

Next Generation Photodynamic Therapy (PDT) and Sonodynamic Therapy (SDT)

Role of Treatment in Cancer

Photodynamic therapy is the use of light sensitive substances, which accumulate selectively in cancer cells and when exposed to light of an appropriate wavelength causes an excited state, which is able to transfer its energy to oxygen. This transfer of energy causes the electrons in oxygen to rearrange and assume a different electronic configuration, where all electrons in the oxygen molecule have paired up, resulting in a particular electron spin configuration. This is highly reactive and initiates a series of events that leads to the release of Cytochrome C from the mitochondria (these are the engines of the cell and are present in large numbers in all cells) and this initiates tumour cell death. Tumours tend to be hypoxic (lacking in oxygen), so in treatment protocols in some cases, we use ozone auto-haemotherapy, which is a method of increasing oxygen at the tumour site.

Sonodynamic Therapy is the use of low-level ultrasound and this produces tumour destruction from the non-thermal effects of ultra sound, especially cavitations in malignant cells. Ultra sonic cavitations generate free radicals from the breakdown of water molecules. The Photodynamic agent we use is also sensitive to ultrasound frequencies. This approach allows deeper penetration into the body. Sonodynamic therapy is carried out using a simple therapeutic ultrasound machine with an especially designed treatment head known as a manipule, which is applied over the affected area with some ultrasound gel placed on the skin. This is done after the light bed exposure; (see 'A review of research into the uses of low level ultra sound in cancer therapy', Uyu Wang & Mason in Ultra Sonics Sonochemistry, Vol 11, issue 2, April 2004, pages 95 — 130).

Most photo-sensitizers come from a class of naturally occurring compounds called porphorins. Natural porphorins are breakdown products from recycled haemoglobin and are inherently light sensitive. These accumulate in tumours and cause cancer cells to auto-fluoresce.

PDT has several advantages over surgery and radiotherapy: it is comparatively non-invasive, it can be targeted accurately and repeated doses can be given without the total dose limitations associated with radiotherapy, and the healing process results in little or no scarring. PDT can always be done on an out-patient/day case setting as the treatment has no side effects. Possible side effects occur due to tumour breakdown, these are as follows:

1. Tiredness – feeling exhausted which can be treated symptomatically and is quite commonly observed.
2. Discomfort or pain around the tumour site due to inflammation.
3. Occasional mild bruising over tumour site is sometimes observed on the skin following PDT.
4. **If the tumour is attached to a blood vessel, bleeding can occur during treatment because of tumour breakdown. If it is attached to a major blood vessel the consequences can be life threatening**

No photosensitivity from normal ambient light, artificial or natural, has been noted with the use of Sonalux. **As a precaution however**, we advise you to not go out in direct sun light for periods of over half an hour for 1 week following administration of Sonalux.

In prostate cancer, there is a small risk of incontinence and impotence. This has not been noted in any case of prostate cancer treated with this method so far. However, it is noted significantly when fibre optics are inserted into the prostate and PDT is given in this manner. This is not the method we use.

The next generation of Photodynamic Therapy is a significant advance on previous PDT. This uses a specific agent which does not have to be given intravenously and can be given orally. It accumulates selectively in tumour sites and it does not persist in the skin. It is also a whole body treatment, and it does not require the use of lasers. The agent is sensitised by a specialised light bed consisting of several tens of thousands of light emitting diodes, emitting in the red light region and the infra-red region of the spectrum. The treatment programme can be repeated as often as is necessary, and for advanced tumours it is best to treat slowly so as to avoid too rapid a tumour break down in too short a time.

Method of Treatment Using Next Generation Photodynamic Therapy

The patient is assessed clinically. Then the agent is taken orally, with the drops being absorbed under the tongue. 48-72 hours then elapse whilst the agent clears from the skin and accumulates selectively in tumour sites. Following this the patient is exposed on the light bed to appropriate light frequencies from light emitting diodes. The time of exposure is important and can vary from 5 minutes up to 15 minutes for patients with less advanced tumours, to only a few minutes for patients with more advanced tumours (the more advanced the tumour, the slower the treatment programme). Exposure on the light bed initially occurs consecutively on three days following the 48-72 hours after administration of the oral agent.

Further light bed exposure is then calculated on an on-going clinical basis. The patient is given enough oral agent to cover one treatment cycle.

Anecdotally there has been the best success using Next Generation PDT with breast cancer and prostate cancer. Ultrasound is then administered over the tumour area.

We often combine ozone auto-haemotherapy with PDT. PDT relies on the production of singlet oxygen (O). This is derived from oxygen (O_2). Tumours are characteristically hypoxic (showing low oxygen levels). Ozone auto-haemotherapy is an effective way of increasing oxygenation just before light bed exposure, therefore increasing the effectiveness of the PDT.

**OBSERVATIONAL OUTCOMES ON 12 MONTHS OF CASES
TREATED USING A BACTERIOCHLORIN PHOTODYNAMIC AGENT
SENSITIVE TO (660 NANOMETRES), AND TO ULTRASOUND.**

SUMMARY

The results of patients having undergone photodynamic therapy over the last 12 months have been encouraging. In the majority of cases, based on biochemistry pre and post PDT, there has been some tumour cell destruction. We also have regularly achieved some tumour cell destruction in tumours deep in the body.

In the case of bone secondaries, as in practically all cases with bone secondaries they develop increased pain in the bone secondaries post PDT, it is hard to explain this. The reason is that ultrasound does not transmit through bone and red light cannot penetrate into bone either. However, having said that, it appears that we are having results in this situation but the mechanism is unclear. It is too early to say whether the treatment of bone secondaries in this way, from time to time in any particular patient will lead to longer median survival. Currently we have no evidence that our bone secondaries disappear but a clinic based in Australia using a similar approach uses Photodynamic diagnosis and can measure the fluorescence from tumours situated relatively close to the skin using this specific method. In that particular clinic they have been able to show convincingly, one particular patient with non small cell lung cancer with bony metastases in the lumbar 4 vertebra, to show that this disappeared and no longer showed up following photodynamic diagnosis following photodynamic therapy. We are looking into the use of this diagnostic method in order to look at the bone secondary situation in more detail.

In the case of a small number of patients who have had a complete response, it is impossible to say at this stage as to whether they will or will not recur.

It would seem that a sensible way forward with patients with significant tumour, is to repeat this form of photodynamic therapy from time to time to cope with tumour mass or increasing tumour mass.

We are continuing to audit these cases in as detailed a way as possible.

INTRODUCTION

We use a bacteriochlorin agent which is sensitive to red light (616 nanometres) and ultrasound. We have animal studies using the mouse sarcoma 180 model, showing significant tumour destruction from red light and ultrasound (in the case of ultrasound, experiments were done in complete darkness using ultrasound only) and this demonstrated that the agent is sensitive to ultrasound and to red light (616 nanometres).

Where there is significant tumour mass, we have to control the inflammatory response which occurs following PDT. Practically all tumours swell initially if the PDT has been successful, due to a release of large concentrations of pro inflammatory cytokines. The most effective way of controlling this is to use Dexamethasone at a varying dose depending on the severity of the symptoms post PDT in each particular patient.

We have begun to fractionate treatments, as a result of our clinical experience with patients with significant tumour mass.

Judging results from photodynamic therapy, can be challenging as when initially the tumour swells, the tumour could, initially, look bigger on scanning. Because private scans are relatively expensive, doing scans before and after each course of PDT is not an every day option for us. Therefore, we tried to look at biochemistry pre and post PDT. We have looked at tumour markers, relevant to the particular patient being treated and also tumour marker 2 Pyruvate Kinase and cell free DNA. We have compared these to controls of the same tests in patients with stable cancer. Broadly speaking, if we get a significant change in any of these readings pre and post PDT, this corresponds clinically to a useful response. In those patients with no significant change before and after, generally there has not been a significant response to the PDT.

