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Photodynamic therapy in superficial bladder cancer: past, present and future

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Abstract For many reasons, such as toxicity and lack of selectivity of photosensitisers, as well as complexity of technical procedures and inconstant therapeutic results, photodynamic therapy of highly recurrent superficial bladder cancer never gained wide acceptance in the urological community. However, the 25 years of experience combined with the recent discovery of new photosensitisers, such as protoporphyrin IX (PpIX) induced by 5-aminolevulinic acid (ALA) or ALA-derivatives or hypericin open new, very interesting perspectives in this therapeutic field.

Keywords Bladder cancer · Photodynamic therapy · Dihaematoporphyrin derivatives · Protoporphyrin IX · 5-aminolevulinic acid · Hexyl-ester of aminolevulinic acid · Hypericin

Introduction

In cancer diseases, photodynamic therapy (PDT) aims at inducing a cytotoxic reaction in tumours that have previously accumulated a photoreactive chemical compound or photosensitiser. The light–photosensitiser interaction induces in the presence of oxygen a chain reaction leading to death of the cells [1, 26, 70, 71, 72].

To avoid the surgical removal of a diseased organ and lastingly maintain its physiological function, this therapeutic concept appears extremely attractive. In urology, superficial bladder cancer proceeds from a field origin disease of the whole urothelium [14, 75] and seems particularly prone to this type of treatment. Actually, it is characterised by a long course of recurrences necessitating numerous endoscopic surgical operations associated with diverse topical chemotherapeutic and/or immunotherapeutic agents [28, 50].

Since the first report of a photodynamic treatment of a bladder cancer by Kelly and Snell in 1976 [39], a considerable amount of research has been performed. However, despite interesting clinical results in patients whose cancers are refractory to BCG and mitomycin C, PDT of superficial bladder cancer remains experimental [7, 17, 25, 35, 47, 62, 68, 74, 83, 91, 94]. Its technical realisation is difficult because of the very high number of chemical, physical and biological variables that have to be taken into consideration.

Our purpose is to review the experience with PDT over the last 25 years and bring to light research that may justify a renewal of interest in this field.

Clinical experience of PDT over the last 25 years

Principles of PDT

As previously mentioned, three components are essential to induce the cell death mechanisms: a sensitiser, light and oxygen. The choice of a specific treatment modality results from the optimalisation of a compromise between many different parameters, such as the toxicity, the tissue distribution and light-absorption characteristics of the photosensitiser, the performance of the light-source systems, the specific clinical situation, the localisation of the tumour inside the tissue, the tumour oxygenation and metabolism, the production of active photo-products or reactive oxygen species and, finally, the characteristics of the tissue-repair processes [1, 26, 69, 70, 71, 72].

Of course, photosensitisers have different biochemical properties corresponding to their light absorption/emission characteristics and to their cellular localisation and tissue distribution [73]. The penetration of the light

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within tissues depends on its wavelength, which has to correlate with the absorption spectrum of the photosensitiser and the optical properties of the illuminated tissue. The energy released during the light-tissue interaction is linked to these parameters [13, 58, 82].

After adequate light excitation of the tumour, the photosensitiser reacts with molecular oxygen and forms reactive oxygen species [free radicals and reactive singulet oxygen ($^1O_2$)] within cells. In turn, these photoproducts react with molecules of different organelles, such as mitochondria, cellular or nuclear membranes, lysosome, Golgi apparatus, endosplasmic reticulum, disrupting the bioenergetic cellular pathways. The cytotoxic mechanism involved induces necrosis and/or apoptosis of the incriminated cells [65, 69, 70, 71].

Haematoporphyrin derivatives

In bladder cancer, the history of PDT is closely related to the haematoporphyrin derivatives' family: haematoporphyrin derivatives (HpD) or Photofrin I, dihaematoporphyrin ether/ester (DHE), Photofrin II or Photosan [21, 70]. Although imperfect, these photosensitisers got licensed approval for clinical trials in many countries because of their wide range of medical applications [56]. The understanding of the biological effects of the light-sensitised tissue interaction, linked to the photosensitising agent chemical, tissue-distribution properties and the available physical systems of bladder illumination, is essential to appreciate the clinical results obtained in the specific indication of superficial bladder cancer.

