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REVIEW

Photodynamic therapy for chest wall recurrence from breast cancer

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Review

Summary Breast cancer is common with over 230,000 new cases diagnosed each year in North America alone. While great strides have been made to achieve excellent cancer control and survival, a significant minority of patients fail locally. While initial salvage to regain disease control is of the utmost importance, it is not universally successful. This leads to a therapeutic quagmire. Additional surgery, radiation and chemo-hormonal therapy are possible, but they are usually highly morbid with low success rates. Photodynamic therapy appears to be an underutilized salvage modality for this unfortunate patient population. This report analyzes and reviews the role of photodynamic therapy for patients with chest wall re-recurrence from breast cancer.

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Introduction

Dramatic advances have occurred in the early detection and treatment of breast cancer. However, even with 90% or higher local control rates reported at 5-year follow up, a considerable number of women still suffer local regional failure [1]. Potentially, in North America alone, this translates to nearly 20,000 of the 230,000 new breast cancer cases diagnosed each year requiring salvage therapy for local-regional failure. Further, it is well documented that local failure increases with longer follow-up. Eventually more than 15% of these patients will require local salvage by 15 years post-treatment despite ''curative'' therapy [2].

Generally initial salvage for patients who fail breast-conserving therapy of lumpectomy and radiation is modified radical mastectomy [3]. For patients who fail mastectomy full course radiation therapy is employed to the chest wall and regional lymphatics. Fortunately in both situations salvage therapy is generally successful with minimal acute morbidity for most patients. Salvage in these situations usually incurs risk of arm edema as the most common chronic side effect. Overall, several large series show that nearly 90% of patients undergoing salvage will regain local control [2,4–6]. For lumpectomy and radiation patients with isolated recurrence at the initial tumor site survival is nearly equivalent to similar patients who did not recur. Most patients who experience recurrence will undergo additional chemotherapy though no randomized series exist to examine this important question and the benefit of this treatment.

Given the large number of patients diagnosed with breast cancer, the real risk of local failure, and the fact that local control from salvage does not approach 100%, a significant minority of breast cancer patients will re-recur loco-regionally. These individuals will most likely have already undergone one or more major surgical procedures for local control, full dose radiation and multi-agent chemo-hormonal therapy. Clearly, additional salvage options with these modalities are limited. Photodynamic therapy (PDT) [7,8] has had considerable success in the treatment of cutaneous primary and metastatic malignant lesions and should be considered for these unfortunate individuals. PDT has the additional benefit of being a potentially painless outpatient procedure that is repeatable. PDT can work in combination with other salvage regimens or as a stand-alone therapy. In a simplistic overview, PDT has three main components: first a sensitizing agent, which preferentially accumulates in malignant/pre-malignant tissues and/or clears faster from surrounding normal tissue; second, a source of intense illumination, which at the appropriate wavelength will activate the sensitizer. This leads to the third component of PDT, oxygen, which in the course of the photodynamic reaction is transformed into singlet oxygen. The generation of singlet oxygen allows for the rapid cytotoxic/vasculotoxic activity associated with PDT. We will analyze and review the PDT literature, based on published peer reviewed papers, concerning this important patient population.

Natural history of chest wall lesions

Once tumor cells have invaded dermal lymphatics, they appear free to travel extensively in this cutaneous system [9]. As these lymphatics are without direction, due to lack of valves, metastasis originating from the chest wall can spread to the contralateral chest, abdomen and even the back. This extensive spread explains the virtual complete failure of nidusectomy, attempted at what appears to be a solitary metastasis. As these lesions grow, they often cause intensive signs and symptoms. Commonly, patients report an unrelenting itching which is not relieved by topical steroids or shots. Many patients report pain from these lesions as well as motion limitation due to discomfort. Eventually, the lesions begin to weep and bleed causing further distress. Open tumor infiltrated wounds and infections that are poorly controlled follow. Lesions may impinge on the brachial plexus and remaining axillary nodes leading to additional neurologic difficulties and edema. The quality of life for these individuals and their caretakers can become poor. As lesions progress uncontrollably, psychological and physiological distress occurs as might be expected from individuals watching their cancers grow in front of their eyes. Some patients will succumb due to the combination of infected wound, pain and tumor burden [10,11].

Salvage for re-recurrence: options

Surgery

With the extensive dermal lymphatic involvement of the skin, a local approach to excision virtually always fails [9]. As it is impossible in many patients to obtain clear margins, which would allow for wound healing, further surgery must be approached cautiously. Even highly selected patients who have been deemed candidates for chest wall resection often followed by additional radiation and chemotherapy generally fail at the margins of resection [12,13]. Further, these patients have fairly high morbidity even in the best surgical hands [14]. It would be clinically more efficacious to excise and close wounds in a sterilized field than to leave a tumor infested wound and expect healing. Should the tumor bed be sterilized, for example by PDT, a variety of plastic surgery grafts could be employed to close defects, if needed. In this situation, as no viable tumor would prevent healing, potentially one could expect excellent clinical and cosmetic effects.

Radiation

Radiation is a highly effective modality for patients with initial recurrence post-surgery [15,16]. Radiation has the benefit of treating the recurrent field and regional lymphatics with excellent clinical and cosmetic outcomes [17]. Patients with recurrence post-radiation are extremely difficult to re-irradiate. This is due to the well-established tolerances of tissue to radiation. After a first course of radiation therapy, the lung, soft tissue, ribs, lymphatics and nerves in the prior radiation field are near tolerance levels. An additional course of radiation to recurrent disease will likely bring these critical normal structures beyond tolerance. This can have severe clinical complications in terms of symptomatic pneumonitis, arm edema, plexopathies, fibrosis and wound healing difficulties [18—20].

