Patient Responses to Cytoluminescent Therapy® for Cancer: An Investigative Report of Early Experiences and Adverse Effects of an Unconventional Form of Photodynamic Therapy

Ralph W. Moss, PhD

Cytoluminescent Therapy® (CLT) is an unconventional form of photodynamic therapy (PDT), utilizing a second-generation chlorophyll-derived photosensitizing agent and whole-body illumination. Starting in late 2002, CLT was administered in Ireland to 48 patients. Illumination with lasers and light-emitting diodes followed the administration of an initial bolus IV. After returning home, patients continued self-administered treatment using oral agent activated by infrared lamps. CLT proponents claimed that these procedures were beneficial to patients with advanced cancer. An organization devoted to making information on alternative therapies available to the public was engaged to contact these CLT patients and assess the outcome. In informal contacts, patients reported that initial side effects were generally mild and transient. However, especially after commencing self-treatment, many reported unanticipated effects, including fatigue and general weakness, increased pain, cough, dyspnea, diminished appetite and weight loss, tissue necrosis, and other major symptoms. At a minimum of 6 months after initial CLT, no patient has reported an objective response, and some have complained of deterioration on the home treatment. There have been 17 deaths among the 48, with a mean survival after initial treatment among decedents of 4.2 months. CLT, in this group, was a qualified failure, with a high incidence of aftereffects. The mode of action of these aftereffects has yet to be explored. In the future, CLT should be administered to patients only in carefully managed medical facilities, by fully trained and licensed professionals, under the supervision of relevant regulatory agencies, and with meticulous follow-up care.

Keywords: ***cancer; complementary; alternative; CAM; photodynamic therapy; cytoluminescent; PDT; CLT; aftereffects***

The aim of this report is to investigate the effects, subjective as well as objective, of Cytoluminescent Therapy® (CLT), an unconventional method of administering photodynamic therapy (PDT), in 48 patients with cancer. CLT utilizes a second-generation photosensitizing agent (Radachlorin®, also trademarked as Photoflora®) primarily activated through whole-body illumination of patients using lasers, light-emitting diodes (LEDs), and commercially available infrared lamps.

This report is the result of a follow-up study by Cancer Communications, Inc (CCI), a Pennsylvania-based company devoted to the publication of accurate information on complementary and alternative therapies in cancer. The study was requested by Dr William H. Porter and his colleagues of the Cytoluminescent Therapy Centre, Killaloe, County Clare, Ireland (presently called CLT Clinics, Ballina, County Tipperary, Ireland). Information on CLT was circulated through an online newsletter published by CCI in October 2002. The author of the present report, president of CCI, was engaged by the Cytoluminescent Therapy Centre to give a series of educational lectures to 48 patients and later to contact these same patients to determine the outcome of their CLT treatment.

History of PDT

In the winter of 1897-98, a Munich medical student, O. Raab, discovered the phenomenon of biological photosensitivity.[1,2] Photosensitizing agents by themselves were found to cause minimal toxicity to cells, becoming cytotoxic only upon activation by specific wavelengths of light. Photosensitizers preferentially accumulate in abnormal tissue. When such chemicals are activated by light, highly energetic singlet oxygen is released, causing damage to cellular membranes and intracellular microstructures and proteins. When oxidative damage exceeds threshold levels, affected cells begin to die.

RWM is at Cancer Communications, Inc, Lemont, Pennsylvania.

Correspondence: Ralph W. Moss, PhD, Cancer Communications, Inc, PO Box 1076, Lemont, PA 16851. E-mail: rwm@cancerdecisions.com.

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The effectiveness of PDT depends on a number of variables, including

- the ability of the agent to accumulate preferentially in target tissue,
- the reactivity of the agent to light,
- the depth of penetration of the light,
- the interval between application of the photosensitizer and its activation,
- the rate of drug and light interaction, and
- the field of illumination achieved.

Over the following decade, Raab's professor at Ludwig-Maximilians University, H. von Tappeiner, together with A. Jesionek, used this phenomenon to treat cutaneous malignancies with preliminary success.[3] The first photosensitizers were coal tar dyes, such as acridine and eosin, but porphyrins were soon substituted, due to their greater sensitivity to light activation. In 1955, S. Schwartz found that a derivative of hematoporphyrin (HpD) had greater selective tissue-localizing properties than HpD alone.[4]

In 1978, T. J. Dougherty et al published the results of the first human clinical trial of PDT, using HpD with a filtered xenon arc lamp as the activating light source. Out of a total of 113 lesions treated (including malignant melanoma; mycosis fungoides; soft tissue sarcomas; carcinomas of the breast, colon, endometrium, and prostate; and squamous and basal cell carcinomas of the skin), there were 111 complete or partial responses.[5]

Since 1995, Photofrin (porfimer sodium), a photosensitizer derived from HpD, has been approved by the Food and Drug Administration (FDA) for the treatment of micro-invasive endobronchial non-small-cell lung cancer[6]; advanced, partially or totally obstructing cancer of the esophagus[7]; early-stage esophageal cancer with Barrett's esophagus[8]; and various malignant and premalignant skin lesions.[9,10] In addition, PDT is also FDA approved as a treatment for multiple actinic keratoses[11] and age-related macular degeneration,[12] using the photosensitizer aminolevulinic acid and vertiporfin (Visudyne®), respectively. The European Union (EU) has approved the HpD derivative, Photosan®.[13] In October 2001, the photosensitizer Foscan® was also approved by the EU, Norway, and Iceland as a local therapy for the palliative treatment of patients with advanced head-and-neck cancer who had failed prior therapies and were unsuitable for surgery, radiotherapy, or systemic chemotherapy.[14]

For skin and superficial tumors, PDT can be administered using an external light source such as a laser attuned to the absorbency peak of the corresponding photosensitizer and delivered in a highly targeted way. In the case of deep-seated tumors, the light source generally must be applied either (1) endoscopically, (2) interstitially, or (3) intraoperatively. In these ways, PDT may also be used in the treatment of larger internal areas, including the pleura and peritoneum.

There are presently more than 8500 scientific articles in Medline on the topic of PDT, at least half of which relate to cancer. There are also more than a dozen US clinical trials of PDT recruiting patients with various types of cancer, including recurrent malignant supratentorial gliomas, malignant mesothelioma, solid tumors metastatic to the skin, locally recurrent prostate cancer, obstructive esophageal tumors, lymphoma or chronic lymphocytic leukemia, cervical intraepithelial neoplasia, intraperitoneal cancer, and cutaneous T-cell lymphoma, as well as various benign conditions.[15,16]

PDT is thus of potential use in the treatment of a large percentage of tumor types. However, the most commonly used agent, Photofrin, is a variable mixture of HpDs that is not chemically defined or fully standardized. Despite the fact that it was the first photosensitizer to be approved by the FDA, its use has not increased as rapidly as might be expected. This is because of its limited tumor-tissue specificity, relatively low peak absorbance of light (630 nm, a wavelength that does not penetrate tissue deeply), the obligatory need for systemic administration (precluding its use as a topical agent), and the persistent skin photosensitivity that it induces, sometimes lasting up to 6 weeks posttreatment. For such reasons, there is a worldwide search for more effective second-generation photosensitizing agents to replace the first-generation agent, Photofrin.

A considerable number of new photosensitizers are under evaluation. These include mono- and diasparyl chlorin e_6 (MACE, NPE_6, and DACE),[17] lysyl-chlorin p_6, lutetium texaphyrin derivative (Lutrin),[18] tin ethyl etiopurpurin (SnET2),[19] and tetra-meso-[m-hydroxyphenyl] chlorin (THPC or Foscan).[20] Photosensitizers presently in US clinical trials also include silicon phthalocyanine 4,[21] benzoporphyrin derivative monoacid ring A (Verteporfin),[22] HPPH, methoxsalen (PUVA), and dihematoporphyrin derivative (DHP).[23] Most of these are chemically pure agents, which absorb light at 650 to 800 nm or greater (into the infrared range) and induce less skin photosensitivity than Photofrin.[24]

Development of Radachlorin

Radachlorin is one such second-generation agent. It was developed from chlorophyll derived from the microalga *Spirulina platensis* in 1994-2001 by Andrei V. Reshetnickov, PhD, et al and is produced by Rada-

Pharma Co, Ltd, Moscow, Russia.[25] It is described by its inventor as the "the first natural, water-soluble chlorin-type photosensitizer derived from *Spirulina platensis*" (A. Reshetnickov, personal communication, July 23, 2003). The major component of Radachlorin is sodium chlorin e_6 (90%-95%). One of the minor components is sodium chlorin p_6 (5%-7%). The third chlorin constituent (1%-5%) is kept as a trade secret by the company. The drug substance is prepared as a 7% aqueous solution.[26] (The term *Photoflora* has been used at the CLT Web site. This is a commercial name being used for marketing and approval purposes in the West. Photoflora and Radachlorin are synonymous terms.)

