Intralesional Therapy for Metastatic Melanoma

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Disclosures

- Consultant for Amgen
Objectives

- Understand the role of Intralesional therapy
- Learn the types of Intralesional therapies for treating metastatic melanoma including treatments previously used and therapies currently being used
- Clinical trials studying intralesional therapy in combination with immunotherapy
- The benefits of intralesional therapy
Staging melanoma

- **TNM**
  - **T**: Tumor depth/thickness, known as Breslow’s depth, and presence of ulceration
  - **N**: Nodal involvement and intransit melanoma located within subdermal and dermal lymphatics between the primary tumor and draining nodal basin
  - **M**: Metastasis to distant lymph nodes, distant skin sites, or organs such as the lungs, brain, bone, intestines, etc.
Stages of Melanoma

- **Stage 0**: Melanoma confined to epidermal region of skin
- **Stage I**: Localized disease, only in skin and very thin
- **Stage II**: Localized disease, thicker than Stage I
- **Stage III**: Spread to lymph nodes
- **Stage IV**: Spread to other organs
Stages of melanoma treated with Intralesional Injection Therapy

- **Stage III**
  - IIIB: Satellitosis, > 2 cm from the primary tumor located within lymphatics that have not yet reached the nodal basin
  - IIIC: Regional nodal involvement

- **Stage IV: Distant metastasis**
  - M1a: distant skin and nodal basin metastasis
Treatment Options for Stage III Melanoma

- Surgery
  - Lymph node dissection
  - Resection of dermal/subcutaneous metastasis

- Systemic Therapy
  - Immunotherapy
    - Anti-PD-1 therapy
    - Anti-CTLA-4 therapy
    - Combo Anti-PD-1 + CTLA-4
  - Targeted Therapy for BRAF mutated
    - BRAF/MEK inhibitor

- Isolated Limb Infusion
Role of Intralesional Therapy

- Progression of disease despite therapy
- Toxicity from systemic therapy
- Unresectable dermal/subcutaneous nodules and/or nodal disease
  - Visible
  - Palpable
  - Visualized with ultrasonography
Goal of Intralesional Therapy

- Locoregional disease control
- Induce a systemic anti-tumor immune response
- Limit systemic toxicity
History of Intralesional Therapy

- Intralesional Bacillus Calmette-Guerin (BCG)
  - Attempt to eradicate in transit disease with potential to generate a systemic response
  - Caused severe toxicity leading to reduced clinical use
  - Early reports revealed tumor regression in about 90% of injected lesions with regression of 20% of uninjected lesions

- Cytokines: IL-2, Interferon Gamma, Interferon Alfa, GM-CSF
  - Associated with a high local response at site of injection, but no systemic response
  - Fell out of favor due to side effect profile, treatment cost, injection frequency, and efficacy
Phase III Trial: TVEC vs. GM-CSF

Talimogene Laherparepvec Improves Durable Response Rate in Patients With Advanced Melanoma

TVEC vs. GM-CSF

- TVEC is a modified oncolytic herpes simplex virus (HSV-1)
  - Anti-tumor Effect - direct lysis of the tumor
  - The lysed tumor releases virus infecting other tumor cells
  - The virus includes the gene for GM-CSF
  - This stimulates local immune cells

- GM-CSF - granulocyte macrophage colony-stimulating factor
  - Cytokine that stimulates an immune response
Overall Survival in ITT Population included Stage IIIB –IVC melanoma

Andtbacka et al JCO 2015
Overall Survival Stage IIIB/C – MIa

Andtbacka et al JCO 2015
Talimogene Laherparepvec (TVEC) for the Treatment of Advanced Melanoma: A Single-Institution Experience

Matthew C. Perez, MD¹, John T. Miura, MD¹, Syeda Mahrukh Hussain Naqvi, MD, MPH², Youngchul Kim, PhD², Amanda Holstein, BS¹, Daniel Lee, BS¹, Amod A. Sarnaik, MD¹, and Jonathan S. Zager, MD, FACS¹

