Acute Lymphoblastic Leukemia (B-ALL)
 - Chronic lymphocytic lymphoma (CLL)
 - Follicular Lymphoma (FL)
 - Diffuse Large B-cell Lymphoma (DLBCL)
 - Mantle Cell Lymphoma (MCL)

Ghorashian S, et al. Br J Haematol 2015;169: 463-478.
 Kim SJ, Korean J Hematol. 2011; 46: 211-213.
 Kim SJ et al. Blood 2014; 124: 1622.

Car T-cells

- Advantages in hematologic malignancies:
 - Established cell surface antigens
 - Less invasive tumor sampling
 - Natural homing of t-cell to malignancy site
 - Blood, bone marrow, lymph nodes
- Studied in heavily pretreated, relapsed, refractory and post- allogeneic transplant patient population
 - 100 trials were registered with ClinicalTrials.gov with the search term "chimeric antigen receptor,"
 - United States, Europe, China, Japan, and Australia

Im A et al. J Hematol Oncol. 2017 Apr 24;10(1):94.

Acute Lymphoblastic Leukemia (ALL)

Reference	Number/Age	Complete Remission Rates
Brentjens RJ et al.	5 adults	100%
Grupp SA et al.	2 children	100%
Davila ML et al.	16 adults	88%
Lee DW et al.	20 children	70%
Maude S et al.	25 children 5 adults	90% 100%
Frey NV et al.	12 adults	89%
Park JH et al.	27 adults	89%

Brentjens RJ et al. Sci Transl Med. 2013;5 (177):177ra138.
Grupp SA et al. N. Engl. J. Med. 2013; 371:1509-1518.
Davila ML et al. Sci Transl Med. 2014;6(234):234ra225.
Lee DW et al. Lancet. 2015; 385: 523-528. e382.
Maude S.L et al. N. Engl. J. Med. 2014; 371: 1507-1517.
Frey NV, et al. ASH. 2014; Paper 76315.
Park JH et al. ASH. 2014; Paper 76373.

ELIANA Trial- Efficacy

- Global Phase II trial reporting on 63 pediatric/young adults
 - CD19+ R/R B-cell ALL with ≥5% bone marrow lymphoblasts by morphology
 - Median follow-up 6.4 months
- 83 % (52/63) achieved CR or CRi within 3 months
- Relapse free probability after remission
 - @ 6 months 75% @12 months 64%
- Survival probability
 - @ 6 months 89% @12 months 79%

CRi: CR with incomplete blood count recovery

Buechner J, et al. European Hematology Association Annual Meeting, Abstract 5476. Presented June 24, 2017.

ELIANA Trial- Safety

- Cytokine Release Syndrome (CRS)
 - 78% of pts (21% grade 3; 27% grade 4); no CRS-associated deaths occurred
- Neurotoxicity
 - 15% (grade 3 neuropsychiatric AEs) with no grade 4 events and no cerebral edema reported
- Deaths:
 - 2 within 30 days of infusion
 - ALL progression, n=1; cerebral hemorrhage, n=1
 - 9 more than 30 days after infusion
 - ALL relapse/progression, n=6; HHV-6 encephalitis, pneumonia, systemic mycosis, n=1 each

Buechner J, et al. European Hematology Association Annual Meeting, Abstract 5476. Presented June 24, 2017

Tisagenlecleucel (Kymriah™)

- First gene therapy approved in the United States by the FDA
 - “Breakthrough therapy status”
- One-time treatment of relapsed/refractory B-cell precursor ALL patients up to 25 years old
- REMS which include elements to assure safe use (ETASU)
 - Available at 20 centers in September
 - 32-35 centers by end of 2017

https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm540568.htm

Pricing

- Cost: \$475,000
- Pay for Performance deal
 - First of its kind with CMS
 - Free of charge in children on Medicaid with no response after 1 month
- Patient assistance program
 - Co-pay discounts, travel assistance, free treatment
- P&T implications
 - Regulated as a drug
 - Available prescribing information

http://fortune.com/2017/08/31/novartis-kymriah-car-t-cms-price/

Non Hodgkin's Lymphoma (NHL)

Reference	Number/Age	Complete Remission Rates
Sauter CS et al.	6 adults	100%
Schuster SJ et al.	8 adults	38%
Kochenderfer JN et al.	11 adults	55%
Turtle CJ et al.	9 adults	11%

Chronic Lymphoblastic Leukemia (CLL)

Reference	Number/Age	Complete Remission Rates
Porter DL et al.	23 adults	22%
Kochenderfer JN et al.	4 adults	25%
Park JH et al.	7 adults	29%

Sauter, C. S. et al. Blood. 2014; 124, a677.
Schuster, SJ et al. Blood. 2014; 124, a1087.
Kochenderfer, JN et al. J. Clin. Oncol. 2015; 33: 540-546.
Turtle, CJ et al. J. Blood. 2014; 124, a384.
Porter, DL et al. Blood. 2014; 124, a1062.
Kochenderfer, JN et al. Blood. 2012; 119, 2709-2720.
Park, JH et al. J. Clin. Oncol. 2014; 32 (5a Suppl.), a7020.

