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Carbon Dot-Based Photodynamic Therapy for Clinical Treatment of Nonmelanoma Skin Cancer

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ABSTRACT

Introduction: Nonmelanoma skin cancer (NMSC), mainly including basal cell carcinoma (BCC) and squamous cell carcinoma (SCC), is the most often diagnosed malignancy worldwide, frequently necessitating substantial healthcare resources due to its elevated incidence and recurrence rates.

Objective: This study evaluated a combined procedure of curettage and carbon dots-photodynamic therapy (CDs-PDT) to treat skin cancer superficial BCC (S-BCC), nodular BCC (N-BCC), invasive microglandular BCC (IMG-BCC), solid surface extension BCC (SS-BCC), and in situ SCC (Bowen).

Methods: Twenty-two patients (15 male and 7 female) with 27 lesions were treated with this combined procedure. In all cases, curettage was performed first, followed by CDs-PDT. Previously, CDs had been used as cream or hydrogel vehicles for photodynamic treatment. PDT was administered in four or eight sessions, depending on each patient's response. The results indicate that PDT-based cream/CDs achieved complete responses in S-BCC, N-BCC, and SS-BCC and partial responses in the elimination of Bowen's lesions. PDT-based hydrogel-cream/CDs showed partial responses in S-BCC and SS-BCC.

Results: This research found, for the first time, that PDT-based cream/CDs have better results than hydrogel-cream/CDs for the treatment of nonmelanoma skin cancers BCC and Bowen disease. Rapid healing was noted following each PDT session-based CD, and no pain was reported during irradiation.

Conclusion: These results indicate that CD-based PDT could be used in the clinical setting for the treatment of non-melanoma skin cancer.

Introduction

Skin cancer, including melanoma and nonmelanoma skin cancers (NMSC), has become a prominent and escalating public health concern globally. The incidence of NMSC and melanoma has been steadily increasing due to factors such as an older population, more UV exposure, and increased awareness that improves early detection. Their combined dual impact is highlighted by this increasing load, which poses a complex challenge for healthcare systems worldwide [1]. NMSC arises from epidermal keratinocytes, has the highest mutational burden of all solid tumors, and is the most common epithelial malignancy. The most common treatment for this disease is excision surgery, Mohs surgery, cryotherapy, electrodesiccation and curettage, and photodynamic therapy [2, 3].

Photodynamic therapy (PDT) shows promise for cancer patients. It has several advantages, including the ability to elicit antitumor immune responses, low systemic toxicity, and limited invasiveness [4]. It has demonstrated promising outcomes with few adverse effects for specific cancer types [4]. PDT works by generating reactive oxygen species (ROS) and singlet oxygen ($^1O2$) by administering a photosensitizer (PS), a light source, and molecular oxygen ($3O2$). Singlet oxygen ($^1O2$) and other ROS are produced by these combination's regulated photochemical reactions (photodynamic processes).

For specific nonmelanoma skin cancers, the following photosensitizers have been used in clinical trials: Metvix® (methyl aminolevulinate, MAL) has been FDA-approved for the treatment of actinic keratosis (AK) and BCC worldwide; MAL-based PDT (MAL-PDT) for the treatment of AK, SCC, and BCC; 5-Aminolevulinic acid (5-ALA, Levulan®) has received FDA approval for the treatment of various diseases, including cutaneous superficial and nodular BCC, in situ SCC, and AK; Radachlorin® has been approved by the Ministry of Health of the Russian Federation (MHRF) for the treatment of skin cancer [5].

Carbon dots (CDs) are carbon-based materials that are quasi-0D and have diameters less than 10 nm. Due to their excellent tunable photoluminescence, high quantum yield, low toxicity, small size, notable biocompatibility, and plentiful, inexpensive sources, CDs have garnered significant attention [2]. Several publications have confirmed that CD conjugates in PDT have an anticancer impact in studies in vivo and in vitro when used to treat cancer [6 - 8].

Methods and Patients

Twenty-two patients (15 male and 7 female) with 27 lesions diagnosed as superficial BCC (S-BCC), nodular BCC (N-BCC), invasive microglandular BCC (MG-BCC), solid surface extension BCC (SS-BCC), or in situ SCC (Bowen). In all cases, the diagnosis was defined by biopsy. The lesions were located in different parts of the body, including the head, face, neck, chest, back, and arms. To carry out the treatment with informed consent, the skin lesions were first cleansed with saline solution and subjected to curettage under local anesthesia (lidocaine 2%). CDs were applied in a thin layer using two vehicles: base cream and hydrogel, both at a concentration of 114 mg/ml. After applying the CDs to the skin lesions, they were occluded for three hours. Then, the treated areas were cleaned and irradiated with a 650 nm light source at 100 mW/cm² for 20 minutes, followed by a 450 nm light source at 100 mW/cm² for 30 minutes.