The vast majority of our patients are late stage cancer patients. All post surgery chemotherapy and radiotherapy.

The form of PDT used was well tolerated.

Treatment - the main disadvantage is that where there is significant tumour load, a marked release of pro-inflammatory cytokines occurs and the resulting inflammatory response has, in some cases, to be controlled by the use of Dexamethasone, in a varying dose depending on the specific clinical situation.

We carried out, in as many cases as possible, pre and post PDT, standard bloods, cell free DNA, tumour marker 2 Pyruvate Kinase and an appropriate tumour marker, depending on the case. The laboratories measuring cell free DNA and Pyruvate Kinase have, in each case, one specific biochemist dealing

with these tests. When this biochemist was away on holiday, or where one of the periods when patients were having PDT coincided with public holidays such as Christmas, Bank Holidays, in these situations the blood tests could not be done.

We also looked at using Telomerase but found that the results obtained differed wildly both in the control subjects and in the PDT patients, so this was found not to be a useful measure.

We did control tumour marker 2 Pyruvate Kinase, cell free DNA and standard tumour markers in a range of stable cancer patients. We are currently having these results statistically evaluated. When this has been done we will put in the P value (probability value) for each case.

Tumour Marker 2 Pyruvate Kinase

Cell proliferation is a process that consumes large amounts of energy. A key sensor for this regulation is the glycolytic enzyme, Pyruvate Kinase, which determines whether glucose carbons are channelled to synthetic processes or used for glycolytic energy production. The mammalian tumour marker 2 Pyruvate Kinase isoenzyme, can switch between a less active dimeric form and a highly active tetrameric form which regulates the channelling of glucose carbons either to synthetic processes (dimeric form) or to glycolytic energy production (tetrameric form). Tumour cells are usually characterised by a high amount of the dimeric form leading to a strong accumulation of all glycolytic phosphometabolites above Pyruvate Kinase. Therefore, this looks at glycolytic activity in the body. Tumours tend to be glycolytic.

Essentially, what we have found in our observational study is that Pyruvate Kinase may go up or down in any particular patient but this usually corresponds to a clinically useful response. In other words, there isn't a clear direction as to whether it goes up or down post PDT.

Standard Tumour Markers

Standard tumour markers, such as CA 125 (ovary), CA (oesophagus, lung, bile duct, pancreas, bladder, colon) CA 19.9, (oesophagus, bile duct, pancreas), CA 15.3 (breast) and prostate specific antigen (prostate), tend to go up post PDT but this is not always the case. We find that a significant change up or in some cases down post PDT as compared to pre PDT correlates with a clinical response.

Cell Free DNA

The term 'Free-DNA' is widely used, but Cell-Free DNA is more correct. Most of the non-related DNA in blood plasma is likely to be down to protein molecules (2). Hence, before measuring Cell-Free DNA it is appropriate to use a reagent that uses a proteinase to assist in freeing DNA that is bound to proteins (3). Most circulating DNA has been released from degrading cells and is mainly present as nucleosomal elements from the enzymatic chopping-up of the genomic DNA (4). In healthy people the circulating Cell-Free DNA is at a very low level (2, 5). The top end of normal is 9 units. Higher concentrations are found in malignancy (6 – 11). Autoimmune disorders (4), severe infections (12, 14). Burns and traumatic injuries can also show high levels of Cell-Free DNA. In other words increases are associated with significant disease (15).

The Use of Ozone Autohaemotherapy Together With PDT

We found significantly better results by using ozone autohaemotherapy before each light bed treatment with PDT. Tumour hypoxia is often marked, and during PDT oxygen is consumed as shown in Sitnik et al's (16) paper on the reduction of tumour oxygenation during and after photodynamic therapy.

Immune Response

There is increasing evidence that killing tumour cells using photodynamic therapy resulting in tumour cell necrosis, increases expression of tumour antigen. This should lead to more effective anti-tumour vaccines. It is impossible to say at this early stage whether increased expression of tumour antigen leads to antigen specific T cell responses (17).

Tumour Cell Necrosis

Method of cell death in PDT is by tumour cell necrosis; this as pointed out above produces a marked increase in pro-inflammatory cytokines with an accompanying marked inflammatory response. This can last for several weeks. The use of Dexamethasone, in particular is especially useful in terms of controlling this reaction.

RESULTS FROM PATIENTS WHO HAVE RECEIVED PHOTODYNAMIC THERAPY

BREAST CANCER

CASE 1

Right breast with fungating skin secondaries with liver metastases and a large open area over the right breast.
C8 15.3 pre PDT 201, CA 15.3 post PDT 214.
PK and cell pre DNA not done. Clinically no result.

CASE 2

Breast cancer with bone metastases.
PDT carried out in August 2005.
C15.3 176 pre PDT, went down to 36 post PDT.
Cell free DNA and PK not done.
Some 3-4 weeks following all the bone secondaries were significantly more painful. This patient continued to progress well and we repeated the PDT in July 2006.
C8 15.3, PDT was 76, post PDT went down to 35.
Cell free DNA and PK not done.
Again all the bone secondaries caused increased pain for 3 – 4 weeks following PDT.
This patient remains clinically well.

CASE 3

This patient has a strong family history of breast cancer with several family members having died from breast cancer. She wished to carry out PDT on a prophylactic basis. She also has co-existing Chronic Fatigue Syndrome of many years duration.

Specific bloods before and after were not done in this case. After the PDT the Chronic Fatigue Syndrome improved significantly and has remained better since.

CASE 4

AEG metastatic breast cancer with metastases in the bone and liver.
pre PDT PK 6.3 – post PDT PK 16.9.
Pre PDT cell pre DNA 9.1 – post PDT cell free DNA 16.9.
At the time metastases were more painful from 1 – 5 weeks post PDT.
This patient had a median survival time of 9 months. She is still alive and has a good quality of life over a year later post PDT (at the time of writing this paper).

CASE 5

Breast cancer with multiple bone metastases.
Pre PDT CA 15.3 56 - post PDT CA 15.3 74 – pre PDT cell free DNA 12.4. Post PDT cell free DNA .7. Pre PDT PK 10.2. Post PDT PK 111.
All bone metastases were more painful from week 2 of PDT treatment until 3 weeks after PDT.

This patient is still alive and relatively well some 15 months after carrying out the PDT.

CASE 6

Breast cancer, affecting the skin over the left breast. There is a wide spread tumour over the skin all over the left side of the chest.
Pre PDT CA 15.3 67. Post PDT CA 15.3 133. PK and cell free DNA were not done.

There was significant local improvement in her skin cancer, but this was preceded after the PDT with a marked local inflammatory response which is a common reaction to PDT. This gradually settled down. On grounds of cost she was unable to have a further course of treatment.

CASE 7

CA breast with bony metastases.
Pre PDT cell pre DNA 12.7. Post PDT cell free DNA 21.7.
Pre PDT PK 2.5. Post PDT PK 16.5.
This patient, 9 months following the PDT, remains clinically well and has good quality of life. She has stable disease. All her bony metastases were more painful 2 weeks after PDT.

CASE 8

Metastatic breast cancer in bones and liver.
Median survival 2 months.
Pre PDT CA 15.3 296. Post PDT CA 15.34 111.
This patient died 3 months post PDT.

CASE 9

Carcinoma of the right breast.
This patient decided to do PDT pre lumpectomy. The diagnosis had been made on needle biopsy. On pathology, when the tumour was removed it was found that the tumour had been completely replaced by necrotic tissue, clearly as a result of the PDT which had essentially killed her tumour. We didn't do bloods before and after in this case.

CASE 10

Metastatic breast cancer in liver and bones.
No pre and post bloods were done in this patient (PK and cell free DNA).