Car T-cell Clinical Trial Design

- Numerous distinctions between trials by various groups including:
 - scFvs derived from separate hybridomas
 - Disparate signaling domains (CD28 vs. 4-1BB)
 - Genetic modification methodology
 - Dose/preparative regimen prior to cell infusion
 - Prime t cells for expansion
 - T-cell dose

Namuduri M et al. Expert Rev Hematol. 2016 Jun;9(6):511-3.

Car T-cell Lessons

- Cells work where drugs fail
 - Capable to clear CNS disease
 - Durable remissions are possible
- No GVHD in post-allogeneic patients
- Response correlates with in vivo expansion of cells and presence of CRS
 - Not degree of CRS

Im A et al. J Hematol Oncol. 2017 Apr 24;10(1):94.
Sadelain M. J Clin Invest. 2015 Sep;125(9):3392-400.
Yang X et al. Blood. 2014 Jun 12; 123(24): 3750-3759.

Car T-cell Persistence

- Benefit of ongoing disease surveillance
- Disadvantage of long-term B-cell aplasia
 - Surrogate marker for persistence
- Optimal duration unknown
 - May vary based on antigen target
 - Documented up to 4 years after infusion in CLL patients
- Complex picture
 - Linked to co-stimulatory domains and cell culture system

Maus MV et al. Clin Cancer Res. 2016 Apr 15;22(8):1875-84.

CAR T Cell Response and Resistance

- ALL has high response rates and relapse rates
 - 25-50% will relapse with CD-19 negative disease
 - CD-19 positive relapse occurs when cells no longer present
- CLL has lower response and relapse
 - Less intrinsically active T-cells
- NHL falls in the middle
 - Target downregulation not as apparent as a mechanism for resistance
- Therefore, need different strategies to improve efficacy and prevent resistance

Sadelain M. J Clin Invest. 2015 Sep;125(9):3392-400
Im A et al. J Hematol Oncol. 2017 Apr 24;10(1):94.

Car T-cell Resistance: ALL CD-19 Negative disease

- Selective pressure by CAR T-cells yields antigen escape variants
 - Not seen in NHL or CLL
- Dual Antigen Targeting
 - Targets include CD12 and CD22
 - 2 antigens would mean that escape of CAR T-cell-mediated destruction would require simultaneous mutations in two genes

Sadelain M. J Clin Invest. 2015 Sep;125(9):3392-400

Dual Antigen Targeting

- Increased antitumor function compared with a T-cell expressing a single CAR
- Multiple co-stimulatory domains may result in:
 - Lower vector titers
 - Lower expression of CAR at cell surface
 - Decreased functionality due to requirement of accessory signaling apparatus proximal to cell the membrane

Maus MV et al. Clin Cancer Res. 2016 Apr 15;22(8):1875-84.

CAR T-Cell HEADLINES

“ASCO 2017: CAR T Cell Therapy Shows Incredible Results in Myeloma”

<https://www.myelomacrowd.org/asco-2017-car-t-cell-therapy-shows-incredible-results-in-myeloma/>

BCMA- Plasma cell specific antigen

- Phase 1 clinical trial in China
 - 33/35 pts with response (14 CRs)
 - 5 patients followed out 12-14 months still in remission
- Bluebird Bio/Celgene Phase 1
 - 11 patient, dose-finding, 78% ORR
 - Expanded to CRB-401 2-part, non-randomized, open label, multi-site Phase 1 study of bb2121 in adults with relapsed/refractory multiple myeloma (MM)
 - Enrolling at 7 sites in US

<https://www.myelomacrowd.org/asco-2017-car-t-cell-therapy-shows-incredible-results-in-myeloma/>

“CRISPR Turbocharges CAR T Cells, Boosts Cancer Immunotherapy”

<http://www.genengnews.com/gen-news-highlights/crispr-turbocharges-car-t-cells-boosts-cancer-immunotherapy/81253925>

CRISPR/Cas9

- Custom genome editing technology used for removing, adding or altering sections of the DNA sequence
- Consists of 2 key molecules
 - Cas9 Enzyme
 - Acts as a pair of molecular scissors that can cut 2 strands of DNA to remove or add DNA
 - Guide RNA
 - Small piece of pre-designed RNA sequence within a longer RNA scaffold. Scaffold binds to DNA and the pre-designed sequence “guides” Cas9 to right spot in genome to cut

<http://www.genengnews.com/gen-news-highlights/crispr-turbocharges-car-t-cells-boosts-cancer-immunotherapy/81253925>
<https://www.yourgenome.org/facts/what-is-crispr-cas9>

CRISPR/Cas9

- After Cas9 makes cut in DNA the cell uses natural repair mechanisms to fix
- Preliminary work of CAR T-cells designed with technology report:
 - Uniform CAR expression
 - Enhanced T-cell potency
 - Delayed T-cell differentiation and exhaustion
 - Potentially safer and more effective cells
- “off-target” effects
 - More specific guide RNA, single strand Cas9 enzyme

<https://www.yourgenome.org/facts/what-is-crispr-cas9>
Eggem J et al Nature. 2017 Mar 2;543(7643):113-117.

