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COMMENTARY

Texaphyrins

NEW DRUGS WITH DIVERSE CLINICAL APPLICATIONS IN RADIATION AND PHOTODYNAMIC THERAPY

Jonathan L. Sessler† and Richard A. Miller‡*

*Department of Chemistry & Biochemistry, University of Texas, Austin, TX 78712; and
‡Pharmacyclics Inc., Sunnyvale, CA 94086, U.S.A.

ABSTRACT. The texaphyrins are quintessential metal-coordinating expanded porphyrins. They constitute a new series of synthetic porphyrin analogues that show promise as drugs for use in a range of medical therapies. Currently, two different water-solubilized lanthanide(III) texaphyrin complexes, namely the gadolinium(III) and lutetium(III) derivatives **1** and **2** (Gd-Tex and Lu-Tex, respectively), are being tested clinically. The first of these, XCYTRIN™, is in a pivotal Phase III clinical trial as a potential enhancer of radiation therapy for patients with metastatic cancers to the brain receiving whole brain radiation therapy. The second, in various formulations, is being tested as a photosensitizer for use in: (i) the photodynamic treatment of recurrent breast cancer (LUTRIN™; Phase II clinical trials complete), (ii) photoangioplastic reduction of atherosclerosis involving peripheral arteries (ANTRIN™; now in Phase II testing), and (iii) light-based treatment of age-related macular degeneration (OPTRIN™; currently in Phase I clinical trials), a vision-threatening disease of the retina. Taken in concert, these two metallotexaphyrins provide a powerful new class of experimental drugs whose diverse potential utility is abetted by a combination of well-optimized physical features, favorable tissue biolocalization characteristics, and novel mechanisms of action. Interestingly, these mechanisms may alter conventional wisdom regarding mechanisms of radiation therapy and the pathophysiology of atherosclerosis. BIOCHEM PHARMACOL **59**;7:733–739, 2000. © 2000 Elsevier Science Inc.

KEY WORDS. texaphyrins; radiation sensitization; photodynamic therapy; photoangioplasty

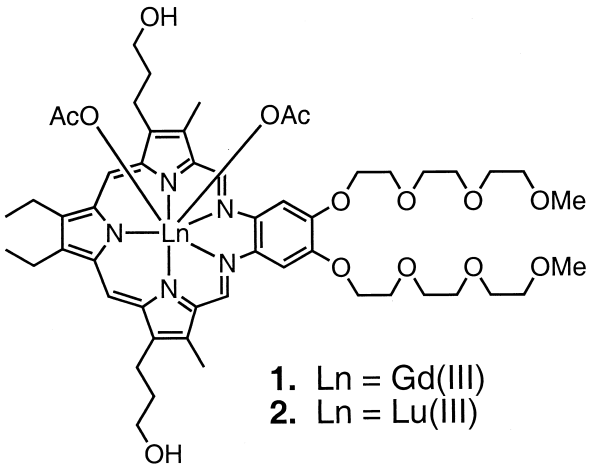
Chemical agents that can improve or potentiate the efficacy of various therapies constitute an important area of interest to medicinal chemists and medical practitioners alike [1]. Such agents not only can make existing treatment modalities more effective and render various experimental therapies viable, they can also, in a more generalized sense, provide insights into the mode of action of various treatments whose chemical or biological basis for action remains but poorly understood. In this commentary, a new class of seemingly powerful agents, the lanthanide texaphyrins [2–4], is discussed. These systems, now in advanced stages of clinical testing in diverse diseases, show promise in making radiation-based cancer therapy more effective, while enhancing, or even enabling, photodynamic treatments of tumors, atherosclerosis, and diseases of the retina.

