Photodynamic Therapy (PDT) in Cancer Therapy

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Dr. Shafirstein:
Hi, I’m Gal Shafirstein. I’m a Professor of Oncology and the Director of the Photodynamic Therapy Clinical Research at Roswell Park Cancer Institute. I’m responsible to work with physicians and design clinical studies and use of the PDT in the treatment of patients at Roswell Park Cancer Institute.

I would like to have the following disclosures. I have been serving on an advisory board for Pinnacle Biologics. This is a company that sells only FDA-approved drugs in the US for PDT. I am receiving research support from the following companies: Pinnacle Biologics and Apocare Pharma. They contract with Roswell Park Cancer Institute. I have been receiving research support which supports much of my current research from the National Cancer Institute and the National Institute of Health in the US, and I have received in kind support such as lasers and drugs from the following companies. I
also have patent applications owned by Roswell Park Cancer Institute.

The objective of this talk is to describe photodynamic therapy, explain how to use it, how to administer photodynamic therapy in the treatment of patients, when we can consider PDT in lung cancer, which is the primary use for photodynamic therapy, and it’s an FDA-approved indication, and I would like you to be aware of future applications of PDT in the treatment of head and neck cancer.

So, what is PDT? PDT is a treatment where a light-sensitive photosensitizer is excited with external light. The light is visible light between 400 to 700 nanometer, but sometimes we use near infrared, which is between 700 to 800 nanometer. When the photosensitizer is being absorbed, it produces singlet oxygen that can induce the destruction of live cells.

Short history: PDT actually has been discovered about 100 years ago, in Germany first, but it was never actually used and refined for the treatment of patients. In the early 1970s, Dr. Dougherty at Roswell Park Cancer Institute refined and developed a modern PDT that’s being used today. He found Photofrin. It’s a porfirm sodium that’s being used and received FDA approval for PDT in the treatment of lung and esophageal cancer. Later on in the ’90s and in the 2000s, there was a development of other drugs such as the mTHPC (Foscan) that is now approved, has been approved in Europe for the treatment of head and neck cancer, and there is a bacteriopheophorbide (Tookad), which was developed, actually, in Israel, in Europe, and received approval for the use in prostate cancer in Mexico.

So, PDT is a 2-step therapy. You start with photosensitizer that’s being administered either intravenous or topical, or sometimes you drink it. You wait 15 minutes to 96 hours. Fifteen minutes is some drugs that we call vascular drugs where the drugs reach the tumor and they clear most of the healthy tissue within 15 minutes. Other drugs require 48 hours such as the Photofrin or 96 hours such as the Foscan. The time that you wait is allowing for the drug to be more retained in the tumor compared to normal tissue. Then you shine light. You use typical laser light, red laser light. What is oxygen in the tissue, and it interacts with the photosensitizer, and there’s a production of singlet oxygen. The singlet oxygen is limited in terms of distance for less than 0.35 micron, and in terms of time, it’s only active for about 0.2 microseconds. What does it mean? It means that in terms of PDT, the action goes very, very fast and very, very local, and the action, of course, only where there’s enough drug, light and oxygen. Outside this area there’s no PDT. And as the laser is continuously shining and activating the photosensitizer, you continuously have the PDT, but once you stop, within less than a microsecond, nothing happened. And away from the action area, which is less than half a micron, there is nothing that is going to happen, so it’s very local. You wait a little bit longer, 24 hours to 1 to 7 days, and there is cell death.
At the time that the PDT occurs, there’s always a chance that there will be fluorescence. The fluorescence is that when the photosensitizer basically fluoresce, and we can use it to detect the presence of the photosensitizer. There’s also a chance that there will be heat, that the light is going to heat the photosensitizer. What we’re trying is to minimize the heat by controlling the PDT process, which I’ll explain shortly.

The damage mechanism is via apoptosis and necrosis. The tumor blood vessels are being unstable and damaged. PDT also induces inflammation that in specific settings can lead to anti-tumor immunity, and importantly, the clinically approved photosensitizer has been shown to have no limiting DNA damage. A good paper to read about PDT was published in 2011 by a group of experts, and please, if you want to read more, go ahead and look at this paper.

