Cancer Immunotherapy: Promises and Challenges

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Disclosures

Consulting: Celldex, Nektar, Nanostring, Endopredict

Research: IRX Therapeutics, Merck, BMS, Medimmune
LONG-TERM SPONTANEOUS REGRESSION OF MALIGNANT MELANOMA WITH VISCERAL METASTASES

Report of a Case with Immunologic Profile

GREGORY B. BULKLEY, MD, Max H. COHEN, MD, PHD, Peter M. BANKS, MD,Devron H. CHIAR, MD, and Alfred S. KETCHAM, MD

A case of a 58-year-old woman with viscerally metastatic malignant melanoma is presented 12 years after spontaneous and complete regression of disease. Diagnosis of primary and metastatic lesions was confirmed by review of tissue sections. The presence and subsequent absence of visceral metastases were documented by open liver biopsies. Sections of metastatic lesions revealed extensive necrosis of tumor and infiltration by lymphocytes and plasma cells. Skin testing showed a strongly positive delayed hypersensitivity response to dinitro-
The Immune System to treat cancer?

Stage I-III Triple Negative Breast Cancers

0% Lymphocytes  50% Lymphocytes
70% 5-yr Survival  90% 5-yr Survival

Adams S, et al, JCO 2014
Agenda

• FDA approved immunotherapies & how they work
  • Toxicity management of immunotherapy
    • Future directions

Selected Immunotherapy Approvals

- IL-2
- Sipuleucel-T
- Blinatumomab
- T-VEC
- CAR T-cell


- Trastuzumab
- Ipilimumab
- Nivolumab
- Ipi+Nivo

“Immune checkpoint antibodies”
### Classes of Immunotherapy: Antibody Therapy

**Example: Trastuzumab**

- **Metastatic**
  - Increase median survival from 20.3 mo to 25.1 mo

- **Early Stage**
  - Reduce recurrence rate by 36%

*Hudis C, et al, NEJM 2007*

### ADCC

<table>
<thead>
<tr>
<th>Antibodies bind antigens on the surface of target cells</th>
<th>NK cell CD16 Fc receptors recognise cell-bound antibodies</th>
<th>Cross-linking of CD16 triggers degranulation into a lytic synapse</th>
<th>Tumour cells die by apoptosis</th>
</tr>
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<tbody>
<tr>
<td>Rituximab</td>
<td>Daratumumab</td>
<td>Cetuximab</td>
<td></td>
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*Wikipedia, ADCC, accessed 5/29/2017*
Classes of Immunotherapy: Cytokine therapy

Example: high dose IL-2 \rightarrow “go for the gold”

- IV high dose cytokines in 5d. Cycles, up-titrated to toxicity
- Complete response rate: 5%; partial response rate: 10%

\[ \text{Atkins MB, et al, JCO 1999; Alva A, Cancer Immunol Immunother 2016} \]

Th1 versus Th2 T-cell responses

\[ \text{Bailey SR, Front Immunol 2014} \]
Classes of Immunotherapy: Vaccine Therapy

Vaccine = exogenous tumor antigen

- Peptide / carbohydrate
- DNA/RNA, vector
- Cellular

Example: Sipuleucel-T

- Metastatic Prostate Cancer
- Survival: 25.8 v. 21.7mo
- No change in tumor growth
- $100k = 259k/life year?


Antigen Presentation

Classes of Immunotherapy: Antibody conjugates

Example: Blinatumumab

- ALL (B-cell leukemia)
- Survival 7.7mo, v 4.0mo for chemotherapy
- May also eradicate minimal residual disease

Kantarjian H, et al. NEJM 2017

Genetic Engineering of Antibodies

Bispecific antibody
BITE “Bispecific T-cell engager”
Blinatumumab

Antibody drug conjugate
T-DM-1 = trastuzumab + chemo

Classes of Immunotherapy: Immune Checkpoint Antibodies

Classes of Immunotherapy: Immune Checkpoint Antibodies

- MSI-High Colorectal
- Melanoma
- NSCLC
- RCC
- Bladder Ca
- Hodgkin’s Lymphoma
- Merkel’s Cell
- HEENT Ca
Classes of Immunotherapy: Oncolytic Viruses

- Viral vector (HSV1)
- Replicate and lyse injected tumor
- Manipulate genome to enhance effect: - suppressive genes; + GM-CSF

**Example: T-VEC**
- Metastatic Melanoma
- Survival: 23.3 v. 18.9mo
- Responses in injected, non-injected, and viscera


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**CAR T-cell Therapy: Tisagenlecleucel**

Maude S, et al. NEJM 2014
Adoptive T-cell therapy

1. Tumor sample
2. DNA sequencing
3. Identify somatic mutations
4. Isolate and grow T-cells that react to mutation
5. Re-infuse into patient

Tran E et al, Nature Immunology 2017; Tran E et al, NEJM 2017

Agenda

Types of immune-related toxicity & Management

An Anecdote: Patient AR
Immune related toxicities: what

- Hypophysitis
- Thyroiditis
- Adrenal Insufficiency
- Enterocolitis
- Dermatitis
- Pneumonitis
- Hepatitis
- Pancreatitis
- Neuropathy
- Arthritis

• Any organ!
• Distinct mechanism of action
• May be exacerbated by underlying autoimmune conditions/presence of autoantibodies

Boutros et al, Nat Rev Oncol 2016
Immune related toxicities: what

Boutros et al, Nat Rev Oncol 2016

Immune related toxicities: when?

