Photoimmunotherapy

Near infrared photoimmunotherapy: A new light-based treatment for cancer

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Disclosures

- No financial conflict of interest
- Patents on photoimmunotherapy
- Licensed to Rakuten Asypirian.com
- Indebted to Hisataka Kobayashi (HK)
History

Brief History of Light Therapy

• Laser Ablation
  – Thermally burns tissue
  – In plastic surgery laser light can be tuned to selectively ablate discolored lesions
  – Requires expert control of laser.

• Photodynamic therapy
  – Inject a photo-porphyrin
  – Slightly greater uptake in tumors than normal
  – Narrow therapeutic window
PDT

**Photodynamic therapy (PDT)**

- **Step 1**: Inject photosensitizer
- **Step 2**: Concentrates in the tumor
- **Step 3**: Activated by light
- **Step 4**: Tumor is selectively destroyed

**Non specific uptake (normal tissue accumulates)**
- Side effects limit efficacy

Kills by apoptosis - non immunogenic
Photosensitivity for 2-8 weeks post injection
PDT in humans

First Person to Receive PDT

Inject hematoporphyrin derivative (HPD),
wait 10 min, move to direct sunlight
From: Meyer-Betz Deutsches Klin Med 112: 476, 1913
Drug administration
Surgery

Surgery Conducted by Dr. William Sindelar, Surgery Branch NCI (mid 1980s to early 1990s)
Thoracic malignancies

Clinical PDT Studies
Disseminated Intra-peritoneal Malignant Neoplasms

Thoracic Malignancies PDT: Dr. Harvey Pass, Surgery Branch NCI (late 1980s to early 1990s)
Light therapy

Light Therapy: Is there a better way?

Excitation
(Energy of a single photon)

Emission
(Fluorescence
Heat
Chemical reactions)
Targeted imaging with fluorescent dyes
NIR dyes

Trastuzumab – NIR dyes

% fluorescence

Trast-dye combination

Tras-IR700

Dead cells!!!
Near infrared photo-immunotherapy (NIR-PIT)

- Humanized monoclonal antibody (biology/medicine)
  Highest binding specificity, greatest in vivo target delivery; applicable to the clinical practice.

- Hydrophilic phtalocyanine (chemistry)
  Great absorber of 700nm light, great urinary excretion. Works as a "nano-dynamite" to damage only binding cell membrane.

- Near-infrared light of 700 nm (physics)
  Non-ionizing radiation, great tissue penetration, high energy photon to ignite targeted cytotoxicity.

Release of cellular contents
NIR-PIT kills targeted cells
Cell swelling

NIR-PIT induced cell swelling and release of intracellular contents

Low coherent quantitative phase microscope (QPM)

-3.6 sec.

20 µm
Photoimmunotherapy
Filopodia

Alterations in Filopodia in 3T3/HER2+ cells

NIR-PIT

Control
Alterations in Filopodia in MDA-MB-468 cells

NIR-PIT

Control
Tumor reduction

NIR-PIT reduces tumors in nude mice

- PAN-IR700
- PAN-IR700/White

Pre

Day0

NIR light

Day2

Tumor volume (mm²)

Time after Ab-IR700 injection (days)

Survival

Target: EGFR

Time after Ab-IR700 injection (days)
Toxicity studies of cetuximab-IR700 in NHPs showed no cutaneous toxicity

No systemic toxicity

Phase 1 dose finding study in inoperable recurrent Head and Neck Cancer was approved by FDA
  • Cetuximab-IR700 dose finding
  • Light dose finding
Head and neck cancer

644,000 new cases each year,
Two thirds are in developing countries
In the US, 12,460 deaths per year

Organs That Are Affected by Head and Neck Cancers
- Palate
- Lips
- Tongue
- Sublingual salivary gland
- Nasal cavity
- Parotid salivary gland
- Pharynx
- Submandibular salivary gland
- Esophagus
- Larynx
Treatment Initial: Chemoradiation and surgery

- Recurrence:
  - Combination chemotherapy: 10-36% RR
    - Duration of response: 5.5 months
  - Immunotherapy, antibody therapy
  - Re-irradiation: significant toxicity
    - Quality of life strongly affected.
  - Photodynamic therapy (Foscan)
    - Improves median survival
    - Significant side effects-normal tissue damage
    - Carotid rupture, fistulas, perforations, etc.
Phase I/II trial

**Phase I/II, Head and Neck Cancer Study Design**

Phase I study, recurrent/unresectable Head and Neck Cancer that failed conventional therapies. (Two parts: part I drug dose escalation, and part II light dose escalation.)

