Curricular Track I—Manipulation of the Immune System in Transplantation and Oncology

Activity No. 0217-0000-11-086-L01-P (Knowledge-Based Activity)

Tuesday, October 18

10:15 a.m.–11:45 a.m. Convention Center: Spirit of Pittsburgh Ballroom A

Moderator: Kellie L. Jones, Pharm.D., BCOP

Clinical Associate Professor, Purdue University School of Pharmacy and Pharmaceutical Sciences, Indianapolis, Indiana

Agenda

| 10:15 a.m. | Solid Organ Transplant Immunosuppression: Maintaining the Balance | | | | |
|------------|---|--|--|--|--|
| | Steven Gabardi, Pharm.D., FCCP, BCPS Abdominal Organ Transplant Specialist, Program Director, PGY2 Organ Transplant Pharmacology Residency, Brigham and Women's Hospital, Department of Transplant Surgery/Renal Division; Instructor of Medicine, Harvard Medical School, Boston, Massachusetts | | | | |
| 11:00 a.m. | Modulating the Immune System in Oncology: The Evolution of Therapy <i>R. Donald Harvey III, Pharm.D., FCCP, BCPS</i> Assistant Professor of Hematology and Oncology, Director, Phase I Unit, Winship Cancer Institute, Emory University, Atlanta, Georgia | | | | |

Faculty Conflict of Interest Disclosures

Steven Gabardi: no conflicts to disclose. R. Donald Harvey III: no conflicts to disclose.

Learning Objectives

- 1. Review current trends in transplant immunosuppression.
- 2. Discuss strategies for managing T and B cell activation.
- 3. Differentiate immunosuppressive regimens based on the recipient's disease state and organ transplanted
- 4. Review the evolving therapies in oncology targeting the immune system.
- 5. Describe how immunomodulatory agents are incorporated either as single agent or in combination with chemotherapy in the treatment of cancer.

Self-Assessment Questions

Self-assessment questions are available online at www.accp.com/am



Transplant Immunosuppression

Steven Gabardi, Pharm.D., FCCP, BCPS Abdominal Organ Transplant Specialist Brigham and Women's Hospital Instructor in Medicine Harvard Medical School

Conflict of Interest

- I have no financial relationships to disclose within the past 12 months relevant to my presentation
- My presentation does include discussion of off-label or investigational use

Objectives

- Review current trends in transplant immunosuppression
- Discuss strategies for managing T and B cell activation
- Differentiate immunosuppressive regimens based on the recipient's disease state and organ transplanted.

Introduction

Advances in transplant immunosuppression have contributed to:

- A decrease in acute rejection and an increase in graft survival
- Longevity for kidney allograft recipients

Proliferation of agents means:

- More options
- More complicated management

Principles of Immunosuppression - 1

Elimination of acute rejection would be ideal (if there were no side-effects)

Humar et al^{1,2}

 studied long-term outcome (rejection vs. no rejection) of recipients transplanted at a single center from 1984-1998

- immunosuppression – cyclosporine, prednisone, azathioprine

- excluded graft loss to technical failure, primary nonfunction, death, recurrent disease

10-Year Death-Censored Allograft Survival Rates



Patients were excluded from the analysis if they experienced death with graft function, primary non-function, technical failure, or recurrent disease.

Humar A, et al. Transplantation 1999;68:1842-6

Costs of Acute Rejection

- Actual costs
 - multiple lab tests (for diagnosis)
 - return to the transplant center
 - kidney biopsy
 - cost of treatment
- Long-term costs
 - increase rate of CAD; decreased allograft survival
 - increased risk of infection and malignancy (from anti-rejection treatment)
 - other side-effects from anti-rejection treatment

Principles of Immunosuppression - 2

Maintenance of excellent kidney function is important

Meier-Kriesche et al*

- analyzed 58,900 adult US patients who received a primary renal transplant between 1988 and 1998 and who had at least 1 year of allograft survival. The primary study endpoint was death from a cardiovascular event beyond 1 year of transplantation.
- Serum creatinine values at 1 year after transplantation were strongly associated with the risk for cardiovascular death. Above a serum creatinine value of 1.5 mg/dL, there was a significant and progressive increase in the risk for cardiovascular death.

Cardiovascular Death and Graft Function



Meier-Kriesche HU, et al. Transplantation 2003;75:1291-5

Principles of Immunosuppression - 3

Lowest Risk: Identical twin, BMT

<u>Highest Risk</u>: Highly sensitized, Expanded-criteria donor

a) Among transplant recipients, there are continua of risk - e.g., for acute rejection episodes, drug side-effects

 b) There are also immunosuppressive agents with greater vs. lesser efficacy and greater vs. lesser risks (side-effects)

Goals for Achieving the Best Long-Term Outcome

Minimize acute rejection (AR)

Minimize chronic rejection/chronic allograft nephropathy: minimize AR, CNI nephrotoxicity

Minimize cardiovascular risk factors Minimize other drug-related side-effects

Classification of Immunosuppressive Agents

1) Induction agents* - powerful drugs used for a short time at the time of transplant 2) Maintenance agents* - drugs given long-term (indefinitely) to prevent rejection 3) Anti-rejection agents* - drugs given to reverse a rejection episode 4) Drugs used in special situations – e.g., ABO incompatible transplants or transplants across a positive crossmatch

* Agents used in different settings may be the same.

