Light against cancer

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Photodynamic therapy (PDT) uses a photosensitizing agent, light and oxygen to destroy malignant cancer cells. Professor Jacques Piette has been working for a number of years on photosensitizing molecules and the cellular mechanisms implicated during PDT. Together with an international consortium he has written a recent article (1) which summarizes the main driving forces of this treatment in the field of oncology.

In what ways can light interact with our bodies? One example of interaction could be provided by certain medications and chemical substances, called photosensitizing or photosensitizers (PS) that become active in the presence of light and cause cell damage whose classical manifestation are skin rashes, burns or even necrosis. To limit these side effects it is necessary to protect oneself from light during therapy with photosensitive drugs.
Another example: some molecules produced through cellular metabolism are also sensitive to certain wavelengths of light. That is true for porphyrins, molecules found in haemoglobin which ensure the transport of oxygen and CO$_2$, or cytochromes involve in cellular respiration. The absorption of certain wavelengths of light can excite the porphyrins in triggering a series of biological reactions. Fortunately the cells possess different defence and repair mechanisms which serve to limit damage. For various reasons, connected to amongst other things their abnormal proliferation and metabolism, malignant cells accumulate porphyrins whilst healthy cells rapidly eliminate them. 'From that came the idea that in administrating a photosensitizing agent which has procured a certain selectivity as far as malignant cells are concerned, it would subsequently be possible, by lighting them up with an appropriate wavelength, to destroy them without harming the healthy tissues: that is the principle of photodynamic therapy!' summarises Professor Jacques Piette, FRS-FNRS Research Director and the Director of the GIGA-Research Unit at the University of Liège. It was in the 1970s that researchers showed for the first time a total tumor eradication in mice, without any side effects, through the action of hematoporphyrin derivatives and red light. Since these early times photodynamic therapy has been the subject of numerous research programmes and clinical trials which have confirmed its value in the fight against cancer.

The treatment protocol is not very aggressive and relatively simple. A photosensitizer, inactive whilst it is not illuminated, is administered either through direct injection into the tumour in the case of superficial cancers or into the bloodstream for deeper cancers, or applied locally, as it is done in the case of skin cancers. After a certain period of time, called the drug-light interval, the tumour has accumulated a large quantity of the PS - it has become photosensitive - whilst the healthy tissues have eliminated it for the greater part. The doctor then applies a red light to the tumour by lighting it up for a few minutes through direct illumination in the case of superficial cancers or with the help of a laser beam by endoscopy for deeper cancers. The side effects are limited: at the very most a localised pain or a residual photosensitivity during which patients have to avoid being exposed to sunlight.

A photosensitiser and red light

The first generation PS were porphyrins whose selectivity for malignant cells was pretty low. To limit the risk of causing lesions in the healthy tissues around the cancerous tissues being treated, researchers developed PS which had a greater affinity for the malignant cells, whilst being non-toxic and rapidly eliminated by normal cells. They are for the main part derivatives of porpyrhrs, chlorines, bacteriochlorines or phthalocyanines.
But it is also possible to bring about a significant accumulation of endogenous porphyrin within the malignant cells through the aid of 5-aminovulinic acid (5-ALA). ‘In a normal cell,’ explains Professor Piette, ‘during the different enzymatic processes, this amino acid is converted into protoporphyrin IX and then, thanks to heme synthase, into a heme which will be incorporated into haemoglobin. Yet this enzyme is inhibited or very weakly expressed in the majority of malignant cells. Thus if the latter are placed in contact with 5-ALA they will accumulate protoporphyrin IX, which is photosensitive, enabling the malignant cells to be killed through illumination with red light.’

Why red light? Because it is the only one capable of penetrating tissues deeply. In effect the majority of UVCs and UVBs are absorbed by the keratinous layer of the skin. UV-A radiation and visible light pass through the epidermis, but are in part stopped by the haemoglobin of the blood cells and the melanin responsible for skin pigmentation. In the end, only red and infrared cross the epidermis and the dermis to reach the hypodermis, but infrared is to a great extent absorbed by water. The spectral range enabling sick tissues to be treated by light is thus situated in the red.
Oxygen, a toxic agent

In concrete terms the PS present in the malignant cancerous cells absorbs this red light, becomes excited and transmits the energy to molecular oxygen $O_2$. There follows a series of reactions within the cells leading to the formation of reactive oxygen species. The reactive species derived from oxygen which is formed by energy transfer is \textit{singlet oxygen}, $^1O_2$. The latter has a short life span but is very destructive to cells. It reacts with amino acids, oxidizes lipids, alters \textit{proteins}, the \textit{mitochondrions} or the cell nuclei and causes irreversible damage to \textit{DNA}. It is the real cytotoxic agent of PDT. These photodynamic reactions cause tissue necrosis, \textit{apoptosis} and autophagy of the malignant cancer cells. They also have indirect effects which increase the effectiveness of treatment such as the destruction of tumour vascularisation and the induction of inflammatory and immune reactions.

For their part the malignant cells have cell protection mechanisms to limit the cytotoxic effects of PDT. In trying to understand these mechanisms, the GIGA Research Unit’s Laboratory of Virology and Immunology has brought to light the role played by several enzymes which control cell defence mechanisms. In inhibiting these enzymes it is thus possible to deprive malignant cells of their defences. \textit{The results obtained concerning glioblastoma, which are amongst the most aggressive brain tumours, shows that the inhibition of certain key enzymes increases very significantly the tumour's sensitivity to PDT;} says Jacques Piette enthusiastically.
The principle of Photo Dynamic Therapy (PDT)

A photosensitiser (PS) is administered. At the end of a certain lapse of time the PS has accumulated in the malignant cells. Being illuminated by red light activates the PS which, in the presence of oxygen, generates photodynamic reactions which cause irreparable damage to the malignant cell.
**Therapeutic applications**

Compared to surgery, **radiotherapy** and **chemotherapy**, PDT can appear miraculous. It nevertheless only allows small sized and easily accessible tumours to be treated, for example skin, bladder, oesophagus, lung, stomach or cervical tumours. For cancers which are at a more advanced stage or which are more difficult to reach, PDT can be used as a supplement to classic protocols, particularly if the latter prove to be insufficiently effective or provoke resistance. *There are currently effective treatments for numerous cancers. Nevertheless certain amongst them have to be abandoned because the tumours become resistant to chemotherapy or to radiotherapy, for example. One of the major advantages of PDT is that it does not induce any resistance. It allows the volume of the tumour to be reduced and the patient's vital prognosis to be improved,* points out Jacques Piette.

PDT can also be used to diagnose tumours, a procedure named 'photodiagnosis.' Excited by blue light, the PS emits red fluorescence, which enables not only tumours to be located with great precision but also enables surgeons to be guided during tumour ablation (fluorescent guided resection). *Oncology surgeons use PDT to locate the tumour and remove a maximum of sick tissues. If there are still fluorescent cells left after surgery they change their wavelength (from blue to red) and increase the power of the laser beam to eradicate the remaining tumoral cells by photodynamic therapy and thereby obtain an improvement of the effects of dissecting the tumour only,* describes the researcher.

Despite these very encouraging results and the numerous research projects which are still underway, PDT is still under used, apart from in dermatology (certain skin tumours), for bladder tumours or to help in diagnosing brain tumours. Several centres, in England, Germany and France for example use PDT in a repeated manner in the case of tumours which are multi-resistant to classic forms of treatment. No-one doubts that it is just a question of time; more and more university and hospital centres are becoming interested in photodynamic therapy. Recently, PDT has also demonstrated its effectiveness in the fight against **bacterial** infections which are multiresistant to antibiotics.

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