**Step 1:** RM-1929 infusion

**Step 2:** Tumor illumination at 24 h

**Part I**

<table>
<thead>
<tr>
<th>RM-1929 Dose Escalation, fixed light dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Expected Duration: 6 months</td>
</tr>
<tr>
<td>Total Patients: up to 24 → 12</td>
</tr>
</tbody>
</table>

Description: dose escalation study of RM-1929 in various cohorts to determine the **safety profile and the anticancer activity of the treatment with NIR light 50 J/cm²**.

- Cohort 1: 160 mg/m² of RM-1929
- Cohort 2: 320 mg/m² of RM-1929
- Cohort 3: 640 mg/m² of RM-1929
- Cohort 4: 1280 mg/m² of RM-1929

**Part II**

<table>
<thead>
<tr>
<th>Light Energy Escalation, fixed drug dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Expected Duration: 6 months</td>
</tr>
<tr>
<td>Total Patients: up to 18 → 12</td>
</tr>
</tbody>
</table>

Description: light escalation study various cohorts to determine the **safety profile and the anticancer activity of the treatment**

- Cohort 1: 150/200 (J/cm² or J/cm)
- Cohort 2: 250/300 (J/cm² or J/cm)
- Cohort 3: To be determined

Target: EGFR

Clinical Sites: up to 5 clinical sites in the USA
LED laser system

Optical engineering
LED of ~$180 (~100 mW) for preclinical
→ Laser of $30k (< 8W) for clinical
Remarkable Data from First 4 Patients

Very well tolerated, no significant AEs. No damage to normal tissue and good healing. Now >40 patients have been treated

<table>
<thead>
<tr>
<th>Patient</th>
<th>Tumor</th>
<th>Safety</th>
<th>Anticancer Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>#1</td>
<td>Large cancer in the throat and nasopharynx: 3x6 cm</td>
<td>No AEs</td>
<td>&gt;70% tumor reduction at 1 month</td>
</tr>
<tr>
<td>#2</td>
<td>Large throat cancer 3x6 cm</td>
<td>No AEs</td>
<td>Complete response (100% tumor death)</td>
</tr>
<tr>
<td>#3</td>
<td>Large 3x3x2 rapidly growing recurrent tongue cancer</td>
<td>No AEs</td>
<td>&gt;70% tumor reduction at 2 weeks</td>
</tr>
<tr>
<td>#4</td>
<td>Large cancer in the throat: 9x4 cm</td>
<td>No AEs</td>
<td>Complete response (100% tumor death)</td>
</tr>
</tbody>
</table>
Tissue repair

NIR-PIT is highly effective and tissue repairs after therapy

Multiple surgeries X, chemo-radiation X, -> recurrence

Before

Immediately after

Target: EGFR
“Almost immediately, you can see the tumor start dying. It turns white and melts away,” Stenson says. Because the payload drug remains inert unless activated by a specific wavelength of light that doesn’t damage human tissue, destroying the cancer cells causes almost no damage to surrounding cells. “The drug/dye combination (the monoclonal antibody combined with the photosensitizer) is not toxic until activated by near infrared light, thus is very safe from a systemic perspective,” Stenson explains.
Phase II study

Clinical Trial Results Ph1/II
AEs have been minimal
No Photosensitivity
100% Response rate
57% Durable response rate

NCI Trial in the Clinical Center:
Optical/PET/MRI imaging after PIT
PI: Valia Saloura MD ACI
To start in 1st quarter 2019
### Overall response rates (Phase 2: NIR-PIT RM-1929)

<table>
<thead>
<tr>
<th>Best overall response (n=29)</th>
<th>RM 1929 (640mg/m²): n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete response</td>
<td>4 (13.8)</td>
</tr>
<tr>
<td>Partial response</td>
<td>9 (31)</td>
</tr>
<tr>
<td>Stable disease</td>
<td>11 (37.9)</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>5 (17.2)</td>
</tr>
<tr>
<td>CR+PR</td>
<td>13 (44.8)</td>
</tr>
<tr>
<td>CR+PR+SD</td>
<td>24 (82.8)</td>
</tr>
</tbody>
</table>