The texaphyrins, represented by prototypic complexes **1** and **2** [Gd-Tex§ (motexafin gadolinium) and Lu-Tex (motexafin lutetium), respectively], are pentaaza, Schiff base macrocycles that bear a strong, albeit "expanded," resemblance to the porphyrins and other naturally occurring tetrapyrrolic prosthetic groups. For instance, like the porphyrins, the texaphyrins are fully aromatic and highly colored. They are, however, dark green rather than purplish-red (the lowest energy transition falls, for instance, at >700 nm, rather than at *ca.* 620 nm). Also, in contradistinction to the porphyrins, the texaphyrins are monoanionic ligands that contain five, rather than four, coordinating nitrogen atoms within their central core. The fact that this central core is roughly 20% larger than that of the porphyrins further endows the texaphyrins with an ability to form stable, nonlabile 1:1 complexes with a range of larger metal cations, including specifically those of the trivalent lanthanide series. Abetting this special stability is the fact that, in the case of texaphyrins, metal insertion is accompanied by ligand oxidation. As a result, the macrocyclic skeleton tightens up around the metal cation, resulting in a very high barrier for disassociation that is not observed in the case of the corresponding lanthanide(III) porphyrin complexes [2].

One other way in which the texaphyrins differ from porphyrins is in terms of their redox potential. While both systems are reasonably hard to oxidize, texaphyrin complexes such as **1** and **2** are far easier to reduce than typical metalloporphyrins {$E_{1/2}$ = −0.041 V and −0.044 V vs normal hydrogen electrode (in dimethylformamide) [5] vs −1.41 V for zinc(II) octaethylporphyrin (normal hydrogen

† Corresponding author. Tel. (512) 471-5009; FAX (512) 471-7550; E-mail: sessler@mail.utexas.edu

§ *Abbreviations*: Gd-Tex, gadolinium(III) texaphyrin (**1**); Lu-Tex, lutetium(III) texaphyrin (**2**); XRT, x-ray radiation therapy; MRI, magnetic resonance imaging; PDT, photodynamic therapy; and ARMD, age-related macular degeneration.



STRUCTURE 1.

electrode in dimethylformamide) [6]}. It was a recognition of this fact, coupled with the expectation that the texaphyrins would show the tumor selectivity characteristic of many porphyrins [1], that led to the consideration that Gd-Tex (**1**) might function as an XRT-enhancing agent [3]. Another appealing feature of this compound was its MRI detectability [3], allowing non-invasive evaluation of tissue localization and clearance. These particular applications of gadolinium(III) texaphyrin are discussed immediately below.

GADOLINIUM(III) TEXAPHYRIN—A RADIATION ENHANCER

Improving the clinical benefit of radiation therapy has been a long-standing goal in cancer research. One approach has been to administer agents to enhance the sensitivity of tumors to radiation therapy [7–11]. Currently, there is no Food and Drug Administration (FDA)-approved radiation sensitizer. Nonetheless, the need for an agent, or agents, that could help potentiate the efficacy of XRT is cogent and real. Every year, more than 750,000 patients in the United States undergo radiation treatment for cancer. Unfortunately, in many patients the treatment is of limited value because of inadequate efficacy or serious toxicity. It is believed that this oftentimes limiting therapeutic benefit both reflects damage to normal cells and derives from the presence of hypoxic cells within the tumor. Hypoxic cells are typically 2.5 to 3 times less sensitive to radiation than oxygenated cells. Not surprisingly, therefore, several different approaches to overcoming the radioresistance of hypoxic cells, e.g. radiation fractionation or administration of hyperbaric oxygen, have been pursued. Whereas some success has been encountered using some of these strategies, an alternative approach, involving the use of radiation sensitizers, is also attractive [7–11]. In this context, the halogenated pyrimidines and the nitroimidazoles have been studied extensively [12, 13]. However, at present neither class of agents has been demonstrated to result in a clinically beneficial outcome because of inadequate activity *in vivo*, toxicity, and non-selectivity for tumors. Thus, the search for improved radiation sensitizers continues. Ideally, such improved sensitizing systems should demonstrate low inherent toxicity, operate in both the presence and absence of oxygen, not require incorporation into DNA, and possess tumor selectivity [1].