The laboratory process for preparing Radachlorin was presented in 2000 at SPIE, the International Society for Optical Engineering.[27] The final pilot technological process was patented in Russia by Rada-Pharma in March 2001.[28] Radachlorin is included as a drug substance in the Russian Pharmacopoeia (A. Reshetnickov, personal communication, June 20, 2003).[29] It was first applied clinically as a photosensitizer in Russia in 2000-2001 and has gone through phase I studies there, primarily for use with superficial skin lesions.[30,31] In 2003, protocols were approved in Russia for phase II studies of basal cell carcinoma, squamous cell carcinoma of the skin and mucosa, and melanoma of the skin and its superficial subcutaneous metastases (A. Reshetnickov, personal communication, July 4, 2003).[32]

The development of Radachlorin is part of a larger trend within the scientific community. Other chlorin-based photosensitizers, such as MACE, are in development at the present time.[33,34] To date, however, Radachlorin remains experimental. Although it has been approved as a photosensitizer in Russia for use in clinical trials, it is not approved for general use. Nor is it approved for use in Russia for the treatment of deep-seated tumors or metastatic disease.

History of CLT

William H. Porter, MD, who has registered the name Cytoluminescent Therapy, is primarily responsible for the idea of using Radachlorin as a systemic treatment for metastatic disease. He is an American-born and trained ophthalmologist, now residing in Ireland, who first began working with PDT in mid-2000. He is not presently a licensed physician but works as a technician under another doctor's supervision. Porter initially employed Photofrin and other compounds as photosensitizers. In 2002, he began using Radachlorin in agreement with the Russian manufacturers and renamed the substance Photoflora for use in the West. No peer-reviewed articles on CLT or PDT by Porter are found in PubMed or other major indexes, and he does not claim to have published any. In articles, Web sites, and interviews directed primarily at lay audiences, however, he has claimed that CLT represents "a major shift away from localized treatment to systemic treatment."[35]

Table 1. Characteristics of Photodynamic Therapy (PDT) Versus Claims Made for Cytoluminescent Therapy (CLT)

Conventional PDT (using Photofrin)	*Claims for CLT (using Radachlorin)*
Inadequately selective for cancer cells	Preferentially accumulates in cancer
Skin photosensitivity up to 6 weeks	Rapidly excreted from skin
Long waiting period before light administration	Light administered within 3 hours
Limited number of tumor targets	Useful in treating any kind of cancer
Light must be pinpointed at tumors	Can be given as whole-body treatment
Peak absorbance at 630 nm	Peak absorbance at 662 nm
Stand-alone treatment, no home component	Home treatment to enhance initial effects
Requires posttreatment scans and tests	Scans and tests discouraged for months
Curative only for superficial/ limited cancer	Beneficial for advanced cancer

Certain major differences between PDT and CLT have been postulated by Porter. These are summarized as shown in Table 1.

Claims of CLT's uniqueness are based both on its novel photosensitizing agent (Radachlorin) and the manner in which that agent and the various activating lights are administered. Radachlorin is said to have a much greater selectivity than Photofrin, to be "both more cancer-selective and more powerful than the agents typically used in PDT."[36] Being slightly lipophilic in nature, it is carried into the cell via membrane lipoproteins and is precipitated in an acid environment, which helps it accumulate preferentially in cancer cells.[35(p116)] Radachlorin is also claimed to be more rapidly excreted from the skin than Photofrin and to produce fewer phototoxic side effects.[36] With Radachlorin, as used in the CLT setting, light activation is started within hours of administration. While Photofrin has its peak absorption of light at 630 nm, a wavelength that allows only for a superficial penetration of effective light, Radachlorin has a peak of light absorption at 662 nm, according to its manufacturers.

Porter has stated that CLT is effective in treating most kinds of cancer, using external light sources without the need for endoscopy or other invasive techniques.[35(p114)] In contrast to conventional PDT, which is generally given as a local treatment targeting known

areas of malignancy, CLT is given as a whole-body treatment using lasers and arrays of LEDs in the visible red range that are specially manufactured for this purpose.

Standard PDT is given as a stand-alone medical treatment, without any self-administered component. CLT is also given in an initial therapeutic session, but thereafter patients are expected to take a smaller daily oral dose of the photosensitizer, followed by self-administered broad-spectrum infrared light exposure, starting approximately 3 weeks after returning home. Porter suggested that this home treatment continue "for three to four months following the initial intensive treatment."[35(p119)]

Conventional PDT requires and encourages post-treatment scans and tests to track the effectiveness of the treatment. However, CLT patients have reported that Porter discouraged them from undergoing such tests for several months after treatment, expressing a concern that it was impossible to distinguish between radiolucencies arising as a result of tumors and those due to the expected and desirable CLT-induced inflammation accompanying tumor necrosis. He has been quoted as saying, "This process of tumor breakdown may last for up to 6-8 months following treatment and it is only after the passage of active inflammation that the PET scan, in our opinion and experience, can be considered an accurate determinant of tumor activity." He added that "elevated tumor markers are commonly seen following this CLT therapy from fragmentation of tumor so this too early on may be confusing if not seen in the light of the treatment dynamics."[37]

While conventional PDT may be curative for superficial or early-stage cancers, it is universally recognized as palliative, or experimental at best, for advanced cancers. By contrast, CLT explicitly claims to be therapeutically beneficial for most types of cancer, including deep-seated, recurrent, and/or metastatic tumors. Porter has stated,

> I haven't found any tumor that there hasn't been a favorable response to. . . . There seems to be a consistently favorable response to virtually every type of tumor that we've treated. . . . Truthfully, many people with advanced-stage cancers just seem to be carrying right on.[35(p119)]

Early Clinical Experiences With CLT

From mid-November 2002 until mid-January 2003, 4 groups of 12 cancer patients were treated with CLT in Killaloe, Ireland. The first 24 patients (2 groups of 12 each) were treated in a building owned by, and adjacent to, the East Clinic. The next 24 patients (2 groups of 12 each) were treated in rooms of the nearby hotel in which they were staying. In addition, the first 24 patients were treated with herbal and/or vitamin injections and extracts by Dr Paschal Carmody, medical codirector of East Clinic. The second group of 24 did not receive any such treatment (a point to which we shall return).

Table 2. Four Cytoluminescent Therapy Groups in Ireland: Periods of Treatment

Treatment Group	*Period of Treatment*
1	November 17-23, 2002
2	November 30-December 6, 2002
3	January 5-11, 2003
4	January 19-25, 2003

During each of the 4 treatment periods, a program involving educational lectures was offered. While other patients were treated with CLT before, after, and even during this time period, the focus of the present study is exclusively on the 48 patients who attended these lectures and constituted these 4 groups.

Typically, each group of participants arrived on a weekend, was treated for 2 or 3 days of that week, and then departed on the following weekend (Table 2).

Composition of the Patient Groups

Twenty-eight (58.3%) of the 48 patients were female; the remaining 41.7% were male. Two patients (4.2%) were Hispanic, 1 (2.1%) was Asian American, and the remainder were Caucasians. The average age was 53.4 years (calculated on the basis of 25 patients who provided this information). All patients came from the English-speaking world. Four came from Canada, 3 from the United Kingdom, 1 from Australia, and the rest from the United States. The great majority of patients in the 4 groups had advanced or recurrent cancer, and most had exhausted all conventional treatment options. All signed treatment consent forms stating that "no guarantees have been made or implied regarding results of the treatment."

