Intratumoral Immunotherapy

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Disclosures

• I am an employee of Ankyra Therapeutics
• I served on advisory board for Castle Biosciences
Intratumoral Immunotherapy Definitions and Rationale
What is intra-tumoral Immunotherapy?

- Therapeutic approach that delivers IO drugs directly into the tumor
  - May be physical or chemical
  - Can be given by direct injection; or
  - Systemic delivery with local activation in the TME
- In most cases, focuses on generating local immune responses
  - May also induce systemic immunity
- Expected to have a more favorable safety profile compared to systemic drug delivery
A major goal of modern IO therapy is to establish immune-inflamed ("hot") tumor microenvironments.
IO agonists are limited by poor therapeutic windows

- Limited clinical success of systemically administered cytokines and antibody agonists
- On-target, off-tumor toxicity restricts dosing
- Transport barriers and immunosuppressive microenvironment of solid tumors limit efficacy

Intratumoral administration has potential to greatly expand therapeutic window by increasing relative tumor vs systemic exposure
History of Intra-tumoral Therapy of Cancer

1893

1904
First viral infection–induced tumor regression (leukemia)[35]

1912
Rabies (cervical)[36]

1956
Adenovirus (cervical)[40]

1971
Measles (leukemia)[38,39]

1974
Mumps (solid tumors)[37]

1997
First clinical trials with engineered virus (HNC, pancreatic)[43]

2000

2003
HSV-1 + GM-CSF (T-VEC) (melanoma)[78]

2005
Engineered adenovirus approved in China (nasopharyngeal carcinoma)[78]

2010

2011
First phase III trial fully enrolled (T-VEC, melanoma)[80]

2015
First approval of an oncolytic virus in the US (T-VEC, melanoma)[80]
# Global Approved Oncolytic Viruses for Cancer

<table>
<thead>
<tr>
<th>Name</th>
<th>Virus</th>
<th>Indication</th>
<th>Country</th>
<th>Year Approved</th>
</tr>
</thead>
<tbody>
<tr>
<td>H101 (Oncorine®)</td>
<td>Adenovirus</td>
<td>Nasopharyngeal carcinoma (with chemotherapy)</td>
<td>Peoples Republic of China</td>
<td>2005</td>
</tr>
<tr>
<td>Talimogene laherparepvec (T-VEC; Imlygic®)</td>
<td>HSV-1-GM-CSF</td>
<td>Melanoma</td>
<td>United States, Europe, Israel, Australia</td>
<td>2015</td>
</tr>
<tr>
<td>ECHO-7 (Rigvir®)</td>
<td>Echovirus (picornavirus family)</td>
<td>Melanoma</td>
<td>Latvia, Georgia, Armenia</td>
<td>2019</td>
</tr>
<tr>
<td>Teserpaturev</td>
<td>HSV-1</td>
<td>Malignant Glioma</td>
<td>Japan</td>
<td>2021</td>
</tr>
</tbody>
</table>
Number of Intratumoral Clinical Trials in Oncology as of 11/30/2021

- 82 active IT clinical trials
  - 65 active
  - 17 planned
- 42 trials in the U.S.
- 45 trials in Phase I or I/II
Intralesional approaches Induce immunogenic cell death

Galluzzi et al. Nature Immunol. 2017
Contemporary definition of ICD

Fig. 1: Immunomodulatory CAR T-cell therapy in mice.

Bommareddy et al. Science Transl Med 2018
Intratumoral immunotherapy may have an *in situ* vaccination effect

- Antigens defined
- Tumor not needed
- Use normal immune cells

- Uses native antigens
- Must access tumor
- Uses local immune system

Sheen and Fiering WIREs 2018
Benefits of Intra-tumoral Immunotherapy

• Allows direct access to multiple cells in the tumor microenvironment
• Able to use established tumor features (e.g., in situ vaccine effect)
• No need to identify tumor-associated antigens
• Generally, has been associated with limited toxicity
• Easy to promote serial biopsy and biomarker analyses
• Less expensive
• May preclude or delay need for more toxic systemic agents
Intratumoral Immunotherapy

Types of Intratumoral Therapy
Types of Intra-tumoral therapy

• Physical (Ablative) therapies
• Drug-related therapies
• Intravenous delivery with local activity
• Combination therapy
Physical Intratumoral Therapy
Cryotherapy

Toxicity:
- Pain
- Hemorrhage
- Edema
- Numbness
- Neuropathy
- Alopecia
Microwave and Radiofrequency Ablation

- Tumor entered with thin needle and probe
- Apply electrical current (radiofrequency) or microwave energy
- Tumor necrosis induced
- Residual scar left behind
High-intensity Focused Ultrasound

• Non-invasive therapeutic technique
• Uses lower frequency and continuous waves
• Induces thermal damage in tissue (65-85 °C)
• Pulsed waves induce mechanical damage
• Can use with ultrasound or MRI imaging
• HIFU approved in U.S. for prostate cancer treatment in 2015
• Many other tumors under study
Hyperthermia
Radiation Therapy

1. Cell kill via irradiation

2. Antigen presenting cells (APC) present tumor antigens to CD8 T-cells

3. CD8 T-cells circulate through the body, destroying both directly irradiated and “abscopal” tumors

X-ray Irradiation

Directly Treated Tumor

Secondary “Abscopal” Tumor

Destroy secondary
Electroporation

Electrochemotherapy

- Electric pulse surrounds the cells
- Anticancer drug allows access to the cytosol
- Membrane ressealed, anticancer drug exerts cytotoxicity

Electric Field
- ~1kV/cm: Irreversible
- ~50V/cm: Reversible
- ~100us: Thermal
- ~20ms: None