Immunosuppressant Action and the Immune Cascade



Critical Questions

1) Should we give the same immunosuppression to all recipients (one size fits all)?

or, if not

2) Who should receive antibody induction? -All?

-Selected high risk groups?

-Drug minimization trials?

3) Who should receive aggressive (vs. conservative) maintenance immunosuppression?

Introduction of Immunosuppressants (US)



I - Induction

Goals of induction therapy

- 1. To decrease the rate of acute rejection
- 2. To permit delayed initiation, minimization or avoidance of some of the maintenance agents (i.e. CNI, corticosteroids)

Available agents

- 1) Monoclonal antibodies that react with a single antigen receptor on the lymphocyte
 - Basiliximab (Simulect)
 - Alemtuzumab (Campath)
 - Withdrawn from the market: muromonab-CD3 (OKT3) and daclizumab (Zenapax)
- 2) Polyclonal antibodies: react with multiple antigen receptors
 - Equine polyclonal IgG antibody (ATGAM)
 - Rabbit polyclonal IgG antibody (Thymoglobulin)

I - Induction

Pharmacologic Classification of the Induction Agents

1. Non-Depleting Proteins

- Basiliximab (Simulect®)

1. Depleting Proteins

- Equine antithymocyte globulin (ATGAM®)
- Rabbit antithymocyte globulin (Thymoglobulin[®])
- Alemtuzumab (Campath[®])

Non-Depleting Proteins: Basiliximab

- A chimeric monoclonal antibody that competitively inhibits the activation of lymphocytes by IL-2
- This agent has low immunogenicity potential because of the incorporation of human protein sequences.

Human

Mouse

Non-Depleting Proteins: Basiliximab

• Dosing:

- Loading dose: 20 mg ~2hrs prior to transplantation.
- Maintenance dose: 20 mg dose 4 days post-op.
 - After this dosing regimen the agent stays bound to the CD25 receptor for up to 10 weeks
- <u>Drug-Drug Interactions (DDI)</u>: none reported
- <u>Adverse Drug Reactions (ADR)</u>: incidence of ADR in clinical trials were similar to those seen with placebo.

Depleting Proteins: Antithymocyte Globulins (Horse and Rabbit)

- These agents are purified gamma globulin obtained by immunizing horses/rabbits w/ human lymphocytes.
 - Cytotoxic antibodies directed against a broad array of surface antigens expressed on T- and Blymphocytes:
 - CD2, CD3, CD4, CD8, CD11a, CD25, CD28, CD45, Human Leukocyte Antigen (HLA) Class I and HLA-DR subsets
 - Causes depletion of peripheral lymphocytes
 - complement-dependent lysis (primary response)
 - clearance by the RES
 - Cellular reconstitution may take up to 3 months

Depleting Proteins: Antithymocyte Globulins (Horse and Rabbit)



What is the difference between the two agents?

Antithymocyte globulin rabbit (r-ATG) not only causes cell depletion, but it also has some secondary mechanisms:

- •immune modulation,
- •B-cell apoptosis,
- actions on adhesion molecules,
- dendritic cell depletion

Depleting Proteins: Antithymocyte Globulin Rabbit

- Dosing:
 - Most common regimens utilize 1.5 mg/kg/day for 3 -5 days
 - Ideally first dose is given prior to graft reperfusion¹
- <u>DDI</u>: none reported
- <u>ADR</u>:
 - myelosuppression (leukopenia)
 - cytokine release syndrome (myalgias, hypotension, tachycardia, fever, etc.)
 - RARE: serum sickness

Depleting Proteins: Alemtuzumab

- Alemtuzumab is an anti-CD52 humanized, monoclonal antibody that has an FDA indication for use in B-cell chronic lymphocytic leukemia.
- CD52 is present on virtually all B- and T-cells, as well as macrophages, NK cells and some granulocytes.
- The alemtuzumab-CD52 complex triggers antibody-dependent lysis.
 - The depletion of lymphocytes is so marked that it takes several months, up to one-year, post-administration for a patient's immune system to be fully reconstituted.

