Update on Management of Melanoma

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Case presentation

- Mr. K is a 63-year-old male presented with a rapidly growing “berry-like” skin lesion on his right shoulder. This is most likely:

A- Superficial spreading melanoma
B- Nodular melanoma
C- Acral-lentiginous melanoma
D- Lentigo maligna melanoma
Types of melanoma

**Superficial spreading melanoma**
- Most common type of skin melanoma (70%)
- Asymptomatic black or brown macule
- Radial growth phase before becoming invasive.

**Nodular melanoma**
- Second most common type of skin melanoma (15%)
- Blue-black “berry-like” nodular lesion
- Vertical not radial growth
- Rapid progression over months
Types of melanoma

**Lentigo maligna**
- Irregularly shaped macule, older patients, size: up to 5-7 cm
- In situ melanoma
- Slowly grows over 5-15 years before becoming invasive
- Invasive changes (lentigo maligna melanoma): the formation of bumps (papules), change in color.

**Acral-lentiginous melanoma**
- Occurs on the palms and soles.
- 2-8% of melanomas in white people
- 75% of melanomas in black and Asian people

**Subungual melanoma**
- 0.7 to 3.5% of all melanomas
Which of these statements is most accurate about familial predisposition to melanoma:

A - Most people with melanoma have an affected first-degree relative.
B - A family history of melanoma increases an individual's chance of getting melanoma, but most melanoma is sporadic.
C - A family history of red hair has no significant effect on risk of melanoma.

QUIZ

B- Correct:

- Around 10% of all people with melanoma have a family history.
- Most melanoma is not inherited but is instead sporadic.
- Two genes have been primarily linked to familial melanoma: CDKN2A and CDK4. A mutation in these genes gives a person an increased risk of melanoma.
Which of these statements best reflects opinion about clinically diagnosing malignant melanoma:

A- There are no typical characteristics of melanoma

B- A combination of shape, pigmentation, and regularity of shape and size can be used to help recognize melanoma clinically

C- Melanoma are always more pigmented than the surrounding skin
All of the following are acceptable methods to biopsy a suspected melanoma lesion except:

A- Excisional biopsy with 1-2 mm margin

B- Shave biopsy should be avoided due to risk of transecting a melanoma and preventing true staging of the lesion

Amelanotic melanoma
Breslow depth & T stage

T1a: <0.8 mm no ulceration
T1b: <0.8 mm with ulceration
0.8-1 mm

T2a: >1-2 mm no ulceration
T2b: >1-2 mm with ulceration

T3a: >2-4 mm no ulceration
T3b: >2-4 mm with ulceration

T4a: >4 mm no ulceration
T4b: >4 mm with ulceration

Melanoma in situ
MKSAP: Prognosis is related to the **depth of invasion**, high mitotic rate, lymphovascular invasion, and **the presence of ulceration**
Case presentation....

• An excisional biopsy was done. Pathology confirmed malignant melanoma, Breslow depth 3 mm and a close surgical margin of 0.5 cm. What would be the next step.

A- Wide local excision

B- Wide local excision and sentinel lymph node biopsy

C- PET CT or CT chest/abdomen/pelvis to rule out metastatic disease

D- No further intervention as the lesion was excised
SLNB should be done when depth of melanoma $\geq 0.8$ mm
Case presentation....

C is correct.

MKSAP: Even if sentinel lymph node biopsy is positive, a completion lymph node dissection is no longer routinely performed, as there is no improvement in survival. Patients with positive SLNB (stage III) may be followed by clinical examination and serial ultrasounds of the nodal basin involved to detect nodal recurrences. These patients are also eligible for adjuvant systemic treatment.
1939 patients with SLNB + melanoma underwent randomization.

24.1% of the patients in the dissection group and 6.3% of those in the observation group had had lymphedema ($P<0.001$)

2 years later our patient presented with fatigue, severe pain in RUQ and mid-back, anorexia, and 20 lbs. weight loss the last 3 months.

- CT c/a/p, MRI spine revealed metastatic disease.
- US-guided liver biopsy and pathology confirmed metastatic melanoma.
What is the most appropriate next step:

A- Initiate immunotherapy with ipilimumab and nivolumab
B- Refer to whole brain radiation therapy
C- High dose IL2
D- Chemotherapy
THE TOXINS OF WILLIAM B. COLEY AND THE TREATMENT OF BONE AND SOFT-TISSUE SARCOMAS

Edward F. McCarthy, M.D.