Costs and Patient Protection

New photosensitizers, like all novel pharmaceutical agents, are usually tested in an orderly progression of studies, with clinical trials under institutional review board (IRB) supervision for patient protection. However, there was no IRB supervision of the treatment of patients described in this report, and CLT was administered strictly on a fee-for-service basis. The cost of this CLT treatment program (including the initial treatment and a 4-month supply of oral medication) was €20,000 (Euro), which was equal to US$23,000 per patient at the time in question.[38]

Nature of the Treatment

Porter has asserted that CLT causes minimal toxicity when carried out properly (ie, by himself or those whom he has trained and certified). "Many patients have told us that they found the treatment to be more comfortable and relaxing than they had expected," states the CLT Web site. The same Web site does warn that "as the diseased tissue breaks down it creates inflammation, which can cause discomfort. Fortunately," it continues, "any pain associated with CLT is usually minimal to moderate, temporary, and can easily be controlled with a mild painkiller."[39]

No criteria for clinical selection of appropriate patients were exercised during the treatment of the first 2 groups; patients were basically accepted on a first-come, first-served basis. While there were relatively few acute reactions to the initial phase of the treatment, some patients in these groups, and others treated during that period, began to report aftereffects, especially with the commencement of the home-administered portion of the program. More stringent clinical selection criteria were thus applied to groups 3 and 4.

Thus, in the latter 2 groups, CLT was discouraged or ruled out for patients who were bedridden, nonambulatory, or confined to wheelchairs; who were receiving supplemental oxygen most or all of the time and were too sick to travel; who were suffering from severe cachexia; who had stents implanted for pancreatic or bile duct cancer; whose tumors compromised a major blood vessel or involved the spinal column; who were suffering from porphyria; who were clinically depressed and therefore unlikely to comply with treatment; who were younger than the age of 18; or who were pregnant or contemplated getting pregnant within 1 year of undergoing treatment. All patients were requested to come with a companion to provide physical and moral support.[40]

On day 1, all patients were administered a 10-ml vial (35 mg) of Radachlorin intravenously as a single bolus dose over a 20- to 30-minute period. Dr Porter has indicated that he increased or decreased the dose by 25% depending on the weight and size of the patient (W. H. Porter, personal communication, August 5, 2003).

Intravenous (IV) administration of Radachlorin was followed 3 hours later by initiation of light therapy in the amount of approximately 20 joules. The exact exposure depended on the extent and location of the patient's tumors. Light irradiation consisted of red LEDs and a dual-frequency laser (both visible 662 nm and infrared 808 nm), again depending on the location and extent of the tumor.

Dr Porter has stated that on the first day, he administered LEDs over the "area of involvement" with additional illumination given over areas of possible or potential metastatic spread. Depending on the type and location of the tumor, the dual-frequency laser was employed.

On the second day, treatment was similar "but usually a reduced amount, depending upon the presence or absence of changes visible through the skin and the patient's reaction to the therapy." Often on day 2, he said, he would also perform an endoscopic light treatment via the rectum for patients with prostate cancer (W. H. Porter, personal communication, August 5, 2003).

During the following days, members of the first 2 groups had 2 additional sessions of infrared irradiation, which was accomplished by utilizing the infrared lamps in a so-called "hyperthermia bed." But there was no elevation in core body temperature and therefore no attempt at hyperthermic treatment per se (W. H. Porter, personal communication, August 1, 2003).

Dr Paschal Carmody has stated that he put all patients in the first 2 groups on an "immune modulating program," which included IV administration of high-dose vitamin C, glutathione (10 cc), factor AF2[41]* (10 cc), a complex of homeopathic medications, and ozone (P. Carmody, personal communication, July 31, 2003). Vitamin C was given both IV and by oral tablet. By IV, patients received 10 cc (500 mg per cc) of vitamin C solution for a total IV dose of 5000 mg per day. By tablet, they received 2×1000 mg tabs, 3 times daily, for an oral total of 6000 mg per day.

Patients in the first 2 groups also received intramuscular injections of thymus extract (5 cc daily), as well as other homeopathic and oxygenation therapies. Some patients were also given IV sodium bicarbonate. Upon departure, each of these 24 patients was advised to continue immune-modulating therapies and an "oral metabolic program" (P. Carmody, personal communication, July 31, 2003).

In early January 2003, Carmody withdrew his support from the CLT program. Thus, the third and fourth groups were not treated by him and did not receive any medically supervised immunomodulation. Because the program no longer had access to East Clinic's facilities, the third and fourth groups could not receive infrared irradiation through exposure to the heat lamps of the hyperthermia beds.

At the end of their treatment week, each patient attended a meeting at which he or she received further instructions from Porter and the attending physician. At that time, patients were given directions for setting up and using infrared light arrays (eg, commercially available heat lamps) when they returned home.

*Factor AF2 is an extract from the spleen and liver of sheep embryos and lambs that has sometimes been used to decrease the side effects of conventional therapy.

It was Porter's belief that by doing so patients could "carry on the same process" (ie, the photodestruction of cancer cells) "on an ongoing basis—even when a person returned home." Patients were therefore given a supply of Radachlorin in an encapsulated or liquid form to take home and were told to wait approximately 3 weeks before initiating self-treatment. Home treatment was to consist of the equivalent of 1 ml Radachlorin orally, on a daily basis, followed by the application for 20 to 30 minutes of a commercially available 250-watt heat lamp emitting a broad spectrum of infrared light. The stated purpose of this follow-up treatment was to augment and continue the tumoricidal effects of the initial treatment, which Porter has described as "massive."[35(p118)]

Altogether, the total proposed treatment period lasted approximately 5 months, including both initial and home treatment. Porter stated that only at the culmination of that period would objective measurements of tumor breakdown begin to be accurate. Until that time, he stated, any scans or other tests were likely to result in false positive readings for cancer, since treatment-induced inflammation would mask or distort radiographic and biochemical values.[37]

Contacts with the Patients

CCI was engaged by the Cytoluminescent Therapy Centre to contact these 48 patients and elicit their experiences with the therapy, for the purpose of developing a preliminary assessment of their responses to, and experiences with, CLT. No quantitative clinical research was planned, and no access to confidential medical records was involved. Informational interviews were also conducted with physicians who have practiced CLT, including Drs Porter and Carmody (Ireland), Wolfgang Wöeppel (Germany), Ralph Ballard (Australia), and Alexander Ovchinnikov (Russia), as well as with Andrei Reshetnickov, PhD, inventor of Radachlorin. CCI staff members have monitored on a regular basis 2 e-mail lists on CLT as well as Web sites discussing this issue.

In early February 2003, the author sent an e-mail letter to all 48 patients, requesting collaboration in recounting their experiences with the clinical effects of CLT. Patients were informed that the effort would result in a publication but that their identities would not be revealed. At least a dozen responded that they were experiencing serious aftereffects of the treatment and that they felt abandoned by their CLT providers, who (they claimed) had been unresponsive to repeated requests for help in dealing with posttreatment problems. Four patients had already died. A subset of half a dozen patients refused to fully participate in the study. One patient was entirely lost to follow-up.

Table 3. Study Status of 48 Cytoluminescent Therapy Patients

Status of Patient	*n*	*%*
Alive and provided sufficient information for inclusion	24	50.0
Died but provided evaluable information before demise	7	14.6
Died before being able to provide information	10	20.8
Too sick or dissatisfied to fully cooperate	6	12.5
Unable to be contacted	1	2.1
Total	48	100.0

In March 2003, these 48 patients (or their survivors) were e-mailed a questionnaire to elucidate both their subjective and objective responses to the treatment. This included a 5-point self-evaluation scale, in which patients were asked to rate their quality of life, with 1 being pain-free and ambulatory and 5 being in constant, incapacitating pain. Those who did not respond were then sent 3 successive e-mail reminders during April and May 2003 as well as a letter to their physical addresses. Some were also contacted by telephone. Another request for follow-up information was e-mailed to all patients in mid-June 2003. Eventually all but 1 patient was located, and 31 of the 48 patients (64.6%) returned completed questionnaires or provided sufficient data to be included in this survey (Table 3). Continuing informal contacts were maintained through August 2003.

