New technologies applicable to bladder hyperthermia

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Learning objectives

• Understand how fever-range hyperthermia can influence cancer biology

• Understand fundamental concepts of heat-targeted drug delivery for bladder cancer

• Describe some novel applications of hyperthermia in bladder cancer
Surgical Section.

July 13, 1909.

Mr. J. Warrington Haward, President of the Section, in the Chair.

The Treatment of Inoperable Sarcoma by Bacterial Toxins (the Mixed Toxins of the Streptococcus erysipelas and the Bacillus prodigiosus).

By William B. Coley, M.D. (New York.)
In the discussion of these cases certain criticism was offered by a surgeon which is typical of the sort of criticism the method received in former days, but which has become less and less frequent in recent years. No criticism was made as to the accuracy of the diagnosis in these cases, nor of the fact that the tumours disappeared and the patients themselves were in perfect health. The patients were present as visible proof of the latter fact, but this was the line of reasoning: (1) The treatment, if of the value claimed, should—after fifteen years—have become generally accepted all over the world and universally adopted. (2) The critic had just returned from Europe, and stated that the treatment was not generally used or accepted there: ergo, it could not be of value. Furthermore, the critic had himself tried it in a certain number of cases many years ago, and had not obtained the same results as myself.
**38–40°C**
- Direct cytotoxic: minimal growth arrest
- Immune: increased heat shock proteins (from danger signal to immune system); activation of dendritic cells, NK cells and phagocytes; cross-priming of CD8+ T cells; improved lymphocyte trafficking (increase cell adhesion molecules, cytokine and chemokine release → adaptive immune response)
- Vascular: improved tumor blood flow (vasodilation)

**40–43°C**
- Direct cytotoxic: linear growth arrest (reversible)- M and S phase cell cycle arrest; brief decrease in RNA synthesis; prolonged reduction in DNA synthesis; impaired DNA repair
- Immune: as above
- Vascular: improved tumor blood flow (improved tumor oxygenation, improved drug delivery)

**>43°C**
- Direct cytotoxic: exponential growth arrest (irreversible); protein denaturation; apoptosis
- Immune: decreased heat shock proteins expressions; immunosuppression (inactivation of lymphocytes and NK cells)
- Vascular: reduced tumor blood flow (endothelial cell swelling, microthrombosis, increased vascular permeability → adjacent vasodilatory “steal”)
The key advantages of hyperthermia

1. Minimal toxicity

2. Can be administered in many ways

3. Can be combined with other therapies
   - Synergistic (not just additive)

4. Can be combined with immunotherapies
<table>
<thead>
<tr>
<th>Drug</th>
<th>Treatment time (min)</th>
<th>TER 41.5 °C</th>
<th>TER 43.5 °C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cisplatin</td>
<td>30</td>
<td>1.48</td>
<td>1.59</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>30</td>
<td>2.28</td>
<td>2.74</td>
</tr>
<tr>
<td>Ifosfamide</td>
<td>30</td>
<td>1.52</td>
<td>–</td>
</tr>
<tr>
<td>Ifosfamide</td>
<td>90</td>
<td>3.60</td>
<td>–</td>
</tr>
<tr>
<td>Melphalan</td>
<td>30</td>
<td>3.60</td>
<td>–</td>
</tr>
<tr>
<td>BCNU</td>
<td>30</td>
<td>2.27</td>
<td>2.71</td>
</tr>
<tr>
<td>Bleomycin</td>
<td>30</td>
<td>1.24</td>
<td>1.65</td>
</tr>
<tr>
<td>Mityomycin C</td>
<td>30</td>
<td>1.05</td>
<td>–</td>
</tr>
<tr>
<td>5-Fluorouracil</td>
<td>30</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Doxorubicin</td>
<td>30</td>
<td>1.00</td>
<td>1.00</td>
</tr>
</tbody>
</table>

Data taken from Urano et al.\textsuperscript{103}
Heating options for the bladder
Deep regional hyperthermia

BSD/Pyrexar

Alba 4D

AMC

Thermotron
## Deep regional hyperthermia

<table>
<thead>
<tr>
<th>PROS</th>
<th>CONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Wider field of heating</td>
<td>1. Large device</td>
</tr>
<tr>
<td>2. Treatment planning</td>
<td>2. RF shielded room</td>
</tr>
<tr>
<td>3. Used for a variety of tumors</td>
<td>3. High cost</td>
</tr>
<tr>
<td></td>
<td>4. Slow heating</td>
</tr>
<tr>
<td></td>
<td>5. Not generalizable for NMIBC</td>
</tr>
<tr>
<td></td>
<td>6. Contraindicated with devices or hip replacements</td>
</tr>
</tbody>
</table>
Intravesical radiofrequency antennae

Synergo SB-TS 101 device
## Intravesical RF antennae

<table>
<thead>
<tr>
<th>PROS</th>
<th>CONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Most well studied</td>
<td>1. Medium size device</td>
</tr>
<tr>
<td>2. Generalizable in NMIBC</td>
<td>2. High cost</td>
</tr>
<tr>
<td>3. No need for physics team</td>
<td>3. Bladder burns (? significance)</td>
</tr>
<tr>
<td></td>
<td>4. Contraindicated with devices</td>
</tr>
</tbody>
</table>
Intravesical conduction