Disease progression was noted some 2 months after PDT, therefore, in this case we assume we have had no effect.

CASE 11

Metastatic breast cancer in liver and bones.
Pre PDT CA 15.3: 62. Post PDT CA 15.3:63.
The patient had a median survival of 3 months.
No useful clinical affect was observed in this patient.
She died 4 months after the PDT.

CASE 12

Metastatic breast cancer, with many bony metastases.
Pre PDT cell free DNA 13.4. Post PDT cell free DNA 10.3.
Pre PDT PK 30.7. Post PDT PK 37.9.
As with all our other patients with bone secondaries she noticed increased pain in all her bone secondaries post PDT which lasted 3 weeks.
She is still alive and with a good quality of life some 6 months post PDT.

CASE 13

Metastatic breast cancer with lung secondaries, multiple skin secondaries and some bone secondaries.
Median survival 6 months at the time we first started her on PDT.
Pre PDT cell free DNA 14.8. Post PDT cell free DNA 20.3 .
Pre PDT PK 55. Post PDT PK 32.
On grounds of cost this patient was unable to have a further course of PDT. In the event, she lived for 13 months following the PDT.

CASE 14

Metastatic breast cancer, with multiple bone metastases.
Pre PDT CA 15.3 28. Post PDT CA 15.3 15.
Pre PDT cell free DNA 17.7. Post PDT cell free DNA 21.9.
Pre PDT PK 34.1 . Post PDT PK 23.5.
This patient noticed increased pain in all her bony secondaries for some 2-3 weeks following PDT. Seven months post PDT she is alive and has a good quality of life.

CASE 15

Metastatic breast cancer with multiple bone metastases.
Median survival at the time of starting PDT, 3 months.
Pre PDT cell free DNA 11.4. Post PDT cell free DNA 13.0.
Pre PDT PK 12.7. Post PDT PK 75.
Pre PDT CA 15.3 1336. Post PDT CA 15.3 861.
We do know that this patient was still alive 6 months after PDT, but she had a big inflammatory reaction to the tumour cell death caused by the PDT, and she has been lost to follow up.

CASE 16

CA breast with brain metastases.
Median survival 2 months.
Pre PDT cell free DNA 12.6. Post PDT cell free DNA 10.3.
Pre PDT PK 14.3. Post PDT PK 79.3.
This patient was alive 5 months post PDT, but she remained with symptoms from the brain secondaries.

CASE 17

Metastatic breast cancer with skin, bone and lymph metastases.
Pre PDT cell free DNA 14.4. Post PDT cell free DNA 12.6.
Pre PDT PK 45.9. Post PDT PK 96.9.
This patient had a big inflammatory reaction following the PDT which made her feel significantly unwell. This lasted for some 3-4 weeks.
This patient has been lost to follow up.

CASE 18

Metastatic breast cancer with a fungating lesion in the right axilla.
Pre PDT cell free DNA 17.7. Post PDT cell free DNA 9.1.
Pre PDT PK 13. Post PDT PK 16.4.
Following PDT the fungating area in the right axilla cleared up completely.

CASE 19

Breast cancer with bone metastases.
Pre PDT CA 15.3 73.3. Post PDT CA 15.3 71.3.
Pre PDT PK 29.3. Post PDT PK 70.2.
This patient noticed increased pain in all her bony metastases following the PDT. She is alive with a good quality of life a year post PDT.

COLORECTAL CANCER

CASE 1

Colorectal cancer with liver and lung metastases.
Pre PDT cell free DNA 31.4. Post PDT cell free DNA 20.4.
Pre PDT PK 5.6. Post PDT PK 63.9.
This patient had a median survival of 3 months when we carried out the PDT.
She, in fact, lived for 6 months.

CASE 2

Metastatic colorectal cancer
Cell free DNA pre and post not done on this patient.
Pre PDT PK 39.9. Post PDT PK 26.7.

We did another course of PDT soon after the first course as he was over in the UK from Canada .
The second course of pre PDT PK was 24.7. Post PDT PK was 20.
He had a median survival of 3 months when we started the PDT. He lived for 6 months.

CASE 3

Biorectal cancer with lung metastases
Pre PDT cell free DNA 18.9. Post PDT cell free DNA 11.9.
Pre PDT PK 247.1. Post PDT PK 144.2.
This patient has a median survival of 6 months. At the time of writing this study she is within that time and remains clinically reasonably well with a good quality of life.

CASE 4

Colorectal cancer with lung metastases
Pre PDT cell free DNA 21.9. Post PDT cell free DNA 19.2.
Pre PDT PK 36.2. Post PDT PK 19.7.
She had a CT scan done some 2 months after the PDT and this showed that she was free from secondaries. Her median survival, when we saw her, was 6 months. She is still alive and well 14 months post PDT.

CASE 5

Metastatic colorectal cancer with liver and lung metastases.
Median survival 2 months at the time of doing PDT. No bloods were done before and after (PK and cell free DNA).
This patient lived for 4 months.

CASE 6

Metastatic colorectal cancer with liver metastases.
CEA pre PDT 58.5. Post PDT CEA 127.7.
This patient has been lost to follow up.

CASE 7

Metastatic colorectal cancer with liver secondaries.
Pre PDT cell free DNA 21.7. Post PDT cell free DNA 22.6.
Pre PDT PK 17.1. Post PDT PK 58.9.
When we saw him he had a median survival of 6 months. At the time of writing it is 5 months post PDT.

CASE 8

Metastatic colorectal cancer with liver secondaries.
Pre PDT cell free DNA 16.7. Post PDT cell free DNA 25.2.
Pre PDT PK 138.6. Post PDT PK 83.
This patient has a median survival of 6 months at the time of doing PDT.
She has been lost to follow up.

CASE 9

Colorectal cancer with a tumour situated in the rectum.
He has refused surgery. He complained of a good deal of bowel discomfort.
Pre PDT cell free DNA 18.8. Post PDT cell free DNA 21.7.
Pre PDT PK 25.7. Post PDT PK 4.5.
Following the PDT all the discomfort and disorder eg. bowel habit disappeared. He has been advised to have the tumour restaged but has not done this as yet (as of the time of writing).

PROSTATE CANCER

CASE 1

CA of prostate Gleason 7 with extra capsular spread.
Pre PDT cell free DNA 17.2. Post PDT cell free DNA 7.2.
Pre PDT PK 35.6 Post PDT PK 61.5.
This patient had another course of PDT 3 months after the first course.
Results for this were –
Pre PDT cell free DNA 17.7. Post PDT cell free DNA 20.7.
Pre PDT PK 55.7. Post PDT PK 22.6.
On scanning 2 months after the last PDT he had a complete clearance of his tumour.

CASE 2

Metastatic prostate cancer with bone secondaries and a metastases in the pelvis.

Pre PDT PSA 5.85. Post PDT PSA 5.4.

No other bloods were done before and after in this case.

This patient was having symptoms, all of which cleared up following this course of PDT and he remained clinically well for 18 months. He has now had a recurrence and we are treating him currently.

CASE 3

CA prostate confined to the prostate.

Pre PDT cell free DNA 16.2 Post PDT cell free DNA 17.5.

Pre PDT PK 46. Post PD|T PK 96.4.

This patient remains well and symptom free one year after PDT.

CASE 4

Metastatic prostate cancer with multiple bony metastases in the pelvis and both femurs. Hormone resistant.

Median survival at the time of starting PDT 3 months.

PSA pre PDT 8.3. PSA post PDT 150.

This patient died 2 ½ months post PDT.

CASE 5

Metastatic prostate cancer with multiple bony metastases, hormone resistant.

PSA pre PDT 71. PSA post PDT 108.

Cell free DNA pre PDT 70.4 Cell free DNA post PDT 60.7.

PK pre PDT 51.2 PK post PDT 65.1.

This patient had a median survival at the start of PDT of 4 months.