The selectivity is achieved by the fact that the photosensitizer is preferentially retained in the cancer cell compared to the normal tissue. The ratio is about 3:1. It doesn’t mean that there is no photosensitizer in the normal tissue, but it means there is more photosensitizer that’s being retained in the cancer tissue or our target tissue. It’s important to know that the fact that we have photosensitizers in the normal tissue is not necessarily a bad thing because that allows us to treat the margins in addition to the cancer. The PDT-induced photoreaction is directly proportional to the therapeutic light dose.

The selectivity in the first-generation or second-generation photosensitizers such as the mTHPC, or it will be Photofrin as well, there is not so much selectivity of the PDT, as you can see here. In the newest photosensitizer, such as the HPPH, there is selectivity, and the drug actually disappears from the entire system within 48 hours. That means that there’s less photosensitivity issues with administering HPPH versus mTHPC, but at the same time, you need to be aware to the fact that when you have better selectivity, it’s also likely that you can miss margins or you can miss cancer, because the fact that you have a targeted therapy doesn’t mean that you will be able to target the entire tumor. As we all know, tumors are very heterogeneous entities and sometimes you can miss the tumor, so it depends on which disease you want to treat with PDT, and then you’ll choose the appropriate photosensitizer.

In terms of absorption curves, so these are several absorption curves for several photosensitizers. Important thing, Soret band, this is in the area of about 400 nanometers. There’s a high absorption of almost all the photosensitizers. This absorption peak can be used for fluorescence. You shine the light at 400 and you get a strong fluorescence peak in around 690 or a nanometer in the red. The absorption—depending on the photosensitizers. As you can see, this is the Photofrin. The maximum absorption is at 630. It’s very low, but still there’s enough absorption. And then there are several
photosensitizers that absorb at the higher wavelength.

What is the importance of the wavelength when you are talking about the PDT? Typically, we want to have photosensitizers that absorb light between 630 and 763 nanometer. Why do we want to do this? Because if you look, this is the absorption curve for skin. In skin this is the absorption curve for the dermis, the epidermis and blood. As you can see, the blood has a very high absorption in the 400. It also has high absorption in the 600. Here between 630 and 800 there is a dip where there is minimal absorption in the blood, which is associated with deeper penetration of the light. That’s why we want to work with photosensitizer absorbing light in the area of 630 to 763 nanometer, which is mainly red and near infrared. The effective treatment depth is between 3 to 8 mm depending on the light and the photosensitizer that one uses. We use a continuous laser, typically. The important parameters in a continuous laser is their fluence rate, the irradiance, which is the W/cm$^2$. The W/cm$^2$ tells you how fast you actually deliver the photon to the target tissue. The energy, the joules, which is basic integration of the power over time, in this case it’s actually described how many photons and total number of photons are basically being delivered and absorbed by the photosensitizer. So, you want to control both, you want to control the power, you don’t want to be the power too high to avoid heating, and you want to control another power, the fluence rate, and you want to control the joules and primarily the radiant exposure so you have enough photons that will activate the light and cause the damage. The typical spot size is between 0.5 to 5 cm. We typically define the spot size as the diameter. It is typically around a spot size. We can do smaller spot size or larger spot size. This is just a typical spot size that we use in the treatment of PDT.

Light sources: In the early days, about 30 years ago, the light sources occupied almost an entire room. As you can see here, this is the laser. This is monochromator.

Nowadays, we have desktop lasers, so we have a laser... This is a laser that’s being used in Europe. It's a desktop laser that can deliver laser from 4 channels at the same time. It’s not approved in the US, but it’s being used to treat head and neck cancer in the European Union. This is an FDA-approved laser, a Diomed, that delivers 630 nm, and it’s being used in the treatment of PDT with Photofrin. The third laser that I’m showing here is a laser that comes from Finland. It’s a Modulight laser. They can deliver this laser for research with different wavelengths. This typical model delivers 665 nm from 4 channels. Each channel we can connect fiber and we can control the fiber, the power for each fiber independently.