Depleting Proteins: Alemtuzumab

Dosing:

- 30 mg, given as a single dose intraoperatively
- In some settings, a second 30 mg dose is given.
- DDI: none reported
- <u>ADR</u>:
 - Myelosuppression
 - Infusion-related reactions: nausea (54%), vomiting (41%), diarrhea (22%), headache (24%), dysthesias (15%) and dizziness (12%)
 - RARE: autoimmune hemolytic anemia

Comparative Analyses of Induction Therapies

- e-ATG vs. r-ATG¹⁻³
 - Efficacy: Significantly lower rates of BPAR and improved allograft/patient survival with r-ATG at 1-, 5and 10-years
 - Safety: Significantly lower rates of CMV infection with r-ATG, despite higher early rates of leukopenia. Similar rates of PTLD.
- Basiliximab vs. r-ATG (high risk recipients)⁴
 - Efficacy: Similar composite end point of BPAR, DGF, allograft/patient survival
 - Significantly lower rates of BPAR associated with r-ATG
 - Safety: Significantly higher rates of myelousppression and overall infections seen with r-ATG
 - Significantly fewer cases of CMV infection seen with r-ATG, despite higher early rates of leukopenia.
- Alemtuzumab vs. Basilximab (low-risk); vs. r-ATG (high-risk)⁵
 - Efficacy vs. Basiliximab: Lower rates of BPAR at 6, 12 and 36 months with alemtuzumab. The composite endpoint of freedom from rejection, graft loss or death was significantly better at 3-years with alemtuzumab.
 - SAFETY: lower rates of serious infectious complications seen with basiliximab.
 - Efficacy vs. r-ATG: The composite endpoint of freedom from rejection, graft loss or death was similar between both agents.
 - SAFETY: overall, more infectious disease seen with r-ATG, but similar rates of serious infectious complications.

Brennan DC, et al. *Transplantation* 1999;67:1011-8.
 Hardinger KL, et al. *Transplantation* 2004;78:136-41.
 Hardinger KL, et al. *Transplantation* 2008;86:947-52.
 Brennan DC, et al. *N Engl J Med* 2006;355:1967-77.
 Hanaway MJ, et al. *N Engl J Med* 2011;364:1909-19.

Biologic Agent Overview

| | | Clinical Use | | | |
|-------------|--|--------------|-------------|-----------|----------------------------------|
| Agent | Class | Induction | Maintenance | Treatment | Cost |
| Basiliximab | Anti-CD25 Antibodies (non- depleting) | | | | 20 mg = \$2000 |
| Alemtuzumab | Anti-CD52 Antibody (depleting) | | | | 30 mg = \$1700 |
| e-ATG/r-ATG | Polyclonal Antibodies (depleting) | | | | 1.5 mg/kg x 70 kg = \$1600 |

Current Trends in Antibody Induction Use in Kidney Transplantation

--- eATG --- rATG --- OKT3 --- Daclizumab --- Basiliximab --- Alemtuzumab



Andreoni KA, et al. Am J Transplant 2007; 7:1359-75

II – Maintenance Immunosuppression

- Calcineurin Inhibitors (CNI)
 - Cyclosporine (Sandimmune[®] / Neoral[®])
 - Tacrolimus (Prograf[®])
- Inhibitors of T-cell Proliferation
 - Azathioprine (Imuran[®])
 - Mycophenolate mofetil (CellCept®)
 - Enteric-Coated Mycophenolic Acid (Myfortic[®])
- Mammalian Target of Rapamycin (mToR) Inhibitors
 - Sirolimus (Rapamune[®])
 - Everolimus (Zortress[®])
- Co-Stimulation Blockade
 - Belatacept (Nulojix[®])
- Non-specific immunosuppressants
 - Corticosteroids

Common Combinations of Immunosuppressive Regimens



AZA = azathioprine, CSA = cyclosporine, EC-MPA=enteric-coated mycophenolate sodium, MMF = mycophenolate mofetil, TAC = tacrolimus

Common Combinations of Immunosuppressive Regimens

Dual- or triple-therapy (most common)

Benefits: Lower doses of each drug; maximize efficacy (↓ acute rejection episodes) while minimizing toxicity of each drug Risks: Overimmunosuppression Increased costs

<u>Monotherapy</u>

Benefits: Potential for limiting side-effects of multiple drugs
Risks: Increased rejection
Increased doses (levels) of the single drug are
needed → side-effects

Achievement and Maintenance of Optimal Immunosuppression

Not just the choice of drugs but how they are used; blood levels are important for some

Early posttransplant protocols may differ from late:
a) dose reduction over time
b) minimization/elimination of one drug
c) unexpected events may call for changes
d) flexibility is important

Understanding the Importance of Calcineurin Phosphatase



Understanding CsA and TAC



Calcineurin Inhibitors: CsA and TAC

Numerous studies have compared efficacy and side-effects. in general (though there is some variation between studies):

<u>Efficacy</u>

- Patient and allograft survival has been similar for the 2 CNIs
- Acute rejection rates have been similar or ↓ with TAC

Safety/tolerability

- CsA has been associated with greater increases in lipid levels and blood pressure
- TAC has been associated with greater incidence of newonset posttransplant diabetes
- Each has drug-specific side-effects