Chemo-hormonal therapy

Re-recurrent lesions often bode for systemic failure. Most patients should undergo additional staging for extent of disease work-up. This includes

chest, abdomen, pelvic CT and bone scan. Tumor markers may be of benefit. Patients with widespread and progressing systemic disease may not need local treatment in as urgent a fashion as they need systemic therapy. Most patients who have chest wall re-recurrence have already failed primary and salvage chemo-hormonal treatment [21—23]. Many have failed additional salvage courses of chemotherapy as well. It is rare for third-line treatments to effectively control chest wall failure for any prolonged period. Further, no clear data exists that correlates systemic response with chest wall response for these patients. Even in the face of systemic improvement, local re-control can be poor. This may be due to the poor hematologic delivery of chemotherapeutic agents to the chest wall as its blood supply may be compromised due to surgery and radiation, most likely on several occasions. It is recognized that certain chemotherapy agents are potentially radiation sensitizers and perhaps PDT sensitizers. This may complicate the treatment of chest wall disease. It may also increase normal tissue morbidity [24].

PDT

As currently practiced, PDT involves a photosensitizing agent that is activated optimally by a particular wavelength of light [7,25—27]. Ideally this results in a photodynamic reaction. The reaction creates highly cytotoxic and vascular toxic free radicals leading to tumor cell death and immunomodulation. As PDT has been employed to a wide variety of cutaneous neoplasms with excellent clinical and cosmetic outcome, it is reasonable to hypothesize that chest wall lesions would be amenable to this therapy. As PDT works well even in operated upon and radiated fields, this would be a means for additional salvage options. We will review the treatment and outcome results in the published literature for each photosensitizer.

PDT for chest wall recurrence/re-recurrence from breast cancer

Photosensitizers

Photosensitizers are substances that transfer and translate light energy into a type II photodynamic reaction [28]. The oxygen-based reaction creates toxic singlet oxygen species for tumor ablation. Photosensitizers may be natural or synthetic. In general the three main families for photosensitization are porphyrin based, chlorophyll based or dye based [29—33]. The porphyrins are ring structures. Those tried in breast cancer treatment included hematoporphrin derivatives (HPD; Photofrin®), aminolevulinic acid (ALA) — a prodrug which stimulates the production of the naturally occurring photosensitizer Protoporphyrin IX (PPIX) — and the synthetic porphyrin TPPS4. An open ring porphyrin based texaphyrin, Lutex, has also been examined. Chlorophyll based compounds have also been explored including Foscan® (MTHPC) and HPPH, which are chlorines and Purlytin ($SnET_2$), a purpurin, which is a degradation product of chlorin. As yet, no dye has been tested for this indication and reported in peer reviewed literature.

Illumination

Appropriate illumination should allow for activation of the photosensitizer. The longer the wavelength of light, the deeper the penetration into and through the skin. As most chest wall lesions can approach 1cm or more in depth, one generally will require an activation wavelength to readily penetrate this deep. Photofrin® and ALA/PPIX activate around 630 nm. This allows for at least 1 cm light penetration and should be adequate for most situations. ALA has a lesser penetration depth because it is applied locally, and the drug only diffuses to a few mm depth. Deeper lesions may require interstitial therapy; however, even lesions approaching 2 cm were successfully treated by superficial means using Photofrin®[25,34,35]. Purlytin's (660 nm) and Foscan®'s (652 nm) should behave similarly to Photofrin® in depth penetration. Lutex with 732 nm treatment wavelength may have deeper penetration. Illumination to activate the photosensitizers can be by multi-wavelength light or more efficiently by monochromatic light at the appropriate wavelength. This can be generated by intense white light with filters or more accurately by laser light at the specific wavelength. Light is transmitted from the source (i.e. laser) by fiberoptics for illumination. The illumination may be done using a diffusing fiber for multi-directional illumination, which is good for interstitial and intraluminal work, or a micro lens, which like a flashlight projects in a single forward direction. Many other types of fibers also exist. All lesions are more selectively activated by using a micro lens aimed at the treatment field. This will illuminate a circular field, and appropriate light blocking can be added. By blocking light from surrounding or reflected surfaces, one will minimize normal tissue toxicity. Inappropriate blocking of light may block illumination of tumor. One should avoid light field junctions over tumor beds to minimize light

inhomogeneity due to gap or overlap of the light fields. This could allow for under-dosage in the tumor bed and treatment failure. Overlapping light fields can allow for over light dosage and severe morbidity, particularly to normal tissue. Light emitting diodes can also be used as a substitute for the laser in the treatment of superficial lesions. One advantage is that they can be manufactured to treat a large area in one setting, making the treatment shorter and more comfortable to the patient. The efficacy of the LED as a replacement for a laser has been studied by Ferreira et al. (Lasers Med Sci 2004, submitted for publication).

PDT reaction

While it has been demonstrated that most photosensitizers induce PDT by a photodynamic reaction, the location of this reaction may be of clinical consequence. Photofrin® accumulates at the outer cell membrane and upon activation may induce apoptosis as well as cell death by cell membrane destruction. This may then lead to cytokine release and immune system activation. Clearly this may benefit patients with systemic disease. Other sensitizers are more selective in their location of concentration and may cause mitochodrial destruction leading to apoptosis without systemic immune activation since they don't destroy the cell membrane leading to cytokine release. This may well avoid immune stimulation and have clinical ramifications [36].