We think that XCYTRIN™ injection, a gadolinium(III) texaphyrin (**1**) drug, not only fulfills the above criteria but also constitutes a promising new therapeutic agent that can enhance significantly the efficacy of radiation therapy. To date, its utility in this regard has been demonstrated *in vivo* in three murine tumor models (EMT6, SMT-F, and MCa) having very different biological behavior [3, 14]. As illustrated in Fig. 1 for one representative tumor model, these *in vivo* model systems have demonstrated a drug dose–response effect for both single-fraction and multi-fraction radiation treatment regimens. In these studies, substantial tumor growth delay and cures result from using drug dosing and radiation fractionation schedules similar to those used clinically. Recently, a Phase Ib/II clinical trial in patients with brain metastases was completed [15]. It demonstrated improved survival in 61 patients receiving XCYTRIN™ plus radiation compared with two independent case-matched historical controls involving radiation therapy alone.* Patients receiving XCYTRIN™ were less likely to die of complications related to tumor progression in the brain, indicating that the drug improved local control by radiation therapy. MRI scanning confirmed that XCYTRIN™ accumulates in and is retained selectively in tumors and does not localize appreciably in adjacent normal tissue [16]. The drug also was found to be well-tolerated, with hepatocellular damage as the dose-limiting toxicity, presumably related to the known clearance and excretion of the drug by the liver. In any event, the results of these clinical trials, together with the efficacy demonstrated in animal models, provide the rationale for expeditiously testing this agent in recently commenced randomized Phase III clinical trials where its efficacy and safety can be proven definitively. In addition to studies in patients with brain metastases, the National Cancer Institute has recently begun Phase I testing of XCYTRIN™ as a radiation enhancer in several other tumor types.

Given these promising results, it is not surprising that considerable effort has been devoted to understanding the underlying mechanisms of action of XCYTRIN™ [5, †, ‡] While these efforts are still ongoing, it is becoming increasingly clear that this unique XRT enhancer operates in a way that has little precedent within the confines of traditional approaches to radiation sensitizer development. Spe-

* Carde P, Timmerman B, Koprowski C, Arwood D, Ford J, Mehta M, Tishler R, Larner J, Nieder C, Downs M, Scott C, Murray K, Miles D, Miller RA and Renschler MF, manuscript in preparation.
† Sessler JL, Tvermoes NA, Guldi DM and Mody TD, manuscript in preparation.
‡ Sessler JL, Tvermoes NA, Guldi DM, Mody TD and Magda DJ, manuscript in preparation.