At the time of writing he is still alive and relatively symptom free 7 months post PDT.

CASE 6

Prostate cancer with some extra capsular spread .

Cell free DNA pre PDT 12.6. Cell free DNA post PDT 17.2.

Pre PDT PK 14.9. Post PDT PK 13.7.

PSA pre PDT 4.4. PSA post PDT 3.2.

Currently it is hard to determine what degree of tumour cell destruction has occurred.

CASE 7

CA prostate confined within the Capsule
Pre PDT cell free DNA 16.4. Post PDT cell free DNA 20.7.
Pre PDT PK 16.2. Post PDT PK 32.5.
This patient remains well.

NON SMALL CELL LUNG CANCER

CASE 1

Non small cell lung cancer with bony metastases at T8 and T12.
Pre PDT PK 42. Post PDT PK 14.
This patient remained well for one year post PDT and now has stable disease.
She repeated the PDT one year later. On the second round of PDT
Pre PDT cell free DNA 28.2. Post PDT cell free DNA 28.6.
Pre PDT PK 14.3. Post PDT PK 40.7.
At the time of writing she remains well.

CASE 2

Non small cell lung cancer with liver metastases.
Pre PDT cell free DNA 14.9. Post PDT cell free DNA 8.2
Pre PDT PK 49.7. Post PDT PK 10.8.
Median survival at the time of first PDT 3 months. This patient lived for 6 months.

CASE 3

Non small cell lung cancer.
Pre PDT cell free DNA 15. Post PDT cell free DNA 20.
Pre PDT PK 26.9. Post PDT PK 25.1.
Median survival 4 months at the first PDT.
She is still alive and clinically well 6 months post PDT.

CASE 4

Non small cell lung cancer.
Median survival 3 months at time of first PDT.
No PK or cell free DNA done before and after on this patient.
This patient is still alive but breathless 6 months later. However, he claimed he was less breathless from 4 weeks after PDT until 12 weeks after PDT.

CASE 5

Non small cell lung cancer with right pleural effusion.
Median survival 3 months at the time of first PDT.
Pre PDT cell free DNA 11.3. Post PDT cell free DNA 22.6.
Pre PDT PK 53. Post PDT PK 83.
This patient is still alive but is breathless 6 months following the PDT.

SMALL CELL LUNG CANCER

CASE 1

This patient had PDT prior to chemotherapy. In this patient PK and cell free DNA before and after weren't done.
She had a remarkable response to chemotherapy post PDT in that she had 90% of tumour clearance. It is highly likely that the PDT contributed to this.
This patient has been lost to follow up.

NON HODGKINS LYMPHOMA

CASE 1

We didn't do PK and cell free DNA before and after PDT in this patient.
She had chemo-resistant recurrent non Hodgkins lymphoma in the abdomen. She had a complete clearance of her tumour following the PDT.

HODGKINS LYMPHOMA

CASE 1

Recurrent Hodgkins lymphoma with a large swelling in the neck.
This tumour is chemo resistant.
Pre PDT and post PDT PK and cell free DNA not done.
This patient had a complete clearance of her tumour. The tumour initially swelled 50% larger than initially, and then gradually over the next month decreased in size. The patient is alive and well currently.

CASE 2

Recurrent Hodgkins lymphoma, chemo and radio resistant.
Large swelling in the left side of the neck extending into the left supraclavicular fossa.
Post PDT this lump swelled to 50% bigger than previously. Then after two and a half weeks it began to diminish in size and at that time was significantly smaller than before we started treating him. Unfortunately, this patient died, probably with liver and kidney failure as a result of too much tumour cell death. (tumour lysis syndrome).

STOMACH CANCER

CASE 1

This patient had a recurrent stomach cancer which was chemo resistant.

Pre PDT PK 70.7. Post PDT PK 6.3.

Cell free not done.

This patient had a marked inflammatory reaction post PDT, and he had a Gastroscopy which revealed marked tumour necrosis inside the stomach.

Unfortunately, this patient was unable to cope with the degree of tumour cell death and eventually died three months post PDT.

CASE 2

Chemo resistant stomach cancer.

Median survival 2 months at the time of treatment.

No PK or cell free DNA done before and after.

This patient died at 4 months post PDT.

PANCREATIC CANCER

CASE 1

This patient had recurrent carcinoma of the pancreas and had previously had two courses of chemotherapy. He also had secondaries in the larynx.

Pre PDT cell free DNA 10.7. Post PDT cell free DNA 10.

Pre PDT PK 66.2. Post PDT PK 61.9.

This patient had no response clinically to PDT.

OVARIAN CANCER

CASE 1

Recurrent ovarian cancer.

This patient has had three previous courses of chemotherapy.

Pre PDT CA 125 29. Post PDT CA 125 45.

This patient had a median survival of 3 months when he saw her. She lived 4 months.

CASE 2

This patient had a granulosa cell ovarian cancer with metastases in the porta hepatis. Cell free DNA weren't done before and after.

This patient's tumour became stable for 10 months following PDT and then began to grow again.

Bloods were not done on this patient. The tumour became stable for 10 months and then started to regrow.

CASE 3

This patient had surgery in 2005 followed by chemotherapy. Then a reoccurrence in early 2006, treated with more chemotherapy. She had several side effects to the second round of chemo from which she only got a partial response.

She decided to try PDT.

Cell free DDNA pre PDT – 14.2

Cell free DNA post PDT – 20.7

Pre PDT PK – 58.7

Post PDT PK – 20.8

Ca 125 pre PDT - 90

Ca 125 post PDT – 133

MRI scan carried out 6/52 after PDT showed large cystic area, consistent with tumour necrosis in the case of her pelvic recurrence situated above and behind the vagina. She wished to do another course of PDT

CASE 4

Stage IV CA ovary.

CA 125 pre PDT 50. CA 125 post PDT 66.

Pre PDT cell free DNA 8.9. Post PDT cell free DNA 14.

Pre PDT PK 32. Post PDT PK 15.

This patient has been lost to follow up.

ADENOCYSTIC CARCINOMA OF THE HARD PALATE

CASE 1

This is an unusual tumour. This patient refused surgery and radiotherapy. She had a large tumour in the hard palate, extending up into the maxillary antrum, causing some blockage of the nose which made it difficult for her to breath.

Post PDT she had increased pain in the tumour for some 2-3 months. Five months later the whole tumour dropped out, and she was able to breath again. However, there has been a local recurrence of the tumour and she is returning for more PDT.

MALIGNANT MELANOMA

CASE 1

This patient had a malignant melanoma with wide spread metastases. He had a median survival of 3 months.

Pre PDT PK 35.7. Post PDT PK 93.1.

This patient died 3 months from when we first saw him.

CONTROLS

These are patients with stable cancers in whom we have carried out either a tumour marker or cell free DNA or PK or all three, at the time intervals we would normally do these tests before and after with our patients who have had PDT.

CASE 1

Mesothelioma of the pleura cell free DNA 12.7, PK 24.3.

One month later cell free DNA 11.2. PK 23.

CASE 2

Uterine cancer.

Cell free DNA 27.7. One month later cell free DNA 27.8.

PK 13.6. One month later PK 14.

CASE 3

Metastatic colorectal cancer.

Cell free DNA 17.2. One month later cell free DNA 17.7.

PK 154.4. One month later PK 156.8.

CASE 4

Breast cancer.

Cell free DNA 19. One month later cell free DNA 18.6.

PK 9.3. One month later PK 9.5.

CASE 5

Carcinoma of the ovary.

Cell free DNA 34. One month later cell free DNA 32.

PSA 4.2. One month later PSA 4.

CASE 6

Prostate cancer.

PSA 5.3. One month later PSA 5.4

CASE 7

Carcinoma of the prostate.

PSA 1.1. One month later PSA 1.4.