This PDT session was held once per week for four weeks. The control was performed two months post-PDT by biopsy. In patients where clinical or histopathological signs of skin cancer were detected, an additional four sessions of PDT were administered. These additional PDT sessions were performed using CDs in the cream vehicle.

Results

Table 1 shows the results obtained in this study for skin cancers: S-BCC, N-BCC, IMG-BCC, SS-BCC, and Bowen. All patients, after curettage, received four sessions of PDT-CDs, either with cream or hydrogel as the CD vehicle. Following the initial treatment, if cancer cells remained evident, four additional sessions of PDT with cream/CDs were applied.

For S-BCC, complete response (100% response) was observed for the application of PDT-based cream/CDs (10 lesions) and PDT-based hydrogel/CDs (one lesion) and partial response (75% response) in PDT-based hydrogel-cream/CDs (three lesions). For N-BCC, complete response (100% response) was observed with the application of PDT-based cream/CDs (one lesion). For IMG-BCC, no response was observed with PDT-based hydrogel/CDs (one lesion). For SS-BCC, complete response was observed for the application of PDT-based cream/CDs (one lesion) and partial response (50% response) for PDT-based hydrogel-cream/CDs (one lesion).

In the case of Bowen lesions, partial response (80% response) was observed with the application of PDT-based cream/CDs (four lesions) and PDT-based hydrogel/CDs (one lesion), and 100% response was observed with the application of PDT-based cream/CDs (one lesion). During PDT treatment, no pain was observed during irradiation, and rapid healing was observed after each PDT session-based CD.

Figure 1 A–D show the changes in the skin appearance before and after the procedure. The lesion improved two months after PDT treatment.

The results obtained showed, for the first time, that PDT-based cream/CDs have better efficacy than hydrogel-cream/

Table 1. Overall results of treatment of S-BCC, N-BCC, IMG-BCC, SS-BCC, and Bowen lesions based on hydrogel/CDs, base cream/CDs and hydrogel-cream/CDs by PDT.

	Superficial BCC (S- BCC)		Nodular BCC (N-BCC)		Invasive Microglandular BCC (IMG-BCC)		Solid surface extension BCC (SS-BCC)		In situ SCC (Bowen)	
PDT Response Yes/No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No
Hydrogel (CDs (4 PDT)	1 (100%)	0	0	0	0	0	0	0	1 (100%)	0
Base cream/CDs (4 PDT)	10 (100%)	0	1 (100%)	0	0	0	1 (100%)	0	4 (80%)	1 (20%)
Hydrogel-cream/ CDs (8 PDT)	3 (75%)	1 (25%)	0	0	0	1 (100%)	1 (50%)	1 (50%)	0	1
Total Patients	**14**	**1**	**1**	**0**	**0**	**1**	**2**	**1**	**5**	**2**

*In all cases, curettage was carried out first.