Chemical properties and tissue distribution of HpD

HpD and DHE are relatively impure compounds whose composition and stability may vary from one preparation to another [36, 56, 63, 72]. Tissue-distribution studies on animal models have demonstrated that they are retained in normal, as well as in neoplastic, tissues. Administered intravenously, Photofrin II has been found at decreasing sensitiser levels in the following normal tissues: liver, adrenal gland, urinary bladder, pancreas, kidney, spleen, stomach, bone, lung, heart, skin, muscle, brain [26]. Only brain, muscle and skin tissues had lower sensitiser levels than tumour tissue [70]. The tumour-to-normal tissue ratio remains low, imprecise and unpredictable. It seems related to different mechanisms, such as leaky tumour vasculature, poor lymphatic drainage and selective attachment of these porphyrins to lipoproteins. These complexes are retained by the vascular endothelium or interact via a receptor-mediated endocytosis mechanism on malignant cells [26, 37, 70].

Although the half-life of these porphyrins in human serum is considered tolerable (20–30 h for a 5-mg bolus), some components remain present in the skin, or even in the serum at a low level (2–5%), for at least 4–6 weeks [70]. This explains the adverse long-term skin photosensitisation effect.

In human bladder cancer, a good correlation was found on cystectomy specimens between fluorescence and dysplasia or carcinoma in situ following bladder photosensitisation by 2.5 mg/kg of HpD 2 to 48 h prior to bladder wall light excitation [8]. However, no information exists on HpD and DHE in terms of depth and homogeneity of their tumour accumulation, distribution and clearance as opposed to the normal bladder wall in humans. The drug light time interval arbitrarily defined in clinical studies relies on animal tumour models, and the lack of human data partly explains the irreversible fibrosis of the bladder wall observed in some clinical studies [17, 25].

Bladder-illumination techniques developed in combination with HpD

The choice of the light specifications relies on a compromise between the localisation of the tumour in the depth of the bladder wall and the photosensitiser physical properties. HpD, as other porphyrins, may be excited by a spectrum of different wavelengths. Red light (λ: 630 nm) matches a minor peak of the HpD or DHE absorption spectrum and allows a light penetration up to 10 mm through the bladder wall [26, 70, 72]. Green light (λ: 540 nm) may also be used but in principle only for carcinoma in situ because it is associated with a shorter tissue penetration (3–5mm) [63].

Bladder wall illumination may be achieved by two different techniques: directional or whole-bladder irradiation. The first one, easy to manage in terms of a light dose, aims at the treatment of visible tumours but has proven poorly effective for this indication [74]. PDT is essentially designed for the treatment of flat slightly or invisible urothelial neoplasia. Therefore, a whole-bladder illumination technique must be considered.

This implies that the light is uniformly and homogeneously distributed within the whole-bladder cavity. In this situation, the light power per tissue area (fluence rate) is not only determined by the technical properties of the illuminating device, but also by the optical properties of the irradiated tissue, which may change from one patient to another or even from one area to another in the same patient [13]. Assuming that the bladder is a sphere, a spherical bulb-tipped light emitter is placed at the centre of the bladder under echographic and/or endoscopic control. Some authors advise the use of a lipid solution as an intravesical medium to enhance the uniformity of the light distribution [5, 56, 63, 66]. As the light dose should be precisely evaluated for each patient, sophisticated, sometimes computer-assisted, light-delivery systems with light detection sensors placed in contact with the mucosa, allow one to take into consideration the light-refractive index, common denominator of the bladder wall optical properties. But of course, all different parameters (absorption coefficient, scattering

coefficient, anisotropy factor and refractive index, etc.) have to be taken into account for an adapted estimation of the light dose in each patient. [9, 55, 58, 85].

