Cell Therapy 101

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Types of Cell Therapy

Tumor Infiltrating Lymphocytes (TIL)

- Immune cells found with in the tumor that are often capable of targeting the cancer

T Cell Receptors (TCRs)

- T cells that are engineered to include the receptor that enables them to target specific cancer antigens

Chimeric Antigen Receptor T Cells (CAR-T)

- T cells that are modified to express a CAR complex and target different specific surface proteins

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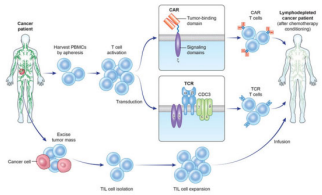
Adoptive T cell therapy can involve engineered (CAR, TCR) or patient-derived (TIL, PBMC) T cells



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Advantages for use of Cell Therapy

- Administer larger numbers of cells with high avidity to tumor antigens
- Shorter treatment times
- Durability of treatment

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TIL

Uses:

- solid tumors (Melanoma, lung, breast cancer)

Limitations for use:

- Must have an easily accessed tumor that can be removed to harvest the TIL cells from
- Relies on good growth of the T cells that recognize the tumor, other T cells could outgrow the tumor specific ones

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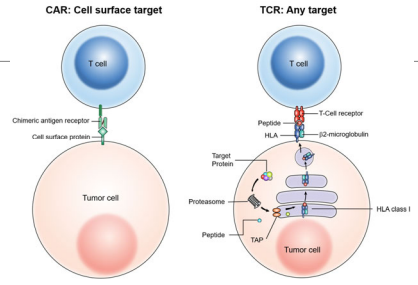

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TCRs

Uses:
- Solid Tumors (sarcomas, HPV related cancers)
- Cancer that express germline antigens (MAGE and NY-ESO)

Limitations of Use:
- HLA restriction
- Tumor must have target present
- Side effects

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CAR T cells

Uses:
- Blood cancers
- research expanding into solid tumor

Limitations for use:
- Tumor must have target present
- Side effects

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Why Give Chemotherapy Prior to T Cell Administration?

- NON MYELOABLATIVE INTRAVENOUS LYMPHODEPLETING CHEMOTHERAPY CONDITIONING REGIMEN PROMOTES INFUSED T CELL GRAFTMENT
- ELIGIBILITY PARAMETERS FOR WBC, HGB, PLATELETS, NEUTROPHILS TO ENSURE THAT BONE MARROW CAN RECOVER
- EXPECTED SIDE EFFECTS: LYMPHODEPLETION (DESIRED!) BUT ALSO LOW BLOOD COUNTS ACROSS THE BOARD, RISK FOR INFECTION, POSSIBLE NEED FOR TRANSFUSIONS, RISK FOR BLEEDING, N/V/D, ANOREXIA, FATIGUE, MUCOSITIS
- MOST COMMON CONDITIONING REGIMEN: CYCLOPHOSPHAMIDE, FLUDARABINE (BORROWED FROM STEM CELL TRANSPLANT)

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Patient management during conditioning chemotherapy

Conditioning chemotherapy may be given inpatient or outpatient depending on drug dosing and required management – CAR T cells protocols often contain lower dose chemotherapy regimens and therefore can be done outpatient

Central lines – Tunneled or non tunneled lines, non valved PICCs

Mesna, IV fluids, frequent voids to prevent hemorrhagic cystitis from high dose cyclophosphamide

Twice daily weights/lasix to prevent fluid overload

Labs – monitor/correct electrolyte imbalances, daily CBCs to monitor counts

Anti-emetics, monitor for constipation

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Rationale for intravenous IL-2 (Aldesleukin)

To promote T cell expansion

More does not equal better

Dosed to individual patient tolerance

Once you stop dosing, side effects don't go away immediately

CAR T cells do not give IL-2 due to excess toxicity

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IL-2 side effects

- Fatigue
- Fever
- Chills/rigors
- Poor PO intake, nausea (rarely vomiting), diarrhea
- Electrolyte abnormalities
- Renal and hepatic dysfunction
- Capillary Leak Syndrome (3rd spacing)
  - Not the same as Cytokine Release Syndrome from CAR T cell therapy
- Confusion
- Hypotension
- Tachycardia
- Dyspnea/Pulmonary Edema

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IL-2 Patient Management

Primary team will green light each dose of IL-2

- Premedications start 24 hours prior to 1st dose of aldesleukin
  - Tylenol 650 PO q4hrs
  - Indomethacin 50 mg PO q8hrs
  - Famotidine (H2 blocker)
  - Zofran 12 mg IV q12hrs
- 5% Dextrose + 0.45% NaCl at 50 cc/hr
- Accurate I/O's and twice daily weights
- Neuro assessments
- Higher risk for falls during IL-2 dosing due to fluid shifts
  Low blood pressure is generally acceptable during admin if mentation is appropriate (compare to baseline pressures)

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Cell Processing – what happens on day of infusion (CCE)

Some trials have manufacturing done elsewhere, CCE still has a role for thawing

Research team enters CRIS orders for cell infusion and vital signs frequency.

