Immunotherapy in Hematologic Malignancies: Past, Present, and Future

Annie Im, MD
Assistant Professor of Medicine
University of Pittsburgh Cancer Institute
Allogeneic hematopoietic stem cell transplantation (SCT):

• One of oldest forms of immunotherapy

• Proof of sensitivity of hematologic malignancies to immunotherapy, i.e. “graft-versus-leukemia” effect
  – Efficacy in chemo-refractory disease
  – Use of donor lymphocyte infusion (DLI) to treat relapse after SCT
  – Development of reduced-intensity conditioning SCT for older or unfit patients
Immunotherapy in hematologic malignancies: Past (and Present)

Gooley et al., N Engl J Med 2012
www.cibmtr.org
Unique features of immunotherapy in hematologic malignancies

Advantages:
• Immune responsiveness (as demonstrated by SCT and DLI)
• Close and constant apposition of malignancy to sites of immune monitoring
• Cellular origins of malignancy are related to immunity \( \rightarrow \) same origin
• Feasibility of isolating and manipulating malignant cells, i.e. pre and post immunotherapy

Challenges:
• Malignant cells can be stimulated by inflammation and thrive off of same stimulatory signals as immune system
• By nature, the malignant cells are corruptions of normal hematopoiesis and thus the immune system
• Exceptional ability of malignant cells to suppress and evade the immune system
Immunotherapy in hematologic malignancies: Present (and Future)

Novel strategies in immunotherapies:

1) Direct targeting of tumor antigens
   – Monoclonal antibodies and antibody-drug conjugates
   – Bispecific T-cell engagers (BiTE)
   – CAR T-cells

2) Augmentation of immune effectors
   – CAR T-cells
   – NK cell therapy

3) Activation of tumor antigen-specific immunity
   – Vaccines

4) Overcoming tumor-derived immune inhibition
   – Immune checkpoint inhibitors
Direct targeting of tumor antigens:

Monoclonal antibodies
Antibody-drug conjugates
Bispecific T-cell engagers
Monoclonal antibodies

Mechanisms of action: antibody-dependent cellular cytotoxicity (ADCC), antibody-dependent phagocytosis (ADP), complement-dependent cytotoxicity (CDC), direct cytotoxicity

FDA approved agents: FDA

- **Rituximab**: the prototype for anti-CD20 monoclonal antibodies and a backbone of B-cell lymphoma regimens
- **Ofatumumab** (anti-CD20): single agent efficacy in relapsed/refractory CLL, or combined with chlorambucil in newly diagnosed CLL
- **Obinutuzumab** (anti-CD20): combined with chlorambucil in newly diagnosed CLL
Monoclonal antibodies

**In development: Multiple myeloma**

- **Daratumumab** (anti-CD38)
  - Preliminary results of Phase 1/2 study showed ORR 42% in heavily pretreated population
  - Combined with lenalidomide/dexamethasone showed ORR 75%
  - Main toxicities are infusion-related
  - FDA breakthrough-therapy designation in 2013

- **Elotuzumab** (anti-SLAMF7 or CS1)
  - Single agent use showed no objective response and stable disease in 26%
  - Combined with lenalidomide/dexamethasone showed ORR 79% and median PFS 14.9 months in randomized Phase 3 study in heavily pretreated population
  - FDA breakthrough-therapy designation in 2014

- Others in development: mAbs against CD38, CD138, CD56, CD40, Bcell activating factor (BAFF)

Plesner et al., ASH 2014
Lonial et al., N Engl J Med 2015
Antibody-drug conjugates

- Immunoconjugate – a targeting antibody linked to an effector molecule (cytotoxic agent), providing direct delivery to malignant cell

- **Brentuximab vedotin** (anti-CD30 and a microtubule inhibitor): FDA approved for relapsed/refractory Hodgkins lymphoma and anaplastic large cell lymphoma

- **In development**: ADCs targeting CD138, CD19, CD33, and others

Palanca-Wessels and Press, Blood 2014
Bispecific T-cell engagers (BiTE)

- Dual specificity for CD3 (T cells) and tumor surface antigen → passive recruitment of cytotoxic T cells to catalyze formation of the immunologic synapse

- Polyclonal T cell response and independent of MHC expression, thus overcoming a common mechanism of tumor immune escape

Rogala et al., Expert Opin Biol Ther 2015
Bispecific T-cell engagers (BiTE)