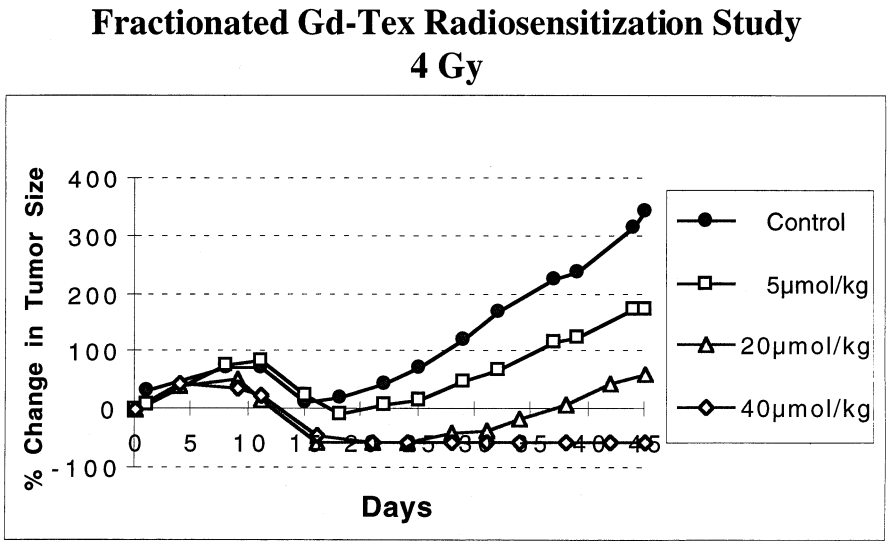


FIG. 1. Multiple-fraction radiation sensitization study following i.v. administration of XCYTRIN™ injection, a Gd-Tex-based radiation sensitizer. Balb/c mice (six per group) were injected intravenously via the tail vein with 5, 20, or 40 µmol/kg of XCYTRIN™, 7 days after intramuscular injection of EMT6 tumor cells into the hind flank of the right rear leg. Two hours later, a dose of 4 Gy of radiation was administered. Administration of the XCYTRIN™ drug and radiation were repeated daily for 4 more days. A control group of six Balb/c mice with implanted EMT6 tumors were treated with radiation only. Data acquired included tumor-free (at primary site) survival and periodic measurements of tumor size. Not only do the results show that the combination of the XCYTRIN™ agent and multiple-fraction radiation significantly decreased tumor growth as compared with treatment by radiation only, but all mice receiving the highest dose of 40 µmol/kg and five of the six mice receiving 20 µmol/kg showed no evidence of disease after 45 days. Reproduced with permission from *Proc Natl Acad Sci USA* 93: 6610–6615, 1996. Copyright (1996) National Academy of Sciences, U.S.A. [Ref. 3.]

cifically, it is believed, on the basis of pulse radiolytic model studies, that Gd-Tex (the active dicationic ingredient in XCYTRIN™ injection), an easy-to-reduce macrocycle (*vide supra*), acts to "sponge up" electrons formed as the result of the interactions of x-rays with water. As a consequence, the combination of x-rays and Gd-Tex leads, in the absence of oxygen, to an augmented concentration of hydroxyl radicals (the other and more cytotoxic daughter product formed from the reaction of x-rays with water) while concurrently preventing the "pseudo-recombination" of electrons with sublethal products formed from the reaction of hydroxyl radicals with various biological substrates. In the presence of oxygen, this same initial electron capture event produces a metastable reduced texaphyrin product ($Gd\text{-}Tex^{+\cdot}$) that reacts with oxygen to form superoxide anion. Thus, depending on the conditions, XCYTRIN™ can form two different kinds of so-called reactive oxygen species.

The fact that the combination of Gd-Tex and x-rays serves to produce, *inter alia*, reactive oxygen species has important biological consequences. This is because such species, when formed in lysosomes and mitochondria (sites where Gd-Tex is believed to localize), will not only trigger apoptosis but also release so-called messenger factors that may induce the programmed death of other nearby cells [17, 18]. Thus, a multi-center cascade effect can be induced that is very different in its mode of action from the classic, enhanced DNA cleaving mechanism proposed for nitroimidazoles and other so-called hypoxic cell sensitizers. In particular, such a cascade-based cell-killing process, as well as possible concomitant changes in cell-cycle checkpoint-dependent function [19], are expected to lead to high *in vivo* efficacy but little or no activity in simple clonogenic or *in vivo–in vitro* assays. To the best of our knowledge, such predictions are fully consistent with experimental results.

The above dichotomy is of more than academic interest. Specifically, the finding that XCYTRIN™ works well *in vivo* but demonstrates minimal activity *in vitro* compared with hypoxic cell sensitizers raises the highly intriguing question of whether simple *in vitro* or *in vitro–in vivo* screening methods should continue to be used exclusively for the identification of potential anti-cancer treatments. Certainly, our own experience with XCYTRIN™ leads us to argue that they should not.

LUTETIUM(III) TEXAPHYRIN—A NOVEL PHOTOSENSITIZER WITH DIVERSE APPLICATIONS

PDT is an emerging modality that shows considerable promise for the treatment of solid tumors and a range of other disorders [1, 20–23]. It is predicated on the use of a sensitizing dye (photosensitizer) that is administered, usually via intravenous injection, and allowed to localize selectively in a cancerous region or other tissue sites of interest (e.g. atheromatous plaque and neovascularized regions). Visible light irradiation is then used to activate the sensitizer and produce singlet oxygen, the main putative

cytotoxic agent. The potential specificity derived from combining drug selectivity with targeting of light activation makes PDT particularly appealing.

Unfortunately, in marked contrast to x-ray radiation-based therapy of cancer, the photodynamic treatment of tumors has been limited. In part, this reflects the barrier associated with the introduction of any new treatment modality. However, the main reason why PDT is not widespread is that suitable photosensitizers are not available. Currently, only one PDT photosensitizer, PHOTOFRIN® (porfimer sodium), has been approved by the FDA [1, 24]. This drug, being a complex mixture of porphyrinic species and plagued with a uniformly high level of induced cutaneous phototoxicity, is far from ideal. Indeed, it has been approved for only a limited set of indications (e.g. obstructing esophageal cancers and superficial bronchial lung cancer).