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Response to Therapy

- Overall Response Rate: 58%
  - 46% CR and 12% PR
- Overall disease control rate: 79%
- Median Time to Response
  - 2.1 months
- Median Time to Complete Response
  - 2.8 months (range: 0.9-8.5 months)
  - 6 cycles (range: 2-14 cycles)
- Median Follow Up
  - 10 months
Pre Treatment

SOX10, showing nuclear positivity in viable cell

- Brown areas are melanophages
- Red areas are melanoma

Post Treatment

Sox10, negative nuclear staining in pigmented cells

- No Cells Stained Red
Case #1

- 77 year old female
- Stage IIC of the lower leg and medial thigh
- Prior treatments:
  - superficial and deep groin dissection
  - PV-10 intra-lesional injections
  - Isolated Limb Infusion
  - temozolamide chemotherapy
  - nivolumab immunotherapy.
- 11 injections of TVEC over a 9 month period (11/2016 – 8/2017)
Pre Treatment
Administering TVEC

- Amount of medication injected based on size of tumor
  - Inject up to maximum 4 cc’s of medication per treatment

- Inject biggest lesions first then biggest and newest lesions during subsequent cycles

- Side Effects: Mild to moderate flu-like symptoms within 48 hours managed with Tylenol. Incidents decrease with each injection.

- Imaging studies every 3 months
  - Disease may not respond to therapy in 3 months; therefore, we prefer to administer 6 months of therapy to determine results of therapy
6 Cycles of TVEC
Bystander Effect
Case #2
Case #3
COSMUS-1 and 2 Trials

- Evaluated the real-world use of TVEC with availability of checkpoint inhibitors, specifically anti PD-1

- 83 patients
  - 26.5% received TVEC after failure of anti PD-1
  - 38.6% received TVEC concurrently with anti PD-1
  - 34.9% received TVEC alone

- Of all the patients, 25.3% completed treatment with no remaining injectable lesions in a median time of 4 months

- TVEC after failure of immunotherapy is further characterized in a paper in press in Annals of Surgical Oncology by Carr et al.
  - >50% ORR and >30% CR after failure of IO for intransit melanoma

Sun et al. Melanoma Management 2019
Carr et al. Melanoma Management 2020
PV-10

- 10% solution of Rose Bengal disodium, a xanthene dye
- Preferentially enters melanoma cells causing lysosomal disruption and subsequent cell necrosis
- Antigen is released from the tumor cell stimulating an immune response and leading to the destruction of bystander lesions.
Phase 2 Study of Intrallesional PV-10 in Refractory Metastatic Melanoma

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Phase 2 study in Refractory Metastatic Melanoma

- International, multicenter, single-arm trial assessed efficacy and safety of PV-10 in 80 patients with refractory cutaneous or subcutaneous metastatic melanoma.

- Stage III and Stage IV melanoma refractory to a median of 6 prior interventions.
Administering PV-10

- Injected up to 20 cutaneous and subcutaneous lesions, up to 4 times a week, over a 16 week period

- Patients followed for 52 weeks to:
  - Determine best overall response rate in injected target lesions and uninjected bystander lesions
  - Assess durability of response
  - Characterize adverse events.
Effects of PV-10
Findings

- Overall response rate for Target Lesions: 51%
  - Complete Response: 26% in target lesions
- Median time to response: 1.9 months
- Median duration of response: 4 months
  - 8% of patients having NED after 52 weeks
- Response of target lesions correlated with bystander lesion regression and occurrence of locoregional blistering.
- Adverse effects were mild to moderate and locoregional to treatment site
  - No treatment associated grade 4 or 5 adverse events
Case

Subject 0014: Male, age 48, Stage IIIb (N2c) since 2008, Sx of 1° and mets
Single treatment with 1.3 mL PV-10 to 10 lesions; 1 untreated bystander lesion (B1)
CR of Target and Bystander Lesions at Week 24
Benefits

- Effective for local disease control
- Can be combined with systemic immunotherapy
  - Currently being evaluated in combination with Pembrolizumab in Phase 1b/2 study
Combination PV-10 and Pembro

- Ongoing study including both checkpoint blockade naïve and refractory patients

- Preliminary response in 21 checkpoint blockade naïve patients
  - Overall Response Rate: 67%
  - Complete Response: 10%
  - Partial Response: 57%

- Preliminary response in 14 checkpoint blockade refractory patients
  - Overall Response Rate: 29%
  - Complete Response: 7%
  - Partial Response: 21%

Zager et al Combination PV-10 and Pembro 2020
TAVO and Electroporation

- Tavokinogene telseplasmid, a plasmid encoding IL-12, intratumoral injection. IL-12 is a pivotal regulator of innate and adaptive immunity.