**Blinatumomab** (CD19/CD3)

- Anti-CD19 and anti-CD3 variable fragments joined by a linker
- Phase 2 study of blinatumomab in 189 patients with relapsed/refractory Ph-negative acute lymphoblastic leukemia (ALL) – CR/CRi rate 43%, half of whom went on to allogeneic SCT
- FDA approved for relapsed/refractory Ph-negative ALL in December 2014
- Toxicities:
  - Cytokine release syndrome
  - Neurotoxicity
  - Guidelines have been developed for management of toxicities and dose reduction
- Administration is continuous infusion (inpatient or outpatient)

Topp et al., Lancet Oncol 2015
In development

- Evaluating blinatumomab for other B-cell malignancies
- CD3-CD33 BiTEs for AML
- Bispecific NK cell engagers (BiKE)
Augmentation of immune effectors AND
Direct targeting of tumor antigens:

CAR T-cells
CAR T-cells

- Autologous T-cells engineered to express synthetic chimeric antigen receptor (CAR) against tumor surface antigen – antigen specific, HLA independent

Advantages in hematologic malignancies:

- Known cell surface antigens (i.e. CD19)
- Easy sampling of tumor
- Natural T-cell homing to hematologic organs – blood, bone marrow, lymph nodes

Lee et al., Clin Cancer Research 2012
• Lymphodepletion with chemotherapy enhances homeostatic expansion of infused T-cells

• Engagement of tumor antigen by CAR to T-cells leads to cytotoxicity and massive T-cell proliferation independent of MHC

Maude et al., Blood 2014
| Author                | Center            | No. patients | Disease (all relapse/refractory) | Outcomes                                                                 | Duration of CARs | Best duration of response | Comments                                      |
|----------------------|-------------------|--------------|----------------------------------|--------------------------------------------------------------------------|------------------|--------------------------|-----------------------------------------------|
| Jensen *et al* (2010) | City of Hope      | 4            | NHL                              | No responses (2 with CR after autoSCT)                                  | 1 week           | -                        | 1st generation CAR                           |
| Kochenderfer *et al* (2010, 2012) | NIH              | 8            | NHL (4) and CLL (4)             | 80% RR (1 CR, 5 PRs)                                                    | Up to 6 months   | >18 months               | 5/8 CRS 4/8 Bcell aplasia                   |
| Savoldo *et al* (2011) | Baylor           | 6            | NHL                              | 2 SD                                                                      | 2nd generation – up to 6 months | -                        | Infusion of 1st and 2nd generation T cells in same patient |
| Brentjens *et al* (2011) | MSKCC            | 10           | CLL (8) and ALL (2)             | CLL – 1 PR, 2 SD ALL – 1 durable Bcell aplasia                          | Up to 6 weeks (correlated with burden of disease) | 8 months                   | Most with CRS                                |
| Porter *et al* and Kalos *et al* (2011) | U Penn           | 3            | CLL                              | 2 CR, 1PR                                                                | Up to 6 months (↑ expansion) | >11 months                | All with CRS                                 |

NHL: Non Hodgkins Lymphoma, CLL: Chronic Lymphocytic Leukemia, ALL: Acute Lymphoblastic Leukemia, SCT: Stem Cell Transplant, CR: Complete Response, PR: Partial Response, SD: Stable Disease, RR: Response Rate, CRS: Cytokine Release Syndrome
# Clinical trials for CD19 CAR T-cells (1)

| Author            | Center                | No. patients | Disease (all relapse/refractory) | Outcomes | Duration of CARs | Best duration of response | Comments                        |
|-------------------|-----------------------|--------------|-----------------------------------|----------|------------------|---------------------------|--------------------------------|
| Jensen et al (2010) | City of Hope          | 4            | NHL                               | No responses (2 with CR after autoSCT) | 1 week | -               | 1st generation CAR          |
| Kochenderfer et al (2010, 2012) | NIH                  | 8            | NHL (4) and CLL (4)               | 80% RR (1 CR, 5 PRs) | Up to 6 months | >18 months | 5/8 CRS 4/8 Bcell aplasia |
| Savoldo et al (2011) | Baylor               | 6            | NHL                               | 2 SD     | -                | -                         | Infusion of 1st and 2nd generation T cells in same patient |
| Brentjens et al (2011) | MSKCC                | 10           | CLL (8) and ALL (2)               | CLL – 1 PR, 2 SD ALL – 1 durable Bcell aplasia | Up to 6 weeks (correlated with burden of disease) | 8 months | Most with CRS     |
| Porter et al and Kalos et al (2011) | U Penn              | 3            | CLL                               | 2 CR, 1PR | Up to 6 months (↑ expansion) | >11 months | All with CRS    |