In view of the problems inherent in PHOTOFRIN®, considerable effort is being devoted to the synthesis and study of new, so-called second generation PDT sensitizers that might make PDT more useful [24]. Of the various second generation systems being developed, we think that lutetium texaphyrin (Lu-Tex, **2**) stands out as being among the best; it is endowed with attributes that make it particularly attractive, not just for the photodynamic treatment of cancer but also for the photoangioplastic reduction of atherosclerotic plaque and the treatment of ARMD [4, 25–35].

The most obvious and, in some respects, important feature of Lu-Tex is that it is water-soluble and easy to administer via i.v. injection [4]. In contradistinction to PHOTOFRIN™, it is also a single unique compound that possesses a lowest energy maximum (at λ_{max} = 732 nm) in the far-red portion of the visible spectrum, where blood and bodily tissues are most transparent [36]. This provides for one of the major advantages of Lu-Tex, namely activation by light that is capable of penetrating through tissue and blood. Being diamagnetic and containing a *bona fide* heavy atom (lutetium), it also produces singlet oxygen in good quantum yield (between 10 and 70%, depending on conditions [31, 37]) when irradiated at this lowest energy maximum. Further, and on a very different level, Lu-Tex exhibits low inherent dark toxicity, which is related primarily to its more rapid clearance from the plasma. Specifically, in humans this agent is cleared on a time scale that is measured in hours [27], whereas PHOTOFRIN® is cleared on a time scale that is measured in months [38]. The more rapid clearance of Lu-Tex is likely responsible for its reduced cutaneous phototoxicity as compared with PHOTOFRIN®. Nonetheless, in spite of its relatively rapid clearance, it still is retained selectively in neoplastic sites (by factors of 10:1 relative to surrounding normal tissues) as well as in macrophages present in atherosclerotic plaque and in the neovasculature associated with ARMD [25–35]. While the origins of this selectivity remain the subject of ongoing mechanistic investigations, they are thought to reflect in part the fact that Lu-Tex binds well to, and presumably modifies, low density lipoproteins [24]. Once modified in this way, these latter blood components are believed to be taken up by rapidly proliferating cells, macrophages, and the neovasculature of ARMD.

LUTRIN™ injection is the Lu-Tex drug formulation being developed for use as a photosensitizer in the PDT treatment of cancer. As illustrated in Fig. 2 for one particular tumor model, it shows remarkable activity in the PDT of cancer in animal models [4]. LUTRIN™ also was found to be active in a Phase I clinical study for the treatment of metastatic tumors to the skin and subcutaneous tissues [28] and was the subject of a recently completed Phase II clinical trial for recurrent breast cancer to the chest wall.

Potentially more important than even PDT is a new application of light and photosensitizing drugs that we are terming photoangioplasty or photoatherolysis [1]. Photoangioplasty resembles more classic PDT in its photophysics if not in actual application-related details. Briefly, the basic idea is to administer a photosensitizing agent that localizes to atherosclerotic plaque and then use light-based activation (through, for example, an optical fiber catheter inserted into the blood vessel) to effect plaque removal. Given that this is a procedure that needs to be effected in the presence of blood, the requirement for an agent that not only localizes to plaque but also is activated by blood/tissue penetrating non-thermal far red light becomes clear. This makes Lu-Tex and ANTRIN™, the photoangioplastic agent derived from it, seemingly ideal. Such materials are retained selectively in atherosclerotic plaque [30] and display a lowest energy λ_{max} of 732 nm, a wavelength that is transmitted through blood [31].