Among all systems available at the present time, the double concentric balloon catheter coupled with a light dosimeter [9] represents probably the best compromise because it ensures a homogeneous light distribution while minimising different sources of errors, such as modification of the bladder shape and/or optical properties of the bladder fluid content during therapy [36, 66]. This device consists of a catheter with two concentric transparent balloons. After determination of the bladder volume, the outer balloon is filled up to lie against the bladder wall. When this balloon is in contact with the bladder mucosa, the inner balloon is placed at approximately the centre of the bladder. A fat emulsion as scattering medium is injected into the inner balloon, which serves as an isotropic emitter. Light supply occurs by a fibre with a conical end radiating perpendicular to the axis into the scattering medium. The space between the bladder wall and the outer balloon can be rinsed to remove blood and urine during therapy. As the outer balloon is filled with clear water, the reflected light from the bladder wall may propagate undisturbed within the bladder volume, improving considerably the homogeneity of the total light distribution. At the surface of the outer balloon, a fibre (light sensor) placed halfway between the centre and the bladder outlet, detects the reflected light from a circular stripe of the bladder wall, assuming that the light condition of the stripe is representative of the whole bladder wall. All registered parameters are sent to the dosimeter, which calculates the light dose necessary for the treatment [9, 36].

Light–tissue interaction with HpD

In fact, light–tissue interaction with HpD is far more complex than the principle of PDT, cited above.

As retention of HPD or DHE occurs in cancer cells as in elements of tumour vessels, such as endothelial and/or blood cells, different mechanisms are identified: a direct cytotoxic effect on cancer cells, an indirect tumour death by hypoxia and nutritional deprivation due to vascular collapse, blood flow stasis with acute inflammation, oedema and necrosis, and an immunological response by release of cytokines linked to these previous processes [21, 22, 67, 69]. All these mechanisms interact, compete or even inhibit each other. A reduction of tissue oxygen following early vascular damage may paradoxically protect living cancer islets within tumours, which will originate future recurrences [84].

Clinical results with HpD

All these reasons explain the difficulties encountered in establishing a standardised clinical protocol. Mainly, phase I and II studies are reported (Table 1) [7, 17, 25,

Table 1 Synopsis on clinical experience with haematoporphyrin derivatives (HpD) or dihaematoporphyrin ether/ester (DHE)-induced photodynamic therapy. *WBD*, *CR*

Reference	Year	Ta,T1	cis	Photosensitizer (mg/kg)	Time interval	Focal (J/cm^2)	WBD (J/cm^2)	CR: Ta,T1 (3 months)	CR: cis (3 months)	Follow-up (months)	Recurrence group Ta,T1	Recurrence group cis
Benson [7]	1988		15	HPD: 2.5–5	3 ± 48	150			15 (100%)	6–32		8 (53%)
	1988		12	HPD: 4–5	3 or 48		25–45		8 (66%)	3–9		3 (37%)
Prout [74]	1987	17	2	DHE: 2	48	100–200	5.5–10	8 (47%)	2 (100%)	3	n.a.	n.a.
Harty [25]	1989	7		DHE: 2	72	100	25	5 (71%)		6–12	2 (40%)	~
Stamp [83]	1990	10		HPD: 2	72		10–20	7 (70%)		24	8 [b] (80%)	
Jocham [35]	1990		20	HPD: 3×10	48		15–70 (35)		16 [a] (83%)	60		14 [c] (70%)
				DHE: 2×8	60–72							
				DHE: 1.5×2								
Windhal [94]	1993	4	7	HPD: 2.5×8			30–53	3 (75%)	7 (100%)	6–30	2 (66%)	2 (28%)(4 deaths)
				DHE: 2	48		15					
D'Hallewin [17]	1995		15	DHE: 2	48		15 (tot 75–100)		15 (100%)	9–36	~	6 (40%)
Kriegmair [47]	1995	17	5	DHE: 2	48–53		15–30	9 (53%)	4 (80%)	6–42	6 (66%)	2 (50%)
Uchibayashi [91]	1995		34	HPD: 3×21	?		?		25 (73%)	24	~	14/18 (77%)
				DHE: 2×13	?							
McClellan [62]	1997	20		DHE: 2×6	48		5–25	9(45%)		6–56	5 (55%)	~
				DHE: 1.5×14							8 [b] (40%)	~
Nseyo [68]	1998		36	Porf. Sod: 2	40–50		15		21 (58.3%)	12	~	10 (47%)
Total		75	146					41 (54%)	113 a (77%)			

