Intratumoral and Local Immunotherapy

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Disclosures

• I am an employee of Immuneering Corporation
Intratumoral Immunotherapy

Definitions and Rationale
A major goal of modern IO therapy is to establish Immune-inflamed (“hot”) tumor microenvironments.
What is intra-tumoral Immunotherapy?

• Therapeutic approach that delivers IO drugs directly into the tumor microenvironment
  • May be physical or chemical
  • Can be given by direct injection; or
  • Regional intra-vascular injection
  • Systemic delivery with local activation in the TME?

• Focuses on generating local immune responses
  • May also induce systemic immunity

• Expected to have a more favorable safety profile compared to systemic drug delivery
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]

2000

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

2004
Imiquimod approved for basal cell cancer

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]
Intra-tumoral immunotherapy mediates anti-cancer activity through multiple mechanisms

• Direct tumor cell cytotoxicity
  • May also impact other cells in the tumor microenvironment [1]

• Induction of host anti-tumor immunity
  • Local/regional immune responses [2]
  • Systemic (i.e., abscopal/anenestic) immune responses [3]
1. Immunogenic cell death
Traditional ICD measured by release of DAMPs

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Courtesy Dr. Cory Hogaboam
Bommareddy et al. Oncolimmunol. 2018
Ecto-calreticulin exposure denotes ICD
2. Intratumoral therapy promotes local and regional immune activation
Pre-clinical strategies for demonstrating immunity with local immunotherapy agents

Bommareddy et al. Science Transl Med 2018
3. Intratumoral therapy *may* induce systemic immunity (i.e., abscopal or anenestic effect)

- Local effect
  - Drug X injection site
  - Recruitment and activation of dendritic cells
- Systemic effect
  - Tumor-cell killing
  - Distant tumor site
- In situ “vaccination” effect
Intratumoral immunotherapy may have an *in situ* vaccination effect

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

- Uses patient tumor neoantigens
- Must access tumor
- Uses local immune system

Sheen and Fiering WIREs 2018
Bilateral flank tumor model to assess systemic anti-tumor activity with local immunotherapy
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
Intratumoral Immunotherapy

Types of Intratumoral 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
How does hyperthermia mediate anti-tumor activity?
Radiation Therapy

1. Cell kill via irradiation

Directly Treated Tumor

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

Secondary "Abscopal" Tumor

X-ray Irradiation

Destroy secondary
Electroporation

**Electrochemotherapy**

- Electric pulse surrounds the cells
- Anticancer drug is injected
- Increased membrane permeability allows access to the cytosol
- Membrane reseals, anticancer drug exerts its cytotoxicity

**Degree of Electroporation**

- Electric Field:
  - ~1kV/cm: Thermal
  - ~50V/cm: Reversible

- Pulse Length:
  - ~100us: Irreversible
  - ~20ms: Reversible

© 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

45 patients
- 87% ORR
- 42% CR

In-transit mets

Read et al. J Surg Oncol 2018
Oncolytic Viruses

- Selective cytotoxicity
  - Tumor ICD
- Induction of immunity
- Favorable safety profile

Diagram:
- Oncolytic virus infects healthy cell, leading to virus replication.
- Healthy cell becomes damaged and releases virus progeny.
- Local inflammation occurs, releasing tumor antigens.
- Systemic anti-tumor immune response initiated.
- Destruction of tumor microenvironment.
- Infects more tumor cells.
Intratumoral cytokines: IL-2

Phase 2 study of 24 stage III and IV melanoma patients with IL-2 IT
• 245 lesions treated in 24 patients
• CR seen in 85% (n=209) of lesions and 62.5% of patients (n=15)
• PR seen in 6% (n=21) of lesions and 21% (n=5) of patients
• Toxicity limited to grade 1-2 events

Meta-analysis of 49 studies of intra-lesional IL-2 for in-transit melanoma
• Six studies met criteria for analysis
• Overall, 2,182 lesions in 140 patients were treated
• CR occurred in 78% of lesions
• CR occurred in 50%
• Treatment well tolerated
  • Local pain and swelling
  • Mild flu-like syndrome
• Only three grade 3 adverse events
  • Rigors, Headache, Fever and Arthralgia

Radny et al. BR J Cancer 2003
Byers et al. J Surg Oncol 2014
A phase I study of intratumoral ipilimumab and interleukin-2 in patients with advanced melanoma

Abhijit Ray¹, Matthew A. Williams², Stephanie M. Meek², Randy C. Bowen³, Kenneth F. Grossmann¹, Robert H.I. Andtbacka¹, Tawnya L. Bowles², John R. Hyngstrom³, Sancy A. Leachman⁴, Douglas Grossman¹, Glen M. Bowen¹, Sheri L. Holmen¹, Matthew W. VanBrocklin³, Gita Suneja⁷ and Hung T. Khong⁷

• 12 patients; 3+3 design; 8 weeks of tx
• IL-2 at 3 MIU and dose escalation of ipilimumab (0.5 – 2 mg)
• No DLTs
• Grade 3 events of hyponatremia (1) and local ulceration (5)
• Local response 67%
• Abscopal response 89%
• ORR by irRC 40%
Intratumoral cell therapy (DC, T cells, etc.)