To date, the efficacy of ANTRIN™ photoangioplasty has been demonstrated in various animal models [30, 32, 33], and this same agent is now in Phase II clinical trials for the treatment of peripheral arterial disease. Impressive results have been obtained in a recently completed Phase I trial as reported by Kramer *et al.* [39]. Patients treated with ANTRIN™ photoangioplasty demonstrated overall improvement in angiograms, ankle-brachial index, and clinical outcomes assessments. An illustrative result is seen in Fig. 3. This procedure is performed using standard percutaneous endovascular techniques in a catheterization laboratory. To the best of our knowledge, this is the first non-mechanical clinical technique effective in reducing atherosclerosis. Current procedures, such as balloon angioplasty, are hindered by thrombosis, restenosis, or their inability to treat diffuse disease. Thus, we like to think our results and the progress they represent augur well for the use of texaphyrins in photoangioplasty. Indeed, in conjunction with appropriately administered red light they could be used to help control several of the most widespread and debilitating of all medical conditions, namely atherosclerosis of peripheral arteries and coronary arteries, as well as, potentially, diseases associated with impaired cerebrovascular circulation.

Many of the same attributes that make drugs derived from Lu-Tex (viz. LUTRIN™ and ANTRIN™) so attrac-

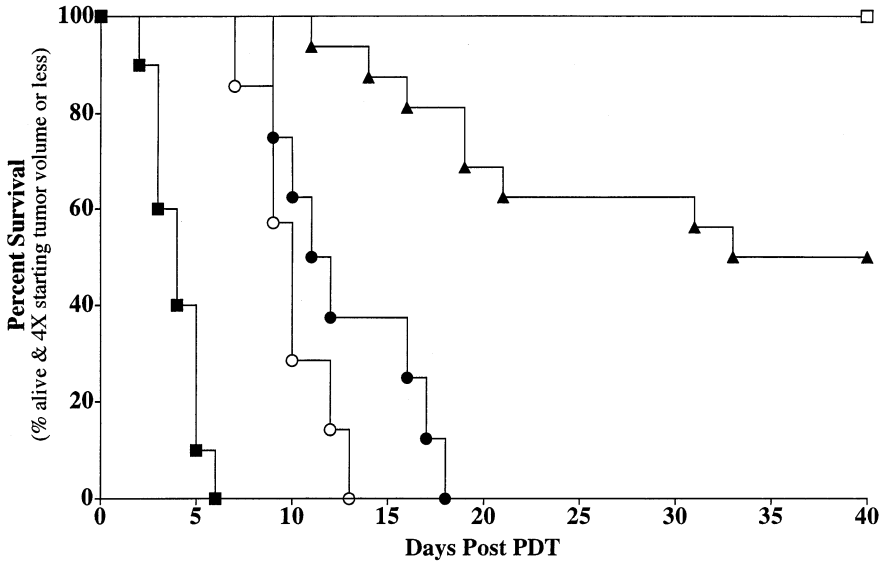


FIG. 2. Kaplan–Meier curve for survival or time for tumor to reach four times starting volume for SMT-F tumor-bearing mice treated with 10 μmol/kg of LUTRIN™, a Lu-Tex-based photosensitizer. The mice were irradiated 3 hr (N = 9, □), 5 hr (N = 16, ▲), 12 hr (N = 8, ●), and 24 hr (N = 7, ○) after injection of LUTRIN™ photosensitizer with 150 J/cm^2 at 150 mW/cm^2 at 732 nm. A matched set of control animals received light irradiation alone (N = 10, ■). Initial tumor volumes were 70 ± 35 mm^3. During the study, all animals whose tumor volume increased to four times the initial tumor volume were subjected to euthanasia. On the other hand, all animals that were still in the study at day 40 displayed no evidence of disease at the tumor site. Reproduced with permission from *Photochem Photobiol* 63: 892–897, 1996. Copyright (1996) American Society for Photobiology. [Ref. 4.]

tive in terms of treating cancer and atherosclerosis also make Lu-Tex of interest in terms of treating ARMD. This condition, which is the leading cause of severe visual impairment and blindness in Americans over age 60, is caused by angiogenesis of abnormal vessels in the choroid of the retina. These diseased vessels leak fluid, which results in visual impairment. While currently there is no cure for ARMD, the use of a photosensitizing drug that localizes in this neovasculature in conjunction with site-specific red-light photoactivation offers the possibility for clinically

