Interventional Immu-oncology

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Recommended Citation
Costin J. Interventional Immu-oncology. 2nd year resident presentation at Aurora St. Luke's Medical Center; April 27, 2023; Milwaukee, WI.

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Interventional Immuno-oncology

HIT-IT

Human intratumoral immunotherapy

James Wade Costin
The story of Dr. William B. Coley and tumor regression

- Bone surgeon practiced 1891 -1936 and credited as the godfather of immunotherapies.

- Young patient sarcoma died 2 weeks after amputation from pulmonary metastatic disease.

- Researched case reports of cancer remission and found multiple examples throughout history of tumor regression following acute infection. (St. Peregrine the catholic patron saint of cancer)
Coley found a living patient 0

**Fig. 1.**

Recurrent round-celled sarcoma. Spontaneous recovery following accidental erysipelas. Photograph taken seven years after the cure.
Coley’s toxin

• First 10 patients were injected with live S. Pyogenes bacteria at tumor site. Several patients had tumor regression but 2 patients died from infection.

• Later went on to create the first cancer vaccine: Coley’s toxin a mix of dead Streptococcus pyogenes and Serratia marcescens (Gram + and Gram -).

• Patients with prolonged fever had the best treatment response.

• Treated more than 1,000 patients with this toxin. Hard to validate actual numbers but even his critics at the time admitted it was curative for at least small percentage of patients.
The Treatment of Inoperable Sarcoma by Bacterial Toxins (mixed toxins of the *Streptococcus* erysipelas and *Bacillus prodigiosus*)

**Fig. 6.**

Recurrent angio-sarcoma (round-celled).

**Fig. 7.**

Disappearance of tumour under toxins. Patient well eight years later.
What happened to Coley’s Toxin?

• Hard to reproduce results – Coley treated patients for multiple months and sometimes years with numerous intratumoral injections.

• No standard manufacturing process.

• Overshadowed by radiation therapy developed at the same time and later chemotherapy.

• Mechanism of action was not understood and bacteria curing cancer seemed counterintuitive at the time. However, there has been a resurgence of interest last decade.
• Two or more acute inflammatory responses occurring at about the same time in cancer patients with documented spontaneous remission.

• Some of these were related to acute infections but others examples include allergic reaction after vaccine and acute auto immune episode.

• Mechanism of action likely related to negating the inhibitory effect and activating systemic innate immunity.
Basics of Immuno-Oncology

• The immune system is great at killing cancer, specifically CD4 and CD8 T cells.
• Cancer is great at hiding from the immune system.

PD1 and PDL1
CTLA
Miracle Immunotherapy drugs

Pembrolizumab
Nivolumab
Cemiplimab

Atezolizumab
Avelumab
Durvalumab

T cell
Activation

TCR
MHC
Peptide

PD-1
PD-L1

Ipilimumab
CTLA-4
B7
CD28

Dendritic cell

Cancer cell

Cancer cell proliferation
Why shift towards intratumoral injections?

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<td><strong>Advantages</strong></td>
<td>Practical</td>
<td>Practical</td>
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<td>Low therapeutic index, High toxicity</td>
<td>On-target, off-tumour toxicity</td>
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Isolated Limb Perfusion With High-Dose Tumor Necrosis Factor-α in Combination With Interferon-γ and Melphalan for Nonresectable Extremity Soft Tissue Sarcomas: A Multicenter Trial


**Conclusion:** ILP with TNF, IFN, and melphalan is a safe and highly effective induction biochemotherapy procedure that can achieve limb salvage in patients with nonresectable extremity STS. TNF is an active anticancer drug in humans in the setting of ILP.

Cytokine cascade is essential for anti-tumor response but can also be deadly.