[a] Extrapolated value as the study of Jocham only mentioned the number of treated tumours, [b] Patients having developed a progressive disease, [c] all recurrences including dysplasia

35, 47, 62, 68, 74, 83, 91, 94]. Results of a phase III study, announced in 1987, comparing HPD PDT to intravesical Thiotepa [21] were never published. However, a multicentre randomised phase III trial comparing PDT versus BCG intravesical immunotherapy for the prophylaxis of recurrent superficial urothelial carcinoma of the bladder and therapy of carcinoma in situ, initiated in 1995, is now closed and results will be published soon [36].

Because of inadequate light penetration, papillary tumours larger than 1.5 cm (which are better treated by conventional means anyway) respond badly. HPD- and/or DHE-induced PDT are more effective for flat tumours, such as carcinoma in situ. The short-term (3 months) response rate can be considered as good as BCG therapy, but due to recurrences or disease evolution, the long-term disease-free survival is often disappointing. However, it is important to point out that most of the patients involved in PDT protocols were refractory to BCG therapy and presented a high risk of unfavourable evolution. This explains the high rate of post-treatment cystectomy related in some studies [17, 25]. On the other hand, some patients clearly benefit from this treatment with a disease-free survival going longer than 60 months [35]. Irritative bladder symptoms for several weeks are generally the rule after HpD/DHE PDT, in addition to a prolonged cutaneous photosensitivity for some patients. Complications, such as detrusor fibrosis, ureteral reflux and/or bladder shrinkage, as a possible consequence of the photosensitiser accumulation in the bladder muscle, remain relatively unpredictable, [17, 25, 35, 62] despite the considerable amelioration of the whole-bladder light distributors [9, 36, 55, 58]. Therefore, some authors recommend a reduction of the photosensitiser and light dose for prophylactic treatments [35, 62, 63].

Clearly, the role of PDT in superficial bladder cancer cannot be restricted to one concept, and other ways of research have to be explored.

New ways of research

Second-generation photosensitisers

The new ways of research in the field of bladder cancer PDT aim at looking into second-generation photosensitisers (Table 2), characterised by a reduced toxicity, a more favourable tumour selectivity, a light activation in the far red spectra (where light tissue penetration is deeper), other modes or routes of administration (liposome encapsulation, systemic, topical...) [2, 99] and specific cell localisation or cell death mechanisms, etc. [2, 3, 6, 43, 81, 100].

Many of these agents are considered of clinical interest, since they present a lower toxicity with a more rapid clearance from normal tissues, such as skin and muscle, and a much higher molar absorption coefficient at a longer wavelength than DHE. But animal tumour model studies show variable results in terms of tumour response, skin photosensitisation, tumour-to-benign bladder tissue selectivity, fluorescence detection of the photosensitising agent, choice of the critical point of phototoxic activation [2, 3, 72, 73], etc.

Table 2 Second-generation photosensitisers

Exogenous
Benzoporphyrin derivatives (BPD A)
Meso-tetrahydroxyphenylchlorin (mTHPC)
Bacteriochlorin a (BCA)
Phthalocyanines derivatives:
Chlor-aluminum-sulfonated phthalocyanine (CASPc – AlPcS4 – ZnPc, etc.)
Naphthalocyanine (isoBOSINC)
Metallopurpurin
(Cd-texaphyrin, etc.)
Others:
(Calphostin C)
Hypericin
Endogenous
Protoporphyrin IX (PpIX) induced by
Delta-aminolevulinic acid (ALA)
Hexyl ester of ALA (h-ALA)