- Ex vivo modified cells
- In vivo modified cells
- Adoptive transfer and CART depend on recruitment to and function within the TME

Cui and Guo Int J Mol Sci 2016
Intratumoral STING immune agonists

- Stimulator of Interferon Genes
- Identified by expression cloning using IFN-beta reporter
- Allows foreign DNA sensing at the intra-cellular level
- Activates innate immunity
- Potent anti-viral activity
- ‘Senses’ tumor DNA
- Agonizing STING can promote anti-tumor activity

Khoo and Chen EMBO Rep 2018
Toll-like receptor agonists

Danger is represented by:
- Bacteria
- Virus
- Fungi

These have molecular features that distinguish them from our own cells:
- Endotoxin
- DS RNA
- Lipopeptides
- CpG DNA
- SS RNA
- Flagellin
- HMGB1

Our immune systems have evolved to recognize them:
- TLR1, 2, 6
- TLR3
- TLR4
- TLR5
- TLR7/8

LPS
Flagellin
Lipoproteins

TLR2
TLR4
TLR5
TLR7
TLR8
TLR9

dsRNA
CpG DNA
ssRNA

Binds RAGE, LPS; amplifies TLR sigi


Ossenbrug et al. Cell Chem Biol 2017
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Pre-clinical Issues
Pre-clinical Issues

- 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 or anenestic effect?)
- Dose-response relationships should be defined
  - Anti-tumor vs. anti-viral immunity
- Dosing schedule and routes are important to validate
Oncolytic viruses utilize specific cell surface entry receptors
Intratumoral therapy should report injected and un-injected tumor responses

Hamilton et al. Cell 2018
Thomas et al. JITC 2019
Consideration of anti-viral immune response

Anti-HSV-1 Ab titers

HSV-1 Seronegative at Baseline

HSV-1 Seropositive at Baseline

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Clinical and Logistical Issues
Clinical Issues

• 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)
Intratumoral RECIST (itRECIST) for local immunotherapy

• Consider injected and un-injected lesions
• 1 vs 2 dimensions (RECIST vs. WHO)
• Imaging of cutaneous lesions imperfect
• Photography helpful but time consuming
• “Pseudo-progression” may be common
• Complete regression may be hard to define
• Role for biopsy confirmation?
• irRECIST has not been validated

- Modified RECIST
  - Allow treatment post progression
  - Use standard RECIST

Goldmacher et al. JCO 2020
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 (anesthetic) responses may utilize different MOA, kinetics
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

Macedo, et al. JITC 2020
Intratumoral Immunotherapy | Integrating Into Combination Therapy
Phase 1 clinical trial of T-VEC and pembrolizumab in melanoma

Without added toxicity

Ribas et al. Cell 2017
T-VEC induces CD8+ T cell recruitment and PD-L1 expression in the TME
T-VEC + pembrolizumab induces CR in immunologically deserted tumors

Ribas et al. Cell 2017
Randomized Phase 2 Clinical Trial: T-VEC + ipilimumab improves ORR

- T-VEC + ipilimumab vs. ipilimumab alone Stage IIIb-IVM1c melanoma

- Response rates (N=198) more than doubled with T-VEC + ipilimumab vs. ipilimumab alone (38% vs. 18%)

- For visceral lesions (none injected), the response rate was 35% for T-VEC +ipilimumab vs. 14% for ipilimumab alone

- No additional toxicity as compared to ipilimumab alone

Chesney et al JCO, 2017
Outstanding Issues with IT therapy

• How should eligibility be modified from standard clinical studies?
• Regulatory requirements for biodistribution are evolving
• Should all tumor be injected?
• Can IT agents be delivered by intravenous route?
• What are appropriate clinical endpoints?
  • Monitoring of injected vs. un-injected lesions
• What is the optimal schedule for treatment (including when to stop), especially in combination with other agents?
• How should component contributions be confirmed?
  • Clinical vs. biomarker validation
• How long should contact transmission be monitored?
• Is neoadjuvant treatment better?
Conclusions

• Intratumoral immunotherapy is defined as local delivery of agents that induce innate/adaptive anti-tumor immune responses

• There are many types of intratumoral immunotherapy in clinical development
  • Physical approaches
  • Drug-based approaches

• Intratumoral immunotherapy pre-clinical considerations
  • Validate cell entry receptors, extent and type of cell lysis, local and distant anti-tumor activity in immune competent murine systems, immunogenicity

• Intratumoral immunotherapy clinical and logistical considerations
  • Must consider dosing, schedule, volume, biodistribution, anti-viral responses, eligibility and endpoint responses

• Intratumoral immunotherapy as part of a rational combination approach
  • Neoadjuvant, IO combinations, non-IO combinations