Recent case with IL-12 therapy. TNF from previous example was relatively abandoned due to dose limiting toxicities.
Modern Immuno-Oncology is complex

- **Antigen presenting cells (APC)**
  - Tolerogenic
  - DC differentiation & maturation
  - Antigen presentation
  - T cell activation

- **Macrophages**
  - Population expansion
  - Immunosuppressive effects e.g. TCR peroxynitration, T cell apoptosis

- **Natural killer cell**
  - NK-mediated killing by modulating activating or inhibitory receptors
  - HLA-I, NKG receptor, NKp44

- **Dendritic cell**
  - CD80, CD86

- **Myeloid-derived suppressor cell**
  - G-CSF, ENTPD2/CD39L1

- **Cancer stem cell**
  - Stemness markers CD24, CD44, CD47, CD133, EpCAM, ALDH
  - Self-renewal pathways: Wnt/β-catenin, Hedgehog, Notch
  - EMT
  - Drug resistance
  - Tumorigenesis
  - Treatment relapse and tumor reoccurrence

- **T lymphocyte**
  - PD-L1 expression
  - CD4 & CD8 T cell proliferation
  - Antitumor response

- **Regulatory T cell**
  - Population expansion
  - Immunosuppressive effects affect plasticity

**Tumor Immune MicroEnvironment**
Cells that matter just as much as CD4 and CD8 T cells (Cancer’s favorite friends)

Treg – Inhibit inflammation and auto immune responses
• Stop other T cells from killing tumor and tumor specific T cells from proliferating (aka exhausted T cells)

Macrophages – Differentiated monocytes in 2 modes
• Repair – stimulate fibroblasts, angiogenesis, etc…
• Defense – active phagocytosis, proinflammatory cytokines, and antigen presentation

APCs (Dendritic cells) - Prime and proliferate lymphocytes
• Active mature vs. Tolerogenic dendritic cells
• Critical for tumor associated tertiary lymphoid structures
General principle of HIT-IT

Immunogenic intratumoral injections can cause significant local and systemic immune responses. Through a complex mechanism this switches the immune system from tolerating and supporting cancer to killing it.

A shift in paradigm:
Indirectly curing cancer. Akin to poking the bear.
Pathologic features of successful treatment

Increased
• T and B cells
• APC
• TA-TLS organized clusters of the above cells
• Defense type macrophages

Decreased
• Treg
• Repair type macrophages
• Fibroblasts
Abscopal effect – Nontreated tumor bulk regression

69 yo metastatic RCC pre and 5 weeks post 4 injections to neck mass with CFA (Dead Mycoplasma)
Classes of intratumoral immunotherapies
Intratumoral Injection of *Clostridium novyi*-NT Spores in Patients with Treatment-refractory Advanced Solid Tumors
Intratumoral Injection of *Clostridium novyi*-NT Spores in Patients with Treatment-refractory Advanced Solid Tumors
Intratumoral Injection of *Clostridium novyi*-NT Spores in Patients with Treatment-refractory Advanced Solid Tumors
Image guided cryoablation of cancer with intra-tumoral injection of anti-CTLA-4 and PD-1 immune check-point inhibitors

Mark A Rosenberg¹, Jason Williams²

From 30th Annual Meeting and Associated Programs of the Society for Immunotherapy of Cancer (SITC 2015)
National Harbor, MD, USA. 4-8 November 2015

Pre Treatment

2 months Post
Clinical trial NCT03567720
KEYNOTE-890

A Phase 2, Multi-Cohort, Open-Label Study of Intratumoral Tavokinogene Telseplasmid Plus Electroporation in Combination With Intravenous Pembrolizumab Therapy With or Without Chemotherapy in Patients With Inoperable Locally Advanced or Metastatic Triple Negative Breast Cancer (TNBC)

In the previous KEYNOTE-086 trial, treatment with single-agent pembrolizumab led to a modest response rate of 5.3%. Preliminary data from the current study, in which 29% of patients assessed so far have responded, suggest that intratumoral tavokinogene telseplasmid and electroporation may enhance sensitivity to pembrolizumab in this patient population, Dr. Telli said.
Major challenges facing HIT-IT research

• Many novel therapies being tried mostly in phase I and II clinical trials
• Dosage, timing, boost doses
• Combination therapies
• Modified cells and monoclonal antibodies are expensive
• Concurrent treatments (Systemic chemo and immunotherapy agents)
• Concurrent procedures (Ablations, surgeries)
• Patients have variable response
Conclusion

• It’s well documented that triggering the immune system a specific way can lead to tumor regression and cancer remission but it’s really complex.

• Intratumoral immunotherapy is a way to take advantage of this phenomenon and will likely be the future of cancer treatment.


https://clinicaltrials.gov/ct2/show/NCT03567720