Seven patients who died are also included in this analysis, based on information provided by next of kin. In addition to recounting their experiences with CLT therapy, patients also provided details of their medical diagnosis and subsequent medical treatment.

It was felt that a minimum of 6 months of correspondence would permit us to monitor the patients' responses and adequately review any reports of progress following CLT treatment. Over the course of this 6-month contact period, a total of 6 of these patients reported some signs of benefit from the treatment. But at least 9 patients not only believed that they had not benefited but also felt that the treatment had actively accelerated the growth of their malignancy.

In Table 4, we give information on the vital characteristics of the 31 patients who responded to the survey. The "current treatment" and "self-assessment" (on a 1-5 scale) date from the patients' time of presentation for CLT.

Narrative Accounts of Two Patients' Experiences

What follows are narrative accounts of 2 patients' experiences with CLT. These give an idea of the subjective experiences that many of the patients went

Table 4. Vital Characteristics of Responders to Questionnaire at Time of Presentation for Cytoluminescent Therapy (CLT)

Patient	*Gender*	*Age*	*Cancer Diagnosis*	*Presentation Stage*	*Standard Treatment Before CLT*	*Medications at Presentation*	*Self-assessment at Presentation*
1	M	50	Prostate	III	None	PC-SPES	Good (1)
2	F	48	Ductal carcinoma in situ (DCIS)	0	Stereotactic biopsy	Raloxifene, Celebrex	Good (1)
3	F	21	Alveolar soft part sarcoma	IV	Surgery, chemoradiation	IF-a, thalidomide	Fair (2)
4	F	51	Breast: invasive ductal carcinoma	IV	Surgery, chemoradiation	Letrozole, tamoxifen	Poor (4)
5	M	75	Prostate	II	Iscador (mistletoe)	None	Good (1)
6	M	54	Rectal	IV	Surgery, chemoradiation	None	Fair (3)
7	M	52	Colorectal	IV	Surgery, chemotherapy	None	Very poor (4.75)
8	M	54	Prostate	I	Arimidex	Artemisinin	Good (1)
9	M	60	Prostate	III	Surgery, radiation	Lupron	Good (1)
10	F	46	Mantle cell lymphoma	IV	Chemotherapy	None	Fair (2)
11	M	68	Prostate	IV	Surgery, hormonal blockade, brachytherapy	Lupron	Fair (2)
12	M	48	NSCLC	IV	Chemoradiation and Iressa	None	Good (1)
13	F	42	Breast: infiltrating ductal carcinoma	IV	Surgery, chemoradiation, Zoladex, Zometa	Analgesics	Fair (2)
14	F	68	Breast: adenocarcinoma	IV	Surgery, chemoradiation	None	Good (1)
15	F	69	Breast: invasive ductal carcinoma	IV	Surgery, chemoradiation	None	Fair (3)
16	M	52	Colorectal	IV	Surgery, chemotherapy	None	Poor (4)
17	M	56	Colorectal	IV	Surgery, chemotherapy	Irinotecan, Xeloda	Fair (2.5)
18	F	57	Breast: infiltrating ductal carcinoma	IV	Surgery (refused chemotherapy)	Letrozole	Fair (2)
19	F	52	Breast: invasive ductal carcinoma	IV	Surgery, chemoradiation		Fair (2.5)
20	F	44	Breast: invasive ductal carcinoma	IV	Surgery, high-dose chemotherapy + bone-marrow transplant, radiation; tamoxifen, pamidronate, trastuzumab	Tamoxifen, pamidronate, trastuzumab	Fair (2.5)
21	F	52	Non-small-cell lung cancer (NSCLC)	IV	Surgery, chemoradiation	Analgesics	Fair (2.5)
22	F	Age unknown	Breast	IV	Surgery, chemoradiation		Fair (2)
23	F	49	NSCLC	III	Chemoradiation	None	Good (1)
25	F	72	Colorectal	IV	Surgery, chemotherapy	None	Poor (4)
26	M	73	Colorectal	IV	Surgery, chemotherapy, hyperthermia	None	Fair (2)
27	M	36	Melanoma	IV	Chemotherapy, immunotherapy	None	Fair (2.5)
28	F	35	Breast	IV	Surgery, chemoradiation	None	Poor (4)
29	F	74	Pancreatic	IV	Surgery, chemoradiation	Analgesics	Poor (3.5)
30	M	45	Gastric	IV	Surgery, chemoradiation, supportive CAM	Analgesics	Poor (4)
31	M	62	Pancreatic	IV	Surgery, chemoradiation		Fair (3)

through in pursuing this unconventional treatment abroad. (Narrative accounts of other CLT patients are also available at Cancer Communications' Web site, www.cancerdecisions.com.)

Patient 1 was a 50-year-old man who was diagnosed with stage III prostate cancer in 1996, with a prostate specific antigen (PSA) score of 100 and confirmed spread to seminal vesicles and abdominal lymph nodes. He rejected conventional treatment and treated himself with an herbal formula, PC-SPES (with apparent success, based on a decline in PSA and symptoms). However, by November 2002, his PSA was rising an average of 10 points per month and his urinary retention was worsening. When he went to Ireland in January 2003, he was at 1 on the self-evaluation 5-point scale. During the initial treatment, he experienced generalized pruritus that subsided once the lights were extinguished. (With this patient, as with other prostate cancer patients, Porter utilized a supplemental endoscopic administration of the laser light source.)

After commencing home treatment, this patient experienced worsening urinary retention and obstruction (waking 7 or 8 times at night to urinate), marked weakness and fatigue, daily headaches, diminished appetite, and a weight loss of 25 lbs in a single month. He also developed hydronephrosis, kidney pain, and episodic hematuria. On several occasions, he passed substantial amounts of what he surmised to be necrotic tissue in his urine. After he stopped CLT and commenced taking PC Plus (a nonprescription herbal product similar to PC SPES), he experienced a rapid decline in his PSA and substantial symptomatic improvement within a period of weeks.

A transrectal ultrasound examination in May 2003, using color flow and pulsed Doppler evaluations, revealed a prostate gland only slightly larger in appearance than before CLT. The patient stated that the radiologist's report read, "The seminal vesicles appear slightly smaller in size." The report also noted that while "multiple tumor vessels were noted on a prior examination," now "minimal vascularity is identified within the tumor mass on the current study." According to the radiologist, "This represents marked improvement in vascularity compared to prior study."

Just weeks later, however, he received the results of a June 2003 bone scan and MRI of his lumbar/sacral area. These showed widespread metastatic disease throughout his entire skeletal system. The patient wrote,

> I don't think I have ever heard about such a rapid deterioration in any man's prostate cancer over the nearly 7 years that I am battling with this. Maybe CLT caused my cancer to mutate into something bone hungry and virulent. I don't think we'll ever know.

He is now on conventional therapy suggested by his urological oncologist.

Patient 3 is a 21-year-old woman with an extremely rare stage IV alveolar soft part sarcoma. This was diagnosed at stage IIIB in February 2001. In March 2001, she had surgery to remove the primary lesion from her left thigh, followed by radiotherapy. In September 2001, she had surgery to remove metastases from her spine, followed by radiotherapy. In July 2002, she was treated with dacarbazine + doxorubicin + ifosfamide, which was ineffective. This was followed in September and October 2002 by thalidomide and interferon alpha, which slowed the growth of tumors in her lungs and on her skull. The prognosis she was given by her doctors in September 2002 was for ~6 months further survival.

At the time she received CLT in January 2003, she had widely disseminated metastases in her lungs, the largest of which measured 5 cm; she also had 2 large (egg-sized) tumors on her skull and some in her ribs. At the time she presented for CLT, persistent cough was her most prominent symptom, along with dyspnea and pain in her sides. She was still taking thalidomide and interferon alpha. This patient classified herself as 2 on the 5-point scale in terms of pain, mobility, and malaise.