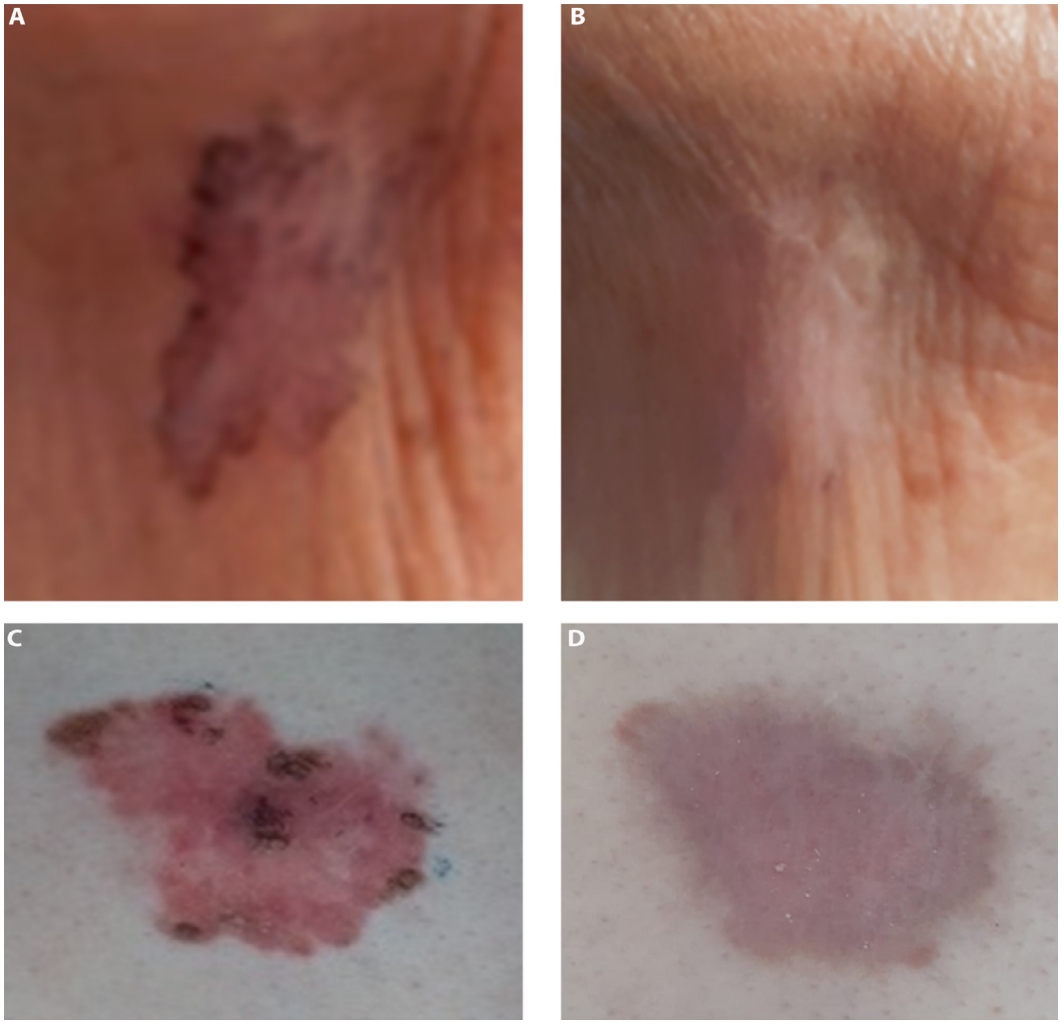

Figure 1. Neck Bowen lesion: A) Initial state (2.5 cm x 4.2 cm); B) Skin appearance after four sessions PDT-based hydrogel-cream/CDs. Superficial lower back BCC lesion: C) Initial state (3.8 cm x 3.0 cm), D) Skin appearance after four sessions PDT-based cream/CDs.

CDs and cream/CDs for the treatment of nonmelanoma skin cancers, BCC, and Bowen disease. Rapid recovery was observed following each PDT session-based CD, with no pain during irradiation.

Discussions

During PDT sessions with both vehicles (cream and hydrogel), no discomfort was observed when irradiated with blue or red light, compared with the photosensitizer Aminolevulinic Acid, ALA, where high levels of pain have been reported during red-light irradiation. In addition, PDT with the ALA also causes burning, stinging, or other sensations during the light exposure phase of the treatment [9]. This allows us to conclude that the CDs used in both vehicles show promising results as photosensitizers for PDT.

The irradiation time (20 minutes with blue LEDs and 20 minutes with red LEDs) is due to the fact that the absorption spectrum of CDs depends on the excitation wavelength, with the greatest light absorption at 405 nm and the lowest at 630 nm [10]. Red light has a penetration depth of up to 5 mm, enabling deep penetration into tumor cells. Meanwhile, blue light has a skin penetration depth of 1 millimeter, allowing complementary treatment at the surface. Blue light is commonly used in antimicrobial PDT treatment of superficial infections [11].

As ex vivo, in vitro, and skin permeation indicated that carbon dots permeate into and through the dermis within hours, suggesting their potential for topical administration, the incubation time of carbon dot in the lesions was three hours [12, 13]. The protocol used in this study included curettage prior to the application of CDs, allowing for better penetration of the CDs into the cancerous tissues. Curettage in PDT has shown better results than PDT alone. The prior curettage provided significant reduction in volume and/or pigmentation of lesions.

Conclusions

This study demonstrates that carbon dot-based photodynamic therapy (CDs-PDT), combined with prior curettage, is a promising, safe, and minimally invasive therapeutic strategy for nonmelanoma skin cancer. The results highlight superior clinical efficacy of cream-based CD formulations compared to hydrogel systems, achieving complete responses in several BCC subtypes and favorable outcomes in Bowen disease. Additionally, the absence of pain during irradiation and the rapid healing observed after treatment underscore its strong potential for improving patient compliance and quality of life. Overall, CDs-PDT represents an innovative and clinically translatable approach that could complement or, in selected cases, serve as an alternative to conventional treatments for NMSC.

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