Cancer Immunotherapy as a Conventional Modality: The Need for Physician and Nursing Education

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IOM Workshop 1 March 2016
INTRODUCING THE LATEST BREAKTHROUGH IN CANCER THERAPY. YOU.

Everyone is born with a defense system against cancer. We’re turning melanoma patients into stronger cancer fighters by harnessing the power of their immune systems with a drug pioneered at Memorial Sloan Kettering. By turning the concept of targeted immunotherapy into a reality for our patients, we’re changing the way the world treats cancer. Learn more at MSKCC.ORG/MORESCIENCE

MORE SCIENCE. LESS FEAR.

Memorial Sloan Kettering Cancer Center
In-network with most health plans. Ask about financial aid.
Outline

- Background (melanoma data)
- Unique toxicities: how to manage?
- Unique response patterns: irRC
- The future: multiple stakeholders have launched helpful efforts
Ipilimumab Augments T-Cell Activation and Proliferation

Adapted from O'Day et al. Plenary session presentation, abstract #4, ASCO 2010.
‘Driving’ An Immune Response

T-cell receptor: Antigen-MHC

CD28: B7

CTLA-4: B7

Vaccine?
Ipilimumab: Unique ‘Immune-Related’ Adverse Events

- Rash (approx 20%)
- Colitis/enteritis (approx 15%)
- Elevated AST/ALT (approx 10%)
- Endocrinopathies: Thyroiditis, Hypophysitis, Adrenal insufficiency (2-5%).

Severity is inversely related to vigilance of surveillance. If detected early, most are easily treated and reversible.

Toxicities are more successfully managed mechanistically, rather than solely symptomatically.
Time Courses are Helpful

Figure 3 Average time to onset of adverse events associated with ipilimumab. Kinetics of appearance of immune-related adverse events by organ class over time. Note: Reprinted with permission. © 2012 American Society of Clinical Oncology. All rights reserved. Weber JS, Kähler KC, Hauschild A. Management of immune-related adverse events and kinetics of response with ipilimumab. J Clin Oncol. 2012;30(21):2691–2697.
Anti-CTLA-4 Induces Regression of Transplantable Colon Carcinoma

Leach DR et al., Science, 1996
Ipilimumab Pattern of Response: Responses After the Appearance and Subsequent Disappearance of New Lesions

Pre-treatment

July 2006

Week 12: Progression

3 mg/kg ipilimumab Q3W X 4

New lesions

Week 20: Regression

Week 36: Still Regressing

Source: 2008 ASCO Abstract #3020 Wolchok.
Unique Kinetics of Response in Patients Treated With Ipilimumab

Images courtesy of Jedd D. Wolchok, MD.
Four Patterns of Response to Ipilimumab Therapy Observed

• 2 conventional:
  -- Response in baseline lesions
  -- ‘Stable disease’ with slow, steady decline in total tumor volume

• 2 novel:
  -- Response after initial increase in total tumor volume
  -- Response in index plus new lesions at or after the appearance of new lesions
CA184-007 Trial: 4 Patterns of Response Observed

- **Response in Baseline Lesions**
  - PD
  - PR
  - CR
  - 3 mos

- **Response in Total Tumor Burden in the Presence of New Lesions**
  - 1.4 yrs
  - 9 mos

- **Slow, Steady Decline in Total Tumor Burden**
  - 6 mos

- **Response After Initial Increase in Total Tumor Burden**
  - 8 mos
  - 5 mos

SPD = sum of the product of the perpendicular diameters (measure of tumor volume).
Reproduced with permission from Weber. ASCO. 2008 (abstr 9010).
Proportion of Response to Ipilimumab

Patients randomized to 10 mg/kg ipilimumab monotherapy: CA184-008 and -022
n = 227

- mWHO PD at Week 12
  n = 123
  Followed beyond mWHO PD
  n = 57

- mWHO Disease control in baseline lesions
  n = 63

- mWHO SD in baseline lesions
  n = 45
  25 ongoing

- mWHO PD
  n = 123

- Unknown (No follow-up scan)
  n = 41

- Response in baseline lesions
  n = 18 *
  12 ongoing *
  1 response with intermittent progression

- “Stable disease” with a slow, steady decline in total tumor volume
  n = 8 **
  6 ongoing
  1 decline with intermittent progression

- Response of index plus new lesions after the appearance of new lesions
  n = 3
  1 ongoing

- Response after initial increase in total tumor volume
  n = 1
  ongoing

- “Stable disease” with a slow, steady decline in total tumor volume
  n = 18
  15 ongoing
  1 decline with intermittent progression

14 patients with evidence of clinical activity
(13 after mWHO PD + 1 w/o follow-up beyond mWHO PD)

* Including 1 patient with confirmation of response in roll-over study CA184-025
** 2 of these patients demonstrated SD compared to baseline after initial increase in total tumor volume (both ongoing). One of these had 24% reduction from peak and 2% increase from baseline at the last evaluable tumor assessment.