For 3 hours after initial CLT, she experienced difficulty breathing and had pulmonary edema for 2 to 3 days after treatment. During the week she was in Ireland, the tumors on her skull softened and reduced in size by approximately 90 percent. After treatment, she also had less pain in her ribs, although her cough continued unabated. Within a few weeks of returning home, the 2 tumors on her skull had reverted to their pretreatment size but remained soft and spongy in consistency. She felt better after CLT, she says, because she was able to stop taking thalidomide, which had made her feel drowsy and fatigued.[42] However, after CLT, she also developed new symptoms of night sweats and hot flashes.

In May 2003, she still reported feeling that CLT had benefited her. Soon after this, however, she had episodes of hemoptysis, and a June 2003 computed tomography scan showed that the pulmonary tumors had increased slightly in both size and number, as had the tumors on her skull. On the other hand, the patient states there were no longer detectable metastases in her bones. "My scan in January before CLT showed cancer in some ribs," she wrote. "My rib pain is now all gone."

In May and June 2003, there was a discussion in a Web-based CLT news group that the oral form of Radachlorin was not living up to its projected shelf life of more than 1 year. Like some others, patient 3 believed that the home product had degraded in qual-

ity. Since May 2003, in her opinion, the oral capsules had been "duds," since "as soon as I started month 4 all side effects, such as night sweats post-treatment, stopped. I think the CLT was working but I don't think it is anymore," she wrote.

She remained a firm believer in the treatment philosophy, and in July 2003, she completed further CLT in Ireland, the only patient (to our knowledge) out of the 48 to do this.

Patient Outcomes

In Table 5, we summarize the outcomes in the 31 patients from whom we managed to obtain sufficient information to evaluate.

Deaths Among Patients

In addition to the 7 deaths among the 31 evaluable patients, we know of 10 more deaths among those patients who could not be fully evaluated. There were 2 deaths per month in January and February 2003, 1 in March, 5 in April, 6 in May, and then a single death in June. We are unaware of any deaths in July or August. The average survival time of the decedents from the date of their initial CLT treatment was 4.2 months.

No patient died during the week he or she was in Ireland, or even in the immediate 1-month posttreatment period. While there were a few early deaths, most of those who died survived 3 to 5 months. However, one odd and disturbing occurrence is that 14 of the 17 patients who died within 6 months of initial CLT were in treatment groups 1 and 2 (Table 6). This represents 82.4% of all the deaths in the observation period. Put another way, more than half (54.2%) of the patients in the first 2 groups died within 6 months of treatment compared to just 12.5% who died in the second set of 2 groups.

For purposes of analysis, groups 1 and 2 (treated with immunomodulation at East Clinic in late 2002) can be designated set A. Groups 3 and 4 (treated, without immunomodulation, at a Killaloe hotel in early 2003) can be designated set B. In set A, 13 patients out of 24 died within 6 months of their initial CLT. (Patient 23, who was in group 1, died in June 2003, 7 months after initial CLT, and is therefore not included in this 6-month analysis.) In set B, a total of just 3 out of 24 died within 6 months.

The simplest explanation for this discrepancy would be that patients in set A presented with more advanced malignancies than those in set B. However, this does not appear to be the case. As can be seen in Table 7, the percentage of patients who presented in stage IV was roughly comparable in the 2 sets (70.8% vs 79.2%). If anything, the percentage of stage IV patients was somewhat higher in set B than in set A, thereby confounding the notion that more patients died in set A because they presented with more advanced disease.

Aftereffects of the Treatment

Most patients reported feeling reasonably well during the week they were in Ireland for initial CLT, and there were relatively few serious immediate side effects of treatment (Table 8). Some even reported a diminution in persistent symptoms, or an increase in appetite, and all were able to successfully return home by commercial airliners.

However, in the weeks and months after returning home, especially after initiation of the home treatment, many respondents reported distressing signs and symptoms, which they generally attributed to CLT. We have tabulated 8 major categories of aftereffects, including 1 category for unique, albeit potentially serious, events (Table 9).

In corroboration of a cause-and-effect relationship with CLT, some patients reported that they could control the incidence and severity of their symptoms by modulating application of the home treatment. For instance, they could control persistent pulmonary symptoms (dyspnea and coughing) by decreasing or avoiding thoracic illumination. Although it is sometimes difficult to distinguish between the sequelae of treatment and the natural progression of a disease, the temporal relationships of treatment and symptoms, and the fact that patients were able to control the severity of their symptoms by reducing or abstaining from home treatment suggests a causal link between CLT and many of these aftereffects, particularly those relating to decreased pulmonary function.

In all, 87.1% of respondents reported at least 1 of these 8 major aftereffects and ascribed it to CLT; 55.0% of respondents reported having 3 or more major symptoms, while 32.2% had 1 or 2 symptoms. Only 12.9% reported none (Table 10).

The following major events were reported by one patient each: diarrhea, dysuria and urinary retention, headaches, hematuria, hemoptysis, kidney pain, nausea and emesis, nerve damage, skin burning, thromboembolism, renal and liver failure, extreme exacerbation of pain following routine radiation therapy, and the sudden, rapid advance of bone metastases.

Some of these events are not unexpected in advanced cancer patients, including thromboembolism, nausea, and diarrhea, and cannot be necessarily attributed to CLT. Nine patients (29%) reported their belief that CLT made their tumors progress more rapidly than expected. However, it is uncertain whether such

Table 5. Treatment Outcomes Among 31 Respondents

Patient	*Gender*	*Age*	*Diagnosis*	*Stage*	*Self-report Pre–CLT*	*Clinical Status 6/12 Post-CLT*	*Self-report Post-CLT*
1	M	50	Prostate	III	Good	Very poor: widespread skeletal metastases, rising PSA	Poor
2	F	48	Doctal carcinoma in situ (DCIS)	0	Good	Good: no recurrence	Good
3	F	21	Alveolar soft part sarcoma	IV	Fair	Lung metastases increased in size and number; coughing and hemoptysis; tumors on head larger; bone scan clear	Fair
4	F	51	Breast: invasive ductal carcinoma	IV	Poor	Stable	Fair
5	M	75	Prostate	II	Good	Stable	Good
6	M	54	Rectal	IV	Fair	Stable	Fair
7	M	52	Colorectal	IV	Very poor	Tumor load stable; considering further chemotherapy	Poor
8	M	54	Prostate	I	Good	PSA within normal limits	Good
9	M	60	Prostate	III	Good	Stable; PSA still elevated	Good
10	F	46	Mantle cell lymphoma	IV	Fair	Deteriorating: splenic enlargement noted; has had further chemotherapy and rituximab	Poor
11	M	68	Prostate	IV	Fair	Symptoms worsened; disease progressed; PSA rose sharply; now undergoing immunotherapy	Fair
12	M	48	Non-small-cell lung cancer (NSCLC)	IV	Good	Tumors enlarging steadily; atelectasis June 2003 with hemoptysis; condition deteriorating	Fair
13	F	42	Breast: infiltrating ductal carcinoma	IV	Fair	Considerable pain from disseminated skeletal metastases	Fair
14	F	68	Breast: adenocarcinoma	IV	Good	Deteriorating: CT shows increase in size and number of metastases; has had further chemotherapy	Poor
15	F	69	Breast: invasive ductal carcinoma	IV	Fair	Condition deteriorating; weight loss, persistent coughing	Poor
16	M	52	Colorectal carcinoma	IV	Poor	Critically ill; liver and kidney failure	Very poor
17	M	56	Colorectal carcinoma	IV	Fair	Tumor load increased 25%; cachexia, anemia, ascites	Very poor
18	F	57	Breast: infiltrating ductal carcinoma	IV	Fair	Primary tumor enlarged, ulcerated, necrotic; skeletal metastases increasing in size and number	Poor
19	F	52	Breast: invasive ductal carcinoma	IV	Fair	Condition deteriorating; patient now undergoing immunotherapy	Poor
20	F	44	Breast: invasive ductal carcinoma	IV	Fair	Condition deteriorating; skeletal metastases; increased pain and tumor progression; impaired liver function	Poor
21	F	52	Small-cell lung cancer (SCLC)	III	Good	Deteriorating; increased pain from skeletal metastases; now undergoing immunotherapy	Poor
22	F	Unknown	Breast carcinoma	IV	Fair	Increased progression, advancing skeletal metastases with increased pain	Poor
23	F	49	NSCLC	III	Good	Critically ill	Poor
24	F	50	Breast: invasive ductal carcinoma	III	Good	Rapid progression; patient incapacitated by skeletal pain	Very poor
25	F	72	Colorectal carcinoma	IV	Fair	Rapid decline	Died 6/12 post-treatment
26	M	73	Colorectal carcinoma	IV	Fair	Very rapid progression; lung metastases; ascites	Died 7/12 after treatment
27	M	36	Malignant melanoma	IV	Fair	Rapid progression	Died 4/12 post-treatment