Weber et al, JCO 2012; Antonia et al, ESMO 2015
Immune related toxicities: general management

Principles for the generalist

1) Always suspect immune-related toxicity
2) Rule out common causes
3) Seek confirmatory diagnosis
4) Grade toxicity and utilize algorithms
5) Oncology consult → clinical trials implications

<table>
<thead>
<tr>
<th>Grade 1:</th>
<th>Grade 2:</th>
<th>Grade 3-4:</th>
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<tbody>
<tr>
<td>- Supportive care</td>
<td>- Withhold drug.</td>
<td>- Discontinue drug.</td>
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<tr>
<td>- Consider drug withhold</td>
<td>- Low-dose corticosteroids (prednisone 0.5-1mg/kg/day or equivalent).</td>
<td>- High-dose corticosteroids (prednisone 1-2mg/kg/day or equivalent) tapered over ≥ 1 month once toxicity resolves to ≤ Grade 1.</td>
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Immune related toxicities: colitis

Diagnostic Workup
- Rule out alternative diagnosis: C. difficile, other GI infections
- Distinguish between diarrhea and colitis
- Consider invasive testing with colonoscopy

Management
- Low threshold for starting corticosteroids
- No benefit for corticosteroid pre-treatment (budesonide)
- Colitis that is slow to improve/refractory to steroids: treat with anti-TNF
- Infliximab 5mg once or twice every 14 days
Toxicities: Pneumonitis

COP-like

Interstitial

Hypersensitivity

GGO
Toxicities: Pneumonitis

Naidoo et al, JCO 2016

Pneumonitis Management Algorithm

1. Asymptomatic, Radiologic changes only
   - Grade
   - Investigations: Radiologic imaging (High resolution CT chest)
   - Management: Continue immunotherapy
   - Follow-up: Repeat CT every cycle

2. Mild/moderate new symptoms
   - Grade
   - Investigations: Microbial assessment where necessary
   - Management: Withhold immunotherapy
   - Follow-up: If improves to ≤Grade 1 within 3 days of supportive care, resume immunotherapy at next dose

3-4. Severe/life-threatening new symptoms or worsening hypoxia
   - Grade
   - Investigations: Consider Pulmonary/Infectious Diseases Consults and Bronchoscopy
   - Management: Discontinue immunotherapy
   - Follow-up: If worsens in 48 hours consider additional immunosuppression (infliximab, cyclophosphamide, mycophenolate mofetil)

Naidoo et al, JCO 2016
Profound Fatigue

Think endocrine!

Pituitary
Hypophysitis

Thyroid
Thyroiditis

Adrenal
Insufficiency

Consider MRI pituitary protocol
TSH, FT4 +/- T3
Cortisol, ACTH Stim

***Check serially!

Treatment:
Hormone Replacement
Endocrinology Consultation

Profound Fatigue

Think endocrine!

Pituitary
Hypophysitis

Thyroid
Thyroiditis

Adrenal
Insufficiency

Consider MRI pituitary protocol
Serial TSH, FT4 +/- T3
Cortisol, ACTH Stim

***Check serially!
Toxicities: Rash

- Maculopapular
- Papulopustular
- Sweet's syndrome
- Bullous Pemphigoid
- Lichenoid Dermatitis

All of the above!
Toxicities: Rash

**20-40% Patients with anti-PD-1**

Rarely serious, <5% Tx d/c rate

**Management:**

- Mild, <10% BSA: topical steroid
- 10-30% BSA: oral steroid, hold Tx
- >30% BSA or severe → derm consult

Antibody mediated (against BP180)
Also found on melanomas

Toxicities: Immune Related Hepatitis

**Presentation**

- Mainly asymptomatic elevations in AST/ALT
- 10% with anti-CTLA4 mAb
- <5% with anti-PD-1/PD-L1 mAb
- Grade 3+ events: 1-2%
- Increased toxicity with combinations (vemurafenib)

**Management**

- Minimize alcohol intake
- Oral steroid taper of at least 3 weeks
- *No infliximab* (FDA Blackbox warning)
- Mycophenolate 500mg-1000mg bid
Can you treat a patient with prior autoimmune conditions?

Yes!

Anti-PD-1 JHU cohort:
52 patients with previous autoimmune disease
• 38% had mild flare of prior condition;
• 4% required discontinuation;
• 29% developed other irAEs, 8% requiring discontinuation
Agenda

Immune related response criteria & implications

Nishino M et al, Nature Reviews Clin Oncology 2017

Agenda: Future Directions

IL-2 + SBRT  Anti-OX40
Pegylated IL-2  Anti-PD-1 + Chemotherapy
Intramammary IRX  Anti-TGFb+
                  Radiotherapy
Thank you!