Calcineurin Inhibitors: CsA and TAC

• <u>Dosing</u>:

- Due to significant inter- and intra-patient variability, therapeutic drug monitoring (TDM) is employed to maximize the efficacy of both CNIs.
 - CsA: overall exposure is best correlated to C_2 or C_3 levels
 - TAC: overall exposure is best correlated to C₁₂ levels
- Appropriate levels are dependent on institutionspecific protocols and concomitant immunosuppressants
- <u>DDI</u>: both agents are substrates for CYP3A4 and P-gp
CNI Side-Effects

Cardiovascular – Hypertension; Hypercholesterolemia

Glucose intolerance

<u>Neurotoxicity</u> – Tremor; Headache; Insomnia; Paresthesia

<u>Nephrotoxicity</u> – perhaps long-term dose and levelrelated

<u>Hepatotoxicity</u>

Malignancy – related to overall immunosuppression

<u>Physical</u> – Gingival Hypertrophy; Hirsutism (CSA); Alopecia (TAC)

Trends in CNI Use

Cyclosporine Tacrolimus



Meier-Kriesche HU, et al, Am J Transplant 2006;6:1111-31

Mycophenolic Acid (MPA): MMF and EC-MPA

- Inhibit lymphocyte proliferation
 Inhibitors of purine and
 - Inhibitors of purine and DNA synthesis
 - cells other than lymphocytes have an alternate synthesis pathway
 - thus, selective antiproliferative effect on T and B cells



MPA: MMF and EC-MPA

- <u>Dosing</u>:
 - MMF: 1 gm BID
 - EC-MPA: 720 mg BID
 - TDM is not routinely recommended
- <u>DDI</u>: divalent/trivalent cation-containing antacids and supplements, cyclosporine
 - MMF only appears to interact with proton pump inhibitors¹

• <u>ADR</u>:

- Myelosuppression
- Gastrointestinal disorders, both upper and lower GI tract
- Associated with significant teratogenic effects

1. Ruppercht K, et al. J Clin Pharmacol 2010;49:1196-201

AZA



- AZA is a prodrug of 6-MP.
- 6-MP is incorporated into DNA where it inhibits purine synthesis and prevents the formation of RNA.
 - Inhibits gene replication and subsequent activation of T-cells.

AZA

- <u>Dosing</u>: 2 5 mg/kg/day to start, titrated to hematological effects (maintenance dose may be between 1 and 3 mg/kg/day).
- DDI: allopurinol, febuxistat
- <u>ADR</u>:
 - Myelosuppression
 - RARE: pancreatitis

mToR Inhibitors: Sirolimus and Everolimus

- Both agents binds to FKBP, but do not inhibit calcineurin phosphatase
- The sirolimus or everolimus/ FKBP complex inhibits mToR, a driver of cell proliferation
 - This inhibition results in a reduction in IL-2 driven lymphocyte proliferation
- Everolimus is a derivative of Sirolimus with slightly different PK parameters.



Understanding the impact of the mToR Inhibitors



mToR Inhibitors: Sirolimus and Everolimus

- <u>Dosing</u>:
 - TDM (C₁₂ levels) is employed to maximize the efficacy of both mToR inhibitors
 - Appropriate levels are dependent on institution-specific protocols and concomitant immunosuppressants
 - Common Doses
 - Sirolimus: 1 2 mg QD
 - Everolimus: 0.75 mg BID
- DDI: both agents are substrates for CYP3A4 and P-gp
- <u>ADR</u>:
 - Cardiovascular (hypercholesterolemia, hypertriglyceridemia)
 - Myelosuppression
 - Dermatologic (rash, mouth ulcers)
 - Musculoskeletal (myalgias, muscle weakness)
 - Interstitial pneumonitis
 - Renal (proteinuria)
 - Hepatotoxicity
 - Decreased wound healing

2005 OPTN/SRTR Annual Report¹



OPTN/SRTR=United States Organ Procurement and Transplantation Network/Scientific Registry of Transplant Recipients

1. In Meier-Kreische HU, et al. Am J Transplant 2006;6:1111-31

Co-Stimulation Blockade: Belatacept

 Belatacept is a fusion protein that acts as a selective T-cell costimulation blocker by binding to CD80/86 receptors on APCs and blocking the required CD28 mediated interaction between APCs and T-cells needed to activate the T-cells.