The light delivery: So, here is a schematic, which is basically showing this is a laser shining a light on a geometry that represents the tumor. The important thing to show here is this is all a computer simulation that if you deliver 630 nm, 150 mW/cm$^2$, which is the typical fluence rate or irradiance that
we use in the treatment of PDT with Photofrin, about half of the power is being absorbed in the first 3 mm, so really, what you can effectively do is treat cancer or tumors that are about 3 mm in thickness, or from the surface you can treat these tumors with PDT and Photofrin.

The approved indications for PDT in the US for lung cancer, the European Union and Japan: This is the approval for Barrett’s esophagus; the bladder cancer is approved for clinical use in Canada, in the European Union head and neck; and recently, people have received companies have received approval to treat early-stage prostate cancer in Mexico.

The PDT in lung cancer: Here is a typical setting how you use the PDT to treat lung cancer. This is a diffuser fiber. This is during the illumination, that the physician put it through a scope. This is after illumination, and this is after treatment 4 weeks. There was a complete clearance of the tumor. Importantly, after you do a treatment in lung cancer, within 24 hours we need to go back and clean away, making sure there’s no debris that is left behind.

There are new photosensitizers and techniques. One of the new photosensitizers that I will discuss today is the HPPH that was developed here as a successor for Photofrin. Its main advantage is its less photosensitivity, because one of the drawbacks of PDT is that there is a photosensitivity. That means that the patients cannot go out in the sunlight after they receive the photosensitizer. In some of the photosensitizers, they need to wait up to 30 or even 90 days. Some others, such as the Photofrin, other photosensitizers, such as the Foscan, you need to wait about 4 weeks, the HPPH about 1 week to 10 days. While we’re saying there’s a photosensitivity, that can cause a burn if the patient goes out to an intense sunlight or exposed to an intense light. It doesn’t mean that the patient needs to be in the dark. It means that the patient cannot receive, cannot be exposed to a strong light. We actually want the patient to receive some light so it slowly, actually, photobleach the photosensitizer until there’s no photosensitizer there. And when patients receive the treatment, they receive specific instructions how to avoid intense light after they receive the drug.

Interstitial PDT is a new technique that has been used in the last 10 to 15 years, and we have some new advancements that I will discuss today. In intraoperative PDT is a PDT where you add this therapy to a surgery. Why interstitial PDT? Interstitial PDT has been shown to be effective in the treatment of refractory head and neck cancer. This is based on a study that was done in Europe with Temoporfin, with Foscan. They reported up to 74% overall response. It was 20% complete response and 54% partial response in patients that failed all therapies, so it was done as a salvage treatment. These results led to the approval of the use of I-PDT with Foscan in the European Union. It has a limited use, and one of the reasons we believe that it has a limited use outside Europe is because they didn’t do proper (inaudible 16:14) and treatment planning. Here at Roswell we use interstitial PDT with
Photofrin, which is an FDA-approved drug in the US for PDT. Our result thus far suggests that it's safe, but we still need to fine-tune and improve the treatment to make it more effective, and this is being done with NCI-funded studies that are ongoing in my laboratory and at Roswell Park Cancer Institute.

How we do interstitial delivery? This is how we do it at Roswell Park. We use catheter. This is a brachytherapy, FDA-approved brachytherapy therapy catheter. We put fiber. This is a diffuser fiber, a laser fiber with a diffuser end. We put it into the catheter, and then we put it into the patient. Prior to putting the fiber in the catheter, the catheter has a core, a metal core to allow the physician to push it through the skin into the target tumor. Everything is done under ultrasound or CT-guided just for the safety of the patient and make sure that we put the fiber wherever the plan is telling us fiber should be placed.

This is a simulation showing that if you have a flat-cut fiber, most of the light is being absorbed in front of the fiber. If you have a diffuser fiber, like we use here, most of the light is absorbed in a radial manner to the fiber itself.

Here is a treatment that we did. This is a simulation, computer simulation, that was generated by CT that reconstructed the entire tumor. This tumor is between the internal and the external jugular. We placed 12 fibers in this case, and we treated the patient in the operating room. This treatment has shown to palliate. We are still working on ways to improve the treatment so we can actually achieve a cure and complete local control of the tumor. This is done as part, as I said, of an NCI-funded study. The important thing here is that you can see although the tumor is in a very sensitive region, we can safely treat the patient. Physicians at Roswell Park have treated several patients with tumors that were not amenable to any other approved therapy successfully in that sense that it was safe, and no serious adverse event was reported.