In fact, this research seldom goes beyond laboratory investigations on in vitro cell cultures or in vivo tumour animal models. In vitro cell cultures with different human transitional cell carcinoma cell lines bring important clues to photosensitiser cellular localisation, light-induced cytotoxicity, cell organelle target and/or death mechanism, influence of oxygen, metabolism or pH on the photodynamic response, etc. [6, 38, 64, 96, 97]; but the biological and physiopathological consequences of a possible photodynamic action on the normal bladder urothelium are seldom studied in an in vitro model [52]. Tumour animal models differ from one study to another. In some, the tumour implantation is orthotopic [3, 30, 31, 81, 89, 99], in others heterotopic [100]. These studies give information on the tumour response to different protocols of the sensitised tumour and help to determine different parameters of illumination, such as the wavelength, fluence rate, interaction time, light dose fractionation, etc. However, these models do not generally reproduce the clinical situation of a flat multifocal bladder cancer because the tumours sometimes become bulky and may induce a dense network of neovessels at the site of implantation that can modify the tumour's response to the treatment. Moreover, as the tumour-to-benign tissue ratio of the photosensitiser is often not identical in animals and humans [11, 24, 99], the lack of human studies on tissue distribution within the bladder for most of these photosensitisers renders the approach of a future possible clinical application very difficult.

Delta-aminolevulinic acid or delta-aminolevulinic acid derivatives induced protoporphyin IX photosensitiser

This new mode of tumour photosensitisation merits special mention, as it is now used for either carcinoma in situ photodiagnosis, or photodynamic treatment of different cancers [10, 23, 40, 41, 48, 57, 77, 90, 98], and research is ongoing in many medical fields.

Basic principle of the photosensitisation with delta-aminolevulinic acid or delta-aminolevulinic acid derivatives

Haeme-containing enzymes are essential for the energetic metabolism of every cell, and protoporphyin IX (PpIX) is the immediate precursor for haeme in the biosynthesis pathway. Under normal conditions, haeme synthesis is regulated so closely that photosensitising concentrations of PpIX are not reached. The cellular concentration of PpIX is determined by the rate of synthesis of delta-aminolevulinic acid (ALA) under the regulation of a feedback control mechanism on the ALA synthetase activity dependent on the free haeme concentration [40, 41, 71].

Three mechanisms are susceptible to inducing high intracellular accumulation of photosensitising concentrations of PpIX [40, 71] in the haeme biosynthetic pathway (Fig. 1). The first one is the administration of exogenous ALA or ALA derivatives, which bypasses the mechanism of feedback control. As the transition of PpIX to haeme is a slow process, a transient PpIX accumulation will occur. The second one is the iron depletion, which inhibits the ferrochelatase and thus PpIX conversion to haeme. The third mechanism increases haeme degradation [71].

The rate of ALA-derived porphyrin synthesis has been shown to be higher in cancer cells than in normal cells, and malignant tumours may accumulate PpIX in a proportion from 8- to 2,410-fold (average 20) in comparison to benign tissues [71]. Disturbed enzymatic activities, such as the reduction of the ferrochelatase activity in cancer cells, which slow down the transition from PpIX to haeme, explain such a ratio. It seems to be the main mechanism in urothelial cancer cells [45]. However, abnormal PpIX accumulation is not fully understood in every cell type [71].

Based on preliminary fundamental studies, this type of endogenous tumour photosensitisation is applied in many malignant diseases, such as treatments of cutaneous tumours (superficial basal cell carcinoma, Bowen's disease, actinic keratosis, cutaneous T-cell lymphoma, etc.) [10, 57, 90], gastrointestinal tumours [77], oral cavity tumours [23], endometrial disease of the uterus [98], and as diagnostic photodetection of hardly visible tumours in bladder cancer [19, 33, 48, 79].