CASE 8

Carcinoma of the prostate.

PSA 1.2. One month later PSA 1.3.

CASE 9

Carcinoma of the breast.

CA 15.3 38. One month later CA 15.3 39.

RESULTS IN TABLE FORM

Case	Tumour marker		PK		cell DNA	
	pre PDT	post PDT	pre PDT	post PDT	pre PDT	pre PDT
Breast cancer	CA 15.3 pre	CA 15.3 post				
1	201.0	214.0	ND	ND	ND	ND
2	176.0	36.0	ND	ND	ND	ND
2R	76.0	35.0	ND	ND	ND	ND
3	ND	ND	ND	ND	ND	ND
4	ND	ND	6.3	16.9	9.1	16.9
5	56.0	74.0	10.2	111.0	12.4	7.0
6	67.0	133.0	ND	ND	ND	ND
7	ND	ND	2.5	16.5	12.7	21.7
8	296.0	111.0	ND	ND	ND	ND
9	ND	ND	ND	ND	ND	ND
10	ND	ND	ND	ND	ND	ND
11	62.0	63.0	ND	ND	ND	ND
12	ND	ND	30.7	37.9	13.4	10.3
13	ND	ND	55.0	32.0	14.8	20.3
14	28.0	15.0	34.1	23.5	17.7	21.9
15	1336.0	861.0	12.7	75.0	11.4	13.0
16	ND	ND	14.3	79.3	12.6	10.3
17	ND	ND	45.9	96.9	14.4	12.6
18	ND	ND	13.0	16.4	17.7	9.1
19	73.3	71.3	29.3	70.2	ND	ND
Colorectal cancer	CEA pre	CEA post				
1	ND	ND	5.6	63.9	31.4	20.4
2	ND	ND	39.9	26.7	ND	ND
2R	ND	ND	24.7	20.0	ND	ND
3	ND	ND	247.1	144.2	18.9	11.9
4	ND	ND	36.2	19.7	21.9	19.2
5	ND	ND	ND	ND	ND	ND
6	58.5	127.7	ND	ND	ND	ND
7	ND	ND	17.1	58.9	21.7	22.6
8	ND	ND	138.6	83.0	16.7	25.2
9	ND	ND	25.7	4.5	18.8	21.7

Case	Tumour marker		PK		cell DNA	
	pre PDT	post PDT	pre PDT	post PDT	pre PDT	pre PDT
Prostate cancer	PSA pre	PSA post				
1	ND	ND	35.6	61.5	17.2	7.2
1R	ND	ND	55.7	22.6	17.7	20.7
2	5.9	5.4	ND	ND	ND	ND
3	ND	ND	46.0	96.4	16.2	17.5
4	8.3	150.0	ND	ND	ND	ND
5	71.0	108.0	51.2	65.1	70.4	60.7
6	4.4	3.2	14.9	13.7	12.6	17.2
7	ND	ND	16.2	32.5	16.4	20.7
Non small cell lung cancer						
1	ND	ND	42.0	14.0	ND	ND
1R	ND	ND	14.3	40.7	28.2	28.6
2	ND	ND	49.7	10.8	14.9	8.2
3	ND	ND	26.9	25.1	15.0	20.0
4	ND	ND	ND	ND	ND	ND
5	ND	ND	53.0	83.0	11.3	22.6
Small cell lung cancer						
1	ND	ND	ND	ND	ND	ND
Non-Hodgkin's lymphoma						
1	ND	ND	ND	ND	ND	ND
Hodgkin's lymphoma						
1	ND	ND	ND	ND	ND	ND
2	ND	ND	ND	ND	ND	ND
Stomach cancer						
1	ND	ND	70.7	6.3	ND	ND
2	ND	ND	ND	ND	ND	ND
Pancreatic cancer						
1	ND	ND	66.2	61.9	10.7	10.0
Ovarian cancer	CA 125 pre	CA 125 post				
1	29.0	45.0	ND	ND	ND	ND
2	ND	ND	ND	ND	ND	ND
3	90.0	133.0	58.7	20.8	14.2	20.7
4	50.0	66.0	32.0	15.0	8.9	14.0

Case	Tumour marker		PK		cell DNA	
	pre PDT	post PDT	pre PDT	post PDT	pre PDT	pre PDT
Adenocystic carcinoma of the hard palate						
1	ND	ND	ND	ND	ND	ND
Malignant melanoma						
1	ND	ND	35.7	93.1	ND	ND
Controls'	PSA pre	PSA post				
Mesothelioma of the pleura cell free	ND	ND	24.3	23.0	12.7	11.2
Uterine cancer.	ND	ND	13.6	14.0	27.7	27.8
Metastatic colorectal cancer.	ND	ND	154.4	156.8	17.2	17.7
Breast cancer.	ND	ND	9.3	9.5	19.0	18.6
Carcinoma of the ovary. ¹	4.2	4.0	ND	ND	34.0	32.0
Prostate cancer	5.3	5.4	ND	ND	ND	ND
Carcinoma of the prostate.	1.1	1.4	ND	ND	ND	ND
Carcinoma of the prostate.	1.2	1.3	ND	ND	ND	ND
Carcinoma of the breast ^{2,3} .	38.0	39.0	ND	ND	ND	ND

¹ PSA values according to record

² CA 15.3 pre

³ CA 15.3 post

ND Not done

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Scientific information regarding Next Generation Photodynamic Therapy:

Although currently not available at The Dove Clinic, it is possible to use a fluorescent camera in order to image the patient's tumour, if it is relatively near the skin.

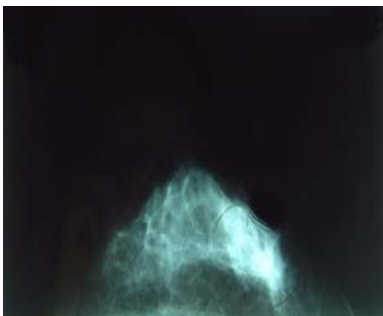
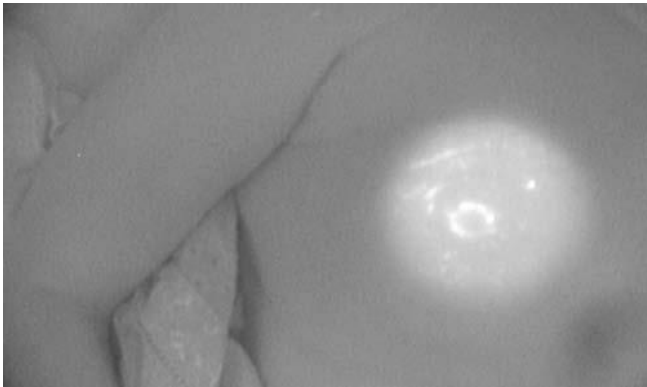
Observational outcomes from Australian clinic using similar methods

The following is a brief summary of results obtained with recent consecutive patients who have been treated with a combination of photodynamic therapy and Sonodynamic therapy (abbreviated in this document as SPDT). These patients are from a clinic in Australia who are using the same approach as ourselves.