ABSTRACT

In 1891, William B. Coley injected streptococcal organisms into a patient with inoperable cancer. He thought that the infection he produced would have the side effect of shrinking the malignant tumor. He was successful, and this was one of the first examples of immunotherapy. Over the next forty years, as head of the Bone Tumor Service at Memorial Hospital in New York, Coley injected more than 1000 cancer patients with bacteria or bacterial products. These products became known as Coley's Toxins. He and other doctors who used them reported excellent results, especially in bone and soft-tissue sarcomas.

Despite his reported good results, Coley's Toxins came under a great deal of criticism because many doctors did not believe his results. This criticism, along with the development of radiation therapy and chemotherapy, caused Coley's Toxins to gradually disappear from use. However, the modern science of immunology has shown that Coley's principles were correct and that some cancers are sensitive to an enhanced immune system.

Because research is very active in this field, William B. Coley, a bone sarcoma surgeon, deserves the title “Father of Immunotherapy.”


patent's immune system can be stimulated or enhanced to attack the malignant tumors. The first systematic
High Dose IL2

Long term remission/cure: 10%

High-Dose Recombinant Interleukin 2
Therapy for Patients With Metastatic Melanoma: Analysis of 270 Patients Treated Between 1985 and 1993

Michael B. Atkins et al. JCO 1999;17:2105
Which of the following agent is a CTLA4 inhibitor:

A- Pembrolizumab
B- Nivolumab
C- Ipilimumab
D- Relatlimab
Checkpoinet Inhibitor

CTLA4

Ipilimumab (Yervoy): CTLA4 inhibitor.

Nivolumab, pembrolizumab: PD1 inhibitors.

Relatlimab: LAG-3 inhibitor.

PD1

LAG-3

James Allison

Tasuku Honjo
Ipilimumab Improved Survival in Patients with Metastatic Melanoma

CheckMate-067

Patients
- Unresectable, stage III or IV melanoma
- Previously untreated
- N=945 patients

NIVO 1 mg/kg + IPI 3 mg/kg Q3W for 4 doses then NIVO 3 mg/kg Q2W
n = 314

NIVO 3 mg/kg Q2W + IPI-matched placebo
n = 316

Ipilimumab 3 mg/kg IV Q3W × 4 doses
n = 315

Treat until progression or unacceptable toxicity
Coprimary endpoints: PFS, OS
The study was not powered for a comparison between NIVO+IPI and NIVO

Wolchok JD. CheckMate 067: 6.5-year outcomes in patients with advanced melanoma. Abstract ASCO 2021
MKSAP: Combining ipilimumab with nivolumab improves response rates compared with either ipilimumab or nivolumab alone but results in significantly more immune-related toxicities.

Wolchok JD. CheckMate 067: 6.5-year outcomes in patients with advanced melanoma. Abstract ASCO 2021
Continue Case Presentation.....

- **04/20/2018 C1 ipi+nivo**
- **05/10/2018 C2 ipi+nivo**
- **05/16/2018**: grade 2 colitis, hypophysitis, and skin rash.
- **5/31/2018**: nivolumab
- **6/2021**: severe colitis.
- Immunotherapy stopped
- Patient is alive as of now (2022) with complete response.
Continue Case Presentation.....

11/04/2019

02/25/2020

06/16/2020
CASE 2: 48 years old male with metastatic melanoma to brain

10/13/2020: Brain mets
Asymptomatic
No steroids
No radiation
Ipi 3 mg/kg+nivo 1 mg/kg
10/15/2020 C1
11/05/2020 C2
11/25/2020 C3
12/17/2020 C4
Maintenance Nivolumab
01/05/2021- until now

7/2019: 1.6 mm depth, left ear helix s/p WLE/SLNB 0/4
9/2020: recurrence. left neck dissection 1/18 LN.
CheckMate-067: Adverse Events

<table>
<thead>
<tr>
<th></th>
<th>NIVO + IPI (n = 313)</th>
<th>NIVO (n = 313)</th>
<th>IPI (n = 311)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Any grade</td>
<td>Grade 3-4</td>
<td>Any grade</td>
</tr>
<tr>
<td>Treatment-related AE, %</td>
<td>96</td>
<td>59</td>
<td>87</td>
</tr>
<tr>
<td>Treatment-related AE leading to discontinuation, %</td>
<td>42</td>
<td>31</td>
<td>14</td>
</tr>
<tr>
<td>Treatment-related death, a n (%)</td>
<td>2 (1)</td>
<td>1 (&lt; 1)</td>
<td>1 (&lt; 1)</td>
</tr>
</tbody>
</table>

Wolchok JD. CheckMate 067: 6.5-year outcomes in patients with advanced melanoma. Abstract ASCO 2021
Immune mediated adverse events