(continued)

Table 5 (Continued)

Patient	*Gender*	*Age*	*Diagnosis*	*Stage*	*Self-report Pre–CLT*	*Clinical Status 6/12 Post-CLT*	*Self-report Post-CLT*
28	F	35	Breast carcinoma	IV	Poor	Rapid progression	Died 4/12 post-treatment
29	F	74	Pancreatic carcinoma	IV	Poor	Rapid progression; liver failure, gastrointestinal bleeding	Died 5/12 post-treatment
30	M	45	Gastric carcinoma	IV	Poor	Rapid decline; liver and kidney failure	Died 4/12 post-treatment
31	M	62	Pancreatic carcinoma	IV	Fair	Rapid progression	Died 4/12 post-treatment

CLT = Cytoluminescent therapy.

Table 6. Cytoluminescent Therapy (CLT): Deaths by Treatment Group

Group	*Number of Deaths*
Group 1 (November 17-23, 2002)	7
Group 2 (November 30-December 6, 2002)	7
Total deaths for groups 1 and 2 (set A)	14 (58.3%)
Died within 6 months of initial CLT	13 (54.2%)
Group 3 (January 5-January 11, 2003)	1
Group 4 (January 19-January 25, 2003)	2
Total deaths for groups 3 and 4 (set B)	3 (12.5%)
Died within 6 months of initial CLT	3 (12.5%)

Table 7. Composition of Groups by Stage

	Stage 0	*Stage I*	*Stage II*	*Stage III*	*Stage IV*	*% Stage IV*
Group 1	0	1	2	1	8	66.6
Group 2	1	0	0	2	9	75.0
Set A	1	1	2	3	17	70.8
Group 3	0	0	0	3	9	75.0
Group 4	0	1	1	0	10	83.3
Set B	0	1	1	3	19	79.2

Table 8. Immediate Effects of Cytoluminescent Therapy

Effect	*Frequency*
Pruritus upon application of light	Common (~90%)
Burning sensation upon application of light	Common (~70%)
Urticaria	Uncommon (~10%)
Increased pain	Rare (~10%)
Dyspnea or swelling in chest	Rare (~2%)
Intense pain and erythema lasting several days	Rare (~2%)

Table 9. Major Aftereffects Ascribed to Cytoluminescent Therapy by 31 Respondents

Patient	*Gender*	*Type*	*Stage*	*Age*	*Fatigue*	*Pain*	*Back Pain*	*Cough*	*Dyspnea*	*Weight Loss*	*Necrosis*	*Sweats*	*Growth Promotion*	*Loss of Appetite/ Weight*	*Other Major Aftereffects*	*Number of Symptoms*
1	M	Prostate	IV	50	X	X	X			X	X		X	X	X	8
2	F	DCIS	I	48	X											1
3	F	Sarcoma	IV	21	X			X	X			X			X	5
4	F	Breast	IV	51												0
5	M	Prostate	II	75												0
6	M	Colorectal	IV	54	X				X							2
7	M	Colorectal	IV	52												0
8	M	Prostate	I	54	X											1
9	M	Prostate	III	60	X											1
10	F	NHL	IV	46	X			X	X						X	4
11	M	Prostate	IV	68												0
12	M	NSCLC	IV	48	X	X	X	X	X	X				X		7
13	F	Breast	IV	42	X	X								X		3
14	F	Breast	IV	68	X	X										2
15	F	Breast	IV	69	X	X	X	X								4
16	M	Colorectal	IV	52	X	X								(improved)	X	3
17	M	Colorectal	IV	56		X				X			X	X	X	5
18	F	Breast	IIB	57	X			X	X				X		X	5
19	F	Breast	IV	52		X	X				X		X			4
20	F	Breast	IV	44	X										X	2
21	F	SCLC	IV	52	X	X						X		X		4
22	F	Breast	IV	40s?		X				X			X	X	X	5
23	F	NSCLC	IV	49				X					X		X	2
24	F	Breast	IV	50	X	X							X			3
25	F	Colorectal	IV	72	X	X							X		X	4
26	M	Colorectal	IV	73	X	X		X	X				X			5
27	M	Melanoma	IV	36	X	X					X					3
28	F	Breast	IV	35	X											1
29	F	Pancreas	IV	74							X					1
30	M	Stomach	III-IV	40s				X						(improved)	X	2
31	M	Stomach	IV	62	X				X						X	3
Total					21	14	4	8	7	4	4	2	9	6	12	
Percentage					67.7	45.1	12.9	25.8	22.6	12.9	12.9	6.5	29	19.4	38.7	

DCIS = ductal carcinoma in situ, NHL = non-Hodgkin's lymphoma, NSCLC = non-small-cell lung cancer, SCLC = small-cell lung cancer.

Table 10. Number of Major Aftereffects per Patient

Number of Aftereffects	*Number of Patients*	*Percentage*
0	4	12.9
1	5	16.1
2	5	16.1
3	5	16.1
4	4	12.9
5	6	19.4
6	0	0.0
7	1	3.3
8	1	3.3

tumor growth might also be due to expected disease progression.

Discussion

The CLT patients surveyed for this report appear to have experienced considerable morbidity and mortality. Whether such morbidity and mortality can be definitely ascribed to CLT is at this time unknown. However, 3 ways in which CLT might have contributed to aftereffects can be proposed: (1) the aftereffects may have been caused by a delayed reaction to the initial bolus agent and light treatment; (2) they may have been brought about through an interaction with the supportive, "immune-modulating" treatments administered at the time of initial CLT (in the case of set A); or (3) they may have arisen as a result of the continued application of home treatment.

A potential explanation for some aftereffects is that the ancillary treatments given to groups 1 and 2 during their week of initial treatment might have either been intrinsically harmful or have interacted in an unknown but deleterious way with CLT. While patients in set A were given these ancillary treatments, no one in set B received them. Extraneous stimulation of the immune system may not be desirable at a time when a large number of immune cells could be killed by the cytotoxic action of photodynamic therapy.

Some further clues to possible causes of CLT-associated morbidity are provided by the fact that conventional PDT is known to suppress immune competence. The ability of irradiated spleen cells from PDT-treated mice to stimulate a mixed lymphocyte response has been shown to be dramatically impaired after PDT. The cell type that mediates this adoptively transferable suppression of contact hypersensitivity responsiveness is in the macrophage lineage.[43] Such decreased immune competence might contribute to a lessened antitumor response. It is possible that this also may be true with CLT using the second-generation agent Radachlorin.

In addition, in a 1999 study of the photosensitizer BPD-MA (Verteporfin: benzoporphyrin-derivative monoacid ring A), it was found that PDT had profoundly inhibitory effects on the immune system. Dendritic cells (DCs) studied after the administration of PDT had a reduced capacity to stimulate the proliferation of alloreactive T cells. In particular, major histocompatibility complex class I and intercellular adhesion molecule 1 levels decreased to 40% of their control levels within 2 hours following PDT. Therefore, the authors concluded, changes in DC receptor expression may contribute to the immunomodulatory action of PDT.[44]

Pulmonary aftereffects were common and seem particularly distinctive of CLT. At least 10 of these patients (32.3%) mention dyspnea, chest pains, or coughing. Although the exact pathology underlying these CLT-associated symptoms has not yet been fully elucidated, there is literature linking conventional PDT to pulmonary symptoms. The appearance of the irradiated area is unchanged immediately after PDT, but within 6 to 48 hours, edema, swelling, and necrosis can occur. Significant coughing, wheezing, and dyspnea may also develop. Many patients expectorate necrotic tissue within several days of treatment.[45] This description is reminiscent of the pulmonary symptoms reported by some of those who utilized CLT as a home treatment.

