Metastatic Melanoma

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Grand Rounds
Case Presentation

- 77 year old male with previous history of scalp melanoma and thyroid carcinoma was referred to outpatient thoracic surgery for workup of newly diagnosed pulmonary nodules that were PET-avid.
  - PMHx: hypertension, hyperlipidemia
  - PSHx: Appendectomy, Excision of scalp melanoma with resection of left parotid gland and left cervical lymph nodes, Thyroidectomy
  - Diagnosed with brain metastases 1 year prior. Undergone brain radiation.

- Physical Exam
  - Elderly appearing man in no acute distress
  - Breath sounds clear bilaterally
  - Abdomen soft, NTND
  - Surgical scars consistent with above surgical history
  - No skin lesions or masses
Case Presentation

- Patient underwent left VATS lung biopsy
- Intraoperative findings
  - Multiple black disseminated lung masses varying in size in left upper and lower lobe.
  - Wedge biopsy obtained from left upper lobe.
  - 32F straight chest tube left in place
- POD0: Foley placed for urinary retention and patient found to have hematuria. Urology consultation placed and CTAP obtained per recommendations. Incidental PE identified in right lower lobe. IVC filter inserted.
- POD1: Chest tube discontinued. Patient discharged home.
- Pathology:
  - Metastatic malignant melanoma (1.2 x 1 x 0.8 cm)
  - BRAF positive, KIT negative
Questions?
Presentation Outline

- Epidemiology
- Diagnosis and Workup
- Systemic Therapies
- Indications for Radiation Therapy
- Clinical Trials
Melanoma

• Develops from melanocytes at epidermal-dermal junction

• In the United States in 2016:
  ▫ 76,380 patients will be diagnosed with melanoma
  ▫ 10,130 patients will die from melanoma

• The majority of patients present with localized disease / stage I-II
  ▫ 4% of patients present with distant metastatic disease
ABCDEs of Melanoma

A: Asymmetry
B: Border
C: Color
D: Diameter
E: Evolution

“ABCDEs of Melanoma: A Guide to Spotting Melanoma” Melanoma Research Foundation
Risk Factors

- Male
- Age > 60
- Fitzpatrick skin type I

History of:
- Multiple sunburns
- Tanning bed use
- Residence near equator / sun exposure
- Precancerous/Cancerous skin lesions
- Immunosuppression
- Xeroderma pigmentosum
- Dysplastic nevus syndrome (B-K mole syndrome)
- Family history
Subtypes of Melanoma

- Superficial spreading
- Nodular
- Lentigo maligna
- Acral lentiginous
- Mucosal
**Molecular Biology**

- **KIT**
  - Activating mutation
  - Receptor tyrosine kinase

- **BRAF**
  - Activating mutation
  - Intracellular signaling kinase in MAPK pathway
Biopsy

• Excisional biopsy is preferred
  ▫ **Margin 1-3 mm**
  ▫ Plan for definitive wide excision following pathological confirmation
  ▫ Longitudinal orientation in extremities parallel to lymphatics

• Full thickness incisional / punch biopsy is acceptable in specific scenarios
  ▫ Palm, sole, digit, face, ear
  ▫ Very large lesions
What should the pathology report mention?

- Breslow thickness
- Ulceration status
- Mitotic rate (#/mm²)
- Margin status
  - Deep
  - Peripheral
- Presence/absence of microsatellites
- Presence/absence of pure desmoplasia
Clark Levels

Prognostic Factors

1. Breslow tumor thickness
2. Presence of ulceration
3. Mitotic rates

*Elevated lactate dehydrogenase (LDH) is usually associated with worse prognosis
Metastatic Melanoma

- Most common sites of distant metastases are lung and liver.
- Other sites include:
  - Brain
  - Gastrointestinal tract
  - Distant skin and subcutaneous tissue
**WORKUP**

- Distant metastatic disease
  - FNA, core, incisional, or excisional biopsy as clinically indicated
  - LDH
  - Imaging for baseline staging and to evaluate specific signs and symptoms

**TREATMENT OF METASTATIC DISEASE**

- No evidence of disease
  - Resect
  - Residual disease → Treat as disseminated pathway (below)

- Clinical trial or Observation

- Limited (Resectable)
  - Observe or Systemic therapy
    - Imaging to assess response or progression
    - Negative for other disease
      - Resect
    - Positive for other disease
      - Residual disease → Treat as disseminated pathway (below)

- No evidence of disease → Resect

- Disseminated (Unresectable)
  - Without brain metastases
    - Consider primary RT or palliative resection ± adjuvant RT for brain metastases
  - With brain metastases
    - Options include:
      - Clinical trial
      - Systemic therapy
      - Intrallesional injection with T-VEC
      - Consider palliative resection and/or RT for symptomatic extracranial disease
      - Best supportive/palliative care
Systemic Therapies