In vitro and in vivo experimental studies on ALA-induced PpIX PDT

In vitro and in vivo models of bladder cancer cells on ALA-induced PpIX PDT arouse the interest of the development of clinical research protocols and confirm a direct cytotoxic effect dependent on the PpIX accumulation inside the cancer cells [4, 12, 15, 29, 30, 46, 80, 89]. Well and moderately differentiated transitional cell carcinoma seems more sensitive to PDT than undifferentiated [80] or squamous carcinoma, which poorly accumulates PpIX [15]. Because of the high complexity of the PpIX cell production and distribution and the presence of additional photoproducts, the exact mechanism of the cytotoxic effect of ALA-PDT is not yet fully understood [71]. But basically, it proceeds through the formation of singlet oxygen and/or other reactive oxygen species similarly to other PDT mechanisms described

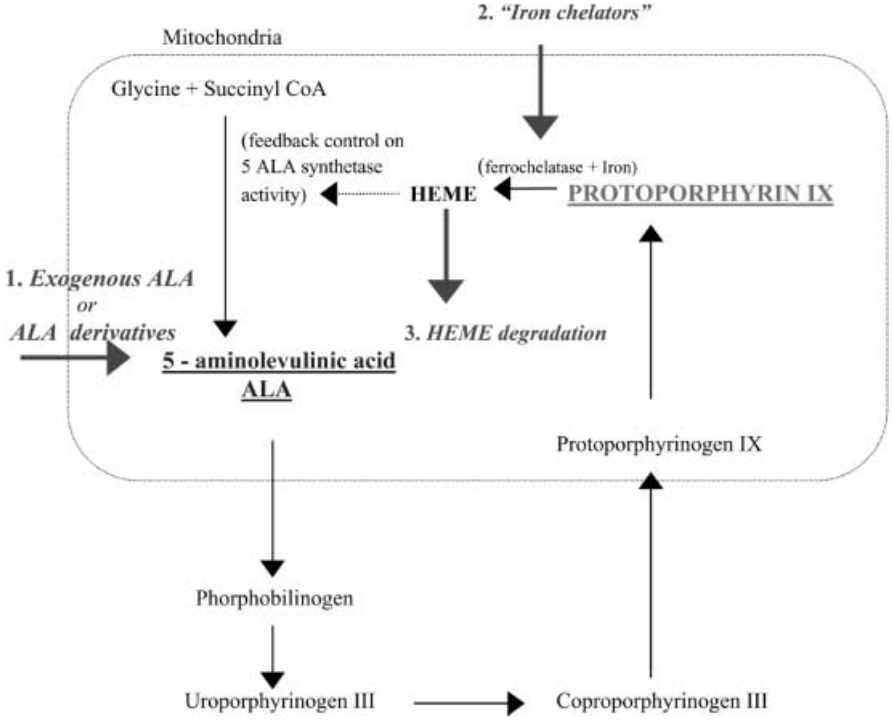

Fig. 1 Schematic diagram of the cellular haeme biosynthetic pathway with three possible mechanisms of protoporphyin IX concentration enhancement

above [71, 96]. PpIX has a $^1O_2$ quantum yield of approximately 0.5 [76]. The cellular localisation of PpIX accumulation in the mitochondria of the perinuclear area [54, 87] suggests that both apoptosis and necrosis are involved in the tumour-killing process, which seems to be confirmed [65]. Other mechanisms induced by a possible retention of PpIX within the capillary vessel endothelium surrounding the tumour or linked to an inflammatory reaction following PDT should be explored [71, 95].

Spectrofluorometric analysis on PpIX tissue accumulation and distribution performed in animals and humans confirms the high selectivity of ALA for the urothelium, independently of the drug administration route: intravenous or intravesical [11, 30, 53, 86, 99]. In animals, according to ALA conditions of administration, the tumour-to-normal bladder mucosa, submucosa and muscle ratio of PpIX goes approximately from 2–3:1; 5:1 and 8–20:1 respectively [11, 12, 46, 99]. In humans, it also rises to 20:1 [24]. In bladder cancer, PpIX is clearly tumour selective and perhaps more than many previously tested photosensitisers. The confirmation of the absence of any deleterious light-dose effect on the detrusor, as well as the choice of the most suitable wavelength between 630 and 635 nm are demonstrated in animal bladder cancer models [12, 30, 89]. This encourages the setting up of clinical trials on ALA-PDT.

