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Review Article

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Topical Therapy For Superficial Basal Cell Carcinoma.

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Abstract

Superficial BCC (sBCC) classically presents as a pink, crusted patch. Histologically, tumor cells are located in the basal layer of the epidermis and form bud-like proliferations with clefting. The gold standard treatment for sBCC is surgery whether it is Mohs micrographic surgery or surgical excision. However, destructive methods and radiation have been used for decades with acceptable cure rates. More recently, topical therapies have been offered for sBCC. Topical therapy is a viable alternative for treatment, as the tumor doesn't extending beyond the papillary dermis. The most common and effective topical therapies offered are imiquimod and 5-flourarocil although ingenol mebutate is also reported in small studies. We discuss topical options for treatment of sBCC and their efficacy.

Keywords: superficial basal cell carcinoma, topical therapy, imiquimod, fluorouracil, ingenol mebutate

Introduction

Basal cell carcinoma (BCC) is the most common type of skin cancer with over 5 million cases diagnosed in the United States yearly [1]. Although there are many histological variations of BCC; the prominent subtypes are nodular, superficial, and infiltrative. Compared to other types of BCC, sBCC presents in a younger patient population [2-4]. Superficial BCC is also most likely to occur on the trunk and extremities while other subtypes of BCC have a higher prevalence on the head and neck [2-4]. Surgery, curettage, and cryosurgery initially were the mainstays of treatments of sBCC. More recently, topical treatments and other non-invasive therapies are being offered.

This article reviews the current topical treatment options and efficiencies available for sBCC. Studies that did not differentiate superficial from other types of basal cell carcinoma were excluded. Studies with over 9 sBCC lesions treated were included unless specified (**Table 1**).

Table 1: Topical Therapies

Study	Design	Treatment	Number of lesions	Regimen	Efficacy	Cure Determined
Geisse et al (2004)	Randomized, controlled, double blind	Imiquimod 5%	185	5x per wk x 6 wks	75%	Histological, 3 mo
			179	7x per wk x 6 wks	73%	
Schiessel et at (2007)	Prospective	Imiquimod 5%	15	5x per wk x 6 wks	87%	Clinical, 14 mo
Gollnick et al (2005, 2008)	Prospective	Imiquimod 5%		5x per wk x 6 wks	89%	Clinical, immediately s/p therapy
					79.4%	2 y
					77.9%	5 y
Dauden et al (2011)	Prospective	Imiquimod 5%	471	5x per wk x 6 wks	83.2%	Clinical, 3 mo
Artis et al (2013) & Roozeboom et al (2016)	Randomized, controlled	Imiquimod 5%	198	5x per wk x 6 wks	83.4%	Clinical, 1 y
					79.7%	Clinical, 3 y

Gross et al (2007)+	Prospective	5-flourouracil 5%	31	BID for up to 12 wks (mean 10.5)		90%		Histological, 3 wks
Artis et al (2013) & Roozeboom et al (2016)	Randomized, controlled	5-fluorouracil 5%	201	BID x 4 wks		80.1%		Clinical, 1 y
						68.2%		Clinical, 3 y
Siller et al (2010)+	Randomized, vehicle-	Ingenol mebutate (%)						Histological
		Day1+2 Day1+8		Day1+2	Day1+8	Day1+2	Day1+8	
		Vehicle	Vehicle	6	6	0	17%	
		0.0025	0.0025	8	8	0	13%	
		0.01	0.01	8	8	25%	0	
		0.05	0.05	8	8	63%	38%	
Izzi et al (2016)+	Prospective	Ingenol mebutate 0.05%	20 patients	Day 1+2		100%		Clinical, 6 mo
Bettencourt (2016)+	Retrospective	Ingenol mebutate 0.05%	9	Daily until 2 tubes used (2-7 days)		100%		Clinical or histological, 2-14 mo
Brinkhuizen et al (2016)	Randomized, controlled			BID x 8 wks (all)				Histological
		Diclofenac 3%	16			64.3%		
		Diclofenac 3% + Calcitriol	16			43.8%		
		Control	16			0		
		Control	16			0		
Bianchi et al (2004)	Prospective	Tazarotene 0.1%	20	Daily x 24 wks		65%		Clinical, 3 yr
Peris et al (2005)	Prospective	Tazarotene 0.1%	41	Daily, up to 20 wks		58.5%		Clinical, Immediately s/p treatment

Imiquimod

Imiquimod 5% cream topically 5 times a week for 6 weeks was approved for the treatment of superficial BCC on the trunk in 2004 in the United States. Imiquimod binds toll-like receptor 7 and 8 which then activates the innate immune system via IFN-alpha [5]. This treatment increases the number of CD4+ T lymphocytes in the vicinity of the tumor, reduces the expression of Bcl-2, and increases apoptosis of tumor cells [6,7]. Imiquimod is pregnancy category C.

Initial studies investigated a variety of treatment dosing schedules, ranging from 3 times a week to twice daily dosing, and evaluated duration of treatment from 2-12 weeks. It was noted that 5 times a week dosing had similar efficacy to 7 times a week dosing with 75% and 73% cure at 3 months respectively [8]. Reported cure rates with 5 times weekly imiquimod treatment ranged from 75% - 89% [8-12]. One long-term study found the overall treatment success to be 77% at 5years [10]. A meta-analysis identified 87.3% tumor-free survival at 12 months with imiquimod treatment [13]. Although not approved for lesions on the head, the majority of the studies included lesions on the face although some excluded the mid-face. Imiquimod was found to be superior to methyl aminolevulinate photodynamic therapy at three years in a randomized control study with a tumor free survival of 79.7% for imiquimod and 58% for methyl aminolevulinate photodynamic therapy [14,15].