- Checkpoint immunotherapy
- BRAF-targeted therapy
- Others:
  - Tyrosine kinase inhibitor (Imantinib)
  - High dose IL-2
  - Cytotoxic Therapy
  - Biochemotherapy
Checkpoint Immunotherapy

- Augment the immune system response
- Increase activation of T helper cells by targeting immunomodulators
  - CTLA-4 (cytotoxic T lymphocyte antigen)
  - PD-1 (programmed cell death protein)
- Antibodies targeted to immunomodulators
  - Ipilimumab (anti-CTLA-4)
  - Nivolumab (anti-PD-1)
  - Pembrolizumab (anti-PD-1)
Systemic Therapies

• Checkpoint immunotherapy
• BRAF-targeted therapy
• Others:
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  ▫ High dose IL-2
  ▫ Cytotoxic Therapy
  ▫ Biochemotherapy
Molecular Biology
BRAF-Targeted Therapies

- BRAF-activating mutations usually occur at residue V600
- BRAF-inhibitors
  - Dabrafenib
  - Vemurafenib
- MEK inhibitors
  - Trametinib
  - Cobimetinib
- BRAF/MEK inhibitor combination therapy
  - Dabrafenib + trametinib
  - Vemurafenib + cobimetinib
Systemic Therapies

- Checkpoint immunotherapy
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Tyrosine kinase inhibitor

- Imatinib
- For melanoma with cKIT mutations
High Dose Interleukin-2

- First-line and second-line therapy
- Warning! Has low efficacy in patients with previously untreated brain metastases. **May worsen edema around brain metastases.**
Cytotoxic Therapy

- Dacarbazine, temozolomide, paclitaxel +/- carboplatin

Biochemotherapy

- Chemotherapy agents + biologic agents
- Dacarbazine/temozolomide, cisplatin/carboplatin, +/- vinblastine/nitrosourea, and IFN-alpha and IL-2
Systemic Therapies

- **Checkpoint immunotherapy**
  - Ipilimumab (anti-CTLA-4)
  - Nivolumab (anti-PD-1)
  - Pembrolizumab (anti-PD-1)

- **BRAF-targeted therapy**
  - Dabrafenib
  - Vemurafenib

- **MEK inhibitors**
  - Trametinib
  - Cobimetinib

- **Others:**
  - Tyrosine kinase inhibitor (Imantinib)
  - High dose IL-2
  - Cytotoxic Therapy
  - Biochemotherapy
SYSTEMIC THERAPY FOR METASTATIC OR UNRESECTABLE DISEASE

FIRST-LINE THERAPY

Metastatic or unresectable disease →

- Immunotherapy
  - Anti PD-1 monotherapy
    - Pembrolizumab (category 1)
    - Nivolumab (category 1)
  - Nivolumab/ipilimumab
  - Targeted therapy if BRAF V600 activating mutation; preferred if clinically needed for early response
    - Combination therapy
      - Dabrafenib/trametinib (category 1)
      - Vemurafenib/cobimetinib
  - Clinical trial

PERFORMANCE STATUS (PS)

PS 0–2 → Disease progression or Maximum clinical benefit from BRAF targeted therapy

SECOND-LINE OR SUBSEQUENT THERAPY

- Anti PD-1 monotherapy
  - Pembrolizumab
  - Nivolumab
  - Nivolumab/ipilimumab
  - Targeted therapy if BRAF V600 activating mutation
    - Combination therapy
      - Dabrafenib/trametinib
      - Vemurafenib/cobimetinib
  - Ipilimumab
  - High-dose IL-2
  - Biochemotherapy
  - Cytotoxic agents
    - Imatinib for tumors with activating mutations of C-KIT
    - Clinical trial

PS 3–4 → Consider best supportive care

OTHER SYSTEMIC THERAPIES

Cytotoxic Regimens for Metastatic Disease
- Dacarbazine
- Temozolomide
- Paclitaxel
- Albumin-bound paclitaxel
- Carboplatin/paclitaxel

Biochemotherapy for Metastatic Disease
- Dacarbazine or temozolomide, and cisplatin or carboplatin, with or without vinblastine or nitrosourea, and IL-2 and interferon alfa-2b

Biochemotherapy for Adjuvant Treatment of High-Risk Disease
- Dacarbazine, cisplatin, vinblastine, IL-2, and interferon alfa-2b (category 2B)
Indications for Radiotherapy

- **Primary disease**
  - Deep desmoplastic melanoma with narrow margins
  - Extensive neurotropism
  - Locally recurrent disease