Systemic or intratumoural drug injection

Degree of Electroporation

DNA delivery

© Renger, 2013
Drug-related Intratumoral Therapy
Intratumoral chemotherapy and electrochemotherapy

Treated with six weekly intra-lesional injections of 5-FU

Electrochemotherapy with bleomycin

Courtesy Julie Gehl
PV-10 in melanoma

In-transit mets
45 patients
- 87% ORR
- 42% CR

Read et al. J Surg Oncol 2018

<table>
<thead>
<tr>
<th>Overall best response</th>
<th>First treatment</th>
<th>Second treatment</th>
<th>Third treatment</th>
<th>Fourth treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete response</td>
<td>13</td>
<td>8</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Partial response</td>
<td>24</td>
<td>12</td>
<td>3</td>
<td>-</td>
</tr>
<tr>
<td>Stable disease</td>
<td>3</td>
<td>4</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>5</td>
<td>5</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Total</td>
<td>45</td>
<td>29</td>
<td>7</td>
<td>1</td>
</tr>
</tbody>
</table>
Oncolytic Viruses

- Selective cytotoxicity
  - Tumor ICD
- Induction of immunity
- Favorable safety profile
Direct injection of IO Agents into the TME

- Cytokines
- Cell therapy
- Immune checkpoint inhibitors
- STING and TLR agonists
Delivering IO through scaffolding platforms

- Increased retention at tumor site
- Local functional immune activity
- Decrease systemic toxicity
Masked IO Delivery
Intratumoral Immunotherapy

Special Considerations
- Pre-clinical Issues
- Clinical Issues
- Logistical Issues
Pre-clinical Issues with Intratumoral Therapy

- Are tumor cells sensitive to drug entry?
- Are tumor cells killed? How?
- Biodistribution is important
  - Does drug remain in tumor (i.e., tumor cell restriction)?
  - Does drug leak to other sites (i.e., other cells in TME, distant tumors, normal tissue)?
- Need tumor model that incorporates injected and un-injected tumor (i.e., Is there an abscopal/anenestic effect?)
- Dose-response relationships should be defined
  - Anti-tumor vs. anti-viral immunity
- Dosing schedule and routes are important to validate
Intratumoral therapy should report injected and un-injected tumor responses

Hamilton et al. Cell 2018
Thomas et al. JITC 2019
Clinical Issues associated with intra-tumoral immunotherapy

• Subject eligibility
  • Tumor size
  • Tumor location (e.g., access)

• Drug delivery
  • Dose vs. volume
  • Schedule
  • Intra-tumoral vs. intra-venous
  • Which lesions to inject or treat?

• Endpoints
  • Injected (treated) lesions
  • Un-injected (un-treated) lesions [abscopal or anenestic responses]
  • Biomarkers (local vs. distant or systemic)
Logistical issues associated with intra-tumoral immunotherapy

• Drug delivery
• Access to visceral sites
  • Image-guided delivery is possible
  • Some sites challenging (e.g., brain, bone, liver dome, etc.)
• Biosafety issues
• Leaking from the tumor site
• Endpoint assessment
  • Need to document injected sites and non-injected sites
  • Abscopal (anenestic) responses may utilize different MOA, kinetics
### Alternative Endpoint Assessments: Intratumoral RECIST (itRECIST)

<table>
<thead>
<tr>
<th>Response</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>T-I lesions</td>
<td></td>
</tr>
<tr>
<td>CR</td>
<td>All nonnodal lesions gone, nodal lesions (&lt; 10 \text{ mm})</td>
</tr>
<tr>
<td>PR</td>
<td>(\geq 30%) decrease in SOD from last imaging assessment</td>
</tr>
<tr>
<td>PD</td>
<td>(\geq 20%) increase in SOD from last imaging assessment ((\geq 5 \text{ mm absolute}))</td>
</tr>
<tr>
<td>SD</td>
<td>Not enough growth for PD</td>
</tr>
<tr>
<td>NE</td>
<td>Not enough shrinkage for PR</td>
</tr>
</tbody>
</table>

| T-NI lesions |
| CR | All nonnodal lesions gone, nodal lesions \(< 10 \text{ mm}\) |
| PR | \(\geq 30\%\) decrease in SOD from baseline |
| PD | \(\geq 20\%\) increase in SOD from nadir (\(\geq 5 \text{ mm absolute}\)) |
| SD | Not enough growth for PD |
| NE | Not enough shrinkage for PR |

**Abbreviations:** CR, complete response; NE, nonevaluable; PD, progressive disease; PR, partial response; SD, stable disease; SOD, sum of diameters; T-I, target injected; T-NI, target noninjected.

Goldmacher et al. J Clin Oncol. 2020
Treatment beyond progression

Goldmacher et al. J Clin Oncol. 2020
Intravenous delivery of IT agents

- Easier route to administer
- Potentially targets all metastatic lesions
- To date, appears safe
- But,
- Limited biodistribution a challenge
  - Immune clearance (i.e. Abs, complement)
  - Protein sequestration
- To date, limited efficacy reported
- Few studies report viable drug at tumor site
Objective Clinical Response with OVs by Route of Administration

For IT treatment:
- 13.3% ORR
- 22.4% DCR
- 1482 total IT treated patients

For IV treatment:
- 4.5% ORR
- 17.6% DCR
- 1147 total IV treated patients

Machedo et al. J Immunother Cancer 2021
Conclusions

• Intratumoral immunotherapy is the local delivery of agents that induce anti-tumor immune responses
• There are many types of intratumoral immunotherapy
  • Physical approaches
  • Drug-based approaches
  • IV delivered and locally activated
• There are unique pre-clinical, clinical and logistical considerations associated with intratumoral immunotherapy
• Rational combination approaches in development
  • Neoadjuvant, IO combinations, non-IO combinations