Dosimetry

Ideally real time dosimetry would exist to assist in therapy. Accurate dosimetry would allow optimization for an appropriate light dose to destroy malignancy with minimal or no normal tissue damage. Optimally, the dosimetry system would inform the user that adequate treatment had been delivered. No such system exists today, although progress have been reported on photosensitizer photobleaching (see photobleaching section below) and other PDT effects as an indication of treatment efficacy. Therefore therapeutic decisions are made with the rather empirical use of drug and light dose. This would explain why some treatments are more successful than others based mainly on clinical skill and judgment rather than accurate information. Until accurate dosimetry is available, clinicians will need to be highly cautious when using extremely active sensitizers or, when high concentrations of less active sensitizers are employed. Low-dose Photofrin® can be successful even when part of the treatment field is illuminated twice (e.g. field junctions). Low-dose Photofrin® is very forgiving in these situations likely due to photobleaching (see below).

Fluorescence

A major issue in any treatment is where the target is located. Clearly symptomatic lesions are easy to identify and response to PDT can be accurately gauged both clinically and by biopsy. Less clear are subtle lesions and areas at risk. In these cases, clinical experience is required. It would be better to have a reproducible ability to detect and define treatment fields [37—39] as well as response [40—43]. It is here that most photosensitizers can shine as most photosensitizers also fluoresce. By visual means or by more sophisticated techniques, it is hoped that fluorescence can be used to better define treatment fields and outcome. This is an area of active research, but results are preliminary. Theoretically the change in fluorescence could also be used as a real time dosimeter. Potentially, sensitizers that fluoresce could be used to optically biopsy lesions [44—53], treat them, dose them appropriately and define a successful therapy without bias.

Photobleaching

Clinically, one can exploit photobleaching to enhance tumor response and minimize normal tissue toxicity [34,54]. Higher photosensitizer drug dose appears to minimize selectivity in PDT response between tumor tissue and normal tissue [55]. This may be explained by photobleaching kinetics. In clinical photobleaching, as little photosensitizer as possible is employed to destroy tumor. Since sensitizers concentrate to a certain degree higher in tumor than normal tissue then one should have more PDT in tumor. Using as little sensitizer as possible spares normal tissue by minimizing PDT at that location. If more sensitizer is infused than needed, more will go to both tumor and normal tissue. Even though more sensitizer is still in tumor than normal tissue enough sensitizer is still in normal tissue to create significant PDT. Therefore, by infusing as little sensitizer as is needed to destroy tumor beds one can minimize normal tissue toxicity and enhance selectivity by photobleaching.

Reported outcomes from clinical trials

Photofrin®

Photofrin®, a hematoporphyrin derivative, is a member of the porphyrin family which has been

employed in a number of trials [34,56—65]. In addition to highly variable drug dose, light dose and drug to light interval time, dissimilar patient populations also appear to exist. Complicating matters even more, the reporting of response varies from series to series, sometimes including lesions response rates, patient response, and volume response among others. These varying endpoints of analysis and treatment techniques make it difficult to compare the published data. As Photofrin® has the longest history of availability, it is not surprising that this photosensitizer has the most clinical reporting. Many of the early works included drug dose, light dose and drug to light interval time variations which are, based on today's 20—20 hindsight, clearly inadequate. However, each series added to our knowledge, and taken as a whole, truly give us impressive insight into appropriate therapy.

Photofrin® (HPD) has been infused from 0.6 mg/kg to 4 mg/kg for breast patients. Illumination has ranged from 20 to 360 J/cm^2. Generally, drug to light interval was about 48 h, but could range to 1 week. Complicating matters further is that current micro lens construction appears more amenable to therapy than older fibers and may offer more homogeneous illumination. Despite all of this, complete response rates of 100% with minimal morbidity is possible. It is also possible to overdose normal tissue with drug or light and induce serious morbidities. These morbidities to normal tissue can present with pain, fibrosis, scarring and altered pigmentation causing serious cosmetic concerns among others. Since most patients treated for chest wall recurrence have tissues injured by prior salvage, healing is of great concern. That is why it is appropriate to analyze data to reveal which techniques offer the best response with least morbidity.

In an elegant series from Roswell Park, infusions of Photofrin® from 0.57 to 2.5 mg/kg with illumination from 30—350 J/cm^2 at 48 h were reported [57,58]. Minimal response at 0.57 mg/kg even with 244 J/cm^2 light was seen. This shows a minimum threshold for response. Further patients infused at 2 mg/kg had much higher treatment related morbidity than patients infused with 1 mg/kg. Particularly, individuals infused at 2 mg/kg illuminated with light doses greater than 72 J/cm^2 were at greatest risk. Interestingly 6 patients infused at 0.75 mg/kg and illuminated at 140—182 J/cm^2 had excellent response with minimal normal tissue toxicity. Similar response was also seen in patients with high light and drug dose, but morbidity in those patients was much more severe. This we feel demonstrates a drug and light dose that not only was threshold for breast PDT but likely exploited photobleaching to minimize normal tissue toxicity. Since Photofrin® for breast metastasis accumulates a bit more in malignancy than normal tissue, the 0.8 mg/kg allows for tumor destruction, but the 0.8 mg/kg is not enough to allow for significant PDT in surrounding normal tissue. Due to normal tissue morbidity found at 2 mg/kg, illumination fields in the Roswell Park report were very tight around lesions. This led to many patients experiencing recurrence at the rim of the illumination field which would require additional salvage treatment. Patients treated at 0.8 mg/kg on this series also had very tight light fields leading to rim recurrence.