1. Stage III breast cancer. Primary breast tumour plus metastases in the axillary lymph node, the other breast and the liver. After SPDT and lumpectomy: no evidence of cancer in all four sites
2. Stage IV breast cancer with rampant bony metastases. Very low energy, not enough to work in the garden. In bed by 7.30 pm. After SPDT (ongoing) weight increased 3 kg and now normal. Normal sleeping time and energy levels. Resumed gardening. Scan shows that the tumours have stopped spreading.
3. Metastatic melanoma grade IV. About 80 metastases visible. Oncologist predicted 2 more months of life. After SPDT (ongoing), Alive and well 4 months after above prediction. Metastases down to about 20. Energy, appetite and weight improved. Physician estimates that about 80 % of the cancer is gone. Further treatment needed.
4. Prostate cancer (large tumour mass), grade IV, urinary infections, bowel infections. Inability to urinate without catheter, impotent. After SPDT/SDT (ongoing) prostate shrinking and softening, urination better, impotence easing. Needs further treatment but improving.
5. Ovarian cancer grade IV. Had hysterectomy and other surgery. No symptoms other than elevated cancer marker. After SPDT cancer marker now normal. No evidence of cancer
6. Squamous cell carcinoma grade I. Lump on upper lip removed surgically. PDD showed 6 metastases on upper lip. After SPDT all metastases have disappeared

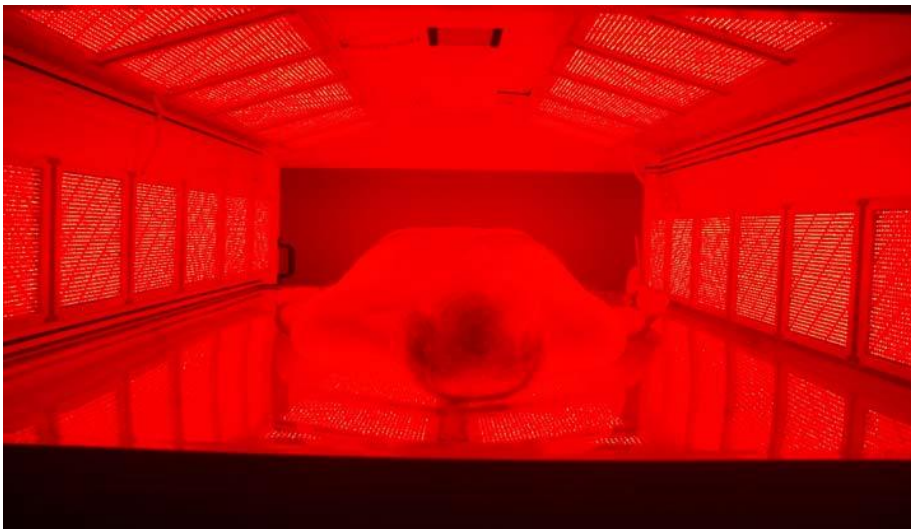
7. Prostate grade IV. Hard prostate with 2 nodules, metastasized outside the gland. After SPDT (ongoing) Prostate shrunk, softened, one nodule disappeared. Better urination. Clear or almost clear of cancer.
8. Mesothelioma and lung cancer. Symptoms include coughing at night, disturbed sleep. Painful breathing, not allowing deep inhalations. Photodynamic diagnosis showed over 12 metastases on the thorax. No noticeable benefits from chemotherapy. After SPDT/SDT (ongoing). Coughing at night has stopped, giving much better sleep. Breathing not as painful, allowing deeper inhalation. "I have an amazing increase in energy ". Visible metastases have dropped from 12 or more to one.
9. Breast cancer grade IV. Lumpectomy. PDD showed metastases in the breast and the axillary lymph nodes. After SPDT (ongoing) Cleared metastases from the breast. Those in the lymph glands remain. Next treatment will be SPDT/SDT
10. Breast cancer grade IV with extensive liver metastases. SPDT failed to halt the progress of the illness. SDT was not available at the time and she has chosen other treatment.

Breast Cancer





A non-toxic treatment for primary and metastatic cancer and other diseases



Next Generation Photodynamic Therapy as well as being used for cancer is also increasingly commonly being used for cardiovascular diseases, generalised hardening of the arteries and calcification of the arteries, as well as for Rheumatoid Arthritis. Recently studies have been carried out on HIV and AIDS, which would imply that it, may be of use in severe Chronic Fatigue Syndrome and also in ophthalmology, particularly macular degeneration. There are many papers on the use of PDT in ophthalmology.

Some scientific papers from several thousand papers in the scientific literature on PDT

Photodynamic therapy for lung cancer: state of the art and expanded indications

T Okunaka and H Kato

Department of Surgery, Tokyo Medical University, Tokyo, Japan.

Nippon Geka Gakkai Zasshi, February 1, 2002; 103(2): 258-62

Commentary: Photodynamic therapy (PDT) has now achieved the status of a standard treatment modality for centrally located, early-stage lung cancer and is introduced on the home page of the US National Cancer Institute. As increasing number of patients consider quality of life after therapy, the indications for PDT are expected to expand. The success in clinical trials of PDT for cancer treatment offers encouragement for its future use.

Generation of effective antitumor vaccines using photodynamic therapy.

SO Gollnick, L Vaughan, and BW Henderson

*PDT Center, Roswell Park Cancer Institute, Buffalo, New York 14263, USA.
Sandra.Gollnick@roswellpark.org*

Cancer Res., March 15, 2002; 62(6): 1604-8.

Commentary: Preclinical studies have shown that photodynamic therapy (PDT) of tumors augments the host antitumor immune response. We found that the PDT-generated tumor cell lysates were potent vaccines and that PDT-generated vaccines are more effective than other modes of creating whole tumor vaccines, i.e., UV or ionizing irradiation, and unlike other traditional vaccines, PDT vaccines do not require coadministration of an adjuvant to be effective. PDT vaccines are tumor specific and appear to induce a cytotoxic T-cell response. Our results show that PDT effects on tumor cells alone are sufficient to generate an

antitumor immune response, indicating that the direct tumor effects of PDT play an important role in enhancing that host antitumor immune response

Photodynamic therapy of loco regional breast cancer recurrences using a chlorin-type photosensitizer.

P Wyss, V Schwarz, D Dobler-Girdziunaite, R Hornung, H Walt, A Degen, and M Fehr

Department of Obstetrics and Gynecology, University Hospital, Zürich, Switzerland. Pius.Wyss@fhk.usz.ch

Int J **Cancer**, September 1, 2001; 93(5): 720-4

Commentary: Chest wall recurrences are a frequent problem in patients treated by mastectomy for breast cancer. Surgery and ionizing radiation are established treatment modalities in these cases. Photodynamic therapy (PDT) provides an alternative treatment modality using a photosensitizer and laser light to induce selective tumor necrosis. PDT using m-THPC resulted in complete response in all patients. Response to treatment did not differ when using the 2 different drug dose protocols. Healing time depended mainly on the size of the illumination field but not on the light dose. Pain score usually rose 1 day after PDT and lasted at higher levels for about 10 days. Healing time usually ranged between 8--10 weeks. Photodynamic technique offers a minimal-invasive, outpatient treatment modality for recurrent breast cancer on the chest wall with few side effects, high patient's satisfaction and with possible repetitive application.

Photodynamic therapy for nonmelanoma skin cancers. Current review and update.

NC Zeitouni, AR Oseroff, and S Shieh

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Mol Immunol, July 1, 2003; 39(17-18): 1133-6.

Commentary: Photodynamic therapy (PDT) is a therapeutic modality involving the use of a photosensitizing agent activated by light to destroy tumor cells. Over the past 25 years, PDT has been shown useful in the treatment of actinic keratoses and certain nonmelanoma skin cancers, such as Bowen's disease and basal cell carcinoma. . PDT offers many advantages including its non-invasiveness and its ability to treat multiple lesions simultaneously and is, therefore, an interesting alternative for treating certain skin malignancies.

[Photodynamic therapy of dysplasias and early carcinomas in Barrett esophagus with a diode laser system--a pilot study]

T Zopf, A Rosenbaum, D Apel, R Jakobs, JC Arnold, and JF Riemann

*Medizinische Klinik C, Klinikum der Stadt Ludwigshafen gGmbH.
thomas.zoepf@t-online.de*

Med Klin (Munich), April 15, 2001; 96(4): 212-6.

