Cellular Therapies: Why Should a PCP Care?

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Learning Objectives

- Recognize the special needs of hematopoietic stem cell transplant patients
- Identify and manage patient expectations and help with their understanding of the risks and benefits of CAR-T therapy
Cellular Therapy

- **Allogeneic hematopoietic cell transplantation**¹
  - N=694 (retrospective)
  - High risk disease
  - 2 yr-NRM (non relapse related mortality) 28%
  - 5 yr EFS (event free survival) 37%

- **CAR-T Therapy**
  - N=16
  - High risk disease
  - Best ORR (overall response rate) (81.3%) and a CR (complete response) rate (43.8%)
  - Responses have deepened over time at 3- and 6-month follow-up
  - CR continues in 5 of 6 patients with at least 3 months of follow-up


Hematopoietic Stem Cell Transplant
Transplant History

- **1958**: First attempted BM transplant
- **1968**: First successful allogeneic BM transplant (University of Minnesota)
- **1980s**: Peripheral blood stem cell (PBSC) transplant
- **1988**: First successful cord stem cell transplant
- **1998**: First unrelated cord stem cell transplant

BM, bone marrow

Stevie Nash

- 55-year-old long-time patient with hypertension had an allogeneic HSCT from his sister for refractory CLL at MDACC and has been discharged at 100 days. He sees you to discuss what follow-up is needed
  - Medications: cyclosporin, allopurinol, trimethoprim / sulfamethoxazole, acyclovir, fluconazole, HCTZ, mg
  - O/E: Thinner but not ill. Shaved head. BP: 130/70; P: 82 T 37.1
  - EENT: Dry mouth and slight inflamed conjunctivae
  - Chest: Hickman catheter, clear to PA, CVS: WNL Abd: WNL Ext: No edema. LAB: Hgb 12 ALC 0.3 ANC 1.2 Platelets 140,000 uric acid 7.8 Mg 2.1 CMP WNL

MDACC, MD Anderson Cancer Center
Best Practices Pearls

- HSCT patients are living longer with complicated medical issues often far from the transplant center
- Allogeneic transplants may have long term concerns related to (Graft Versus Host Disease) GVHD and its treatment
- All transplant patients are at higher risk for many common medical conditions including secondary cancers and psychiatric illness

HSCT (the Vocabulary)

- Allogeneic
  - Syngeneic (identical twin)
  - Related (siblings)
  - Unrelated (MUD or matched unrelated donor)
- Autologous
  - Cells obtained from the same individual
- Donor sources
  - Bone marrow
  - PBSC (peripheral blood stem cells that are “mobilized”)
  - Cord blood
- Conditioning
  - Myeloablative
  - Reduced intensity conditioning (mini-transplant or non-myeloablative)
Before the Transplant
Basic HLA Matching

- Human leukocyte antigen (HLA)
- No relation to blood type
- Encode for cell surface antigen presenting proteins
- Odds of a sibling match: 1/4
- 70% don’t have a family member that matches
- Odds of finding a donor
  - Depends on ethnicity and other factors: Range 1/3 to 1/125,000
  - Potential 18,500,000 donors and 600,000 cord bloods
  - Odds of your donation matching: 1/20,000 to 1/100,000


HLA Matching

Example A shows all the patient’s markers match the donor’s. The 8 of 8 match means that there is a match at A, B, C, and DRB1. A 10 of 10 match means that there is a match at A, B, DRB1, C, and DQ.

Example B shows that one of the patient’s A markers does not match one of the donor’s A markers. Therefore, this is a 7 of 8.

Acute and Chronic Follow up

- Acute GVHD: first 100 days (at transplant center)
- Chronic GVHD: >100 days (at home)
- Relative times of immune recovery are
  - Neutrophils and phagocytes: 2 weeks to 1 month
  - T cells: 6-12 months
  - B cells: 12-24 months

