CAR-T and Other Cellular Therapies in CLL: The Present and Future

August 2, 2022

11 AM PT, 12 PM MT
1 PM CT, 2 PM ET
This program was made possible by grant support from

AstraZeneca

BeiGene

Bristol Myers Squibb

Janssen

Pharmacyclics®

An AbbVie Company
Speakers

Mazyar Shadman, MD, MPH
Associate Professor, Division of Medical Oncology
University of Washington School of Medical Oncology
Associate Professor, Clinical Research Division
Fred Hutchinson Cancer Research Center

Moderator
Brian Koffman, MDCM (retired) MS Ed
Executive Vice President and Chief Medical Officer
CLL Society

Welcome
Robyn Brumble, MSN, RN
Director of Scientific Affairs and Research
CLL Society
CAR-T and Other Cellular Therapies in CLL: The Present and Future

Mazyar Shadman, MD, MPH
Fred Hutch Cancer Center & University of Washington
Seattle, WA

August 2, 2022
Disclosures

- **Consulting, Advisory Boards, steering committees or data safety monitoring committees:** Abbvie, Genentech, AstraZeneca, Sound Biologics, Pharmacyclics, Beigene, Bristol Myers Squibb, Morphosys/Incyte, TG Therapeutics, Innate Pharma, Kite Pharma, Adaptive Biotechnologies, Epizyme, Eli Lilly, Adaptimmune, Mustang Bio, Regeneron, Merck, Fate therapeutics, MEI pharma and Atara Biotherapeutic.

- **Research Funding:** Mustang Bio, Celgene, Bristol Myers Squibb, Pharmacyclics, Gilead, Genentech, AbbVie, TG Therapeutics, Beigene, AstraZeneca, Sunesis, Atara Biotherapeutics, Genmab, Morphosys/Incyte
T-cell immunotherapy tied to 10-year remission in two leukemia patients, study finds

By Jacqueline Howard and Carma Hassan, CNN

Updated 3:23 PM ET, Wed February 2, 2022

Cancer patients cured a decade after gene therapy, doctors say

The two examples show the treatment, called CART cell therapy, can attack cancer immediately, then stay inside the body and evolve there to keep cancer at bay.

This Breakthrough Cancer Treatment Has Prevented Leukemia Relapse for Over a Decade

In most cases, CAR T-cell treatment was incredibly good at killing tumor cells. But now we know it works for a ridiculously long time.

A Cancer Treatment Makes Leukemia Vanish, but Creates More Mysteries

Two early recipients of CART immunotherapy were free of a blood cancer nearly a decade after receiving the therapy.
Outline

- What are CAR-T cells?
- Why do we need them in CLL?
- How are they made?
- When are they used in CLL?
- What are the risks?
- What is the latest on other cellular therapies?
- What is available now in trials?
- What is expected in the future?
- Summary and takeaways
What Are CAR-T Cells?

- Chimeric antigen receptors (CARs) are engineered proteins that enable T-cells to target the cancer cells
- CAR-T cell therapy has been a major advancement in treatment of B-cell lymphoma in recent years
- Currently approved by the FDA for treatment of:
  - Diffuse large B-cell lymphoma
  - Follicular lymphoma
  - Mantle cell lymphoma
  - Acute lymphoblastic leukemia
  - Multiple myeloma
- CAR-T remains an investigational option for CLL in August 2022
  - Patients with CLL can have access to CAR-T by participating in clinical trials
What Are CAR-T Cells?

BEFORE

T-cell

CD19

CD20

CLL cell

ROR-1

AFTER

CAR

T-cell

CD19

CD20

CLL cell

ROR-1

CAR

CLL SOCIETY
What Are CAR-T Cells?

Immune storm

Cancer killing
What Are CAR-T Cells?

- CAR-T is the name of the process not a specific drug
- Different Proteins can be targeted (CD19, CD20, CD22, ROR-1, etc.)
- Different CAR-T products can be designed. Each specific for 1 (or more) protein(s)
What Are CAR-T Cells?

CAR T cells are infused into bloodstream

Cells undergo extensive proliferation

T cells are primed and activated

Endogenous T cell

Antigen-presenting cell

Death of cancer cell and antigen release

Neoantigens

CAR T cells make their way toward tumor cells

CAR T cells

Tumor cell

Recognition of tumor cell

June, NEJM, 2018
Why Do We Need Them in CLL/SLL?

**Immediate Need**
- Treatment of patients with relapsed disease
- Current options:
  - **BTK inhibitors**:
    - Covalent: ibrutinib, acalabrutinib, zanubrutinib * (can’t switch within class after progression)
    - Non-covalent: pirtubrutinib *
  - **BCL2 inhibitor**: Venetoclax
  - **PI3K inhibitors**: duvelisib, idelalisib (unknown future)
  - **Monoclonal antibodies**: rituximab, obinutuzumab
  - **Chemotherapy** (limited role if any in the relapsed setting)

**Future Potential Role**
- A component of combination therapy for fixed-duration regimens
- Important to have an improved safety profile before being used in early lines

* Not FDA approved as of Aug 2022
How Are CAR-T Cells Made?
When Are They Used in CLL?

- A number of factors need to be considered when making a decision about the timing of CAR-T therapy
  - Physical fitness, access, alternative trial options, support, etc.

**Most importantly:**

1. Referral should be made when disease is under control/stable and not with progressive and active disease

2. It is highly recommended that CAR-T is utilized when there are reliable standard options left for the patient and not after exhausting all options
When Are They Used in CLL?