NHL: Non Hodgkins Lymphoma, CLL: Chronic Lymphocytic Leukemia, ALL: Acute Lymphoblastic Leukemia, SCT: Stem Cell Transplant, CR: Complete Response, PR: Partial Response, SD: Stable Disease, RR: Response Rate, CRS: Cytokine Release Syndrome
| Author | Center | No. patients | Disease (all relapse/refractory) | Outcomes | Duration of CARs | Best duration of response | Comments |
|--------|--------|--------------|---------------------------------|----------|-----------------|--------------------------|----------|
| Brentjens et al and Davila et al (2013, 2014) | MSKCC | 16 | ALL | 88% (78% in refractory disease) | Up to 4 months | 3 months (but 7 went on to alloSCT) | 7 CRS CRP, IFNγ, IL6 correlated with CRS |
| Kochenderfer et al (2013) | NIH | 10 | CLL (4) and NHL (6) post-alloSCT | 1 PR, 1 CR, 6 SD | Up to 30 days (used donor T cells) | 9 months | No GVHD |
| Kochenderfer et al (2014) | NIH | 15 | NHL (DLBCL and indolent lymphomas) | 8 CR, 4 PR, 1 SD | Up to 11 weeks | 22 months | 6/7 DLBCL with response |
| Lee et al (2014) | NIH | 21 | ALL (20), NHL (1), 8 post-alloSCT | 14 CR (13 MRD-), correlated with CAR expansion | Up to 8 weeks (most went on to alloSCT) | 19 months | 3 severe CRS CRP, IL6, and CAR expansion correlated with CRS |
| Grupp et al and Maude et al (2013, 2014) | U Penn | 30 | ALL, 18 post-alloSCT | 90% (15 post-alloSCT, 2 post-blinatumomab) | Up to 2 years | 24 months | All with CRS |

DLBCL: Diffuse Large Bcell Lymphoma, MRD: Minimal Residual Disease, GVHD: Graft Versus Host Disease
| Author                          | Center   | No. patients | Disease (all relapse/refractory) | Outcomes                                    | Duration of CARs | Best duration of response | Comments                                      |
|--------------------------------|----------|--------------|----------------------------------|---------------------------------------------|------------------|---------------------------|-----------------------------------------------|
| Brentjens et al and Davila et al (2013, 2014) | MSKCC     | 16           | ALL                              | 88% (78% in refractory disease)             | Up to 4 months   | 3 months (but 7 went on to alloSCT) | 7 CRS CRP, IFNγ, IL6 correlated with CRS     |
| Kochenderfer et al (2013)       | NIH      | 10           | CLL (4) and NHL (6) post-alloSCT | 1 PR, 1 CR, 6 SD                           | Up to 30 days (used donor T cells)            | 9 months                                  | No GVHD                                      |
| Kochenderfer et al (2014)       | NIH      | 15           | NHL (DLBCL and indolent lymphomas) | 8 CR, 4 PR, 1 SD                           | Up to 11 weeks  | 22 months                | 6/7 DLBCL with response                      |
| Lee et al (2014)                | NIH      | 21           | ALL (20), NHL (1), 8 post-alloSCT | 14 CR (13 MRD-), correlated with CAR expansion | Up to 8 weeks (most went on to alloSCT)      | 19 months                | 3 severe CRS CRP, IL6, and CAR expansion correlated with CRS |
| Grupp et al and Maude et al (2013, 2014) | U Penn | 30           | ALL, 18 post-alloSCT             | 90% (15 post-alloSCT, 2 post-blinaatumomab) | Up to 2 years   | 24 months                | All with CRS                                 |