Commentary: Photodynamic therapy (PDT) of dysplasia and early cancer of the esophagus could show good results in the potential of ablation. Unfortunately, the existing expensive and temperamental dye laser systems foiled a broad clinical use. In this pilot study, we investigated the feasibility of an inexpensive and maintenance-free diode laser system for PDT of dysplasia and early cancer in Barrett's esophagus. PATIENTS AND METHODS: Eight patients with Barrett's esophagus and/or early cancer were treated. As light source we used a diode laser system with a maximum power output of 2 W and a wavelength of 633 +/- 3 nm. One patient was treated initially with Photosan-3, seven patients received 5-aminolevulinic acid. RESULTS: In all patients we could achieve reduction in length and/or histologically proven downgrading. In three quarters of the patients, complete eradication of adenocarcinoma could be attained. Columnar-lined metaplastic epithelium could also be completely eradicated. CONCLUSION: PDT using a diode laser system is comparably effective in Barrett's esophagus/early cancer as PDT with dye laser systems. PDT is a gentle and effective technique with little side effects.

An update on photodynamic therapy applications.

TJ Dougherty

*Photodynamic Therapy Center, Roswell Park **Cancer** Institute, Buffalo, New York
14263, USA.*

J Clin Laser Med Surg, February 1, 2002; 20(1): 3-7.

Commentary: Photodynamic therapy (PDT), following health agency approvals throughout the world for various **cancers** and other diseases, is slowly being accepted as a standard treatment to be added to the medical practitioner's armamentarium. Mechanistically, the recognition of apoptosis as an important mode of cell death following PDT and the critical role of the inflammatory process and immunity has only recently been recognized.

Photodynamic therapy for palliation of nonresectable bile duct cancer--preliminary results with a new diode laser system.

T Zoepf, R Jakobs, JC Arnold, D Apel, A Rosenbaum, and JF Riemann

Department of Gastroenterology, Academic Teaching Hospital, Ludwigshafen, Germany.

Am J Gastroenterol, July 1, 2001; 96(7): 2093-7.

Preliminary results of photodynamic therapy (PDT) of bile duct cancer have shown astonishingly good results in the reduction of cholestasis, improvement of quality of life, and even prolongation of the survival time. RESULTS: Four weeks after initial PDT all patients showed a marked reduction of bile duct stenosis. CONCLUSION: PDT with the diode laser system seems to be effective in reducing malignant bile duct stenosis. This treatment is minimally invasive and has a low specific complication rate.

Pancreas, October 1, 2003; 27(3): E42-E45.

Infrared Laser Activation of Indocyanine Green Inhibits Growth in Human Pancreatic Cancer.

William W. Tseng, Romaine E. Saxton, Adriana Deganutti, and Carson D. Liu

Northwestern University, Feinberg School of Medicine, Chicago, Illinois; dagger Department of Surgery, David Geffen School of Medicine at UCLA, Los Angeles, California; and double dagger Department of Surgery, Century City Hospital, Los Angeles, California.

Indocyanine green (ICG) is a clinically approved, water-soluble dye that generates reactive singlet oxygen when activated by infrared light. Infrared light offers the advantage of deeper tissue penetration making ICG photodynamic therapy (PDT) ideal for treatment of intra-abdominal cancers such as pancreatic adenocarcinoma. AIMS CONCLUSION ICG PDT induces consistent and dramatic pancreatic cancer cell death. Since neither ICG nor laser alone caused toxicity, combination therapy may offer effective control of tumor growth with minimal side effects in patients with unresectable primary or metastatic pancreatic cancer.

Phase II clinical study of photodynamic therapy using mono-L-aspartyl chlorin e6 and diode laser for early superficial squamous cell carcinoma of the lung.

H Kato, K Furukawa, M Sato, T Okunaka, Y Kusunoki, M Kawahara, M Fukuoka, T Miyazawa, T Yana, K Matsui, T Shiraishi, and H Horinouchi

Department of Surgery, Tokyo Medical University, 6-7-1 Nishi-shinjuku, Shinjuku-ku, Tokyo 160-0023, Japan.

Lung **Cancer**, October 1, 2003; 42(1): 103-11

Photofrin is the most commonly used photosensitizer for photodynamic therapy (PDT). The major side effect of Photofrin is cutaneous photosensitivity. A second generation photosensitizer, mono-L-aspartyl chlorin e6 (NPe6) has shown anti-tumor efficacy and rapid clearance from skin. The histologic type of the tumor had to squamous cell carcinoma. No serious adverse drug reactions were observed. Complete response (CR) was seen in 84.6% of lesions (82.9% of patients). This study demonstrated excellent anti-tumor effects and safety, especially low skin photosensitivity in patients with early stage lung cancer. PDT using the second generation photosensitizer NPe6 and a diode laser will likely become a standard modality of PDT for central type early superficial squamous cell carcinoma of the lung.

The immunological consequences of photodynamic treatment of cancer, a literature review.

FH van Duijnhoven, RI Aalbers, JP Rovers, OT Terpstra, and PJ Kuppen

Department of Surgery, Leiden University Medical Center, Leiden, The Netherlands.

Immunobiology, January 1, 2003; 207(2): 105-13.

In this review we discuss the effect of photodynamic treatment (PDT) of solid tumors on the immune response. We have summarized the evidence that PDT causes or enhances an anti-tumor response. PDT is a local treatment in which the treated tumor remains in situ while the immune system is only locally affected and still functional in contrast with e.g. after systemic chemotherapy. We conclude that PDT of cancer is a way of in situ vaccination to induce a systemic antitumour response. In general, immune cells are found in the tumor stroma, separated from tumor cells by extra cellular matrix and basal membrane-like structures. We hypothesize that PDT destroys the structure of a tumor, thereby enabling direct interaction between immune cells and tumor cells resulting in the systemic anti-tumor immune response.

The role of apoptosis in response to photodynamic therapy: what, where, why, and how.

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Photochem Photobiol Sci, January 1, 2002; 1(1): 1-21.

Photodynamic therapy (PDT), a treatment for cancer and for certain benign conditions, utilizes a photosensitizer and light to produce reactive oxygen in cells. PDT is primarily employed to kill tumor and other abnormal cells, so it is important to ask how this occurs. Many of the photosensitizers currently in clinical or pre-clinical studies of PDT localize in or have a major influence on mitochondria, and PDT is a strong inducer of apoptosis in many situations

Preliminary report of photodynamic therapy for intraperitoneal sarcomatosis.

TW Bauer, SM Hahn, FR Spitz, A Kachur, E Glatstein, and DL Fraker

*Department of Surgery, School of Medicine, University of Pennsylvania,
Philadelphia 19104, USA.*

Ann. Surg. Oncol., April 1, 2001; 8(3): 254-9.

Sarcomatosis is the disseminated intraperitoneal spread of sarcoma. It is a condition for which there is no effective treatment. Photodynamic therapy (PDT) is a cancer treatment modality that uses a photosensitizing agent and laser light to kill cells. Five patients (45%) have no evidence of disease at follow-up (range, 1.7-17.3 months), including patients at 13.8 and 17.3 months examined by CT. Two patients (18%) died from disease progression. Four patients (36%) are alive with disease progression.

CONCLUSIONS: Debulking surgery with intraperitoneal PDT for sarcomatosis is feasible. Preliminary response data suggest prolonged relapse-free survival in some patients.

Effective treatment of liver metastases with photodynamic therapy, using the second-generation photosensitizer meta-tetra(hydroxyphenyl)chlorin (mTHPC), in a rat model.

JP Rovers, AE Saarnak, A Molina, JJ Schuitmaker, HJ Sterenborg, and OT Terpstra

Department of Surgery, Leiden University Medical Centre, The Netherlands

Br J **Cancer**, October 1, 1999; 81(4): 600-8.