Based on photobleaching and the concept that 0.8 mg/kg with 150 J/cm^2 were near optimal for tumor control with minimal morbidity larger illumination fields were employed in a more recent publication [34]. Here margins well beyond the tumor nodule at risk were illuminated. Rim recurrence was not generally seen and virtually all lesions were eliminated. Overall, it appears that 98% of the time chest wall lesions could be stopped from growing or eliminated. Despite all patients having undergone extensive surgery, high dose radiation and multiple chemo-hormonal therapies, cosmetics was judged to be excellent. Using the same parameters, the East Carolina University (ECU) experience was recently published [61]. Patients, including those with large confluent lesions, who had failed all salvage including radiation were illuminated with wide margins. Drug dose was 0.8 mg/kg with illumination at 48 h by 630 nm light at 150 J/cm^2. All lesions responded and 9 of 14 patients had total elimination of chest wall disease. Five of 14 patients had most lesions cleared, but remained with some areas of non-growing tumors and were called partial responders. Overall out of 500 lesions treated, more than 90% were complete response. As all patients were followed closely, it became apparent that even wider margins of illumination are needed in patients with chest wall metastasis. Several patients failed beyond the edge of the illumination field which generally already included 2 cm margin. With the drug/light dose employed larger margins of illumination were possible without additional normal tissue toxicity. Perhaps larger margins will be required to be illuminated to further increase control rates. High response rates have also been reported with 2—3 mg/kg of Photofrin® and light doses of 100 J/cm^2 [60]. Of note, however, is the significantly higher morbidity seen including wound healing difficulties, fibrosis and treatment related pain. These drug/light doses also do not seem to offer the selectivity in PDT between

normal and tumor tissue requiring tight illumination borders. This would also increase the chance of rim recurrence. Other authors [57,62] have also reported high normal tissue toxicity with high drug and/or light doses, again pointing the way toward lower drug concentrations for these particular patients. Chemotherapy agents may interact synergistically with PDT to potentially enhance response of tumors, however, normal tissues may be sensitized as well leading to enhanced toxicity of normal tissues [24]. The net result may not be of clinical benefit.

While many different Photofrin® drug/light dose schedules can offer high tumor response, normal tissue toxicity can be significant. Further, as dermal invasion leads to widespread disease, wide borders of illumination to seemingly normal appearing but tumor-containing tissue is needed. By exploiting photobleaching, low-dose Photofrin® appears to offer excellent tumor response with minimal normal tissue toxicity. Even heavily operated upon and radiated fields respond well. Low-dose Photofrin® PDT has also allowed for surgical graft placement in a wound defect in the center of a field sterilized by PDT [61]. This clearly offers select patients even more opportunity for salvage.

For patients treated with Photofrin®, the actual illumination procedure appears relatively painless. Some series report a slight stinging towards the end of each field illumination. Most patients have minimal post-PDT related pain as well. Overall, it appears to be a well tolerated procedure. When 2 mg/kg of Photofrin® is used, patients must maintain direct sunlight precautions for a minimum of 4 weeks. At doses of 0.8 mg sunlight sensitization appears rare at 4 weeks.

Lutetium texaphyrin

Lutetium Texaphyrin (Lu-Tex), a member of the texaphyrin family of sensitizers [66], has also been examined in patients with locally recurrent breast cancer [66—68]. Patients who failed salvage, including radiation therapy, were infused with varying drug doses of 0.6—7.2 mg/kg, 3—96 h prior to illumination. Illumination at 732 nm generally at 150 J/cm^2 was then employed. At dose above 5.5 mg/kg, treatment could not be completed due to pain during illumination. Dysesthesia in light exposed areas also occurred. A 27% CR was reported. Additional patients were treated with 1—3 mg/kg. Most patients experienced pain at the treatment site during therapy. Response rates were marginally better. As part of this study dosimetry was examined for patients infused with either 4 or 5 mg/kg and illuminated with 150 J/cm^2. Interestingly fluence rates varied by up to 70% in the treatment field, which may have contributed to the limited CR rates as well as morbidity [69]. This study also revealed that treatment 3-h post-infusion is associated with minimal selectivity and excess toxicity while treatment beyond 24 h was without photo activity.

Npe6

In a phase I study of the chlorin, mono-l-aspartyl chlorin e6 (Npe6), Taber et al. [70] reported on patients with recurrent chest wall lesions who failed prior salvage. In this dose—light finding study 0.5—3.5 mg/kg of Npe6 were intravenously applied to the patients. Approximately 4 h later, lesions were illuminated from 25 to 100 J/cm^2 at 662 nm. Tumor regression and eschar formation were always noted, but patients always failed within this treatment field at doses of drug $\leq$1.65 mg/kg. Patients infused with 2.5 or 3.5 mg/kg and illuminated at 100 J/cm^2 allowed for 66% complete remission (CR) rate. However, at drug dose of 2.5 mg or above no normal tissue selectivity was seen in the treatment fields. While the PDT treatment was tolerated all patients were photosensitive for 2 weeks.