GVHD: Graft-versus-host disease

Transplant Follow up

<table>
<thead>
<tr>
<th>Time Period</th>
<th>Complication</th>
<th>Common Infections</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-1 months</td>
<td>Regimen-related toxicity, Graft failure, Drug reactions</td>
<td>Most bacteria, Candida, Aspergillus, Herpes simplex</td>
</tr>
<tr>
<td>1-3 months</td>
<td>Acute graft-versus-host disease (GVHD)</td>
<td>Candida, other fungi, Pneumocystis jiroveci, Cytomegalovirus</td>
</tr>
<tr>
<td>3-12 months</td>
<td>Chronic GVHD, Relapse</td>
<td>Pneumocystis carinii, Varicella-Zoster viruses, Cytomegalovirus, Encapsulated bacteria</td>
</tr>
<tr>
<td>&gt;12 months</td>
<td>Chronic GVHD, Relapse</td>
<td>Pneumocystis carinii, Varicella-Zoster viruses, Cytomegalovirus, Encapsulated bacteria</td>
</tr>
</tbody>
</table>

Chronic GVHD

- Comes hand-in-hand with graft-versus-tumor
  1. The graft contains immune competent cells (T cells)
  2. The immune compromised host can not reject the graft
  3. The host expresses tissue antigens not present in the donor
- A little bit is good, too much is horrific
- All the treatments are immunosuppressive
- Paradoxical low dose IL2 (interleukin 2)
- Trading one disease for another

“This is not the deal I wanted”

Billingham RE. Harvey Lect. 1966;62:21-78.

Resources

www.marrow.org/md-guidelines

www.BeTheMatch.org/Patient

HCT Quick Reference Guidelines App from
http://marrow.org/Physicians/Medical_Education/Clinical_Guidelines_App/Clinical_Guidelines_App.aspx
Transplant Care

- Biannually 1st year and annual thereafter
  - Clinical assessment including oral, ocular, dental, pysch, sexual, PFTs, CBC, LFTs, Cr/BUN, urine protein, uric acid, Mg, CMV
- Annually
  - Bone density (female and GVHD), ferritin, thyroid, gonadal function, neuro exam
- Immune Issues
  - Prophylaxis for PCP, fungal, encapsulated bacteria, endocarditis, HSV
  - Immunizations for patient and their caregivers
- Cancer Screening
  - Routine plus skin cancer screening
  - Watch CBC for cytopenias and macrocytosis

Vaccines

<table>
<thead>
<tr>
<th>Time After HSCT</th>
<th>Vaccine or Toxoid</th>
<th>12 Months</th>
<th>14 Months</th>
<th>24 Months</th>
<th>Rating</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inactivated vaccine or toxoid</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diphtheria, tetanus, pertussis</td>
<td>Diphtheria toxoid-tetanus</td>
<td>DTP</td>
<td>DTP or DT</td>
<td>BII</td>
<td></td>
</tr>
<tr>
<td>Children aged &lt;7 years</td>
<td>Toxoid-pertussis vaccine (DTP) or diphtheria toxoid-tetanus toxoid (DT)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Children aged ≥7 years</td>
<td>Tetanus-diphtheria toxoid (Td)</td>
<td>Td</td>
<td>Td</td>
<td>BII</td>
<td></td>
</tr>
<tr>
<td>Haemophilus influenza type b (Hib) conjugate</td>
<td>Hib conjugate</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Hepatitis (HepB)</td>
<td>HepB</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>23-valent pneumococcal polysaccharide (PPV23)</td>
<td>PPV23</td>
<td></td>
<td></td>
<td>PPV23</td>
<td>BII</td>
</tr>
<tr>
<td>Influenza</td>
<td>Lifelong, seasonal administration, beginning before HSCT and resuming at ≥6 months after HSCT</td>
<td></td>
<td></td>
<td></td>
<td>BII</td>
</tr>
<tr>
<td>Inactivated Polio (IPV)</td>
<td>IPV</td>
<td>IPV</td>
<td>IPV</td>
<td>IPV</td>
<td>BII</td>
</tr>
</tbody>
</table>

Life-attenuated vaccine

<table>
<thead>
<tr>
<th>Vaccine or Toxoid</th>
<th>Measles-mumps-rubella (MMR)</th>
<th>Varicella vaccine</th>
<th>Rotavirus vaccine</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>-</td>
<td>Contraindicated for HSCT recipients</td>
<td>Not recommended for any person in the US</td>
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</table>