Hepatic
- Autoimmune hepatitis
- ALT/AST increases

Endocrine
- Hypophysitis
- Thyroiditis
- Type 1 diabetes

Renal
- Nephritis
- Renal failure

Respiratory
- Pneumonitis

Skin
- Macropapular rash
- Pruritus

Gastrointestinal
- Colitis/diarrhea

Neuromuscular
- Peripheral sensory neuropathy
Influenmationary Colitis

5wks Post Treatment:
Including:
Infliximab
Short term steroids

Severe inflammation and ulceration c/w Immune mediated colitis

Friable mucosa, but **no signs** of active inflammation or ulceration

Managing Adverse Events With Immune Checkpoint Agents.
Dadu RY, Zobniw C, Diab A. Cancer J. 2016 Mar-Apr;
Case 2: 70 yo male presented with dyspnea and skin rash after cycle 1 of pembrolizumab
Ipilimumab is a CTLA4 inhibitor. All the following are potential adverse events of ipilimumab except one which is less likely to be induced by ipilimumab

A- Hypophysitis
B- Colitis
C- Pneumonitis
D- Skin rash
Immune mediated Hypophysitis

ACTH
Status: Final result
Visible to patient: This result is not viewable by the patient.
09/01/2015 at 09:00 AM in Radiology (UAMS OPC05) Dx: Hypopituitarism

Newer results are available. Click to view them now.

ACTH
Ref Range: 7 - 69 pg/mL
1yr ago: <5 (L)
2yr ago: <2 (L)
2yr ago: 4 (L)

Cortisol, Serum
Status: Final result
Visible to patient: This result is not viewable by the patient.
09/01/2015 at 09:00 AM in Radiology (UAMS OPC05) Dx: Hypopituitarism

Newer results are available. Click to view them now.

Cortisol
Ref Range: AM: 5 - 23 ug/dL PM: 3 - 16
1yr ago: 0.7

Cortisol, 60 min
Status: Final result
Visible to patient: This result is not viewable by the patient.
09/01/2015 at 09:00 AM in Radiology (UAMS OPC05) Dx: Hypopituitarism

Cortisol, 60 Min
Ref Range: AM: 5 - 23 ug/dL PM: 3 - 16
1yr ago: 2.2

Resulting Agency: Softlab
Immune mediated hypothyroidism

56-year-old female with metastatic melanoma developed abnormal thyroid function tests after 2 cycles of combined ipilimumab and nivolumab.

A phase of acute autoimmune thyroiditis with transient hyperthyroidism followed by permanent hypothyroidism.
Complete Vitiligo within Weeks

Receiving first infusion of ipi/Nivo

Weeks later

Slide courtesy of Dr. Isabella Glitza
MDA Houston
Above: Large bullae on foot. Patient was initiated on high dose steroids, and bullae decreased within few days in size and incidence

Right: Separate female patient who developed significant bullae after 9 cycles of pembrolizumab; she also initially presented with a faint rash
Case 3

- Mrs. C is a 55-year-old female with metastatic BRAF V600E mutated melanoma received 3 cycles of ipilimumab and nivolumab; CT a/p 5/16/2019 revealed progression of disease. She presented for second opinion, poor performance status, and her BP in clinic was 80/40.
What would you recommend now:

A- Refer patient to hospice care.
B- Admit to hospital for IV hydration.
C- Start Encorafenib and Binimetinib (BRAF inhibitor plus MEK inhibitor).
D- Enroll in clinical trial.
Follow up visit 08/27/2019
Normal and Abnormal MAPK Pathway:

- Normal Pathway:
  - Growth factor → RTK → RAS → P13K → AKT → mTOR → ERK
  - Nucleus: Survival, growth, proliferation, angiogenesis

- Abnormal Pathway:
  - Growth factor → RTK → RAS
  - BRAF V600 mutation
  - Cytoplasm: P13K → AKT → MEK → mTOR → ERK

Approximately 50% of melanomas harbor the BRAF V600 mutation.