MTHPC

Another chlorin family member, MTHPC, Foscan® has also been evaluated [71,72]. A total of 7 patients with chest wall recurrence underwent PDT in 11 sessions. Most patients had failed radiation, but some did not undergo radiation salvage postmastectomy. Three patients underwent 0.1 mg/kg infusion followed by illumination at 48 h at 5 J/cm^2. Eight treatments on five patients occurred following 0.15 mg/kg infusion with illumination at 96 h at 10 J/cm^2. All illumination was at 652 nm. Normal tissue was covered by plaster with a hole cut out for the illumination field. Six of seven patients had PDT related pain. This pain generally lasted for 2 weeks post-treatment. Narcotic analgesia was needed for several patients. One patient, who had undergone prior radiation treatment, had extreme pain develop within her radiation field. Another patient suffered photosensitivity from a reading light. While all 89 lesions appeared to have CR it is interesting to note that 4 of 7 patients needed additional PDT due to recurrences bordering the prior PDT fields. This rim like recurrence appears to be due to the normal tissue toxicity noted in the illuminated fields requiring the physicians to treat as

small a skin volume as possible. The authors report treatment areas greater than 12 cm^2 cause delayed slough off of necrotic tissue. Tissue healing time for areas treated greater than 12 cm^2 was greater than 3 months. While obviously a very potent and successful treatment for chest wall patients the optimal use of this photosensitizer for this indication is far from known. The very limited treatment fields possible with the drug—light doses used clearly allowed for failure in skin bordering illumination fields. This is not unlike some of the earlier reports on Photofrin®, where drug/light dose combinations were employed and were not optimized. Patients were also sunlight and dark light sensitive for 2 weeks post-infusion. This may have more quality of life limitations than 4 weeks of sunlight photosensitivity from low-dose Photofrin®.

Purlytin

Purpurins, derivatives of chlorines also have been tested. Purlytin, tin ethyl etiopurpurin, was examined on eight patients who had failed conventional salvage regimens including radiation [73]. The drug was infused at 1.2 mg/kg and illumination was undertaken 24 h later at 660 nm with 200 J/cm^2 via micro lens. A complete response rate of 92% with partial response rate of 8% was reported. No patient had lesion re-growth within the illumination fields and cosmetic results were excellent. Good wound healing without fibrosis was noted. Therapy was always as outpatient and with minimal discomfort. Good selectivity was noted within illumination field. Margins of illumination of at least 1 cm were used. No rim recurrences at the borders of the illuminated fields were seen. No sunlight photosensitivity was reported and sunlight precautions were employed for 2 weeks post-infusion. Similar good outcomes were published in case report form [74].

ALA/PPIX

ALA, 5-aminolaevulinic acid is a pro-drug [75,76]. Introduction of ALA overloads the heme synthetic pathway and lead to excess Protoporphyrin IX, an active photosensitizer. This member of the porphyrin family activates around 630 nm and has had excellent response on superficial malignant and pre-malignant skin lesions. However, ALA is generally applied as a superficial cream, which while greatly convenient, is sub-optimal for nodular lesion therapy. The wavelength of light should allow for deep enough tissue penetration, but the cream itself must not be able to diffuse far enough. Even when introduced systemically (orally or intravenous) ALA/PPIX has limited depth penetration. It also loses a significant amount of tumor versus normal tissue selectivity as compared to topical application. This would explain the very poor response rates for breast metastasis, which are usually nodular [77]. Conceivably ALA could be used via a multivisit regimen of repeated topical applications and illumination, but would lose its convenience. It is also quite a painful therapy.

TPPS4

A substituted porphyrin, meso-tetra para sulphophenyl porphin (TPPS4) has also been used for chest wall recurrence [78,79]. This drug was found to be neurotoxic on systemic application. An alternate use has been by intra-lesional injection, without the reported neurotoxicity. In 9 patients who failed initial salvage, including radiation, TPPS4 was introduced into each lesion at 0.15 mg or 0.3 mg via injection. Illumination began 45 min later at 630 nm with fluence of 150 J/cm^2. Only 33% CR rates were reported with follow-up of 6—8 months. Of note, most lesions required an average of 12 injections/illuminations to achieve this result. Clearly, this is not a very convenient treatment regimen for patient or caregiver.

Summary of trials

The results and parameters of the clinical studies used in chest wall PDT are outlined in Table 1 for Photofrin® and other photosensitizers. PDT is active and potentially has an excellent outcome as a salvage tool even in heavily pretreated tissue. The drug can accumulate in tissue damaged by surgery, radiation and chemotherapy. Even with illumination lethal enough to destroy tumors, normal tissue can heal without intervention. Particularly noteworthy is that the healed skin is not fibrotic, and has excellent cosmetic results. It is also very clear that Photofrin®, with its long clinical history, and its published data for this population of patients, can be clinically successful with minimal morbidity. While many drug/light doses can bring success, some appear to have higher side effects. Our experience shows that low-dose Photofrin® at 0.8 mg/kg and illumination at 150 J/cm^2 gives a reliable and excellent outcome.

Other sensitizers are also able to offer good response, but the patient population so far examined is small and follow-up is short. Many of these sensitizers are not always commercially available

Table 1 Clinical Studies for Chest Wall PDT.