Optimisation of the PpIX synthesis and the use of ALA hexyl ester or h-ALA

ALA shows a low liposolubility and passes slowly through biological barriers, such as the cellular membrane, which leads to an inhomogeneous concentration and distribution of PpIX in the deep layers of the tumour following topical application [61]. Theoretically, different ways may improve PpIX concentration and homogeneous tissue distribution:

1. Transformation of ALA into a more lipophilic prodrug (a prodrug is a pharmacologically inactive derivative of a parent drug molecule that requires spontaneous or enzymatic transformation within the body to release the active drug) [42])
2. Combination of ALA with an agent increasing cell membrane permeability, such as dimethylsulfoxide [59]
3. Encapsulation of ALA into liposomes
4. Agents interfering directly with the biosynthetic pathway of haeme [51, 71]
5. Combination of ALA with an iron chelator, such as desferroxamine [59]
6. Iontophoresis or electro-motive diffusion [88]

In superficial bladder cancer, iontophoresis shows, however, no advantage [86]. Among all ALA esters tested, *h*-ALA is the most suitable form to optimise PpIX accumulation and distribution in the urothelium and bladder cancer [51, 59]. At a concentration 20-fold lower than ALA, *h*-ALA produces a two to four times quicker and higher cell concentration of PpIX [51, 59]. Fluorescence microscopic studies on tumour specimens photosensitised by *h*-ALA demonstrate a homogeneous distribution of PpIX through the whole depth of the tumour with an enhanced accumulation in the same order of magnitude [60].

Clinical experience with ALA or h-ALA for photodynamic applications

The main clinical application of both photosensitising agents is fluorescence cystoscopy. The principle of the method is simple. Following a bladder instillation with a solution of ALA 180 mmol or *h*-ALA 8 mmol, the urothelium is inspected with modified endoscopic equipment allowing one to either examine the bladder wall in normal mode (white light) or in fluorescence mode (blue light). All suspicious areas appear bright red, whereas the colour of the normal mucosa remains blue-green [32, 48]. Fluorescence cystoscopy facilitates a precise mapping of most cancerous lesions. It helps to detect early urothelial malignancies, such as carcinoma in situ with a constant sensitivity rate of 89–97% [19, 32, 33, 34, 48]. Exophytic tumours appear more clearly delineated and can be more precisely removed. The benefit of this new endoscopic technique in terms of disease recurrence rate is not yet established, but the residual tumour detection rate at second look transurethral resection seems significantly reduced [79].

By comparison to ALA, h-ALA allows the contraction of the instillation time to less than 1 h [34], which represents a clear advantage in daily practice. This diagnostic tool is becoming a routine procedure in the management of superficial bladder cancer in many urological clinics [19, 34, 48].

In the field of PDT, four clinical trials alone on ALA-PDT are reported. Three concern bladder PDT for superficial bladder cancer or CIS refractory to BCG or mitomycin and one upper urothelial tumours (Table 3) [18, 49, 92, 93]. Whatever the route of administration, ALA PDT induces cytotoxic reactions in tumours of the bladder or the ureter. With some precautions, skin phototoxicity does not occur even after oral administration [78, 93]. As the photosensitiser is mainly retained in the urothelium, no shrinkage or reduction of the bladder capacity is expected. This allows one to perform bladder illumination with a simpler technique than for HpD/DHE without the complex calculation of the reflected light. According to the PpIX-absorption spectrum, a combination of different wavelengths may be used, for example 514 nm and 635 nm, which cover the entire depth of the bladder wall [49, 93]. When ALA is given per os, PpIX is probably better distributed within the tumours, and ALA PDT seems to give better results with a 3-month complete response rate of 100% for carcinoma in situ than following ALA bladder instillation alone [93].