DLBCL: Diffuse Large Bcell Lymphoma, MRD: Minimal Residual Disease, GVHD: Graft Versus Host Disease
| Author                        | Center     | No. patients | Disease (all relapse/refractory) | Outcomes                      | Duration of CARs | Best duration of response | Comments                                      |
|------------------------------|------------|--------------|----------------------------------|-------------------------------|------------------|----------------------------|-----------------------------------------------|
| Brentjens et al and Davila et al (2013, 2014) | MSKCC      | 16           | ALL                              | 88% (78% in refractory disease) | Up to 4 months   | 3 months (but 7 went on to alloSCT) | 7 CRS CRP, IFNγ, IL6 correlated with CRS    |
| Kochenderfer et al (2013)     | NIH        | 10           | CLL (4) and NHL (6) post-alloSCT  | 1 PR, 1 CR, 6 SD              | Up to 30 days    | 9 months                   | No GVHD                                      |
| Kochenderfer et al (2014)     | NIH        | 15           | NHL (DLBCL and indolent lymphomas) | 8 CR, 4 PR, 1 SD              | Up to 11 weeks   | 22 months                  | 6/7 DLBCL with response                      |
| Lee et al (2014)              | NIH        | 21           | ALL (20), NHL (1), 8 post-alloSCT | 14 CR (13 MRD-), correlated with CAR expansion | Up to 8 weeks (most went on to alloSCT) | 19 months       | 3 severe CRS CRP, IL6, and CAR expansion correlated with CRS |
| Grupp et al and Maude et al (2013, 2014) | U Penn     | 30           | ALL, 18 post-alloSCT              | 90% (15 post-alloSCT, 2 post-blinatumomab) | Up to 2 years    | 24 months                  | All with CRS                                 |

DLBCL: Diffuse Large Bcell Lymphoma, MRD: Minimal Residual Disease, GVHD: Graft Versus Host Disease
Complete remission of chemo-refractory primary mediastinal B-cell lymphoma ongoing after 35 months in Large Cell Lymphoma Patient 1

Before treatment

23 months after treatment

Courtesy of James Kochenderfer, MD
Complete remission of chemo-refractory primary mediastinal B-cell lymphoma occurred despite 10 prior treatments and is ongoing after 21 months in Large Cell Lymphoma Patient 4

Before treatment

9 months after treatment

Courtesy of James Kochenderfer, MD
Patient 2 had a PR of chemotherapy-refractory triple-hit DLBCL after infusion of anti-CD19 CAR T cells

Resolution of a large malignant pleural effusion and lymphoma masses
CAR T-cells: Lessons learned

• Durable remissions have been seen in ALL, CLL, NHL - persistence of circulating CAR T-cells has been seen >3 years after infusion in CLL

• In ALL, CR rates of 90% in a relapsed/refractory population are remarkable, especially compared to historical controls

• CAR T-cells have been effective pre- and post-transplant (relapse after allogeneic SCT) and in chemo-refractory disease

• Responses are correlated with expansion of CAR T-cells (not cell dose at infusion) and presence of cytokine release syndrome (CRS)
CAR T-cells: Lessons learned

- CNS disease has been cleared with CAR T-cell therapy
- B-cell aplasia is a surrogate for persistence of CAR T-cells
- Antigen-positive relapses occur after CAR T-cells are no longer circulating; antigen-negative relapses occur in the presence of CAR T-cells
- It is not clear which costimulatory domain is best (CD28 vs 4-1BB)
CAR T-cells

- **CTL019** – FDA breakthrough therapy designation in July 2014 in relapsed/refractory ALL 🇺🇸

- Antigen discovery is leading to development of CAR T-cells for other malignancies (i.e. anti-BCMA in multiple myeloma)

- 41 trials actively enrolling for CAR T-cells in hematologic malignancies
CAR-T cells: Cytokine release syndrome (CRS)

- Inflammatory process related to exponential T cell proliferation associated with cytokine elevation
- Occurrence of CRS correlates with response, but severity of CRS does not
- Mild: high fevers, myalgias, flu-like symptoms
- Severe: Vascular leak, hypotension, multi-organ failure
- Only predictor of CRS – high disease burden at time of treatment (IL6, CRP?)
- Management guidelines exist – steroids, tocilizumab (anti-IL6)

Lee DW et al., Current concepts in the diagnosis and management of cytokine release syndrome. Blood 2014;124(2):188-195.