Drug	Number of patients	Number of fields	Number of Tx sessions per patient	Drug dose (mg/kg)	Wavelength (nm)	Fluence (J/cm^2)	DTI[a] (h)	CR[b] (%)	PR[c] (%)	MR[d] (%)	Morbidity[e] (%)	Photosensitivity patients	Follow-up months	Reference
Photofrin®	14	500	1	0.8	630	150	48	91*	7	2	7	0	>6	[61]
Photofrin®	9	102	1	0.8	630	150	48	89	8	3	0	0	>6	[34]
Photofrin®	4	4	1	0.57	630	30—244	48	0	0	0	0	0	>6	[57,58]
	6	6	1	0.75	630	140—180	48	66	16	16	0	0	>6	
	27	NR	1—6	1—2.5	630	36—288	48—120	19	48	33	50	2	>6	
Photofrin®	7	11	1—3	1—2	630	≤100	48	73	18	9	9	1	>6	[60]
Photofrin®	14	33	1—4	1.5**	630	<50	48, 72, 96	14	42	42	50	0	>6	[59]
	6	47	1—4	1.5	630	≥50	48, 72, 96	33	50	16	50	0		
Photofrin®	15	NR	1	2—3	630	25—200	48	20	80	0	50	0	>6	[62]
Lutex	16	16	1	0.6—7.2	732	150	3—96	27	33	37	50	0	3	[68,69]
	25	38	2	1—3	732	150	3	47	29	24	25	1	3	
Npe6	3	3	1	1.65	664	25—100	4	0	0	0	0	0	3	[70]
	8	11	1	2.5—3.5	664	100	4	66	0	33	100	0	3	
MTHPC	7	89	1 or 2	0.1—0.15	652	5—10	48—96	100	0	0	100	1	4	[72]
Purlytin	8	86	1	1.2	660	200	24	92	8	0	15	0	>6	[73]
ALA	5	14	1	20%	630	150	4	35***	0	35****	30	0	6	[77]
TPPS4	9	NR	12	0.15—0.30	630	150	1	33	22	44	0	0	6	[79]

[a] Drug infusion to light illumination interval.
[b] Complete response.
[c] Partial response >50%.
[d] Minimal response.
[e] Morbidity for Photofrin® includes: severe Tx pain, wound healing problems, scar; morbidity for other drugs includes: severe Tx pain, wound healing problems, scar, normal tissue injury (or or more of each).
* 91% (465/511 lesions); 9/14 patients with CR, 5/14 with PR.
** Highly active version of photofrin, potentially equivalent to 3 mg/kg.
*** Isolated nodules <1 cm.
**** Minimal response to nodules >1 cm.

and appropriate wavelength light sources may not be available either. Clearly, the potential for these photosensitizers to outperform Photofrin® is possible, but has not yet been reliably shown. Only larger multi-institutional clinical trials will be able to ascertain this type of information.

One also should be cautious about the patient population examined. Most of the published literature was for patients with recurrent chest wall disease. However, some studies included a re-recurrent patient population. These individuals have undergone multiple surgeries, radiation courses, and chemotherapies. They are more likely susceptible to normal tissue morbidity but excellent results are still possible [34,61].

Treatment techniques

Patient positioning

Unlike many patients who undergo PDT, patients with chest wall disease pose certain unique considerations. First and foremost patients generally have numerous lesions requiring therapy. Since ideally each lesion should be treated appropriately, a system of identifying the lesion and ensuring it is illuminated is essential. As some individuals will have 50 treatment fields, memory will not suffice. We recommend an anatomical drawing to be used in conjunction with patient coordinates and landmarks. The suprasternal notch and tip of xyphoid process are easily defined and can serve as reference, as can the clavicle. Surface marking by ink at even intervals can assist. This grid will allow for systematic rather than haphazard treatment and avoid geographic misses as well as treatment of the same anatomy twice by mistake. Additionally, patients who have numerous lesions will require comfortable positioning to minimize movement during illumination. Since chest wall PDT is accomplished in a fully conscious outpatient setting we recommend a very comfortable treatment couch or bed. Following along these lines, setting up for illumination is time consuming so making the most efficient use of the micro lens set-up is important. Stands that allow for easy adjustment of the light are needed. Mobile stands that can be rapidly moved and locked into place for the next illumination are very important. Critically, patients who have widespread lesions may need to be turned over or around to reach treatment sites. As PDT can give rapid therapeutic outcome with treatment lesions becoming very tender or weeping, one must use considerable forethought deciding which lesions will be treated first and which last. One does not want to treat the asymptomatic lesions, cause them to become tender, and thus prevent treatment of symptomatic anatomy. With patients requiring multiple planes of illumination and multiple anatomical regions (i.e. chest wall, abdomen, shoulder, etc.) considerable treatment planning must be done prior to patient positioning, otherwise therapy will not be able to be completed.

Illumination

As critical as patient positioning, and deciding which anatomical region is to be treated in which sequence, is the ability to deliver homogeneous illumination. It is important that the light source be incident to the anatomy, otherwise over and under light dosage could occur in each field. Further, the light sources must be able to reach each anatomical area, thus light source mobility and location is part and parcel of patient set-up. Since it is important not to overlap light fields (i.e. over illuminate) it is critical that accurate placement of fibers be maintained throughout therapy. As patient anatomy varies dramatically it is easy to over and under dose. Further, patients may move during illumination and a means to re-position patient/and or light in real time is critical. It is also critical that illumination fields not cut through or partially illuminate tumor beds for this will potentially under dose lesions. As palpable lesions only represent the tip of the iceberg, it is also critical that generous illumination margins around disease be used. In consideration of the added uncertainty of patient motion, we suggest at least 2 cm margin. If indicated, following illumination, an ice patch applied to the treatment fields while the next treatment field is being illuminated will usually eliminate any acute treatment related pain.