Co-Stimulation Blockade: Belatacept

- <u>Dosing</u>:
 - Initial Phase: 10 mg/kg/dose on Days 1 (day of transplant, prior to implantation), and 5, then again at Week 2, 4, 8 and 12.
 - Maintenance Phase: 5 mg/kg/dose every 4 weeks (<u>+</u> 3 days) beginning at Week 16
- <u>DDI</u>: none reported
- <u>ADR</u>:
 - BLACK BOX: increased risk for PTLD when given to EBV seronegative recipients
 - Cardiovascular (edema)
 - CNS(fever, HA, insomnia)
 - GI (diarrhea, constipation, nausea, abdominal pain)
 - GU (UTI)
 - Hemataologic (myelosuppression)
 - Musculoskeletal (arthralgias)
 - Respiratory (cough, dyspnea)

Corticosteroids

- The exact MOA is still not fully understood. Some believe... \bullet
 - <u>High dose</u>: > 100 mg of prednisone equivalents.
 MOA = directly toxic to T cells
 - Low dose: \leq 100 mg of prednisone equivalents.
 - nonspecific immunosuppressive agents inhibit IL-1, IL-2, IL-3, IL-6, IL-15, TNF-alpha and INF-gamma at low doses. Decreased activation of T cells.
- What we do know:
 - Blockade of Cytokine Gene Expression
 - T-cell and APC cytokine expression
 - Bind to heat shock protein \rightarrow translocates to nucleus \rightarrow binds to GRE \rightarrow inhibits transcription of cytokine genes \rightarrow inhibition of IL-1, IL-2, IL-3, IL-6, INF- γ , and TNF- α
 - ↓ cytokine-receptor expression
 - Nonspecific Effects
 - Antiinflammatory effects

Corticosteroids

- <u>Dosing</u>: doses vary widely from institution to institution.
 - Highest doses at time of transplant or as treatment of an acute rejection episode.
- <u>DDI</u>: CYP 450 inducer (dexamethasone) and inhibitor (methylprednisolone).

• <u>ADR</u>:

- Cardiovascular (hypertension, hyperlipidemia)
- Endocrine (hyperglycemia)
- CNS (mood changes, anxiety)
- Osteoporosis
- Weight gain
- Edema
- Lipodistrophy

Relative Side-Effect Profile

| | CSA | TAC | mToR | Pred | MPA |
|----------------------|-----|-----|------|------|-----|
| Hypertension | ++ | + | _ | ++ | _ |
| Renal dysfunction | +++ | ++ | + | - | _ |
| Hyperlipidemia | ++ | + | +++ | ++ | — |
| Glucose intolerance | + | ++ | — | ++ | _ |
| Hyperkalemia | +++ | +++ | — | — | — |
| GI side-effects | _ | + | + | + | ++ |
| Tremor | + | ++ | — | — | — |
| Malignancy | + | + | ? | _ | ? |
| Osteoporosis | Ι | — | - | ++ | — |
| Hirsutism | + | | _ | + | _ |
| Gingival hypertrophy | + | _ | _ | _ | _ |
| Alopecia | _ | + | _ | _ | _ |

Treatment of Acute Rejection

- The biggest changes in kidney transplantation since the turn of the 21st century have been in the understanding of acute rejection.
- Historically, antibodies were thought to attack the allograft immediately (hyperacute rejection) or not be particularly important. The long-term emphasis has been on cellular-mediated rejection and its consequences.
- Recent data (and development of new techniques in pathology) have shown that antibody-mediated rejection can play an important role both early and late posttransplant.

Acute Cellular-Mediated Rejection

 Acute cellular rejection is most common during the first 6 months posttransplant

- Becomes substantially less common over time

- The transplant center should be notified immediately if acute cellular rejection is suspected
- Because treatment is associated with significant sideeffects, most suspected acute rejection episodes are biopsied to confirm the diagnosis

Treating Acute Cellular Rejection

| Agent | Dosage |
|---|--|
| Pulse corticosteroids ¹ | Intravenous methylprednisolone 125 mg to 1 g or 3 to 5 mg/kg body weight daily for 3 to 5 days |
| Antithymocyte globulin, rabbit (Thymoglobulin) ² | 1.5 mg/kg in 500 mL of dextrose or saline infused over 4 to 8 hours for 4 to 14 days |

*Initiation of therapy often requires hospitalization.

1. Pescovitz MD, et al. Am J Transplant 2003;3:1581-6.

2. Thymoglobulin prescribing information. rev. April 2002.

Antibody-Mediated Rejection (AMR)

- A significant form of rejection not amenable to standard immunosuppressive therapy aimed at modifying T-cell function
- Acute antibody-mediated rejection tends to be seen early posttransplant
- Diagnosis is made by kidney biopsy and special stains



C4d Staining in Peritubular Capillaries

Terasaki P, Mizutani K. *Clin J Am Soc Nephrol.* 2006;1:400-3. Racusen LC, Haas M. *Clin J Am Soc Nephrol.* 2006;1:415-20.