CRNs follow Administration of Cellular Therapy Products SOP

CRNs contact DTM CCE the morning of infusion to coordinate timing – infusions usually in the afternoon

Double checks occur with CCE technologist, then another CRN at bedside

Cells administered per protocol and SOP keeping in mind expiration time

CRNs document in Cell Therapy Administration Note

Image courtesy bethematch.org

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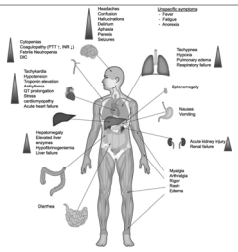
Expected side effects of T cells

All T Cells: Hypoxia, Fever, Chills/Rigors

Toxicities can vary between cell types

- CAR T cells – Cytokine Release Syndrome (see graphic)
- Off target toxicity if antigen is present in healthy tissues



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Post T cell infusion

Patients may be inpatient for 1-2 weeks while blood counts and symptoms recover.

- Response and safety assessments per protocol
  - Solid tumor - RECIST tumor measurements
  - Lymphoma response criteria has multiple factors
  - Leukemia response criteria includes peripheral blood flow and bone marrow biopsies
  - Multiple myeloma response assessment may include bone marrow biopsies and aspirates

Follow up on study until disease progression.

Some protocols allow re-treatment if certain criteria is met.

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No Steroids unless it is an emergency – steroids may interfere with T cells.

Irradiated Blood Products Only (if patient received fludarabine) – due to potential for transfusion-related GVHD.

Monitor for signs/symptoms of infection as counts will be recovering from chemotherapy

Report any fevers, rashes, uncontrolled nausea/vomiting/diarrhea, unable to tolerate PO, or any new/unusual symptoms to research team

Encourage patients to reach out to research team with any questions or concerns

Discharge education

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Follow Up for Gene Therapy T cells (CAR and TCR)

Lentivirus and gammaretrovirus retroviral vectors are used to genetically modify T cells.

Long term follow up is required for 2 main reasons:

1) Ensuring that these are replication incompetent viruses, by testing blood for replication-competent retroviruses (RCR).
2) Monitoring for insertional mutagenesis (ex: development of leukemia/lymphoma), by monitoring for persistence of T cells in the peripheral blood over time

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FDA guidance

Monitor for neurological, autoimmune, or blood disorders, or any new cancers.

Sponsors are advised to observe subjects for delayed adverse events for as long as 15 years.

Minimum 5 years of annual examinations, then additional 10 years of annual queries of study subjects.

Vectors with an improved risk profile continue to be developed.

Assessment of risk should be a continuous process.

November 2006 FDA Guidance Documents "Gene Therapy Clinical Trials-Observing Subjects for Delayed Adverse Events"and December 2000 "Guidance for Industry: Supplemental Guidance on Testing for Replication Competent Retrovirus in Retroviral Vector Based Gene Therapy Products and During Follow-up of Patients in Clinical Trials Using Retroviral Vectors"

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Example Timeline

3 Month, 6 Month, Years 1-5:

- Most recent history and physical examination and laboratory testing from health care provider
- Annual health check (questionnaire) via telephone or email
- Blood sample
  - May not be required after 1 year – OSRO guidance is to get 3 consecutive timepoint negative results prior to discontinuing blood draws

Years 6-15: Annual health status check (questionnaire) via telephone or email

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Current FDA approved cellular therapies

as of 3/1/22)

- ABECMA (idecabtagene vicleucel)
  Celgene Corporation, a Bristol-Myers Squibb Company
- ALLOCORD (HPC, Cord Blood)
  SSM Cardinal Glennon Children's Medical Center
- BREYANZI
  Juno Therapeutics, Inc., a Bristol-Myers Squibb Company
- CARVYKTI (ciltacabtagene autoleucel)
  Janssen Biotech, Inc.
- CLEVECORD (HPC Cord Blood)
  Cleveland Cord Blood Center
- Duoxel, HPC Cord Blood
  Duke University School of Medicine
- GINTUIT (Allogeneic Cultured Keratinocytes and Fibroblasts in Bovine Collagen)
  Organogenesis Incorporated
- HEMACORD (HPC, cord blood)
  New York Blood Center
- HPC, Cord Blood
  Chimerscan Labs, University of Colorado Cord Blood Bank
- HPC, Cord Blood - MD Anderson Cord Blood Bank
  MD Anderson Cord Blood Bank
- HPC, Cord Blood - Lifeliveli
  LifeSouth Community Blood Centers, Inc.
- HPC, Cord Blood - Bloodworks
  Bloodworks
- IMLYGIC (talimogene laherparepvec)
  BioVex, Inc., a subsidiary of Amgen Inc.
- KYMRIAH (tisagenlecleucel)
  Novartis Pharmaceuticals Corporation
- LAVIV (azficel-T)
  Fibrocell Technologies
- LYTURSA
  Spark Therapeutics, Inc.
- MACI (Autologous Cultured Chondrocytes on a Porcine Collagen Membrane)
  Vericel Corp.
- PROVENGE (sipuleucel-T)
  Dendreon Corp.
- RETISYNC
  Ensyvant Therapeutics GmbH
- STRATAGRAFT
  Stratatech Corporation ...
- TECARTUS (brexucabtagene autoleucel)
  Kite Pharma, Inc.
- YESCARTA (axicabtagene ciloleucel)
  Kite Pharma, Incorporated
- ZOLGENSMA (onasemnogene abeparvovec-xioi)
  Novartis Gene Therapies, Inc.

https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products/approved-cellular-and-gene-therapy-products

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