- Tocilizumab does not appear to impact anti-tumor response
CAR-T cells: Other toxicities

Acute:
• Neurotoxicity
  – Global encephalopathy, seizures, mostly self-limited and without long term sequelae
  – Not related to CRS and not prevented by tocilizumab

Long term:
• B-cell depletion
  – Useful surrogate for CAR-T cells
  – Can be managed with IVIg infusions
• TBD?
CAR T-cells: Challenges and future directions

- Optimizing CAR and graft engineering: intracellular signaling domain, CD4:CD8 ratio, presence of Tregs
- Identification of targets – antigen discovery
- Ideal duration of engraftment
- Impact of tumor microenvironment (combine with PD1/PDL1 inhibition)
- Strategies to approach antigen-negative relapse
- Technical, regulatory, and financial obstacles – manufacturing on a wide scale
Augmentation of immune effectors and Activation of tumor antigen-specific immunity

Other strategies:

• **NK cell alloreactivity**
  – UPCI 12-151 (PI: Michael Boyiadzis): Phase I study of adoptive immunotherapy using the natural killer cell line, Neukoplast (NK-92) for the treatment of refractory or relapsed AML

• **Vaccines: AML in CR or PR**
  – Known intracellular tumor-associated antigens exist in AML (i.e. WT1, PRTN3, MAGE, etc)
  – Vaccines trials have not been successful in patients with high tumor burden
  – WT1 and hTERT dendritic cell vaccines have induced cellular immune responses and were associated with durable remissions

van Tendeloo et al., Proc Natl Acad Sci 2010
Khoury et al., ASCO Annual Meeting 2015
Overcoming tumor-derived immune inhibition:

Immune checkpoint blockade
Immune checkpoint blockade

Pardoll, Nat Rev 2012
1) Hodgkins lymphoma (HL): observations suggest that it is uniquely vulnerable...

- Reed-Sternberg cells typically surrounded by extensive (but ineffective) immune infiltrate

- HL characterized by genetic alteration in 9p24.1, which results in PDL1 and PDL2 copy gain and overexpression

- Epstein-Barr virus (EBV) infection, common in HL, also leads to PDL1 overexpression (mechanism to allow viral persistence in the host)

- Increased surface expression of PDL1 in HL tumors has been observed

Armand, Blood 2015
Immune checkpoint blockade

**Nivolumab** (anti-PD1)
- Phase I study in relapsed/refractory MM, NHL, HL; expansion cohort for HL
- 23 patients with median 5 lines of prior therapy
- ORR 87% (CR 17%)
- PDL1 and PDL2 expression observed in all tumor samples tested
- FDA breakthrough therapy designation in 2014

**Pembrolizumab** (anti-PD1)
- Phase 1 study in relapsed/refractory MDS, MM, NHL, HL; expansion cohort for HL
- 15 patients with median 4 lines of prior therapy
- ORR 65% (CR 21%)
- Responses for both agents appear durable, though longer follow up is needed

Ansell et al., N Engl J Med 2015
Moskowitz et al., ASH 2014
2) **After stem cell transplant (SCT): pros and cons...**

- Minimal residual disease state
- Immune reconstitution leads to increased lymphocyte subsets that are targets of PD1 inhibition
- Augmentation of graft-versus-tumor effect in allogeneic setting
  
  *but*

- Impact on risk of graft-versus-host disease in allogeneic setting
Immune checkpoint blockade

**Pidilizumab** (anti-PD1)
- Phase 2 study in 72 patients with diffuse large B-cell lymphoma (DLBCL) after autologous SCT
- 18-month PFS 72% (51% RR in patients with measurable disease after SCT)

**Ipilimumab** (anti-CTLA4)
- CTLA4 blockade not as well studied in hematologic malignancies, but may have a role in post-SCT setting
- Phase 1 study in 29 patients with relapse after allogeneic SCT
- No severe GVHD or DLTs
- Some evidence of anti-tumor activity (2 CRs and 1 PR)

Armand *et al.*, J Clin Oncol 2013
Davids *et al.*, Blood 2014
Immunotherapy in hematologic malignancies: The Future!

Future Directions:

• Ongoing development and refinement of antigen discovery and novel immunotherapies

• Broadening the availability of novel immunotherapies beyond highly specialized centers

• Developing experience in the management of complications of immunotherapies

• Developing appropriate clinical endpoints and response assessments

• Combining immune therapies
Immunotherapy in hematologic malignancies: The Future!

Best role for novel immunotherapies?
- As a bridge to SCT
- To treat post-SCT relapse
- Treatment for transplant-ineligible or lack of donor
- As a complement to SCT (enhancement of graft-versus-leukemia effect)
- In place of SCT...? (durability of response)

Chemotherapist’s bluntest weapon ➔ magic bullet
Timeline of major immunotherapeutic advances in hematologic malignancies

Bachireddy et al., Nat Rev 2015