The only curative treatment for patients with liver metastases to date is surgery, but few patients are suitable candidates for hepatic resection. The majority of patients will have to rely on other treatment modalities for palliation. Photodynamic therapy (PDT) could be a selective, minimally invasive treatment for patients with liver metastases. . Damage to normal liver tissue was mild and transient as serum aspartate aminotransferase and alanine aminotransferase levels normalized within a week after PDT treatment. Long-term effects of mTHPC-PDT were studied on day 28 after treatment. Regardless of drug dose and drug-light interval, PDT with mTHPC resulted in complete tumour remission in 27 out of 31 treated animals (87%), with only four animals in which tumour regrowth was observed. Non-responding tumours proved to be significantly larger ($P < 0.001$) in size before PDT treatment. This study demonstrates that mTHPC is retained in an intrahepatic tumour and that mTHPC-PDT is capable of inducing complete tumour remission of liver tumours.

Photodynamic therapy: a novel treatment for primary brain malignancy.

TT Goodell and PJ Muller

Oregon Medical Laser Center/Providence St. Vincent Medical Center, 9205 SW Barnes Road, Portland, OR 97225, USA.

J Neurosci Nurs, December 1, 2001; 33(6): 296-300

Providing therapy that conserves healthy brain tissue while effectively killing cancerous tissue remains a major challenge in the treatment of primary malignant brain tumors. The most common primary brain malignancies tend to recur despite intensive therapy, and the side effects of radiotherapy and chemotherapy can have considerable influence on health and quality of life. Photodynamic therapy (PDT) is a new technology being investigated to fulfill the need for a targeted cancer treatment that may reduce tumor recurrence and extend survival with few adverse effects. An investigational treatment, PDT employs wavelength-specific light in combination with a photosensitizing agent. The photosensitizing agent accumulates in tumor cells and is activated by nonthermal light, producing radical oxygen species that locally kill tumor cells. The selectivity of the process makes PDT appealing in the brain, where conservation of healthy tissue is vital. Many new photosensitizing compounds and varying methods of light delivery are being studied. This technology shows promise for the treatment of primary brain malignancies.

Scientific References in the Use of Photodynamic Therapy in Cardiovascular Diseases

Motexafin Lutetium (Cardiovascular Diseases) Phase II Trial

A Phase II, Double blind, Multicenter, Randomized Clinical Trial of Motexafin Lutetium Injection and Far-Red Light Activation for the Prevention of Restenosis and Primary Treatment of De Novo Atherosclerotic Lesions in Femoral and Popliteal Arteries

Principal Investigator: Paul Kramer, MD, Kramer and Crouse Cardiology, Mid America Heart Institute, Kansas City Missouri

Institutional ID Number: PCYC-0502 (Closed)

Motexafin Lutetium (Cardiovascular Diseases) Phase I Trial

A Phase I, Drug and Light Dose-Escalation Clinical Trial of Antrin® (Motexafin Lutetium) Injection and Far-Red Light Activation (Phototherapy) in Subjects with Coronary Artery Disease Undergoing Percutaneous Coronary Intervention (PCI) with Stent Placement

Principal Investigator: Dean Kereiakes, MD, Lindner Research Center, Christ Hospital, Cincinnati, OH

Institutional ID Number PCYC-0551 (Completed)

Kereiakes, et al; Circulation 108: 1310-1315, 2003

Photodynamic Therapy for Prostate Cancer — A Novel Technique for Assessing Light Transmission in the Prostate

*CM Moore, CA Mosse, I Hoh, H Payne, D Rickards, SG Bown, ME Emberton
United Kingdom, National Medical Laser Centre, University College London,
London, UK, Myerstein Institute of Oncology, University College London
Hospitals Trust, London, UK, Department of Imaging, University College London
Hospitals Trust, London, UK, Institute of Urology, University College London,
London.*

Aims:

Photodynamic therapy (PDT) uses a light activated drug to cause necrosis, whose depth depends on the penetration depth (PD) of light. Previous studies have measured PD in up to three positions per prostate with wavelengths of up to 665nm. These wavelengths can be absorbed by haemoglobin, leading to large variation in PD. Newer drugs are activated by light of longer wavelengths. It is predicted that they will have increased PD and will not be absorbed by haemoglobin. We aimed to use a novel technique to determine PD in multiple positions throughout the prostate, with 763 nm light.

Procedures

Patients having high dose rate (HDR) brachytherapy for prostate cancer have multiple transparent plastic needles in the prostate for two days. These are used to carry radioactive iridium wires but are also suitable for carrying optical fibres. Laser light was delivered along the needles using a cylindrically diffusing optical fibre. An isotropic detector was placed sequentially in nearby needles and optical power at different distances from the source was measured with a light meter. Needle separation was measured on CT.

Major Findings

PD is the depth at which 63% of light intensity is lost. It is calculated from the diffusion theory approximation to the Boltzmann transport equation. The mean PD over 600 readings was 5.5 mm (2.7-12.1mm).

Significance

The PD showed greater variability than expected. As this variation is proportional to the depth aimed to treat, absolute variation will need to be minimised by reducing the needle separation to less than 10 mm.

Conclusion

PDT for prostate cancer will require multiple interstitial light sources, similar to the needle configuration used for HDR brachytherapy.

Photodynamic Therapy for Primary Prostate Cancer — A Pilot Study using MTHPC

CM Moore, TR Nathan, WR Lees, A Freeman, CA Mosse, M Emberton, SG Bown

United Kingdom, National Medical Laser Centre, University College London, London, UK, Department of Imaging, University College London Hospitals Trust, London, UK, Department of Histology, University College London Hospitals Trust, London, UK, Institute of Urology, University College London, London

Aims:

To determine whether photodynamic therapy (PDT) using meso tatra hydroxy phenyl chlorin (mTHPC) could be a primary treatment for organ confined prostate cancer.

Procedure

Six men with histologically proven prostate cancer, who were unsuitable for or declined radiotherapy, surgery or active surveillance, were studied. The mean pre-treatment PSA was 7.7 ng/ml (range 2.7-15), with a Gleason score of 3+3 in all patients.

The photosensitiser mTHPC was given intravenously and activated after 2-5 days by 652 nm light delivered transperineally to the prostate using MRI guidance. Areas of cancer were treated under local anaesthetic and sedation according to MRI or biopsy results. The peripheral zone of the same lobe was also treated. 4 out of 6 patients had 2 treatments.

Major Findings

Early MRI changes indicated extensive oedema, with patches of ill defined necrosis. This necrosis was well defined at 1 month and was not seen at 3 months. Histology revealed areas of necrosis and fibrosis at 1 month and fibrosis at 2 months. 8 out of 10 treatments resulted in a PSA reduction (mean reduction per patient 4.0 ng/ml, range 2.0 — 10).

2 treatments led to catheterisation for 9 to 19 days respectively. 1 patient had incontinence requiring 1 pad per day for 4 months following a 2nd PDT treatment.

Significance

This is the first report of the use of PDT as a primary treatment for prostate cancer. Necrosis followed by fibrosis, and a PSA reduction was seen.

Conclusion

PDT for primary prostate cancer merits further investigation.

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Fourteen patients with rising PSA levels and with a proven local recurrence after treatment with the radiation were given PDT. PSA scores decreased in 9 patients, to undetectable levels in two of them. Five patients had no viable tumour when a needle biopsy was taken after treatment and CT and MRI scans showed clear signs of tumour necrosis involving up to 91% of the prostate after treatment with PDT. The authors of this study concluded the photodynamic therapy can destroy localized areas of cancer with safe healing without cumulative toxicity associated with ionizing radiation. This study, and the previous two studies, used fibre-optic cables inserted into the prostate. This itself caused some side effects in that 4 men developed stress-incontinence in the Journal of Urology Study and 4 suffered long term impotence. With the use of Next Generation PDT, because it's so tumour specific, the insertion of fibre-optics into the prostate is not necessary.

Please also see the paper by Duijnhoven et al from Immunobiology January 1st 2003, relating to this issue.