The indications for interstitial illumination are unclear as the majority of reports employ only surface illumination. Even lesions approaching 2 cm depth can be successfully treated with surface illumination when Photofrin® is employed. Photosensitizers such as Foscan and Lutex theoretically can treat even thicker lesions from the surface. In general interstitial implants are done for bulky lesions greater than 2 cm in depth. The implanted illumination source is usually placed at the base of the lesion, close to the skin to ensure deep light penetration. Implanted fibers should be about 1 cm apart. The use of small amounts of local anesthetic may help to ease placement pain. Some anesthetics can impede blood flow, which may alter photosensitizer concentration. Bleeding may absorb treatment light.

Specific precautions

Photosensitivity

All sensitizers will offer sunlight photosensitivity [28]. For Photofrin® at 2 mg/kg, 4—8 weeks of precautions are needed. At 0.8 mg/kg we have found sunlight photosensitivity rare after 4 weeks. Purlytin patients were sensitive for 2 weeks [73] and Foscan® [72] patients to 10 days. In general, sunlight precautions apply only to sunlight or similar intense light. Patients' skin must be covered and wrap around sunglasses as well as a wide brim hat is recommended. Reflected light, for example from a car window, can cause photosensitivity reaction. In general, room light is safe. Foscan® patients may be sensitive even at minimal light levels and reports exist of toxicity occurring from sitting near a light bulb or fireplace. As most patients with chest wall recurrence have undergone multiple surgeries, radiation and chemotherapies, they are well versed in toxicity. We have found in our practice, that the sunlight precautions have not prevented any patient from signing informed consent for therapy. However, if you encounter a patient unable to, or unwilling to accept this precaution, they should not be readily offered PDT.

Illumination

Depending on the photosensitizer and its treatment parameters, morbidity to normal tissue during illumination is possible. Foscan® patients must have non-illuminated regions heavily blocked from scatter of light [72]. As this drug is so active, scattered light is often enough to initiate PDT. While employing Foscan®, one must use significant effort to ensure no scatter to tissue you do not wish to treat. It is also very important to not overlap illumination fields as tissue necrosis may occur. Similarly, when 2 mg/kg of Photofrin® is employed one also must be extremely careful concerning illumination overlap to prevent serious morbidity. Interestingly, likely due to photobleaching, when low-dose Photofrin® (0.8 mg/kg) is employed, no additional morbidity is clinically noted during illumination overlap. Indeed as micro lens illumination is circular and few tumor beds are circular, the ability to overlap illumination fields without undue morbidity is the great advantage to low-dose Photofrin®.

Pain control

Depending on the sensitizers and treatment variables, pain may or may not occur during therapy. With ALA and Foscan® illumination all patients experience pain [31,75]; this is rare with low-dose Photofrin®. In cases where pain occurs an ice patch to the affected area generally works. Numbing the skin prior to therapy has been tried, but failed. We suggest patients be dispensed narcotic or non-narcotic pain pills prior to illumination to minimize treatment difficulties.

Many patients have painful chest wall lesions that impact on their quality of life. PDT is often able to offer pain control via successful therapy. Depending on the photosensitizer and treatment parameters, the actual PDT can be painless or painful. In general excellent pain control from lesion diminishment can be seen within 2 weeks of the PDT session. During this time, however, we recommend continued narcotic or non-narcotic analgesia, as clinically indicated.

Photosensitivity reaction

A photosensitivity reaction occurs when normal tissue is exposed to enough light to activate the photosensitizing agent [7]. As each sensitizer has its own characteristic activation energy and half-life, the ability to have a photosensitivity reaction is sensitizer dependent. In general, this reaction is similar but more rapid to develop and more intense than a sunburn. Even a few moments of sunlight to a powerful photosensitizer such as Foscan® can induce this reaction. Patients complain of pain in the exposed area and swelling with burn can occur. The severity of signs and symptoms will depend on the intensity of light exposure and amount of sensitizer remaining. Treatment to each burn is recommended with ice/cold compress, steroids, elevation and pain control. If critical structures such as airway, neck, orbits, etc. are exposed and begin swelling, emergency treatment may be required, perhaps as an inpatient. It should be emphasized that patients are photosensitive starting from infusion (not treatment). An ounce of sunlight prevention beats a pound of cure.

To enhance elimination of the photosensitizer from the skin one can employ the following procedure, if indicated. We suggest waiting at least 1 week post-treatment to try this. The fully covered patient can carefully expose a 1 cm^2 area of skin (forearm placed in a brown bag with a hole in it) at sunset for a minute or two, but should pain occur, this procedure should then be abandoned. If at 24 h minimal sensitivity occurs, the patient can expose more forearm skin for a bit longer and repeat this several more times. By progressively increasing the amount of skin exposed to limited amounts of twilight sunshine, the photosensitizer can be bleached

out fairly rapidly. Do not attempt this with Foscan® and do not try it at other times of the day.

Post-treatment

All patients' post-therapy should undergo several days of steroids with taper. This minimizes local reaction and swelling. Oral narcotic and non-narcotic analgesia for 1—2 weeks is generally useful, though some patients do not actually need these medications. We suggest a 1-week course of antibiotics such as keflex or Augmenten. Patients are also encouraged to drink plenty of liquids. Every patient must be reminded of sunlight precautions at this point as well.