Table 3 Early experience with delta-aminolevulinic acid (*ALA*)-induced photodynamic therapy in the bladder and ureter. *TCC*, *CIS*. *CR*, *PR*, *NC*, *PD*

Reference	Indications	*n*	ALA administration	Toxicity	Irradiation parameters	Bladder shrinkage or ureteral fibrosis	Results at 3 months CR–PR–NC–PD
Kriegmair 1996 [49]	Bladder refractory TCC	10	Intravesical: 5 g ALA; 4.7–8.3 h (m 5.1 h)	No	Whole bladder illumination 2 pts: 15–30J$\sim$ 635 nm, 8 pts: 40J$\sim$514 nm + 20J$\sim$635 nm	No	4–2–3–1
D'Hallewin 1997 [18]	Bladder refractory CIS	6	Intravesical: 1.5gr. ALA; 3–4 h	No	Whole bladder illumination total light dose: 75 J/cm^2 630 nm	No	2–2–1–1
Waidelich 1998 [92]	Multifocal TCC of the upper urinary tract (pTa – G1–G2)	4 (5) [a]	Per os: 40 mg/kg; 3–6 h	Severe hypo-tension 3/4	Cylindrical diffuser; 3–15 irrad./pt. 514 and/or 635 nm (50 J/cm^2)	No	2–2
Waidelich 2001 [93]	Bladder refractory TCC and CIS	24	Per os: 40 mg/kg 4–6 h	Nausea 12/24 Hypo-tension 19/24	Whole bladder illumination 514 nm 40 J/cm^2 & 635 nm 20 J/cm^2	No	*CR at 3 months:* 19 / 24 CIS: 5/5–100% pap.tum: 14/19–74% *NED at 36 months:* 7/24

[a] Number of treated ureters

The results of the last study are particularly interesting and suggest that the disease evolution profile can be modified for a longer bladder preservation for some patients. However, the toxicity of the oral administration on the cardiovascular system, which can lead to severe hypotension in fragile patients, seems a real problem. [27, 77, 93].

Hypericin

Hypericin is an exogenous fluorochrome extracted from the millepertuis plant family, also named St. John's wort (Hypericum perforatum). This constituent is fluorescent and has interesting photoactive and antineoplastic properties. In the Middle Ages, the millepertuis was used after decoction as a vulnerary or to hunt the Spirit of the Tenebrae and heal the possessed. Nowadays, extracts of this plant serve as an antidepressive agent.

In addition, tumours retain and accumulate hypericin. Based on this knowledge, a new technique of fluorescence cystoscopy, very similar to ALA or h-ALA-induced photodiagnosis, demonstrates excellent accuracy in the detection of bladder high-grade dysplasia or carcinoma in situ [20]. The mechanism of the uptake of hypericin in malignant cells is not yet clearly established, but in vitro cell cultures show that a photocytotoxic process can be induced [38].

The future of PDT in superficial bladder cancer

The question of the future of PDT in superficial bladder cancer remains open. Nevertheless, the experience accumulated over the last 25 years clearly demonstrates that this treatment modality conserves some indications but should only be reserved for the treatment of flat disease of the urothelium. The recent discovery of new photosensitising agents, which spare the bladder muscle, raises great hope in the development of new techniques of treatment. The expectation is still to find a therapeutic tool that allows the preservation of the bladder as long as possible by reducing the disease recurrence rate and eventually modifying its evolution into a more benign form. If ALA-PDT seems safer than HpD/DHE PDT concerning the conservation of the bladder function, its mode and technique of illumination can still be optimised. With respect to the potentially severe hemodynamic effects when ALA is administered orally, the topical route should be preferred. In this perspective, *h*-ALA holds more assets. In addition, other ways of research, such as the combination of PDT with chemo- or immunotherapeutic agents should be explored to overwhelm the eventual resistance of cancer cells to PDT [16, 44, 97].

All these questions require the maintenance of a close collaboration between basic scientists, clinicians and industrial partners. Finally, the best option in PDT shall be compared with the standard therapeutic regimens of superficial bladder cancer.

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