**Major recommendations for vaccinations for hematopoietic stem cell transplant (HSCT) recipients, including both allogeneic and autologous recipients. For these guidelines, HSCT recipients are presumed immunocompetent at ~24 months after HSCT if they are not on immunosuppressive therapy and do not have graft-versus-host disease (GVHD)**

CAR-T Cell Therapy
Role in Chronic Lymphocytic Leukemia

Best Practices Pearls

- CAR-T therapy is the first FDA approved gene therapy
- Response rates can be in the mid 80% for high risk patients
- CAR-T is autologous avoiding GVHD but bringing a whole new set of Adverse Events
- There are little data and less long term data
- 2 of the 1\textsuperscript{st} three CLL (chronic lymphocytic leukemia) patients to receive CAR-T are still alive 7 years later
- CMS has recently agreed to cover CAR-T therapy and clinical trial costs
CAR-T Therapy

- CAR-T = chimeric antigen receptor T cell
  - Reprogrammed patient T cells that selectively identify tumour cells and target them for destruction\(^1\)
- Goal is to harness the power of the immune system to kill CLL cells using 3 main structural units:\(^2\)
  1. scFv for MHC-independent antigen recognition
  2. TCR-activating subunit \(\zeta\) to form activation signal 1
  3. 1 or 2 co-stimulatory motifs to form activation signal 2 (from CD28, 4-1BB, and/or OX-40)
- CTL019 is a CD19-targeted CAR-T therapy\(^1,3\)
  - CD19 is expressed throughout B-cell development
  - CD19 is expressed on almost all B-cell malignancies, but not on haematopoietic stem cells

MHC, major histocompatibility complex; scFv, single-chain variable fragment; TCR, T-cell receptor


The Fight Against Cancer

Takes place in every cancer patient
Between the cancer and the immune system

Immune system

Distinguishes “self” from “non self”

Eliminate Infection

Attack Own Cells

Rejection of Invaders

Autoimmunity
Cellular Therapies: Why Should a PCP Care?

Immune System

Over-active immune response

Under-active immune response

Infection

Autoimmunity
Goal of Cancer Immunotherapy

Bend the immune system curve

Eliminate Cancer
Avoid Autoimmunity

Cross-presentation of tumor antigens
The “War on Cancer” at the individual level...

- Primary Combatants:
  - Malignant cells
  - Host immune system

- The host immune system is an active enemy faced by a developing cancer

- All “successful” cancers must avoid immune destruction

- Weapons
  - Target on surface of cell – Antibody-based treatment
  - Target inside cancer cell – T cell-based treatment

Ideal Cancer Immunotherapy Target

Overcome fact that cancer is “self”

Need to break tolerance (help immune system see the target as “non-self”)

- Expression
  - Selectively on malignant cells (or non-vital tissues)
  - On all malignant cells in a tumor

- Function
  - Necessary for cell survival or malignant phenotype

- Antibodies
  - Administer anti-cancer antibodies to patients
  - Administer antibodies that alter the immune response to the cancer

- T-cells
  - Cancer vaccines
  - Change tumor environment so the immune system recognizes and eliminates the cancer (in situ immunization)
  - Take out T cells, change them so they are specific for the cancer, and give them back to the patient
**Remove cancer’s “invisibility cloak”**

Cancer cells express molecules that prevent the immune system from recognizing and eliminating cancer.

We now can block these molecules with mAb or change the configuration of T cells allowing the immune system to recognize and eliminate the cancer.

**Chimeric Antigen Receptors (CAR) T Cell Therapy**

**CAR T Cell Therapy Production**

The production of CAR T cell therapy involves a number of steps.\(^1\)\(^2\)

1. T cells, a type of white blood cell, are collected from a patient or a donor's blood.
2. The collected T cells are then sent to a laboratory where they are engineered to produce chimeric antigen receptors (CARs) on their surface. The engineered T cells are now called CART cells.
3. CART cells are multiplied in the lab and infused into the patient's bloodstream.
4. CART cells are intended to recognize and kill the cancerous cells that have the targeted antigen on their surface while also continuing to multiply within the body.
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**Approaches to CAR T Cell Therapy Development**

There are two approaches to the production of CAR T cell therapy. More research is needed to better understand the potential benefits and disadvantages of each approach.