The use of PDT with the second-generation agent Foscan has been known to result in even more dire outcomes. In a phase I study at Thomas Jefferson University Hospital, Philadelphia, 4 dose levels of Foscan were explored. One of these levels triggered a systemic capillary leak syndrome "leading to death in 2 of 3 patients treated at that dose."[46†]

The molecular and biochemical mechanism underlying most of the other aftereffects remains uncertain. To understand the possible linkages of the aftereffects with CLT, monitoring of blood changes, liver enzymes, renal function, C-reactive protein, immunological reactions, and other variables in patients undergoing this treatment is suggested.

Many of the symptoms described are consistent with a surge in proinflammatory cytokines. A June 2003 study in the *British Journal of Cancer* postulates that PDT results in the rapid induction of an inflammatory response that, while possibly important for activating antitumor immunity, also "may be detrimental if excessive." In mice, it has been shown that PDT using a second-generation photosensitizer induces proinflammatory cytokines and chemokines. This response is characterized by the infiltration of leukocytes, mainly neutrophils, into the treated

†We are aware of a CLT patient treated in Ireland in April 2003 who, after utilizing the home treatment, developed a clinically confirmed interstitial fibrosis within 3 months. This phenomenon urgently requires further scientific examination and evaluation.

tumor. Ironically, considering the negative impact on the patient, long-term positive results may be dependent on the presence of such neutrophils. Attempts are under way in that case to "optimize PDT through the modulation of the critical inflammatory mediators."[47]

IL-6 seems a particularly relevant marker. A study at the Ludwig-Maximilians University, Munich, found that IL-6 "might be involved in the inflammatory reaction and subsequent immunological anti-tumor responses" to PDT.[48] An increase in proinflammatory cytokines has also been noted following other forms of PDT. Researchers at Roswell Park Cancer Institute, Buffalo, have shown that tumor-directed PDT results in an increase in the expression of IL-6, which has been shown to increase the activity of cytotoxic T cells.[49]

Five patients reported sharp declines in appetite and/or weight after CLT. IL-6 released from cancer cells has been shown to diminish appetite and induce muscle wasting. So too does proteolysis-inducing factor (PIF), the "cancer cachectic factor."[50] Under certain circumstances, PIF is produced by cancer cells and results in rapid weight loss. This mechanism could conceivably also be responsible for the weight loss noted in certain CLT patients.

The severity of the inflammatory reactions seen in patients who have undergone CLT has been extremely debilitating (possibly even life threatening) to them and highly distressing to their caregivers. However, without meticulous clinical follow-up, including biochemical assays, scans, and so forth, it is impossible to evaluate the extent, or the ultimate clinical significance, of the posttreatment symptoms displayed by the majority of patients.

It may seem surprising that such morbidity should have occurred at all, given the ostensibly innocuous nature of chlorophyll derivatives and infrared heat lamps. Yet it is also a sobering reminder of the fact that the whole is often greater than the sum of its parts: without the necessary laboratory studies to anticipate and control for possible synergistic reactions, morbidity will probably remain a serious problem. Phase I dose-finding studies for this purportedly nontoxic therapy, standard in the normal development of drug-based therapies such as CLT, would have detected this possible morbidity and allowed proper medical care and follow-up for patients in whom CLT precipitated undesirable side effects.

Mortality

It is not possible at this time to categorically attribute any deaths to CLT, especially since the majority of deaths occurred in patients with stage IV disease who had received conventional cytotoxic treatments elsewhere, prior to CLT. It is possible that a treatment as aggressive as systemic photodynamic therapy may be too destructive for those who have already been enfeebled by progressive disease and the standard cytotoxic treatments. Even the subjective impression of some respondents that CLT might have actually enhanced tumor progression, or hastened death, is serious enough in nature to urgently warrant research into appropriate prophylactic and regulatory measures.

Conclusions

No patient died in the immediate posttreatment period. But after a minimum of 6 months of follow-up, 17 out of the original 48 patients (35.4%) had expired. The great majority of these (82.4%) were in CLT treatment groups 1 and 2 (set A). None of the decedents experienced objective clinical benefit or prolongation of life. Of the patients who declined to communicate with the author, none are known to have had a beneficial outcome. Quite the opposite: refusal to participate in this study generally correlated with a failure of the treatment and/or dissatisfaction with its practitioners.

Some patients claimed that they had been harmed in another way: by postponing objective testing, they missed the chance to detect progressive disease, wasted time, and precluded other treatment possibilities, even when CLT was clearly not working.

Of the 31 patients for whom there is sufficient data to permit such an analysis, there have been no documented shrinkages of malignant tumors, partial or complete, of more than 1 month's duration. A few patients may have had measurable anticancer effects, for example, devascularization of a primary tumor, but in these cases, the benefit has generally proved transient and of no long-term clinical significance. From a standard oncological perspective, CLT delivered in this manner was without beneficial effect.

In the few cases in which there appeared to be a positive response, there were confounding variables that could have been responsible for the observed benefit. Patient 1 had no conventional treatment, but at the time that his PSA declined and his tumor showed devascularization, he was taking an herbal preparation with documented antiandrogenic activity (possibly due to the inclusion of prescription drugs in the preparation).[51,52] Patient 3 at various times was taking thalidomide and interferon alpha in addition to CLT. Thalidomide is an antiangiogenic agent with known anticancer potency[53] while interferon alpha is an immunomodulatory agent frequently used as an adjuvant cancer treatment.[54] The subjective improvement initially experienced by a few other patients was either not confirmed by objective tests or may have been due to chemotherapy or radiation taken immediately before CLT. It is possible that any objective

Table 11. Patient Beliefs About Value of Cytoluminescent Therapy (CLT)*

Patient Belief About CLT	*n*	*%*
Believe they definitely benefited	5	10.4
Believe they may have benefited but are not sure	4	8.3
Believe they definitely did not benefit	24	50.0
Believe they were directly harmed	13	27.1
Could not elicit response	2	4.2
Total	48	100.0

*Includes opinions of surviving family members.

results in these cases were due directly to the conventional treatments or, at best, to a yet-undefined synergistic action between them and CLT.

Several other patients have ascribed subjective benefit to CLT, and it is possible that such improvement could be sustained and could conceivably translate into proof of objective benefit in the months ahead. At least 2 patients (16 and 28) experienced a marked increase in appetite in the days or weeks after initial CLT, although the long-term clinical significance in both cases was nil. A few other patients reported tumor necrosis, but this did not correlate with any clinical benefit and may have even diminished quality of life.

CLT treatment was also associated with a high level of patient dissatisfaction. The degree of this dissatisfaction can be gauged by the representative comments in the appendix, excerpted from patients' letters and e-mail to the author.

As seen in Table 11, patients complained of the lack of clinical benefit of the treatment, inconsistencies and variations in the home treatment protocol, the unanticipated number and severity of aftereffects, the high cost of this unproven treatment, doubts about the integrity and potency of the oral agent, and feelings of abandonment due to a perceived unresponsiveness on the part of CLT practitioners.

In general, as shown in Table 11, the majority of the 48 CLT patients believe they did not benefit (50%), or were even directly harmed (27.1%), by the treatment.

The objective tests that might have allowed for a proper scientifically based analysis of the clinical course of these patients, and of their aftereffects, were discouraged by Porter and the Cytoluminescent Therapy Centre. The patients' own physicians, knowing little about this new and undocumented treatment, could offer little practical advice. This situation resulted in profound confusion, unease, and suspicion among patients and practitioners about the origin and clinical significance of the treatment's effects.

CLT continues to be given in Ireland. However, Porter reports that at present, he no longer administers Radachlorin in an intravenous bolus dose but instead administers the oral agent over a 3-day period. In fact, the protocols described in this article "are now obsolete in light of our present therapy," he writes.

> The effect of this "improvement" is threefold. First, we eliminate the unpleasantness of the IV. Secondly, the contrast between tumor cell uptake and normal cells is much improved. I feel using the IV technique followed by the treatment 3 hours later . . . did not allow enough time, in retrospect, for the agent to clear from normal tissue and skin. (W. H. Porter, personal communication, July 22, 2003)

The home treatment, to the author's knowledge, remains essentially the same.

