Photodynamic Therapy (PDT)
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History
- Sunlight has been known to be associated with certain effects (mainly sunburn) for centuries
- Egyptian, Chinese and Indian cultures used sunlight to treat diseases including vitiligo, psoriasis – Herodotus pioneered “heliotherapy”
- Naturally occurring plant extracts were used
- However the role of light with a mediator has only been known since the late 1800s

Understanding of phototherapy
- Raab in 1900 reported cell death subsequent to interaction of light with chemicals
- Finsen was awarded Nobel Prize in 1903 for establishing scientific basis of phototherapy (smallpox and red light, cutaneous TB with UV)
- In 20th century, mostly used for UV therapy of psoriasis with psoralen or coal tar
- Phototherapy only blossomed in last 30 years.

What is PDT?
- The interaction of certain light wavelengths with chemicals in or adjacent to cells to bring about cell death
- Three components required – a photosensitiser (PS), light of the appropriate wavelength (range) and molecular oxygen

Other reactions
- Reactions which do not use oxygen as an intermediary - such as photoaddition to DNA - are often called “photochemotherapy”
- Psoralens are a common example of such agents
Light

- For PDT to work, light must be able to reach the target cells
- Three processes occur when light reaches the skin
  - Reflection
  - Scattering
  - Absorption

Reflection

- While useful for diagnosis of skin disease, reflected light can play no part in therapy

Scattering

- Scattering is a change in direction of light
- Certain wavelengths of light, particularly in the red region, scatter strongly in tissue (try a laser pointer on your finger!)
- Result is the distribution of light over a larger volume of tissue than the light source might imply

Absorption

- This is the transfer of light energy to the tissue
- Without absorption, no therapy is possible
- Strong absorption however means shallow penetration of light in tissue, weak absorption means more penetration, but less energy transfer

Absorption by chemicals

- Light-absorbing molecules are called chromophores
- Their light absorption profile of each chromophore is dependent on wavelength
- Common chromophores used are Hb, melanin, water, exogenous agents such as tattoo pigments – and photosensitising drugs
UV Phototherapy

- PUVA
  - Psoralen + UltraViolet A
  - Uses psoralen as a photosensitiser
  - Known by ancient Egyptians, but mechanism not clear

- UV-B therapy
  - Uses narrow band of wavelengths ~311nm
  - Probably related to the suppression of major components of cell-mediated immune function.

Light sources

- Most PS react to a narrow band of light wavelengths
- Lasers can be used, but commonly broadband light sources with appropriate filters are employed

The therapeutic process of PDT

- Two stages:
  - The photon (light) energy is transferred to the chromophore (photosensitiser), raising it to an excited state
  - The energy is then transferred to nearby oxygen, which forms singlet oxygen and other highly reactive oxygen species (ROS)
  - These produce cellular damage, killing cells by necrosis or apoptosis

Tumour destruction by PDT

- Mechanism of $^1$O$_2$ + other ROS
  - Direct cellular damage
  - Indirect damage through damage to tumour vasculature
  - Activation of immune response against tumour cells
  - Radius of action of $^1$O$_2$ about 0.02 μm
  - Mechanism of selective uptake in tumour cells of systemic PS not yet well understood, but research developing rapidly

Other effects

- Damage to tumour blood vessels
- Activation of immune system
- Effectiveness limited by penetration/scatter distance of activation light
The ideal photosensitiser (PS)

- Highly specific for the target cells
- Non-specific for normal cells
- Have a short biological half life
- Be systemically non-toxic (in the absence of the activating light)
- Have high absorption in the red and near infrared regions, with high yield of singlet oxygen

Advantages of PDT

- Can treat non-resectable disease with good specificity
- Healthy cells unaffected
- Less (or no) systemic effect compared to chemotherapy

Photosensitisers

- Haematoporphyrin derivative HpD
- First useful porphyrin
- First of current generation of PS (1960)
  - 630 nm laser activation
  - Cervical dysplasia
  - Lung Ca, superficial gastric/bladder Ca, oesophageal adenocarcinoma

Tumour effects of PDT

- ROS can kill cells directly
- Not complete eradication due to inhomogeneous light intensity or cell uptake of PS, as well as consumption of local oxygen supply
- Damage to tumour-associated vasculature, leading to infarction
- Not yet clear just what the long-term effects are
- Activation of immune response
  - Could contribute to selectivity of PS-induced tissue damage

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**Clinical application of HpD**

- Photofrin® I and currently II (more purified version)
- First approved 1994
- Also an HpD
- Used commonly for HGD Barrett’s oesophagus
- Typical regime is IV injection, followed 48 hr later by light activation
- Sunlight to be avoided for 6/52 following injection

**Other HpD variations**

- Photosan ®
- Photogem ®
- Photohem ®

**Temoporphyrin**

- Foscan ®
  - Palliative head/neck Ca
  - First approved 2001
  - 4 day delay before illumination with red (652 nm) laser light
  - Light avoidance for >15 days post-injection