Treatment of AMR

- Antibody- and cellular-mediated rejection can occur independently or co-exist
- When antibody-mediated rejection is independent, treatment options include:¹⁻³
 - High-dose IVIg
 - Rituximab (Rituxan[®])
 - Bortezomib (Velcade[®])
 - Eculizumab (Soliris[®])
 - Plasmapheresis
 - Plasmapheresis and low-dose IVIg
- When antibody-mediated and cellular-mediated rejection coexist, therapy for each must be utilized

1. Becker YT, et al. Am J Transplant 2004;4:996-1001.

2. Alausa M, et al. *Clin Transplant* 2005;19:137-40.

3. Montgomery R, et al. Am J Transplant 2004;4:1011-2.

Intravenous Immune Globulin

• <u>Indication</u>: treatment of primary immunodeficiency syndrome.

Proposed Mechanisms of Action

Anti-Microbial

Increases antibody levels High-affinity binding; broad neutralization activity

Fc-mediated complement fixation with cell lysis and (C3-b) opsonization

Antibody-dependent cellular cytotoxicity (ADCC)

Synergistic with antibiotics

Immunomodulatory

Neutralizes circulating autoantibodies or superantigens

Blocks Fc receptor-mediated events

Modulates cytokines

Promotes down regulation of antibody

Regulates production of helper or suppressor T-cell cytokines

Anti-Inflammatory

Up regulates an IL-1 receptor agonist on macrophages; in turn down regulates production of inflammatory cytokines (IL-1α, IL-1β, IL-6, TNF-α)

Reduces complementmediated damage

Neutralizes microbial toxins

Contains anti-inflammatory cytokines such as TGF-β

Intravenous Immune Globulin

- <u>Adverse Events</u>: infusion-related reactions (i.e., hypotension, shaking, chills, wheezing, flushing, nausea, anxiety, chest tightness, back pain, hypertension)
 - Patients may require conversion to a different brand of IVIG if they have continued infusion-related reactions after decreasing the rate of administration.
- Renal dysfunction may occur, especially when using IVIG products that contain sucrose. Iso-osmotic and Sucrose-free products are preferred.
- <u>Cost</u>: \$80 / gm
 - 10 gm = \$800.00
 - -2 gm/kg (70 kg patient) = \$11,200.00

Rituximab

- Indication: treatment of
 - B-cell non-Hodgkin's lymphoma
 - CD-20 positive chronic lymphocytic leukemia
 - Moderately to severely-active rheumatoid arthritis
- <u>MOA in Transplantation</u>: chimeric monoclonal anti-CD20 antibody targeting B-cells
 - This directly inhibits B-cell proliferation and induces cellular apoptosis through the binding of complement.
 - Complement, in turn, mediates antibody-dependent cellmediated cytotoxicity and subsequent cell death.

Rituximab

- Adverse Events:
 - BBW: fatal infusion reactions, severe mucocutaneous reactions (including SJS) and PML (also tumor lysis syndrome)
 - Cardiovascular (hypo- and hypertension, peripheral edema)
 - CNS (dizziness)
 - Derm (urticaria)
 - Endocrine (hyperglycemia)

 - GI (diarrhea, vomiting)
 <u>Hematologic (leukopenia, anemia)</u>
 Muscular (back pain, myalgias, arthralgias)
 - Respiratory (bronchospasm, dyspnea, sinúsitis)
 - Misc (rise in LDH)
- <u>Cost</u>: \$6 / mg
 - -375 mg/m^2 (1.73 m²) = \$3,892.50
 - -1000 mg = \$6,000.00

Bortezomib

- Indication: treatment of
 - Multiple myeloma
 - Refractory mantel cell lymphoma
- <u>MOA in Transplantation</u>: a proteasome inhibitor that induces cell-cycle arrest and apoptosis of plasma cells.

Bortezomib

- Adverse Events:
 - Cardiovascular (hypotension, peripheral edema)
 - CNS (fever, HA, insomnia, dizziness)
 - Derm (rash)
 - GI (nausea, vomiting, diarrhea, contipation)
 - Hematologic (leukopenia, anemia)
 - Muscular (weakness, back pain, myalgias)
 - Respiratory (dyspnea)
- <u>Cost</u>: \$370 / mg
 - $-1.3 \text{ mg/m}^2 (1.73 \text{ m}^2) = \832.13
 - One cycle (4 doses) = \$3,328.52

Eculizumab

- <u>Indication</u>: treatment of paroxysmal nocturnal hemoglobinuria to reduce hemolysis
- <u>MOA in Transplantation</u>: a humanized monoclonal antibody against complement protein C5 that inhibits its cleavage to C5a and C5b and preventing the generation of the membrane attack complex (MAC)

Eculizumab

- <u>Adverse Events</u>:
 - CNS (HA, fatigue)
 - GI (nausea, vomiting, diarrhea)
 - Muscular (back pain, arthralgias)
 - Respiratory (nasopharygitis)
- Cost: \$10 / mg
 - -900 mg = \$9,000.00
- Drug is currently classified as an orphan drug and has a REMS protocol requiring prescribing and dispensing restrictions

Risk Evaluation and Mitigation Strategies

- The following agents have an associated REMS:
 - Everolimus
 - Sirolimus
 - Belatacept
 - Eculizumab

Conclusions

Proliferation of new agents (plus improvement in prevention and treatment of infection) has resulted in significantly better short-term outcomes for kidney transplant recipients.