The other thing that we do here and in other centers are being done is intraoperative PDT. Here we use PDT in lung cancer. The idea here is that after the removal of the cancer during a surgery, we want to go ahead and control the margins or whatever cells are left behind. In this technique we actually put saline in the cavity, and then we have detectors here that are placed in specific locations, and we move a balloon with a laser—this is a balloon with a laser—in the water or saline here to treat the area. This treatment takes about between half an hour to 1 hour. It's being done after the standard surgery has been completed, and we believe that can improve outcomes. Studies outside our institute and within our institute have shown that in the treatment of patients with mesothelioma, this approach can actually improve their outcome. Specifically, there is a study that we are doing in collaboration with the University of Pennsylvania that is leading that part for the treatment of mesothelioma.

PDT with HPPH for early-stage oral cancer: This is a study that was done here at Roswell. The
intention was to come up with a treatment that can help to cure patients with early-stage oral cancer. Why we propose PDT? Because PDT has been shown with excellent healing. The HPPH has been shown to be safe with minimal photosensitivity, meaning the patients do not need to be careful with sun exposure more than a week to 2 weeks. Here we are showing an example where dysplasia was treated in the tongue. This is a few days after PDT, and this is how the tongue looks like a few months after PDT. The important thing here is that for surgeons like yourself, if you treat this, you have to remove the lesion and get some margins, and that could affect the functionality of the tongue. In the case of PDT, it seems that there is no effect on the functionality of the tongue. That’s one of the main advantages of PDT. Several studies—and you can look at the literature—have shown that PDT does not effect functionality and is associated with very good healing without an intervention after PDT.

We also in this study found out that the response to PDT is associated with a biomarker. The biomarker that was identified at the Photodynamic Therapy Center is the STAT3. The STAT3 will crosslink due to oxygenation during the PDT, and we found out in the study that I’m reporting here that the patient that had squamous cell carcinoma had a higher STAT3 crosslink than patient that had dysplasia.

And this is an example of one of these patients. Patient A had a squamous cell carcinoma, patient B had dysplasia, and this is the control, and as you can see, the patient that had squamous cell carcinoma and was treated with PDT had a higher crosslink, 28%. Importantly, the crosslink only appears in patients that receive PDT. There is no STAT3 crosslinking in patients before they receive PDT.

So, what this study told us, this was a Phase Ib study. We had an expansion called at a maximum tolerated dose, but the maximum tolerated dose in this case was determined as 140 J/cm, although no toxicities were observed. No maximum tolerated toxicities were observed at this dose. We used that, and it seems to be very effective. The pain at the treatment site, edema was a concern that the physicians were able to control. This treatment was more effective in the treatment of squamous cell carcinoma than in dysplasia, and we believe this is because there is a better retention of the photosensitizer in the squamous cell carcinoma compared to the dysplasia or CIS carcinoma in situ.

In conclusion, which patient could benefit from PDT? Mainly patients that have this kind of indication, microinvasive endobronchial non-small cell lung cancer. This is an approved indication. When there’s a complete obstruction of esophageal cancer, this is another approved indication for PDT with Photofrin in the US. And when radiation and surgery are not a good option in the view of the treating physician, it can be used for these indications.

A lot of PDT is being used off label and in clinical research. It has been shown that PDT can be used
before or after surgery, chemotherapy or radiation, without compromising the response to the standard treatment and with potential benefit. That means that when you use or you consider offering PDT to your patients, you don’t preclude the use of any of the standard therapies, even including the newest immunotherapies. PDT can be added before or after. You just have to be careful, of course, to monitor the safety of the patient. And PDT has also been shown to be promising in the treatment of early-stage head and neck cancer with squamous cell carcinoma.

And I would like to acknowledge the support of the NIH that has been supporting the PDT Center, our Roswell Park Cancer Institute Alliance Foundation, the kind support of the drug and the research from Pinnacle Biologics and BioLitec in Germany. Thank you very much.

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