Ongoing = response or SD ongoing at the last evaluable tumor assessment (prior to alternate non-ipilimumab therapy) unless patient died.
Slow steady decline is defined as a ≥ 25% reduction from baseline in total tumor volume at the last evaluable tumor assessment, unless otherwise noted.
irRC Identifies Survivors in Patients with Progressive Disease by mWHO

Pooled data from phase II studies CA184-008 and CA184-022: ipilimumab monotherapy 10 mg/kg (N=227)

Wolchok et al, Clin Cancer Res, 2009
Role of PD-1 Pathway in Suppressing Anti-tumor Immunity

Recognition of tumor by T cell through MHC/antigen interaction mediates IFNγ release and PD-L1/2 up-regulation on tumor

Priming and activation of T cells through MHC/antigen & CD28/B7 interactions with antigen-presenting cells

Tumor cell

Dendritic cell

Nivolumab
PD-1 Receptor Blocking Ab

IFNγR

IFNγ

MHC

T-cell receptor

PD-L1

PD-L2

PD-1

PD-L1

PD-L2

PD-1

T cell

Shp-2

NFκB

Other

PI3K

CD28

B7

MHC

Nivolumab PD-1 Receptor Blocking Ab

ASCO 2013
Changes in Tumor Burden in Patients with Melanoma Receiving Nivolumab 3 mg/kg

All Mel patients treated with 3 mg/kg nivolumab

Vertical line at 96 weeks = maximum duration of continuous nivolumab therapy
Horizontal line at −30% = threshold for defining objective response (partial tumor regression) in absence of new lesions or non-target disease according to RECIST

Unconventional response = response patterns that did not meet RECIST criteria (e.g., persistent reduction in target lesions in the presence of new lesions, or regression following initial progression)
Atypical Patterns of Response in Patients With Metastatic Melanoma Treated With Pembrolizumab in KEYNOTE-001

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Patient With Melanoma Treated in KEYNOTE-001

Baseline  Week 12  Week 24  Week 52

Case courtesy of C. Robert, Gustave Roussy, Villejuif, France.
Patient With Melanoma Treated In KEYNOTE-001

Baseline
- SLD increased 17%
- SD by RECIST v1.1
- SPD increased 56%
- PD by irRC

Week 4
- SLD decreased 55%
- PR by RECIST v1.1
- SPD decreased 85%
- PR by irRC

Week 16
- SLD decreased 55%
- PR by RECIST v1.1
- SPD decreased 86%
- PR by irRC

Week 24
- SLD decreased 55%
- PR by RECIST v1.1
- SPD decreased 86%
- PR by irRC

Week 60
- SLD decreased 49%
- PR by RECIST v1.1
- SPD decreased 85%
- PR by irRC

SLD, sum of the longest diameters.
SPD, sum of the longest diameter x perpendicular diameters.
Patient With NSCLC Treated in KEYNOTE-001

- **Baseline**
  - SLD increased 3.1%
  - SD by RECIST v1.1
  - SPD increased 38%
  - PD by irRC

- **Week 9**
  - SLD increased 3.1%
  - SD by RECIST v1.1
  - SPD increased 38%
  - PD by irRC

- **Week 18**
  - SLD decreased 34%
  - PR by RECIST v1.1
  - SPD decreased 63%
  - PR by irRC

- **Week 27**
  - SLD decreased 47%
  - PR by RECIST v1.1
  - SPD decreased 64%
  - PR by irRC

SLD, sum of the longest diameters.
SPD, sum of the longest diameter x perpendicular diameters.
Long-Term Follow-Up of Early Pseudoprogressors

*At week 108, tumor burden was 541%.
Analysis cutoff: October 2014
Examples of Delayed Pseudoprogression

Overall, 4 of 327 patients followed by imaging for ≥28 weeks met the criteria applied for delayed pseudopropgression.

Analysis cutoff: October 2014
Association of Overall Survival With Tumor Response (n = 594)

Analysis cutoff: October 2014
Rationale for broad-based education efforts

• Need to ensure rapid adverse event reporting for effective management

• The concept of pseudo-progression and subsequent treatment beyond progression is not yet conventional in oncologic therapy
SITC Physician & Clinical Team Education

The Need for Clinical Education

29% of participants at SITC’s regional clinical programs (ACIs) reported no previous immunotherapy education prior to attending. An additional 35% identified CME/CE Activities as their only source for previous immunotherapy education.