Hong S, Han SB. Arch Pharm Res 2011;34(5):699–701
BRAFi + MEKi for $\textit{BRAF}^{V600}$-Mutant Melanoma

Dabrafenib + Trametinib vs Vem

OS: HR 0.69
PFS: HR 0.56

Robert, NEJM, 2014

12 month OS Rate
D+T 72%, Vem 65%

9 month OS Rate
Vem + Cobi 81%, Vem 73%

FDA Approval, 2014, BRAF$^{V600}$-Mutant Stage IV or Unresectable Stage III Melanoma

Vemurafenib + Cobimetinib vs Vem

OS: HR 0.65
PFS: HR 0.51

Larkin, NEJM, 2014

9 month OS Rate
Vem + Cobi 81%, Vem 73%

FDA Approval, 2015, BRAF$^{V600}$-Mutant Stage IV or Unresectable Stage III Melanoma

Encorafenib + Binimetinib vs Vem

OS: HR 0.61
PFS: HR 0.54

FDA Approval, 2018, BRAF$^{V600}$-Mutant Stage IV or Unresectable Stage III Melanoma
# BRAFi + MEKi for BRAF<sup>V600</sup>-Mutant Melanoma

<table>
<thead>
<tr>
<th></th>
<th>Dabrafenib 150 mg BID + Trametinib 2 mg QD&lt;sup&gt;[1]&lt;/sup&gt;</th>
<th>Vemurafenib 960 mg BID (D1-28) + Cobimetinib 60 mg QD (D1-21)&lt;sup&gt;[2]&lt;/sup&gt;</th>
<th>Encorafenib 450 mg QD + Binimetinib 45 mg BID&lt;sup&gt;[3]&lt;/sup&gt;</th>
</tr>
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<tbody>
<tr>
<td>N</td>
<td>563</td>
<td>247</td>
<td>192</td>
</tr>
<tr>
<td>ORR, %</td>
<td>68</td>
<td>70</td>
<td>76</td>
</tr>
<tr>
<td>CR</td>
<td>19</td>
<td>21</td>
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</tr>
<tr>
<td>PR</td>
<td>49</td>
<td>49</td>
<td>55</td>
</tr>
<tr>
<td>SD</td>
<td>23</td>
<td>18</td>
<td>17</td>
</tr>
<tr>
<td>PD</td>
<td>6</td>
<td>7</td>
<td>7</td>
</tr>
<tr>
<td>DCR, %</td>
<td>91</td>
<td>93</td>
<td>93</td>
</tr>
<tr>
<td>Median PFS, mos</td>
<td>11.1</td>
<td>12.6</td>
<td>14.9</td>
</tr>
<tr>
<td>Median OS, mos</td>
<td>25.9</td>
<td>22.5</td>
<td>33.6</td>
</tr>
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</table>

- Cross-trial comparison limited by differences in trial populations, i.e. % with LDH > ULN (DT: 34%; VC: 46%; EB: 29%)


*Slide courtesy of Dr. Michael Davies MDA Houston*
## Adverse Events

<table>
<thead>
<tr>
<th></th>
<th>Combi-D</th>
<th>Combi-V</th>
<th>Columbus</th>
<th>Co-BRIM</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Toxicity % of all/≥G3</strong></td>
<td>DT</td>
<td>DT</td>
<td>EB</td>
<td>VC</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>52/7</td>
<td>53/4</td>
<td>18/4</td>
<td>26/2</td>
</tr>
<tr>
<td>Photosensitivity</td>
<td>4/0</td>
<td>5/1</td>
<td></td>
<td>28/2</td>
</tr>
<tr>
<td>Nausea</td>
<td>20/0</td>
<td>36/1</td>
<td>41/2</td>
<td>40/1</td>
</tr>
<tr>
<td>Elevated ALT</td>
<td>10/2</td>
<td></td>
<td>13/6</td>
<td>23/11</td>
</tr>
</tbody>
</table>

Dummeoret al. Lancet Oncol May 2018  
Larkin et al. NEJM 201  
Summary

• Most melanoma is sporadic. Around 10% of all people with melanoma have a family history (mutations in CDKN2A and CDK4).

• Prognosis is related to the depth of invasion, high mitotic rate, lymphovascular invasion, and the presence of ulceration.

• Wide local excision is the standard of care procedure for cutaneous melanoma lesions. Sentinel lymph node biopsy is added for melanoma >=0.8 mm depth.

• Ipilimumab is a CTLA4 inhibitor
• Nivolumab and pembrolizumab are PD1 inhibitors.
Summary

• Immunotherapy revolutionized the management of metastatic melanoma
  – 6.5-year OS with ipilimumab and nivolumab (49%) and nivolumab (42%)

• 50% of patients with melanoma harbor the BRAF mutation.

• Targeted therapy for BRAF-mutant melanoma
  – 3 approved regimens (BRAF inhibitor + MEK inhibitor): high response rates.

• Immune mediated adverse events: Skin rash, colitis, thyroiditis, hypophysitis, hepatitis, nephritis, pneumonitis, etc
THANK YOU