**Allogeneic**

- Allogeneic CAR T cells are engineered using T cells from a single donor that are utilized in multiple patients.
- Healthy donor → CART cells → Patients

**Autologous**

- Autologous CAR T cells are engineered using a patient’s own T cells.
- Patient → CART cells

**1) T Cell Collection**

- CD3 T Cells

**2) T Cell Transfection**

1. Binding
2. Fusion
3. Integration
4. Transcription and protein expression
5. CAR cell membrane insertion

**3) T Cell Adoptive Transfer**

+/- Lymphodepleting conditioning

**4) Patient Monitoring**

a) Disease response
   - CT scans
   - Bone marrow biopsies
   - Peripheral blood flow cytometry
b) CAR-T Cell persistence
   - Immunohistochemistry of bone marrow biopsy
   - RT-PCR and flow cytometry of blood and bone marrow aspirate
Cellular Therapies: Why Should a PCP Care?

Why CAR’s?
- Best of both worlds of the immune system
  - B cell specificity
  - T cell cytotoxicity without presentation
- Form of Adoptive T cell therapy
- Synthetically engineered receptors designed to overcome immune tolerance / tumor evasion
- Targets surface molecules in their native confirmation
- Engage target independent of antigen presenting cell (APC) and MHC complex

Ideal CAR Target...
- Tumor specific
- Universally expressed on only tumor cells
- Cell surface molecule
- CD 19
  - Found on B cell malignant cells (NHL, CLL, ALL, etc)
  - Expressed on early B cells but NOT stem cells

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Complications of CAR T Cells

- **Cytokine release syndrome (CRS)**
  - Typically within 5 days and CRP best predictor
  - Exponential T cell proliferation leads to IL2, IL6, IFN
  - Can lead to macrophage activation syndrome and shock / organ failure
    - Treated with IL6 monoclonal antibodies (Tocilizumab) and steroids

- **B Cell aplasia**
  - Immunoglobulin replacement required to keep Ig > 5g/L

- **Encephalopathy**
  - Unclear pathogenesis
  - Self limiting
  - No long term complications
  - CAR T cells in CSF in all patients


Challenges of CAR-T Cell Therapy

- Unclear how well it will work against solid tumors
  - Problem of T cells entering tumor site

- Will tumors lose target antigen and develop resistance?

- Technical and regulatory challenges of producing genetically modified CAR-T cells for each patient

- Exhaustion of transferred T cells
  - Use CRISPR gene editing to delete PD-1 from T cells
  - Increased risk of autoimmune reactions from endogenous TCRs
  - Use CRISPR to delete TCRs
  - Result is PD-1- T cells expressing tumor-specific CAR
CD19-targeted CAR-T therapy in patients with ibrutinib-refractory CLL

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>All patients (N=18)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age, years (range)</td>
<td>60 (40–73)</td>
</tr>
<tr>
<td>Prior fludarabine + R regimen, %</td>
<td>18 (100)</td>
</tr>
<tr>
<td>Prior ibrutinib</td>
<td>18 (100)</td>
</tr>
<tr>
<td>Ibrutinib-refractory, n (%)</td>
<td>11 (61)</td>
</tr>
<tr>
<td>Ibrutinib-intolerant, n (%)</td>
<td>3 (17)</td>
</tr>
<tr>
<td>Venetoclax-refractory, n (%)</td>
<td>4 (22)</td>
</tr>
<tr>
<td>Complex karyotype, n (%)</td>
<td>12 (67)</td>
</tr>
<tr>
<td>del(17p), n (%)</td>
<td>11 (61)</td>
</tr>
<tr>
<td>Median abnormal B-cells in BN, % (range)</td>
<td>77 (0.4–96)</td>
</tr>
</tbody>
</table>

- At day 28, 11/13 (85%) of patients who received Cy/Flu lymphodepletion and 2x10⁶ CAR-T cells/kg had complete elimination of marrow disease.

\* By flow cytometry; † 4 weeks after last CAR-T infusion.


Conclusions

- CAR-T cells are exciting addition to our ability to treat CLL and other cancers
- The quality of CAR’s is improving and further data is accumulating
- However, long term data (Persistence of CAR’s) is lacking
- The cause of toxicity is not clear
- More questions than answers at presence. Where / When / How to use them