Combat BRS

Elmedical BWT
<table>
<thead>
<tr>
<th>PROS</th>
<th>CONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Small device</td>
<td>1. Limited to bladder</td>
</tr>
<tr>
<td>2. Inexpensive</td>
<td>2. Bubble accumulation</td>
</tr>
<tr>
<td>3. Generalizable for NMIBC</td>
<td>3. Not for MIBC (?)</td>
</tr>
<tr>
<td>4. Can trigger heat-targetable drugs</td>
<td></td>
</tr>
<tr>
<td>5. Can be used with other devices and hip prostheses</td>
<td></td>
</tr>
<tr>
<td>6. No need for physics team</td>
<td></td>
</tr>
</tbody>
</table>
Submillimeter fiber optic microprobes and silicone germanium thermistors
Temperature probe placement for heat mapping

- Bladder
- Internal iliac vein
- Urethra
- Vagina
- Rectum
Figure 1. CONSORT trials study diagram.

Figure 2. Cumulative incidence of bladder cancer recurrence.
Intravesical magnetic nanoparticle hyperthermia
Iron oxides (e.g., magnetite)
Figure 4.
Pretreatment MRI image showing: (a) rat bladder filled with 0.25 ml saline/gadolinium, and (b) 0.5 ml of magnetic fluid at 0.5mg/ml. In both images, it is possible to visualize the catheter placement in the Bladder (arrows).
Thermally sensitive liposomes for drug delivery
Why use a thermally sensitive drug?

- Can achieve drug concentrations 10-30X higher in the tumor
- Can target drug delivery to specific anatomical locations (by heating those spots)
- Can reduce drug dose because of better delivery and decrease systemic toxicity
The video you are about to see shows real time delivery of free drug to heated tumor tissue.
Using heat-activated drugs makes sense

- Improve tissue drug levels (increase efficacy)
- Might allow for lower systemic doses
- Target drug to organs/sites of need
- Number of agents growing:
  - Doxorubicin
  - Cisplatin
  - Gemcitabine
  - Others…
Enhancing immune effects of hyperthermia
Antigen presentation to the T cell

APC

MHC/Ag

TCR

B7-1/2

CD28

T cell

T cell response
Coinhibition impairs IL-2 response
Costimulation and Coinhibition

Bladder cancer, BCG failure and B7-H1 (PD-L1)
Targeting the ligand
Targeting the receptor

- APC
- MHC/Ag
- TCR
- B7-1/2
- CD28
- Anti-PD-1
- PD-1
- T cell response

T cell response
Blocking PD-L1 can cure some cancers

Combining HT with immunotherapy makes sense

- HT itself is immunogenic (auto-vaccination)
  - Heat shock proteins
  - Upregulate MHC I

- HT encourages leukocyte trafficking
  - Selectin and integrin regulation
  - Endothelial changes

- HT activates immune cells
  - DCs and NKs
Synergistic immuno photo nanotherapy (Symphony)
Combined Therapy

Laser + Gold Nanostars (AuNS) + Anti-PDL-1 Antibody (Ab)

Targeting and killing primary and secondary tumor cells

Primary tumor Cells → Dying tumor cells

Secondary tumor Cells → Dying tumor cells
Visible Tumor

Dorsal skin-fold chamber

8 mm dia Window Chamber and Clip

Visible Tumor

Marker

FLIR A6703sc

- Best IR camera available (5 μm resolution)
- Can be used with Saphire or BaF₂ windows
- Markers/scratches can be used as references
- Sees nanostars heating (2 min laser exposure)
- Could map fever range immune response
Immune System (CD4) Fluorescence

- Scanning stage microscopy with Zeiss AxioSkop II (fluorescence or bright field)
- Can be used with Saphire or BaF₂ windows
- Diamond scratches can be used as references
- Sees CD4 accrual (30 min after heating)
- Could map fever range immune response
Before treatment 6 days after heating GFP myeloid
Treated side

Synergistic Effect on Nanostar (Intravasc?) Alone

Group F


Mouse 1 Mouse 2 Mouse 3 Mouse 4

Nanostar HT

Group D


Mouse 1 Mouse 2 Mouse 3 Mouse 4 Mouse 5

Immunootherapy

Group A


Mouse 1 Mouse 2 Mouse 3 Mouse 4 Mouse 5

Nanostar HT + Immunotherapy

Untreated side

Abscopal Effect on Nanostar (Intravasc?) Alone

Group F


Mouse 1 Mouse 2 Mouse 3 Mouse 4

Nanostar HT

Group D


Mouse 1 Mouse 2 Mouse 3 Mouse 4 Mouse 5

Immunootherapy

Group A


Mouse 1 Mouse 2 Mouse 3 Mouse 4 Mouse 5

Nanostar HT + Immunotherapy
Summary 1: What does the future hold?

- Different devices for different applications
  - Office devices for NMIBC
  - Hospital (possibly office?) devices for MIBC

- New heat-targeted drugs
  - Deliver drug better (more drug to tumor)
  - Activate drug (same drug works better)
  - Less toxic (lower doses)
Summary 2: What does the future hold?

- Combinations with immunotherapy
  - Use HT as a auto-vaccination method
  - Use checkpoint inhibitors

- Nanoparticles may be useful new agents
  - Could be used intravesically or systemically
Team Science