Patient selection

This is a key issue. One must ultimately ask how local control of the chest wall will impact patients. For patients with highly symptomatic chest wall lesions, even in the face of widespread disease, an improved quality of life might be possible. However, should PDT create open wounds that will not heal in the patient's lifetime, no obvious benefit is to be gained. Given the natural history of recurrent lesions to be poorly controlled and to grow, local control and symptom prevention is an important consideration. The timing of intervention is variable; however, larger PDT fields take longer to heal as does treatment of larger lesions. It is our preference to intervene with PDT prior to the patient's back being against the wall. We have found that many patients will not participate in any social activity due to the physical and psychological problems associated with growing, visible tumors. Successful PDT for these individuals is able to provide extraordinary improvement in quality of life.

Wound healing

Fundamentally, PDT appears to swap ever-progressing non-healing lesions with sterilized wounds that can heal with excellent cosmetics [34,61]. For lesions less than 1 cm in diameter and isolated, healing time is measured in weeks. Larger treatment fields can require months to heal. Thicker and larger lesions often form eschars, which we have found to be protective, painless and infection free. It is our recommendation that PDT fields be kept clean with as minimal intervention as possible. Biopsy and wound surgery should be avoided. In virtually all cases, lesions will close and heal. Time to healing is delayed by chemotherapy. In sterilized fields, the rare non-healing defect caused by very large tumors necrosing can be closed by flaps. This should only be attempted by an experienced surgeon.

Retreatment

As recurrent lesions invade dermal lymphatics, they have a propensity for wide cutaneous spread and clinical re-occurrence. The PDT literature shows patients are readily able to undergo multiple treatment sessions and chest wall lesions are no exceptions. New lesions outside prior illumination fields as well as the rarer rim progression can generally be treated with the same drug/light parameters as accomplished on the first session. Similar good outcomes are expected. For the rarer in field recurrence, more intense illumination should be considered. However, it is likely that the in-field recurrence was due to under-dosage of light during the initial PDT sessions. Several reports indicate that re-treatment is well tolerated with excellent response seen [34,61,72]. One should consider re-treating patients on a case-by-case basis. Those individuals with an isolated small recurrence may benefit from a short course of radiation rather than PDT induced photosensitivity. Also, as normal tissue migration is required for wound healing, one might not want to re-treat until the initial PDT treatment fields have virtually healed. This will prevent the development of excessive open wounds.

Conclusion

PDT can reliably salvage individuals with chest wall recurrence despite fragile tissues from surgical, radiation and chemotherapeutic intervention. PDT can not only control chest wall recurrence, but offer the potential for superior cosmetic results. This is particularly noteworthy as these patients are all too often denied any additional salvage, and are left with daily growing reminders of their mortality.

Local treatment may have an impact on survival, particularly if infected open tumor wounds can be healed. In general survival is a function of control of systemic spread. This is why most patients with recurrent disease, even if thought to be contained on the chest wall are initiated on systemic therapy. No study of PDT for this patient population has been large enough to analyze for improved survival. Even if PDT may not significantly improve survival it can improve the quality of life by eliminating obvious signs and symptoms of disease. PDT also offers ex-

cellent pain control and by this criteria alone should be considered beneficial.

Even with limited dosimetry, patients with chest wall recurrence can be reliably salvaged by a variety of photosensitizing agents used in a variety of treatment paradigms. Each agent and treatment has its own risk to benefit ratio and cannot be interchanged. While excellent results can be obtained, serious consequences can also arise. A large patient literature exists reporting that low-dose Photofrin® can offer high response rates with limited morbidity even when inhomogeous illumination occur. Employing high dose Photofrin® and other sensitizers does not appear to be as forgiving. While a number of trials have allowed for some conclusions on how to optimize light and drug concentrations for Photofrin®, the same cannot be said for other sensitizers. Lower drug dose—higher light dose trials for other photosensitizers to enhance response and diminish side effects are needed.

Additional work needs to be done to enhance outcomes and minimize morbidity for patients with chest wall recurrence. Work on fluorescence will no doubt improve our ability to define what requires treatment rather than relying mainly on clinical observation. Changes in fluorescence may allow better correlation with the success or failure of the treatment. It may also provide the basis for real time dosimetry. This would improve response and diminish side effects. As it stands micro lens fibers can be used successfully, but only a limited field can be illuminated at a time. This requires constant re-alignment and re-positioning for each treatment field. Not only is this time consuming and repetitive, but lends itself to significant errors due to motion and potential geographical misses and overlap. As the micro-lens has limited illumination field sizes, one may by necessity have to cut across tumor or critical tissues which can have significant clinical implications. A large homogeneous illumination field, perhaps created by individualized LED's might offer simple and faster therapy and better outcomes.

Since PDT seems to work well as a last resort, even in heavily treated tissue, one might wonder if earlier intervention with PDT would improve the outcome of the disease. Conceivably PDT could be used as an adjunct to surgery to sterilize the tumor bed. As most failures are local following lumpectomy and radiation, PDT may improve outcome. Finally, many patients who could maintain an intact breast, instead opt for mastectomy due to a lack of radiation services. Possibly lumpectomy bed PDT could offer these individuals breast preservation as PDT treatment is far less expensive and more mobile than the current 6 weeks of linear accelerator based radiation. One can only hope that this review will help stimulate interest in answering these important questions.

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