How I Think About: Melanoma

BWH Resident Oncology Curriculum

What is Melanoma?:

- Malignancy of melanocytes.
- 75% of deaths from skin cancer in western world. Global incidence 1-25/100,000.
- UV exposure is major risk factor, especially low-frequency, high-intensity exposures such as blistered burns.
- Median age 57; among the most common cancers in ages 20-29. Very rare in children.

What are the Major Types of Melanoma:

- Superficial spreading (most common).
- Nodular.
- Lentigo maligna: occurs on face.
- Acral lentiginous: occurs plantar (acral) surfaces of hands and feet as well as under nails (subungual), most common in dark skinned people.
- Less common: mucosal and ocular melanoma.

How is a Patient Diagnosed?:

- Comprehensive skin examination with dermoscopy.
- Gold standard is pathologic diagnosis and confirmation with associated staining.
- FISH-based assays have high specificity and sensitivity.

"Deep Dive" Questions:

1. What factors would influence the choice of adjuvant therapy in high risk melanoma patients?
2. What factors might guide patient selection for immunotherapy in patients with melanoma?
3. What are some of the toxicities associated with immunotherapy and how should they be managed?

Key References:

- Hodi FS, et al. N Engl J Med. 2010; 363: 711-723.
- Chapman PB, et al. N Engl J Med. 2011; 364: 2507-2516.
- Robert C, et al. N Engl J Med. 2015; 372: 30-39.
- Larkin J, et al. N Engl J Med. 2015; 373: 23-34.

How is a Patient Staged?:

- **TNM** staging from AJCC.
- **T**: tumor thickness (T1: ≤ 0.8mm, T1b 0.8-1.0 T2: 1-2 mm, T3: 2-4 mm, T4: >4 mm) **a**: without ulceration, **b**: with ulceration.
- **N**: nodal involvement (N0: no nodes, N1: 1 node, N2: 2-3 nodes, N3: ≥4 nodes) **a**: clinically occult, **b**: clinically detected **c:** in-transit/microsatellite metastasis
- **M**: distant metastasis (M0: no metastases, M1a: skin, subcutaneous or distant node M1b: lung M1c: visceral mets, M1d: CNS mets (0)LDH normal, (1)LDH elevated).
  - **Stage I**: T1a-T2a.
  - **Stage II**: T2b-T4b.
  - **Stage III**: N1-N3.
  - **Stage IV**: M1a-M1c.

How is a Patient Treated?:

Clinically negative nodes: surgical excision.

- Margins: 0.5-1 cm for *in situ*, 1 cm for ≤ 1mm, 1-2 cm for 1-2 mm, 2 cm for ≥ 2 mm.

Sentinel node biopsy (SN): for ≥ 0.8 mm thick; or any thickness with ulceration.

Adjuvant therapy (IIIA-IIID): Stage IIIA-D patients with BRAF mutations can be treated with BRAF/MEK inhibition. Patients with stage IIIA-IV NED disease qualify for adjuvant nivolumab or ipilimumab.

Metastatic disease

- Tumor should be sequenced for BRAF mutations (most common V600E); other common mutations are NRAS and KIT.
- Surgical excision is an option for single visceral metastases.
- Pre-2011
  - Chemotherapy with dacarbazine and temozolomide was used. High dose IL-2 had some efficacy.
  - Brain metastases are treated with surgery, SRS or whole brain radiation, respond to BRAF/MEK inhibitors and immunotherapy.
- Post 2011:

Immune checkpoint inhibitors

- **CTLA-4 blockade** (ipilimumab): prolongs OS compared to dacarbazine. Response rate ~11% but can see durable response, ~20% responders alive at 3 years.
- **PD-1 blockade** (Nivolumab, pembrolizumab): response rate ~40%, lower post-ipi.
- **Combination immunotherapy: PD-1 blockade with CTLA-4 blockade:** response rate ~60% with increased toxicity
- **Immune related adverse events:** colitis, hepatitis, endocrinopathies (hypophysitis, thyroiditis), pneumonitis with nivolumab. Treated with steroids, infliximab, mycophenolate.
- **Injectable immunotherapies:** T-VEC (imlygic) FDA approved for patients with accessible disease.

Targeted therapies:

- **BRAF inhibitors** (vemurafenib, dabrafenib)**/MEK inhibitors** (trametinib): BRAF inhibitors target V600E mutation but also atypical ones. Response rate ~70% but no durable responses. Side effects more manageable with combination therapy than single agents (less cutaneous toxicities).

What is a Patient's Prognosis?:

- Stage IV melanoma has 5 year survival rate of 10-15%, however this is changing drastically with novel agents.
- Prognosis better with normal LDH and spread to skin rather than visceral organs.

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