Major focus of current clinical research is improving long-term outcomes, in particular, increasing patient and graft survival, and decreasing morbidity.

Modulating the Immune System in Oncology: The Evolution of Therapy

R. Donald Harvey, Pharm.D., FCCP, BCPS, BCOP Assistant Professor, Hematology/Medical Oncology Director, Phase I Clinical Trials Program



Learning Objectives



- Review the evolving therapies in oncology targeting the immune system.
- Describe how immunomodulatory agents are incorporated either as single agent or in combination with chemotherapy in the treatment of cancer.





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Immunotherapy Approaches

- Active
 - Vaccination
 - Autologous
 - Allogeneic
 - Cytokines
 - Interferon, interleukin-2, GM-CSF, dinileukin diftitox
- Passive
 - Monoclonal antibodies (exception ipilimumab)
- Immunomodulators
 - Thalidomide, lenalidomide



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Monoclonal Antibodies

| MoAb | Indication(s) | Year(s) Approved |
|----------------------|--|---------------------------|
| Rituximab | NHL, CLL | 1997, 2010 |
| Trastuzumab | Breast, gastric cancers | 1998, 2010 |
| Alemtuzumab | CLL | 2001 |
| Ibritumomab tiuxetan | NHL | 2002 |
| Tositumomab | NHL | 2003 |
| Cetuximab | Colorectal, head/neck cancers | 2004, 2006 |
| Bevacizumab | Colorectal, NSCLC, GBM, renal cell | 2004, 2006, 2009, 2009 |
| Panitumumab | Colorectal cancer | 2006 |
| Ofatumumab | CLL | 2009 |
| Denosumab | Bone metastases from solid tumors | 2010 |
| Ipilimumab | Melanoma | 2011 |
| Brentuximab vedotin | CD30 + lymphomas (Hodgkin, anaplastic large cell) | 2011 |



Ipilimumab



Mechanism of Action



Ipilimumab (MDX-010)

- Fully human IgG1 monoclonal antibody to human cytotoxic T lymphocyte antigen 4 (CTLA-4)
 - Blocks binding of CTLA-4 to ligands CD80 and CD86 (B 7 family)
- Population unresectable or metastatic melanoma
- Approved regimen = 3 mg/kg IV over 90 minutes
 Q3 weeks x 4 doses

Phase III Trial of Ipilimumab Plus gp100 Vaccine Versus gp100 Vaccine Versus Ipilimumab as Secondline Therapy in Advanced Melanoma: Treatment Scheme





Primary endpoint: best ORR (original), changed to OS before unblinding/analysis Secondary endpoints include: best ORR, duration of response, PFS, TTP

Hodi FS et al. N Engl J Med 2010;363:711-723

Phase III Trial of Ipilimumab Plus gp100 Vaccine Versus gp100 Vaccine Versus Ipilimumab as Second-line Therapy in Advanced Melanoma: Efficacy



| | lpilimumab/ gp100 (Arm A) (n = 403) | Ipilimumab/ Placebo (Arm B) (n = 137) | gp100/ Placebo (Arm C) (n = 136) | Arm A vs. Arm C | Arm B vs. Arm C | Arm A vs. Arm B |
|-------------------------------|--|--|---|---|---|---|
| Best Overall Response Rate | 6% | 11% | 1.5% | <i>P</i> = .0433 | <i>P</i> = .0012 | <i>P</i> = .0402 |
| Disease Control Rate | 20% | 28.5% | 11% | <i>P</i> = .0179 | <i>P</i> = .0002 | <i>P</i> = .0429 |
| Median Overall Survival | 10.0 months | 10.1 months | 6.4 months | HR 0.68 (95% Cl, 0.55-0.85) <i>P</i> = .0004 | HR 0.66 (95% CI, 0.51-0.87) <i>P</i> = .0026 | HR 1.04 (95% Cl, 0.83-1.30) <i>P</i> = .7575 |
| Survival Rate | | | | | | |
| 1 year | 44% | 46% | 25% | NR | NR | NR |
| 2 years | 22% | 24% | 14% | NR | NR | NR |

Hodi FS et al. N Engl J Med 2010;363:711-723

Phase III Trial of Ipilimumab Plus gp100 Vaccine Versus gp100 Vaccine Versus Ipilimumab as Second-line Therapy in Advanced Melanoma: Adverse Events



| Adverse Events | lpilimumab/gp100 (n = 380) | lpilimumab/Placebo (n = 131) | gp100/Placebo (n = 132) |
|--------------------------------|-------------------------------|---------------------------------|----------------------------|
| Treatment Related | | | |
| All grades | 89% | 80% | 79% |
| Grade 3/4 | 17% | 23% | 11% |
| Deaths | 2% | 3% | 1.5% |
| Immune Related (All Grades) | | | |
| Dermatologic | 40% | 43.5% | 17% |
| Gastrointestinal | 32% | 29% | 14% |
| Endocrine | 4% | 8% | 1.5% |
| Hepatic | 2% | 4% | 4.5% |