After Trial Deaths, Juno Pivots and Scraps Lead CAR-T Therapy

<http://www.xconomy.com/seattle/2017/03/01/after-trial-deaths-juno-pivots-and-scraps-lead-car-t-therapy/>

Juno Therapeutics JCAR015

- ROCKET TRIAL
 - Phase II trial in relapsed/refractory adult ALL
- Canceled after 5/38 patient deaths
 - All 5 deaths due to cerebral edema, fatal toxicity not reported in prior CAR T trials
 - Initially thought to be due to fludarabine lymphodepleting conditioning
 - 2 more deaths after removing fludarabine
- Further investigation with JCAR015 discontinued
- Juno still investigating JCAR014, JCAR016, JCAR017, JCAR018

<http://www.xconomy.com/seattle/2017/03/01/after-trial-deaths-juno-pivots-and-scraps-lead-car-t-therapy/>

CAR T-CELL Toxicity

CAR T-Cell Toxicity

- Not associated with the infusion of the cells, rather with the expansion and persistence
 - Immune activation that is critical for response rates is also responsible for this therapy's most significant treatment-related toxicity
- Most notable toxicities:
 - CRS
 - Severe CRS
 - CNS toxicity
 - B-cell aplasia

Lee, DW et al. Lancet. 2015; 385, 517-528. A382. <https://am.ascopub.org/optimizing-outcomes-clinical-trials-car-t-cell-therapy-patients-all>

CAR T-Cell CRS

Clinical CRS

- Fevers
- Hypotension
- Capillary Leak syndrome
- Respiratory distress
- Neurologic disturbances

Biochemical CRS (elevated)

- Liver Function Tests
- Ferritin
- Triglycerides
- Hypo-fibrinogenemia
- Interferon-gamma
- Interleukin-6
- Soluble IL-2R α
- IL-10
- C-Reactive Protein (CRP)

- Occurs within 1-3 weeks of infusion
- Incidence 18-100%
- Elevated CRP with clinical symptoms can be a biomarker for severe CRS, incidence 27-53%
- Risk Factors:
 - Higher disease burden at baseline
 - Higher cell infusion quantity
- Treatment
 - Supportive care
 - Tocilizumab- indication expanded
 - Steroids

Davila ML, et al. Sci Transl Med. 2014;6(224):224ra225.
 Group SA, et al. N Engl J Med. 2013;368(16):1509-1518.
 Hylton et al. Biol Blood Marrow Transplant 21 (2015) 535Se5373
<https://am.ascopub.org/optimizing-outcomes-clinical-trials-car-t-cell-therapy-patients-all>
 Hylton et al. Biol Blood Marrow Transplant 21 (2015) 535Se5373

CAR T-Cell Toxicity

CNS Toxicity

- Incidence as high as 50%
- Unknown if CAR T-cells cross into CNS, believe neurotoxicity secondary to an inflammatory state rather than direct affect on neural tissue
- Symptoms
 - Confusion, delirium, word-finding aphasia, coma, seizures
 - May require intubation for airway protection
- Most studies start seizure prophylaxis
 - Keppra 500 mg q12h

B-cell Aplasia

- Incidence 86-100%
- Can last for weeks to months
- Hypothesized as a surrogate marker for CAR T cell persistence
- IVIG replacement can supplement hypogammaglobinemia and reduce infection risk

Namuduri M et al. Expert Rev Hematol. 2016 Jun;9(6):511-3.

Physician Driven Persistence Mechanisms

- “Suicide” switch
 - Incorporation of inducible suicide gene caspase-9 (iCasp9)
 - Cell containing iCasp9 can be depleted by administering a synthetic small molecule to dimerize iCasp9 promolecules and trigger apoptosis
 - Coexpression of protein for which a depleting antibody already exists such as CD20
 - Administer rituximab to “cure” toxicity
- None clinically tested, most investigators prefer to use pharmacologic interventions to manage toxicity versus ablate a potentially curative and expensive therapy

Maus MV et al. Clin Cancer Res. 2016 Apr 15;22(8):1875-84.

FACT Pharmacist Responsibility

- Immune Effector Cells (IEC)
- Training :
 - An overview of hematology/oncology patient care, including the cellular therapy process, cytokine release syndrome, and neurological toxicities
- Development and implementation of guidelines or SOPs for pharmaceutical management of cellular therapy recipients
- Access to medications adequate to treat expected complications, including CRS
 - Tocilizumab available on a 24-hour basis
 - Dispensing it within 30 minutes of a request
- Complete continuing education including, not limited to:
 - Field of HPC transplantation
 - CRS and neurological toxicities

<http://www.factwebsite.org/ecstandards/>

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TOPA