First-in-man Phase I study of $TPCS_{2a}$-based photochemical internalization (PCI) of bleomycin in locally recurrent or advanced/metastatic, cutaneous or subcutaneous malignancies

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Abstract

PCI is a novel technique in which chemotherapeutic cytotoxicity is enhanced with a photosensitizer and light exposure. This dose-escalation study assessed the safety and tolerance of $TPCS_{2a}$ (tetraphenyl chlorin disulphonic acid, Amphinex®) in bleomycin PCI, identified the pharmacokinetic profiles, and determined the maximum tolerated dose (MTD) of $TPCS_{2a}$.

Method. Cohorts of 3 to 6 patients were enrolled and the $TPCS_{2a}$ dose escalated by a pre-specified amount until dose-limiting toxicity (DLT) occurred in at least two patients (≥33%). Patients received $TPCS_{2a}$ at a starting dose of 0.25mg/kg. Four days later they received bleomycin (15,000IU/m^2 IV) and after 3 hours red light laser (652nm) was applied to target lesions for 600 seconds to initiate a therapeutic response. Patients were followed for 3 months.

Results. Nineteen patients were enrolled: four with cutaneous breast cancer, 13 with squamous cell carcinoma (SCC) of the head and neck and other regions, and two other cancers. Eighteen patients (95%) experienced 95 AEs, most commonly pain, photosensitivity and nausea. Most AEs (80%) were mild or moderate. Eight episodes of pain (four severe) were treatment-related. Mean patient-reported pain in the 24 hours after treatment measured using a visual analogue scale declined from 4.9 to 1.3 following the introduction of general anaesthesia during the procedure. Four patients experienced skin photosensitivity reactions; three of these were in the highest dose cohort. Eleven patients (58%) experienced 15 serious adverse events: four(swelling, and blistering of hands, tongue oedema, infection to wound site) were possibly or probably related to treatment.

The MTD of $TPCS_{2a}$ was found to be 1.0 mg/kg.

At day 28, 11/16 patients had a complete response (CR) in target lesions, two had a partial response (PR), two had stable disease (SD) and one had progressive disease (PD). At last visit there were five CRs, two PRs, two SDs and two PDs. During the course of the study four patients died (no relation to treatment) and six were withdrawn prematurely.

Conclusion. With appropriate care (analgesia and anaesthesia) $TPCS_{2a}$-based PCI of bleomycin was well tolerated in these patients with locally advanced cancer. Treatment-related AEs were as expected and can be managed. Preliminary efficacy data are very encouraging and a phase II study in HNSCC has just begun.

Photochemical internalization

Photochemical internalization (PCI) uses a light-activated drug to introduce membrane-impermeable chemotherapeutic agents directly into the cytosol of the cell. Patients are first treated with the photosensitizer, which over time clears from the cell membrane but remains on the internal surface of the endosomal membrane. The chemotherapeutic agent is administered and is internalised via endocytosis, where it co-localises with the photosensitizer in endocytic vesicles. The photosensitizer is activated using laser light, leading to vesicle membrane rupture and drug release into the cytosol, enabling the drug to reach its therapeutic target.

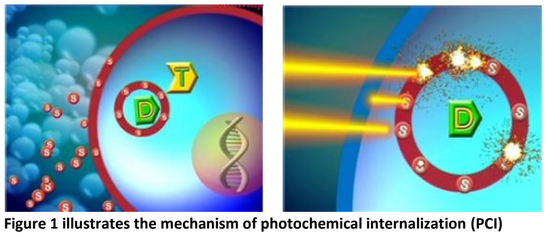


Figure 1 illustrates the mechanism of photochemical internalization (PCI)

Bleomycin is approved for the treatment of several malignancies including squamous cell head and neck cancers. However, relatively high doses are required for therapeutic effectiveness, due in part to its limited penetration through cell membranes. PCI may be a way of improving the efficiency of localised bleomycin delivery into target cells.

Study objectives

The purposes of this study were to explore the safety and tolerability of the newly developed photosensitizer $TPCS_{2a}$ in combination with bleomycin in the treatment of cancers on the body surface and to establish the MTD.

Patients and dosing scheme

Adult patients with local recurrent or advanced/metastatic, cutaneous or subcutaneous malignancies were eligible.

The starting dose of $TPCS_{2a}$ in the dose-escalation was 0.25 mg/kg. The MTD was defined as the dose at which 33% of the patients experienced a DLT or the dose below the dose where more than 33% experienced a DLT. Following identification of the MTD, a lower dose level was selected for expansion in a further six patients. The bleomycin dose (15,000 IU/m^2) and the light dose (60 J/cm^2) were held constant across all cohorts.

Assessments

Safety: Adverse events (AEs), skin photosensitivity, concomitant medications, vital signs, laboratory safety tests, pain and patients' performance status were assessed and recorded at specified intervals throughout the study.

Efficacy: Target lesions were measured by clinical examination and/or ultrasound at the pre-study evaluation, Baseline, Day 28 and Last Visit, and scored according to "Response Evaluation Criteria in Solid Tumors" (RECIST).

Pharmacokinetics: Blood and urine samples for pharmacokinetic analysis were taken on Days 0, 2, 4, 7, 14, 28, and at Last Visit after dosing.

Results

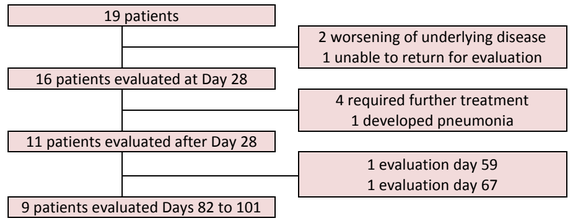
A total of 19 patients (mean age 60.6 years) were enrolled in the study and were treated in four dose groups, Table 1.