- **Regional disease**
  - Extranodal tumor extension
  - # of positive nodes (depends on region)

- **Metastatic disease**
  - Brain metastases
  - Other symptomatic or potentially symptomatic soft tissue or bone metastases
Presentation Outline

- Epidemiology
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Clinical Trials

• Three phases of research:
  ▫ Phase I: safety
  ▫ Phase II: effectiveness
  ▫ Phase III: compares new drug with standard therapy currently being used

• Receive study-related medications and medical monitoring at no or little monetary cost (with some exceptions).
How to Join a Cancer Clinical Trial

If you are thinking about joining a clinical trial as a treatment option, the best place to start is to talk with your doctor or another member of your health care team. Often, your doctor may know about a clinical trial that could be a good option for you. He or she may also be able to search for a trial for you, provide information, and answer questions to help you decide about joining a clinical trial.

Some doctors may not be aware of or recommend clinical trials that could be appropriate for you. If so, you may want to get a second opinion about your treatment options, including taking part in a clinical trial.

If you decide to look for trials on your own, the following steps can guide you in your search. This information should not be used in place of advice from your doctor or other members of your health care team. This guide takes you through the following steps:

**ON THIS PAGE**

- Step 1: Gather Details about Your Cancer
- Step 2: Find Clinical Trials
- Step 3: Take a Closer Look at the Trials that Interest You
- Step 4: Contact the Team Running the Trial
- Step 5: Ask Questions
- Step 6: Make an Appointment
What Information is Available?

- Trial Description
- Condition, Intervention, Phase
- Location
- Eligibility
  - Inclusion Criteria
  - Exclusion Criteria
- Trial Contact Information
  - Principal Investigator
  - Coordinator
A Phase I Study of Ipilimumab and Nivolumab Immunotherapy plus Radiation Therapy for Metastatic Melanoma

For more information and to inquire about eligibility for this study, please contact Dr. Michael Postow at 646-888-4589.

Full Title
A Phase I Study to Evaluate the Safety Blockade (Ipilimumab and Nivolumab) with Stage IV Melanoma

Purpose
Ipilimumab and nivolumab are immunotherapies that work by the brakes on the immune response, and kill cancer cells. Doctors believe these two drugs may further enhance the immune system's ability to fight cancer.

In this study, researchers are evaluating the combination of radiation therapy in patients to determine if the two drugs can increase the success of radiation therapy for patients with stage IV melanoma.

Investigator
Michael A. Postow

Co-Investigators
Christopher A. Barker
Jedd D. Wolchok

Diseases
Melanoma

Locations
Memorial Sloan Kettering Memorial Hospital
Memorial Sloan Kettering Westchester

ClinicalTrials.gov
Visit ClinicalTrials.gov for full clinical trial description
A Pilot Study to Evaluate the Safety and Efficacy of Combination Checkpoint Blockade Plus External Beam Radiotherapy in Subjects With Stage IV Melanoma

This study is currently recruiting participants. (see Contacts and Locations)

Verified October 2016 by Ludwig Institute for Cancer Research

Sponsor:
Ludwig Institute for Cancer Research

Collaborator:
Bristol-Myers Squibb

Information provided by (Responsible Party):
Ludwig Institute for Cancer Research

ClinicalTrials.gov Identifier:
NCT02659540

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History of Changes

Purpose
References

• “How to Join a Cancer Clinical Trial” https://www.cancer.gov/about-cancer/treatment/clinical-trials/search/trial-guide
### Wide Excision of Primary Melanoma

<table>
<thead>
<tr>
<th>Tumor Thickness</th>
<th>Recommended Clinical Margins</th>
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<tbody>
<tr>
<td>In situ</td>
<td>0.5-1.0 cm</td>
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<tr>
<td>≤1.0 mm</td>
<td>1.0 cm</td>
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<tr>
<td>1.01-2 mm</td>
<td>1-2 cm</td>
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<tr>
<td>2.01-4 mm</td>
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<tr>
<td>&gt;4 mm</td>
<td>2.0 cm</td>
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Sentinel Lymph Node Biopsy

- ≤0.75 mm thick – **NOT** recommended
- >1 mm thick – offer SNLB

- In the middle??
  - Offer if there is ulceration or mitotic rate ≥11 per mm².
Talimogene Laherparepvec

- Also known as T-VEC
- Modified herpes simplex virus
- Induces tumor cell lysis and delivers localized expression of GM-CSF to injected lesions
Interferon alpha

- Consistent effect on relapse-free survival
- Little effect on total survival
Pegylated Interferon alpha-2b

- EORTC 18991 trial
- FDA approved for patients with stage III melanoma