- Followed by electroporation
  - Electroporation is a tool for plasmid DNA delivery that uses a pulse of electricity that acts to briefly open the pores of the cell membrane increasing permeability to facilitate plasmid uptake

- Phase 2 Trial of 28 patients
  - ORR: 35.7%
  - CR: 17.9%

Algazi et al Ann Oncol. 2020
Electroporation

**Electric field**: 30-100 V
**Pulse duration**: 10 μs-100 ms

- **Pore formation and electric repulsion**
- **Skin**
- **Blood Vessels**

**Drug ions**
TAVO with Electroporation in Combination with Pembro

KEYNOTE695 is a Phase 2 clinical trial study of intratumoral tavokinogene telseplasmid (TAVO; pIL-12) Electroporation (EP) plus IV Pembrolizumab for patients with pathological diagnosis of unresectable or metastatic melanoma who are progressing or have progressed on pembrolizumab.

TAVO is DNA-based interleukin-12 (IL-12; TAVO), a naturally occurring protein with immune-stimulating functions. IL-12 is an investigational treatment that has not been approved by the U.S. Food and Drug Administration (FDA) for melanoma or any other disease. The process is designed to produce a controlled, localized expression of TAVO in the tumor microenvironment, which in turn, enables the immune system to target and attack tumors throughout the body.

Pembrolizumab, delivered by IV infusion, is a medication that has been approved by the FDA for the treatment of metastatic melanoma. Pembrolizumab is a type of immunotherapy that works by targeting PD-1, a signaling receptor that helps cancer cells hide from the body’s immune system. Pembrolizumab blocks the PD-1 pathway and helps the immune system target and fight cancer cells.

It is believed that the combination will provide more effective response in the body and that will affect tumor growth.

1IL-12 = tavokinogene telseplasmid (TAVO) TAVO

2Reference SITC 2017
Case
TAVO + Electroporation + Nivolumumab
More to come…

- There are other experimental intralesional agents currently being studied in clinical trials:
  - Toll like Receptor agonists (TLR)
  - Immunocytokines
  - Oncolytic viruses
TLR AGONISTS

- Activate an immune response, increasing local antigen presenting cell maturation and expression of immune checkpoints including PD-1 and CTLA-4
- TLR agonists are being combined with immune checkpoint inhibitors to provoke an increased overall response rate
  - Pembrolizumab and Nivolumab: Anti-PD1 inhibitors
  - Ipilimumab: Anti-CTLA4 inhibitor
Immunocytokines

- Daromun- a combination immunocytokine
  - Monoclonal L19 antibody, which has shown to selectively bind to tumor cells present in newly formed blood vessels and neoplastic tissue
  - Fused with IL-2 and TNF-alpha

- The combination has been found to act synergistically through both direct tumor cell necrosis and induction of a systemic anti-tumor response
Oncolytic Viral Therapies

- ONCOS-102: a 5/3 capsid chimeric oncolytic adenovirus engineered to express GM-CSF
- RP-1 and OrienX010: additional genetically engineered HSV1
Summary

- TVEC is effective in treating locoregionally metastatic melanoma with > 50% ORR
  - Very well tolerated, limited side effects

- PV-10 has been shown to be effective as an intralesional monotherapy for locoregionally metastatic melanoma and being studied in combination with systemic IO for metastatic melanoma

- Electroporation and IL12 plasmid injection combined with systemic IO as well as other oncolytic viruses, TLR agonists and immunocytokine agents (TNF and IL-2) are currently in clinical trials to study their effectiveness as intralesional agent monotherapy or in combination with systemic IO for metastatic melanoma