Hodi FS et al. N Engl J Med 2010;363:711-723

lpilimumab (MDX-010)

- Immune-mediated adverse events across trials
 - T cell activation and proliferation leading to enterocolitis (7%), hepatitis (1%), dermatitis (2%), neuropathy (1%), endocrinopathy (hypopituitarism - 4%)
- Monitor LFTs, thyroid function, chemistries before each dose
- Generally appear during induction
- Prednisone 0.5-2 mg/kg/day

Brentuximab vedotin



Mechanism of Action





Multicenter, Open-Label Study of Brentuximab Vedotin in Relapsed/Refractory HL

Eligibility

- Relapsed or refractory CD30+ HL
- Age ≥12 years
- Measurable disease ≥1.5 cm
- ECOG 0-1
- Prior ASCT

Treatment (N=102)

- Brentuximab vedotin
 1.8 mg/kg IV every
 21 days
- Administered outpatient over 30 min
- Max 16 cycles for SD or better
- Restage* at Cycles
 2, 4, 7, 10, 13, 16

Follow-up

Every 12 weeks

* Revised Response Criteria for Malignant Lymphoma (Cheson, 2007)

| Demographics and Bacharacteristics | aseline |
|-------------------------------------|---------|
| | N=10 |
| Age* (years) | 31 (15- |
| Gender (M / F) | 48 / 54 |
| ECOG status (0 / 1) | 42 / 60 |
| Refractory to frontline therapy | 72 (71 |
| Refractory to most recent treatment | 43 (42) |
| Prior chemotherapy regimens* | 3.5 (1– |
| Relapse ≤1 year post ASCT | 72 (71 |
| | |

Time from ASCT to first post transplant relapse*

* Median (range)

N=102 31 (15–77) 48 / 54 42 / 60 72 (71%) 43 (42%) 3.5 (1–13) 72 (71%) 6.7 mo (0–131)

Maximum Tumor Reduction





Adverse Events in ≥20% of Patients



| Preferred Term | All Grades | Grade 3 | Grade 4 |
|-----------------------------------|------------|---------|---------|
| Peripheral sensory neuropathy | 47% | 9% | — |
| Fatigue | 46% | 2% | — |
| Nausea | 42% | — | — |
| Upper respiratory tract infection | 37% | — | — |
| Diarrhea | 36% | 1% | — |
| Pyrexia | 29% | 2% | — |
| Neutropenia | 22% | 14% | 6% |
| Vomiting | 22% | — | — |
| Cough | 21% | _ | _ |

Other Grade 3/4 events in ≥5% of patients: thrombocytopenia (8%) and anemia (6%)



Resolution of Peripheral

Neuropathy

Managed with dose delays and/or reductions to 1.2 mg/kg

- Resolution or some improvement of PN = 80% (45/56)
- Complete resolution of all events of PN = 50% (28/56)
- Median time to resolution or improvement = 13.2 weeks

Sipuleucel-T





Artwork originally created for the National Cancer Institute. Reprinted with permission of the artist, Jeanne Kelly. Copyright 2011.

Sipuleucel-T



- Autologous active cellular immunotherapy product that activates the immune system against prostate cancer
- FDA approval August 2010 for asymptomatic or minimally symptomatic metastatic castrate resistant (hormone refractory) disease.
- Contains a minimum of 50 million autologous CD54+ cells activated with prostatic acid phosphatase (PAP)-GM-CSF

Sipuleucel-T

1. Leukapheresis

~ 40 hours



Dendritic cell Artwork originally created for the National Cancer Institute. Reprinted with permission of the artist, Jeanne Kelly. Copyright 2011.



Primary endpoint: Secondary endpoint: Overall Survival Time to Objective Disease Progression

IMPACT Overall Survival



Schellhammer, Higano, Berger et al, AUA Annual Meeting 2009.

Administration and Monitoring

- Premedication with diphenhydramine and acetaminophen 30 minutes prior
- One hour infusion with no cellular filter
- Adverse events
 - Serious
 - Acute infusion reactions
 - Frequency <u>></u> 15%
 - Chills, fatigue, fever, back pain, nausea, joint aches, headache
 - Typically resolve within 2 days

Conclusions



- Manipulation of the immune system for anticancer treatment has evolved substantially since interleukin-2 was approved in 1992
- Understanding complex immune responses and improvements in bioengineering have and will lead to better therapies
- Real and potential future issues in the field include the uptake of biosimilars, overall healthcare cost and cost-effectiveness, and gene therapy translation to the clinic