**ALA**

- 5-Aminolevulinic HCl (ALA)
  - Levulan ®
  - Used mainly in actinic keratosis (AK), also for acne scars, broken capillaries and rosacea
  - ALA converted to protoporphyrin (the PS) after topical application
  - Blue light (400-450nm, non-laser) used as light source

**BLU-U**

- Commercial light source for ALA
- Surgery procedure
- Good patient acceptance
- Topical drug - no systemic photosensitivity

- Hydrophilic, limiting applications to superficial lesions
- Sunlight (or intense light) avoidance for at least 40 hr post application required
- 50% of pts. report stinging or burning during treatment
- Other known effects include erythema, hyper/hypo-pigmentation, scaling, itching
ALA methyl ester (MAL)

- Used for AK
- Deeper penetration than ALA allows BCC and Bowen's disease (SCC in situ) treatment
- Red light used for activation (non-laser)

Metvix®

- Metvix cream applied and after ~4 hr of occlusive dressing red light activation used for <10’
- Sun exposure to be avoided for ~2 days
- Stinging or burning sensation during illumination - erythema, crusting
- For AK, 1 treatment. For BCC, 2 treatments 1 week apart
Selective Absorption Results in Necrosis of Target Cells

- Individual Lesions Are Treated
- Leaving Normal Tissues Uninvolved
- No Cumulative Effect – Treatment Can Be Repeated
- No Alopecia, Immune Suppression, Toxicity, or GI Symptoms
- Can Be Performed As an Adjunct Therapy

Fluorescence

- Some PS will fluoresce under UV-A light, allowing localisation of uptake, and even visualisation of occult disease

Non-tumour PDT

**AMD (“wet”)**
- PS is verteporfin (Visudyne®) IV
- Uptake of PS by endothelial cells
- Useful in predominantly “classic” subfoveal choroidal neovascularisation, and is angio-occlusive
- Red (689 nm) light used to activate
- Remnant phototoxicity only lasts a few days

**Acne**
- ALA as PS, or use natural PS in *P. acnes*
- Limited evidence for efficacy
- Some evidence that blue or red light produces a PDT reaction in endogeneous *propionibacterium acnes* bacteria resident in skin – temporary (3-12 months) – effects
- Some cytotoxic effects as well, including temporary damage to hair follicles and epidermis

**Superficial fungal infections**
- *Candida albicans* and other related species becoming more resistant to antifungal agents
- Good progress on using various agents as PS, including Photofrin®, but not yet proven effective

<table>
<thead>
<tr>
<th><strong>Sensitizer</strong></th>
<th><strong>Trade name</strong></th>
<th><strong>Potential indications</strong></th>
<th><strong>Active wavelength</strong></th>
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<td>Photofrin</td>
<td>Cervical, endobronchial, oesophageal, bladder and gastric cancer, and brain tumours</td>
<td>630 nm</td>
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<td>HPD-MA</td>
<td>Verteporfin</td>
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<td>m-THPC</td>
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<td>Lumen</td>
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<tr>
<td>Teneplex</td>
<td>Teneplex</td>
<td>Teneplex from diverse origins</td>
<td>644 nm</td>
</tr>
</tbody>
</table>
Non-tumour PDT

- Onchomycosis
  - Two laser treatments available, using near infrared light
  - Noveon® laser works below thermal levels, with dual activation wavelengths (870/930 nm)
  - Effect is still production of reactive oxygen species but without an exogenous PS
  - Pinpointe® UV laser also used, but has a thermal effect, and may not be as effective

Antimicrobial PDT

- Work being done in response to increasing antibiotic drug resistance
- Some in vitro evidence to show that a broad spectrum of PS agents can show antibiotic effects with no development of resistance
- Only immediate use would be in localised pockets of infection such as skin, wounds and in dentistry

Helicobacter pylori

- Some work being done using blue light and endogeneous porphyrin-based PS
- Too early to know how useful this will be

Side effects of PDT

- Most important effect is skin and eye photosensitivity
- Patients must in most cases cover all exposed skin before going into sunlight, even for very short periods – the sun emits great amounts of light in most regions used in PDT
- Even bright indoor light should be avoided (especially dental lights!!!)
- Time ranges from days to 6 weeks
**Side effects of PDT**

- Other PS effects can include nausea and constipation
- Local inflammation or pain can also result
- Local erythema can also result from over-dosing of the activation light, affecting residual PS uptake in normal tissue
- Also from incomplete removal of excess topical PS
- AMD treatment can result in some temporary or permanent vision loss (up to 4 lines) in up to 5% of patients

**The future**

- Clinical trials are under way to evaluate the use of PDT for cancers of the brain, skin, prostate, cervix, peritoneal cavity
- Other research is focused on the development of photosensitizers that are more powerful, more specifically target cancer cells, and which are activated by light that can penetrate tissue and treat deep or large tumors
- Work under way to investigate ways to improve equipment and the delivery of the activating light

**PDT – a summary**

- Targeted means of treating tumours
- Useful in non-tumour disease
- Shows promise for other applications such as anti-fungals and anti-microbials
- Has potential side effects
- Watch this space!

**The End….**

Thank you for your attention