SITC’s Response to the Need for Clinical Education

1) SITC’s Advances in Cancer Immunotherapy (ACI) Cancer Immunotherapy 101 Series*
   - 24 CME/CE programs held in regional U.S. locations since 2013 with an additional 10 scheduled for 2016
   - 73% increase in average attendance, reaching over 3,000 total attendees (17,330 total live credit hours)
   - 36% increase in understanding to implement cancer immunotherapy in clinical practice as result of programs

2) Annual Conferences & Collaborative Live Education**
   - SITC’s Annual Meeting & Associated Programs provide CME/CE options to over 2,400 annual attendees
   - SITC Sessions and jointly-developed programming at dozens of clinical conferences
   - Collaborative international and domestic meetings, reaching clinicians worldwide
3) **Online CME & Mobile Education Game**
   - Over 48,000 learners on SITC-Medscape Immuno-Oncology Portal of 30 activities*
   - Over 700 physicians competing in biweekly jeopardy-style questions on the basics of cancer immunotherapy through a mobile device gaming app, HealthQuest in Immuno-Oncology

4) **Lung Video**
   - Whiteboard animated video with more than 18,500 views since 2014 launch – being expanded in 2016 to include additional education for physicians and nurses to encourage shared decision-making with patients

5) **Resource Guides & Guidelines**
   - SITC Cancer Immunotherapy Guidelines for Melanoma in the 89 percentile (ranked 5th) of the 40 tracked articles of a similar age in *Nature Reviews Clinical Oncology*; revision underway in 2016**
   - 125,000 Cancer Immunotherapy Patient Guides run; being expanded to physicians in 2016
ASCO: I-O Background

• Cancer Immunotherapy is *Science* “Breakthrough of the Year” 2013
• Represents “radical departure” from existing treatment approach
• Plethora of new agents approved and in clinical trials
• “Flood of Information”
ASCO Education Programs

• Integration of immuno-oncology into ongoing education
• ASCO University Course
• Collaborative sessions at ASCO and SITC Annual Meetings
• New ASCO-SITC Clinical Immuno-Oncology Symposium
ASCO University Course

• Cancer Immunobiology
• Classes of Immune Agents
• Potential Predictive Biomarkers
• Clinical Activity
• Response Determination
• Management of Immune-related Adverse Events
Collaborative Sessions: ASCO & SITC

• Hot Topic Session on Value
  – 2015 SITC Annual Meeting

• How to Integrate Tumor Immunotherapy into Your Clinical Practice
  – 2016 ASCO Annual Meeting

• Value Summit
  – 2016 SITC Annual Meeting
  – Program in development
ASCO-SITC Clinical Immuno-Oncology Symposium

- Education and abstract based sessions
- Poster and networking sessions
- Joint planning by ASCO and SITC
- Inaugural meeting February 24-26, 2017
- Orlando, Florida
These treatments are likely to become important treatments for patients with many different kinds of cancer.

—Michael A. Postow, M.D.
Memorial Sloan Kettering Cancer Center
25,000 emails sent to members of the Oncology Nursing Society

- Immunotherapy Clinical Trials: What Patients Need to Know
- Side Effects of Immunotherapy
- Myths About Clinical Trials
- Finding a Clinical Trial That’s Right for Your Patient
Online Resources for Patients, Caregivers, and HCPs

TheAnswerToCancer.org features:

• Immunotherapy Clinical Trial Finder
• Indication-Specific Immunotherapy Information
• Patient Stories
• ImmunoGlossary
• Downloadable Content

~1,600 registered community members

~400 registered HCPs
I-O Policy Working Group

PWG Charge: Led by Friends of Cancer Research, Pfizer & EMD Serono, identify challenges and opportunities in science, regulation, care delivery, education, training & patient access, and prioritize policies to facilitate development & implementation of I-O therapies

Stakeholder Participants: Industry, academia, insurers, advocacy organizations, government, policy makers, patient support networks, research foundations, healthcare networks, and professional societies

Outcome: Group met (December 2015) to develop recommendations to advance the I-O community, including:

- **FDA Oncology Review Activities**: Centralize evaluation of cancer drugs, biologics, and devices to streamline review and approval of complex product combinations

- **Patient Data Collection**: Utilize PROs and learn from broader patient populations through expansion of clinical trial eligibility criteria and collection of post-market data

- **Endpoints for Immuno-Oncology**: Align with current efforts to facilitate development of endpoints that reflect the biology of I-O agents, including standardizing collection of relevant patient data in order to facilitate evaluation of alternative endpoints

- **Immuno-Oncology Education Initiative**: Develop standards to educate the full-spectrum of care-providers and patients on complexities of I-O treatment delivery and unique patterns of response