Failure of first novel agent:
- If a BTKi:
  - confirmed progression while on treatment OR
  - true intolerance to 1st (ibrutinib) and 2nd (acalabrutinib and zanubrutinib) generation drugs
- If venetoclax:
  - confirmed progression while on treatment OR
  - true intolerance

Initiate second novel agent
- While the patient is still responsive to treatment:
  - Introduce the concept of cellular therapy
  - CAR-T: check for availability, eligibility for clinical trials
  - AlloSCT: assessment of comorbidities, prognostic score, donor availability, social barriers and interest

Is CAR-T an option?
- Yes: CAR-T therapy
- No: Is there evidence of measurable residual disease in the marrow or blood by flow cytometry or NGS?
  - Yes: appropriate for alloSCT?
    - Yes: close observation
    - No: consider alloSCT
  - No: consider PI3Kis or clinical trials after progression

Shadman, Hematol Oncol Clin N Am, 2021
What Are the Risks?

- Headaches
- Confusion
- Hallucinations
- Delirium
- Apathy
- Paralytic
- Seizures
- Tachypnea
- Hypoxia
- Pulmonary edema
- Respiratory failure
- Splenomegaly
- Nausea
- Vomiting
- Acute kidney injury
- Renal failure
- Mysalgia
- Arthralgia
- Rigor
- Rash
- Edema

Unspecific symptoms
- Fever
- Fatigue
- Anorexia

Cytopenias
Coagulopathy (PTT, INR)
Febrile Neutropenia
DIC
Tachycardia
Hypotension
Troponin elevation
Arrhythmia
QT prolongation
Sepsis
Cardiomyopathy
Acute heart failure
Hepatomegaly
Elevated liver enzymes
Hypofibrinogenemia
Liver failure
Diarrhea

Shimabukuro-Vornhagen, Journal for ImmunoTherapy of Cancer, 2018
Lisocabtagene Maraleucel (Liso-cel)

- CD19 directed CAR-T
- High-risk features:
  - del17p (35%), mutated TP53 (61%), complex karyotype (48%)
  - Ibrutinib refractory (91%), Venetoclax refractory (65%), double refractory (65%)
- Side effects
  - Grade 3 CRS: 9%, grade 3-4 neurotoxicity: 22%
- Responses:
  - **Overall response: 82%, complete response: 45%**
  - Undetectable MRD in blood (76%) and bone marrow (65%)
- Follow-up
  - Median follow-up 24 months
  - Median duration of response (not reached) – more than half of the responders have not relapsed

Siddiqi, Blood, 2022
CAR-T in Combination With Ibrutinib

- Pre-clinical studies showed that concurrent use of ibrutinib with CAR-T may improve the T-cell quality and function.
- In clinical studies, ibrutinib was successfully combined with CAR-T with no unexpected toxicity.
- There may be some improvement in safety profile of CAR-T when combined with ibrutinib.
- Newer BTKis are expected to be combined with CAR-T in various clinical trials.
What is the Latest on Other Cellular Therapies?

- **Allogeneic CAR-T, CAR-NK or CAR-NKT**
  - Unlike the autologous CARs, immune cells from healthy donors are used
  - Still investigational for CLL and not approved by the FDA
  - Patients with CLL can have access to bispecific antibodies after enrollment in clinical trials

- **Bispecific Antibodies**
  - Bispecific antibodies engage T-cells by physically bringing them to cancer cells
  - Still investigational for CLL and not approved by the FDA
  - Patients with CLL can have access to bispecific antibodies after enrollment in clinical trials
Bispecific Antibodies
Bispecific Antibodies

CD20 B-cell
CD3 T-cell
IgG1

Anti-CD20/CD3 TDB

Target

Minimal modifications

Target+ Tumor cell

T-cell activation
Granzyme & Perforin

Immune synapse formation

Processive killing

Dead Tumor cell
What Is Available Now in Trials?

- **Autologous**
  - CD19
  - CD20
  - CD19/CD20
  - CD19/CD22
  - Kappa light chain
  - CD5

- **Allogeneic**
  - CAR T
  - CAR NK
  - CAR NKT

**Example: CD20 CAR-T Trial**

1. Screening evaluations including tumor biopsy
2. Leukapheresis
3. CD20 CAR T-cell production (~10 days)
4. Lymphodepletion with Cy/flu (36-96 h)
5. T cell infusion
6. Safety assessments (7-16 d)
7. Tumor biopsy
8. Restaging (day 28)
What Do You See as the Future?

- CD19 CAR-T maybe approved for CLL but the timing is not known

- Number of autologous and allogeneic CAR studies are in clinical trials

- An important option for patients with relapsed disease
  - One time treatment with possible long-term remission
  - Effective in patients after BTKi and/or venetoclax

- Ideally and when safety/efficacy profile is optimized, can be utilized in earlier (first?) line of treatment as part of time-limited regimens
Summary and Takeaways

- CAR-T cell therapy is an effective treatment strategy for relapsed CLL
- Still investigational but access is possible by participation in clinical trials
- Optimal time for consideration/referral for CAR-T:
  - When disease is under control/stable
  - Before exhausting all treatment options
- Various targets on CLL cells can be targeted by different CAR-T products
Thank You!

@mshadman

mshadman@fredhutch.org
Audience Questions & Answers
This program was made possible by grant support from

AstraZeneca

BeiGene

Bristol Myers Squibb

Janssen

pharmacyclics®

An AbbVie Company
Thank You for Attending!

Please take a moment to complete our post-event survey, your feedback is important to us.

If you’re question was not answered, please feel free to email asktheexpert@cllsociety.org.

Check out our free CAR-T Therapy brochure and join us on October 26th for our virtual event on therapy sequencing.

CLL Society is invested in your long life. Please invest in the long life of the CLL Society by supporting our work at cllsociety.org/donate-to-cll-society/.