Patients applying imiquimod experience local skin reactions (LSR) during the treatment period. These reactions include itching, erythema, swelling, burning, erosion, and pain [16]. One study found that LSR peaked at the third week of treatment [8]. Less common side-effects include infection, influenza-like symptoms such as myalgia, fatigue, fever [11]. Rarely, eruptive epidermal cysts and vitiligo-like depigmentation can occur [17,18].

5-Fluorouracil

Five percent fluorouracil (5-FU) is approved by the US Food and Drug Administration (FDA) for treatment of sBCC when conventional methods are not indicated or practical. The recommended application is twice daily for 3-6 weeks but therapy may need to be continued for up to 12 weeks [19]. 5-FU inhibits thymidine synthesis by binding to the enzyme thymidylate synthase which blocks DNA synthesis and to a lesser extent RNA synthesis [20]. This effect is most pronounced on rapidly dividing cells such as occurring in neoplasms. 5-FU is pregnancy category X.

A prospective study found that 5-FU twice daily provided a 90% cure with a mean treatment time of 10 weeks [19].All treated lesions were surgically excised to determine cure 3 weeks after treatment [19]. A randomized, single-blind trial evaluating imiquimod, 5-FU, and PDT found an 80% cure rate with twice daily application for 4 weeks with follow-up of 1 year [14]. 5-FU treatment results were non-inferior to imiquimod in this study.

The most common side effects are LSR such as burning, crusting, erosions, erythema, and photosensitivity [19]. Less common reactions include allergic contact dermatitis and ectropion [21,22]. Rarely, individuals with dihydropyrimidine dehydrogenase deficiency can experience severe toxicity [23].

Ingenol mebutate

Ingenol mebutate is derived from Euphorbia peplus (also known as milkweed) [24]. The mechanism of action of ingenol mebutate is thought to be two-fold: necrosis and activation of the immune system with a predominant neutrophil response [24, 25]. Ingenol-induced necrosis is a relatively immediate process occurring 1-2 hours after application with plasma membrane disruption. Due to brisk cell necrosis, the duration of treatment of ingenol mebutate is brief compared to other topical therapies. Ingenol mebutate is pregnancy category C.

Recent studies have evaluated the efficacy of ingenol mebutate for sBCC. In published studies, the cure rate ranges from 63%-100% when treated once daily on 2 consecutive days [25-27]. Depending on the study, the cure was determined by histologically or patients followed clinically. The consecutive day dosing was more effective than treating once on day 1 and day 8 [25]. The higher concentration, 0.05%, was more effective than 0.1% or 0.025% [25]. It should be noted the studies published to date have involved at most 20 patients in a treatment arm.

Local skin reactions are the most common side effects and can include erythema, scaling, crusting, and erosion/ulceration. Severe LSR such as ulceration and vesiculation have also been reported [25]. Other less common side-effects include allergic contact dermatitis, scarring, and conjunctivitis when applied near the eyes [28, 29].

Diclofenac

Diclofenac is a nonsteroidal anti-inflammatory drug that works as a cyclooxygenase inhibitor (COX), which preferentially inhibits COX-2 over COX-1 [30]. It has been approved by the FDA for the treatment of actinic keratosis [31]. COX-2 is increased with UV exposure, and overexpressed in epithelial tumors including BCC. COX-2 is thought to be involved in tumor genesis, promotes inflammation, and inhibition of apoptosis [30, 32]. This upregulation of COX-2 in epithelial tumors is the justification for using diclofenac which has anti-inflammatory and anti-angiogenic properties [33]. There is also evidence that diclofenac induces apoptosis [34]. Diclofenac is pregnancy category B.

Limited data is available on the efficacy of diclofenac 3% regarding the treatment of sBCC. One study found the cure rate for treatment of sBCC with diclofenac twice daily for 8 weeks was 64.3% while diclofenac plus calcitriol twice daily for 8 weeks had a 43.8% cure rate [35].

The most common side effects are mild LSR such as pruritus, erythema, and xerosis. Contact dermatitis and photosensitivity have also been reported [36, 37]. There is a risk of cardiovascular risk with oral COX-2 inhibitors, however, topical diclofenac 2% only has approximately 7% of the systemic exposure of the oral medication [38].

Tazarotene

Tazarotene is a third generation retinoid that acts on retinoic acid receptors (RAR) β and γ [39]. The medication is thought to work by increasing apoptosis due to increase of BAX and decreasing proliferation [39,40]. Both of these functions have been linked to activation of RAR-β [39]. Tazarotene is pregnancy category X.

Tazarotene has been previously evaluated for the treatment of sBCC although cure rates are not as desirable as other topical options. One study with 108 sBCC identified a 65% cure rate after treatment with 0.1% gel daily for 24 weeks [40]. Other smaller studies, found a 50% and 58% cure rate respectively after daily treatment with 0.1% gel for 4 -24 weeks [39,41]. Peris et al. noted an 8% recurrence after 6 months [41].

Local skin reactions are the primary side effect and include erythema, burning, itching, and erosion [40,41].

Conclusion

Surgical removal, destruction via curettage, and superficial x-ray are the most established methods of treatment for sBCC with the highest reported cure rates. More recently imiquimod and 5-fluorouacil are FDA-approved options for treatment of a certain subset of sBCC. Long-term follow up data and head-to-head comparisons are lacking in many studies. Although no flawless treatment for sBCC exists at this time with minimal pain, scarring, and very high cure rates, there are a number of reasonable options to provide patients including topical therapy.

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