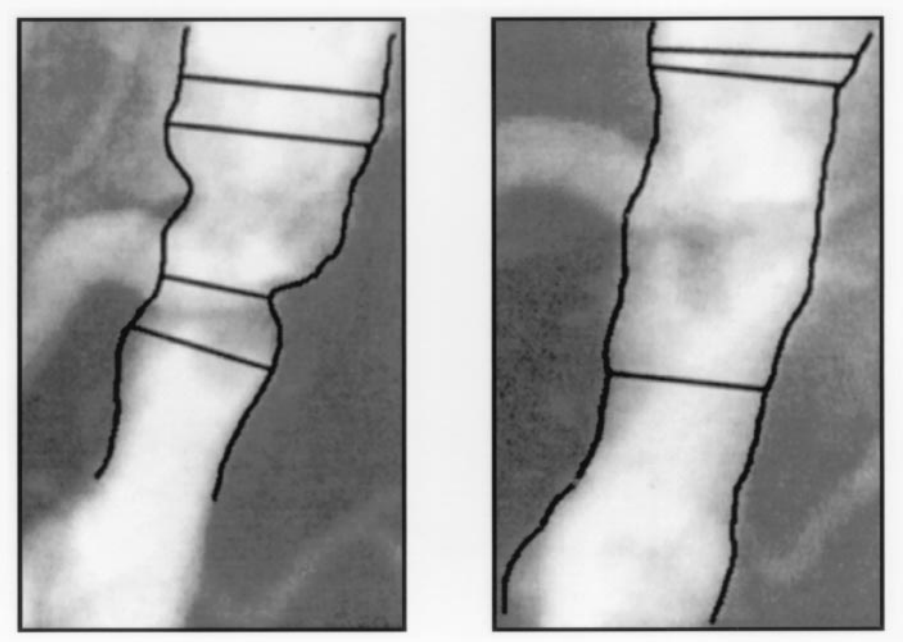


FIG. 3. Left: Pretreatment angiogram of the femoral artery of a patient enrolled in a Phase I study of the Lu-Tex-based ANTRIN™ photosensitizer, showing the severe narrowing of this vessel caused by atherosclerosis. Right: One month after a single treatment with ANTRIN™ photosensitizer-based angioplasty, a repeat angiogram shows a 50% increase in the diameter of the arterial opening and increased blood flow. Reproduced with permission. Copyright (1998) Pharmacyclics Inc.

useful control. To date, the Lu-Tex-derived drug OPTRIN™, an agent being developed specifically for the treatment of ARMD, has been found (when activated with red light) to destroy diseased vessels in preclinical studies [34, 35, *] and is being evaluated currently for safety, drug/light dosing, and efficacy in a Phase Ib/II clinical trial. Meanwhile, a different photosensitizing agent developed by others, namely verteporfin (VISUDYNE™) [40], has completed Phase III randomized clinical trials for the "wet" form of ARMD. Thus, the possibilities for extending the scope of PDT into this important ocular realm look exceedingly attractive at present.

CONCLUDING REMARKS

The unique combination of desirable chemical attributes and highly attractive biolocalization properties makes the texaphyrins a potentially powerful class of new therapeutic agents. While developed so far in the context of the gadolinium(III) and lutetium(III) complexes **1** and **2** only, the diversity of applications to which the photosensitizing drug substance Lu-Tex (**2**) may be applied, coupled with the unique mechanism of action displayed by its XRT-enhancing gadolinium(III) analogue, Gd-Tex (**1**), leads us to propose that these particular texaphyrins will emerge to fill a number of currently unmet medical needs. The fact, however, that a wide range of other texaphyrin complexes are either known or easily envisioned means that the benefit of this series of molecules could extend far beyond the important applications detailed in this commentary. For instance, the possibility of using Lewis acidic lanthanide(III) texaphyrins to effect RNA hydrolysis selectively [41, 42] and thus make more viable the therapeutic utility of antisense technology is currently being explored in our laboratories, as is the use of various texaphyrin complexes to augment, as so-called chemosensitizers, the efficacy of classic anticancer chemotherapy. These new opportunities should continue to make the texaphyrins of interest to all those involved in the fields of chemistry, medicine, biochemistry, and pharmacology.

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