No attempt is made here to analyze these modified protocols or purported results utilizing them. Other CLT-like programs, utilizing wide-area or whole-body illumination and photosensitizing agents similar or identical to Radachlorin, have been planned for clinics in various other countries as well.[55] It is similarly beyond the scope of this article to discuss variants, controversies over competing protocols, or the clinical outcome in patients treated by these methods.

The author's conclusion is that CLT, delivered in the manner described in this article, has been ineffective for the great majority of those who were treated. Nothing in these 48 patients' experiences corroborates the claim that CLT is a major improvement over conventional PDT or that it can be used as a systemic treatment for advanced cancer. In fact, the most conspicuous feature of the CLT protocol discussed in this article has been the frequency and severity of its aftereffects, especially of the home treatment. There are as yet no quantitative biochemical measurements available to guide an understanding of this phenomenon. However, most of the aftereffects are clinically consistent with an increase in proinflammatory cytokines, such as have been noted in rigorous laboratory studies of PDT. Future in vitro and in vivo studies are warranted to understand the basis of CLT's aftereffects.

The present study also points to deficiencies in how the emotional and informational needs of these patients were managed. Standard practice would be to volunteer detailed information concerning past results, the nature of the treatment facility, and the current status of all practitioners' degrees, licenses, and credentials. In this case, there was a lack of timely follow-up care for patients who underwent this treatment. Effective and ethical medical practice dictates that scrupulous attention must be paid to answering all patients' questions in an individualized, profes-

sional, and compassionate manner. This is especially true for a treatment such as this one, given abroad, in which patients are expected to comply with a protracted course of treatment when they return home.

Unlike many complementary therapies for cancer, which stress healthy lifestyle and nutritional support, CLT is clearly a drug-based therapy. As Porter himself has noted, "In the wrong hands, it could be an extremely toxic and harmful treatment."[35(p123)] As such, it should be researched with proper regulatory oversight and supervision by competent IRBs in the countries in which it is being pursued. While in the past, the study of alternative medical techniques has been hampered by limited funding and lack of institutional support, this situation has now begun to change for the better. In the United States, for instance, investigators evaluating alternative therapies can now apply for, and possibly receive, investigational new drug status or federal grants for proper research protocols.

Some patients do believe that CLT, in this or some modified form, has been beneficial to them. Nothing written here is meant to discourage patients from continuing to use any treatment they have reason to believe is helpful. It is not suggested that the qualified failure of the initial clinical explorations with CLT, as documented in this study, necessarily means that this approach could not be modified to become less toxic and/or more successful. Nor is it implied that Radachlorin is less effective or promising than other second-generation photosensitizers.

However, in this cohort of 48 patients, a large proportion found CLT either worthless or harmful or died within a relatively short time of receiving it. This is a sobering conclusion, with implications for other attempts to use novel cancer treatments outside the context of traditional developmental channels and institutional constraints.

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Appendix
Patient Comments About Cytoluminescent Therapy (CLT) Treatment

Patient	*Representative Comment*
1	"I don't think I have ever heard about such a rapid deterioration in any man's prostate cancer over the nearly 7 years that I am battling with this. Maybe CLT caused my cancer to mutate into something bone hungry and virulent."
2	a. "So, perhaps for ductal carcinoma in situ, nascent cancer, there is hope that CLT is an effective therapy." (April 2003) b. "[Diagnostic tests have shown] microcalcifications advancing towards the chest wall and 3 out of 5 serum markers were elevated." (July 2003)
3	"I can't say for sure if my cough or shortness of breath are related to the CLT. They are both exactly the same now as they were before. . . . I have been coughing up blood for 2 weeks."
4	"My quality of life is better than it was before I started treatment."
5	"[Current] indications are that CLT has brought about a significant remission of my prostate cancer."
6	"Physically, I have experienced no change [but] I feel positive; everything is going as expected even though the tumors are slightly larger. I believe my best chance for survival is with a mix of strategies including CLT, herbal, diet and exercise."
7	"Since my treatment [CLT] I have had more pain—up to triple the pain medication—more appetite loss and weight loss; more sluggish and tired days. I stopped home treatment due to pain increase and since stopping, my appetite has been better."
8	"I'm optimistic and awaiting further instructions."
9	"I really wonder if the [CLT] treatment did anything, due to the fact that I was on Lupron and the cancer was already in remission at the time of treatment. Dr Porter assured me this was not the case . . . Well, we will see."
10	"I have faith that CLT will work although I feel my chances of a longer remission would be better if I debulked my lymph nodes and bone marrow with help from conventional treatment."
11	"[Since CLT] my symptoms have worsened and my disease has progressed."
12	[When asked what physical symptoms were there after CLT that had not been there beforehand]: "Productive cough, chest pain, back pain, very short of breath." Nevertheless, he felt that "the treatment is working. When I do the lights I experience symptoms which I feel is caused by inflammation. This will work; I just have to listen to my body and keep the pressure on."

13 "I just need reassurance . . . that it is inflammation causing the flare-ups of pain, not cancer, and that the flare-ups are a positive sign that the tumor is breaking down. I know it is too early for a scan to show the changes yet, but without any kind of marker to show improvement, and without the reassurance of someone who understands CLT it remains a challenge to reassure myself that it is all going to be worth it."

14 "I have slowly felt worse, starting one month after [CLT], with constant pain, desire to sleep, constipation, pain in my arm. I am growing weaker. . . . I just had PET and CT scan. Cancer is spreading."

15 "One week after returning from Ireland I had tons of coughing which caused severe lower back pain and some vomiting. I have never in my life felt so bad. . . . I feel it was caused by the laser which went too deep and powerfully and exploded stuff inside [sic]."

16 "Since there was no change in the status of [my husband's] metastases on the latest scan we can only surmise that the effects of the treatment were what sent him into liver failure and endangered his life."

17 "I fear the light treatment may have made things worse. I had zero signs of improvement and felt the worst I have ever felt."

18 "[My tumor] is weeping a lot more; there is some breakdown of the tissue and the tumor is larger. Because the tissue has broken down the lesion is deeper with some very deep ulcers within the larger lesion itself."

19 "I had severe pain during the treatment. I felt like I was being burned in the area above my right breast at Portacath site extending to the left breast and whole neck area and ears. I as a patient have felt abandoned and felt like no one cared. No support from Dr Porter post-treatment—very disappointing. This shouldn't only be about money."

20 "[The home use of lights] scared me because everyone was feeling so poorly, including myself. I tried to get answers about CLT potentially causing cancer cells to GROW . . . and there was also concern about the inflammation we were all experiencing causing the tumors to grow. The recommended regime changed constantly . . . lots of he said/she said, no real answers due to no real communication. . . . [I have been told that] animal studies show weakened immune systems in those who do whole body light treatments."

21 "The main problem for me was the increase in inflammation which created an increase in the bone pain, which increased the [need for] painkillers, which increased the stomach upsets . . . you see where I am going."

22 No quote available

23 No quote available

24 No quote available

25 "[I] got sick upon return to US [after treatment]. Fatigue, pain, nausea, dehydration, continuing, worsening. Physical level went downhill fast. I don't know if CLT did me any harm, nor any good. I think the progression of my symptoms/disease was something CLT could not stop."

26 "When I arrived in Ireland [for CLT] I was still in good physical condition. . . . Shortly after my return I began to feel progressively worse. Following the advice of Dr Porter I waited four months before getting a chest x-ray. When I did get the x-ray the report started out with the following words: 'Extensive progression of disease in both lungs. . . . ' I was not surprised because I could feel myself growing weaker by the day. I have lost more than twenty pounds, have incessant coughing, loss of appetite, shortness of breath. I feel extremely debilitated. It will soon be five months since I had the CLT and I seem to be in a downward spiral. I am therefore ready to conclude that not only did the treatment not work for me, but it did indeed accelerate the progression of the disease."

27 "In many ways I feel like the end is approaching for me when only a few months ago I was feeling vital and strong."

28 No quote available

29 No quote available

30 No quote available

31 No quote available

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