#### Outcome in 10 patients who previously failed anti-PD1 Rx

<table>
<thead>
<tr>
<th>Confirmed objective response rate</th>
<th>Complete responses</th>
<th>Disease control rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>3/10 (30%)</td>
<td>1/10</td>
<td>9/10 (90%)</td>
</tr>
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</table>

Best ORR 40%
Therapeutic options

**Therapeutic Options for Recurrent HNSCC**

- 30-50K new patients per year (EU, USA) + 10K Japan

**First Line Recurrent**
- Platinum based Chemo
  - ORR 16%, CR 0%
  - PFS 3.3 m
  - OS 7.4 m
- Erbitux + Platinum
  - ORR 36%, CR 0%
  - PFS 5.6 m
  - OS 10.1 m

**2nd Line Recurrent**
- Erbitux single agent
  - ORR 13%, CR 0%
  - PFS 2.8 m
  - OS 6.1 m
- Opdivo single agent
  - ORR 13.3%, CR 2.3%
  - PFS 2 m
  - OS 7.5 m

**3rd Line Recurrent**
- RM 1929 single agent
  - ORR 45%, CR 14%
  - PFS 5.7 m
  - OS 9.5 m
Nude mice tumors

NIR-PIT cannot cure tumors in nude mice

IR700  IR700/White

Pre  

Day0  

NIR light  

Day2  

Tumor volume (mm³)

Time after Ab-IR700 injection (days)

No treatment  Pan-IR700 300 µg iv, no PIT  Pan-IR700 300 µg iv, PIT 30 J/cm²  No Mab, PIT 30 J/cm²  Pan-IR700 300 µg iv, PIT 30 J/cm²

Survival

Target: EGFR

Time after Ab-IR700 injection (days)

Pan-IR700-PIT day 2
NIR-PIT in humans

NIR-PIT in humans-better than mice!

Pre-PIT

2 month after
Xenograft vs. syngeneic model
Cancer immunity cycle

The Cancer-Immunity cycle

1. Release of cancer cell antigens (cancer cell death)
2. Cancer antigen presentation (dendritic cells / APCs)
3. Priming and activation (APCs & T cells)
4. Trafficking of T cells to tumours (CTLs)
5. Infiltration of T cells into tumours (CTLs, endothelial cells)
6. Recognition of cancer cells by T cells (CTLs, cancer cells)
7. Killing of cancer cells (Immune and cancer cells)

Chen and Mellman. Immunity 2013
Immunogenic cell death

NIR-PIT induced immunogenic cell death

- Dying tumor cell:
  - CRT
  - ATP
  - P2RX7
  - HMGB1

- Immature DC:
  - CD91

- Antigen engulfment:
  - TLR4

- Mature DC:
  - Antigen presentation:
    - MHC complex
    - CD86
    - HLA-DR
    - IL-12
    - CD40

- Immunogenic cell death (ICD):
  - Cell swelling and rupture

- Near infrared photoinmunotherapy (NIR-PIT):
  - NIR light
Immunomodulation with NIR-PIT
(NIR-PIT can activate acquired immunity and destroy cancer cells)
Treg cells
Acquired immunity

NIR-PIT induced acquired immunity by local knockdown of Treg cells

CDE6 T and NK cells migrate to other tumor sites

Suppressed

Activated
Cells in tumor

Nguyen et al Nat Rev Uro June 2017
Treg cell elimination

T-reg cell elimination process/ PIT
Why Fab’(2)?
T cell activation

Concern: T-cell activation process/PIT

Diagram showing the activation process involving IL2, IL15, IL2R-α (CD25), and Treg cells.
IL2 receptor

Treg targeted NIR-PIT via CD25
Importance of IL2 receptor

- No Ab
- IL-2 blocking anti-CD25 Ab-IR700
- Non-blocking anti-CD25 Ab-IR700
Combined tumor targeted and Treg targeted PIT:

![Graph showing tumor volume over time for different treatments]
Combined targeted NIR-PIT
Cancer-PIT combination

Cancer-PIT combined with immuno-activation cure local and distant cancers without recurrence

Reinject 5 million cancer cells
Mechanism
Increased permeability

Kobayashi  Nanoscale 2016
PIT: A Disruptive Technology

• Where do we go from here?
  – Combinations of tumor targeted antibodies and immune targeted antibodies
    • E.g. PSMA and MDSC PIT
    • E.g. EGFR and FGF and Treg PIT

• Who will do it?
  – Initially surgeons in ORs
  – Shift to outpatient, IR delivery
    • “A strong arm and a fiber optic catheter....”
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