	$TPCS_{2a}$ Dose Group (mg/kg)			
	0.25, N=4	**0.5,** N=9	**1.0,** N=3	**1.5,** N=3
	Number of Patients (%)			
Diagnosis, n (%)				
SCC, head and neck	3 (75%)	6 (67%)	2 (67%)	2 (67%)
Breast cancer	0 (0%)	3 (33%)	1 (33%)	0 (0%)
Other metastases	1 (25%)	0 (0%)	0 (0%)	1 (33%)

Table 1. Patient and tumour characteristics

The Safety Population contained 19 patients and the Per Protocol (PP) population contained 11. Patients not included in the PP were due to: no lesion measurements taken (N=1), unconfirmed RECIST evaluation (N=3), and lesion measurement not carried out according to protocol (N=4).

Nine patients completed the study as planned to the 3 month assessment.



Dose escalation findings

One AE corresponding to the definition of Grade 2 toxicity was seen in the third cohort (1.0 mg/kg), and dose escalation proceeded at 1.5 times this dose, to 1.5 mg/kg. Two patients (67%) in the 1.5 mg/kg dose group experienced DLTs (see below) and the MTD was therefore agreed to be 1.0 mg/kg. A further cohort expansion was performed at 0.5 mg/kg to confirm findings, and a total of two patients (22%) experienced DLT's (see below) in this dose group .

Safety

The most common AEs were pain related to treatment, and nausea each reported by four patients, followed by tongue oedema, pain in jaw, erythema, and pruritus, each reported by three patients.

	$TPCS_{2a}$ Dose Group (mg/kg)			
	0.25, N=4	**0.5,** N=9	**1.0,** N=3	**1.5,** N=3
	Number of AEs			
	6	47	7	35
	Number of Patients with AEs (%)			
Any AE	4 (100%)	8 (89%)	3 (100%)	3 (100%)
SAEs	0 (0%)	6 (67%)	2 (67%)	2 (67%)
Severity of AEs[2]:				
Mild	3 (75%)	6 (67%)	1 (33%)	3 (100%)
Moderate	0 (0%)	3 (33%)	2 (67%)	3 (100%)
Severe	3 (75%)	6 (67%)	2 (67%)	2 (67%)
Treatment related[1] AEs	3 (75%)	7 (78%)	2 (67%)	3 (100%)

1 Adverse events considered unlikely, possibly or probably related
2 Patients could have AEs of more than one severity or intensity

Table 2. Summary of adverse events

Three patients in the 0.25 and one in the 0.5 mg/kg group experienced severe pain at the treatment site. Following an amendment to permit analgesia and general anaesthesia or sedation, mean pain scores were lower. Other severe treatment related AEs included oedema of the tongue (N=1, DLT), swelling to face, lips and tongue (N=1) and oral cavity fistula (N=1, DLT) in the 0.5 mg/kg group, and infection to wound site (N=1, DLT) and swelling to the hands (N=1, DLT) in the 1.5 mg/kg group.

Four serious AEs in three patients were considered possibly or probably treatment-related: swelling and blistering to the back of hands in one patient (1.5 mg/kg, DLT), infection to wound site (1,5 mg/kg, DLT) and tongue oedema at the treatment site in one patient (0.5 mg/kg). No patients were withdrawn or had treatment interrupted due to AEs.

Efficacy

	Complete response	Partial response	Stable disease	Progressive disease
Safety population				
Day 28, n=16	11	2	2	1
At least four weeks after Day 28, n=11	5	2	2	2
Per protocol population				
Day 28, n=12	10	2	-	-
At least four weeks after Day 28, n=7	5	2	-	-

Table 3. Overall tumour response

Complete clinical regression of target lesions were seen at Day 28 in eight patients in the 0.25 and 0.5 mg/kg groups, and in one patient in each of the 1.0 and 1.5 mg/kg groups. Five of these could be confirmed at least 4 weeks after Day 28.

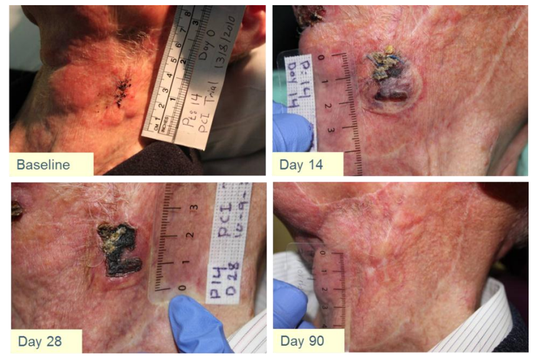


Figure 2 demonstrates an example of a complete response to bleomycin PCI in a patient with a locally recurrent eccrine sweat gland carcinoma

Pharmacokinetics

The maximum blood level of $TPCS_{2a}$ occurs 30 minutes after administration, and the half-life of $TPCS_{2a}$ in blood ranges from 15 to 21 days. There were no signs of $TPCS_{2a}$ in the urine of any of the patients at any of the visits.

Conclusions

$TPCS_{2a}$-based PCI of bleomycin was well tolerated under conditions of analgesia and anaesthesia.

No unexpected safety concerns were raised.

The MTD of $TPCS_{2a}$-based PCI of bleomycin is 1.0 mg/kg.

There are early signs of interesting efficacy of $TPCS_{2a}$-based PCI of bleomycin.

A multisite phase II study in recurrent HNSCC with single treatment of bleomycin, 0.25mg/kg $TPCS_{2a}$ and intratumoural light application has recently been initiated.

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