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LITERARY PERSPECTIVES ABOUT TOPICAL IMMUNOMODULATOR TREATMENT IN SKIN CANCER

Aline Marques Macedo Santos

Filiação Estácio/FMJ

<https://orcid.org/0000-0001-7693-9311>

Elvira Marques da Luz Dias

Universidade Brasil – São Paulo-SP

<https://orcid.org/0000-0001-7966-0877>

José Evandro Santos de Sousa

Estácio/FMJ - Juazeiro do Norte- CE

<http://lattes.cnpq.br/9384173784185323>

Rosa Maria Grangeiro Martins

Estácio/FMJ - Juazeiro do Norte- CE

<https://orcid.org/0000-0002-2516-0719>

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ABSTRACT: Cancer is a serious public health problem in Brazil and worldwide. In this context, skin cancer stands out, classified as non-melanoma or melanoma. Currently, there are several treatment options, to be implemented according to the characteristics of the neoplasm and the general condition of the patient. Among these, topical therapy with immunomodulator has been highlighted as a new form of conservative clinical treatment, and some scientific studies have evaluated, albeit in few publications, the impact of this therapy. The present work aims to carry out a critical narrative of the literature in search of scientific studies that demonstrate the effectiveness of the topical use of imiquimod 5% in the treatment of skin cancer. For this, articles published in the period from 2002 to 2018 were selected, of which the most relevant for this study were used. It was concluded that surgical excision remains the first-line treatment for skin cancer. However, imiquimod may be useful when surgery is contraindicated, for patients who may be able to follow this therapy and tolerate possible adverse skin reactions.

Keywords: Skin cancer. Skin neoplasm. Immunomodulator. Imiquimod.

INTRODUCTION

Cancer is a serious public health problem in Brazil and worldwide. It is estimated that in 2012 there were 14.1 million new cases of cancer and 8.2 million deaths worldwide. Furthermore, the global demographic and epidemiological transition signals an increasing impact of the cancer burden in the coming decades (FERLAY et al., 2013).

In this context, considering that non-melanoma skin cancer is curable in most cases, and that even melanoma can have a good prognosis when diagnosed and treated in its early stages, it is believed that prevention strategies, early diagnosis, effective treatment

and safe follow-up, must be subsidized in order to mitigate the physical, emotional and social repercussions that affect these patients so negatively.

This study aimed to perform a critical analysis of the literature in search of scientific studies that demonstrate the effectiveness of topical use of Imiquimod 5% in the treatment of skin cancer; to know the mechanism of action of the immunomodulator in cancer treatment; to report the contribution of Imiquimod in neotherapy for skin cancer and to demonstrate the scarcity of studies on conservative therapies in the treatment of cutaneous neoplasms.

METHODOLOGY

The present study is a bibliographic narrative about what has already been produced in relation to the treatment of cutaneous neoplasms with topical immunomodulatory therapy.

LITERATURE REVIEW

WHAT IS CANCER?

The word cancer comes from the Greek *karkinos*, meaning crab and was first used by Hippocrates, the father of Medicine. It is configured as a set of diseases that share the disordered growth of cells, and can invade tissues and organs.

Cancer is a pathology of multifactorial etiology resulting from genetic alterations, environmental factors and lifestyle, being an important public health problem in both developed and developing countries (BORATO, 2013).

TYPES OF SKIN CANCER

Worldwide, skin cancer is the most common. It can be classified as melanoma and non-melanoma, the latter has two histological subtypes: basal cell carcinoma and squamous cell carcinoma (INCA, 2016).

DIAGNOSIS

The diagnosis of skin cancer is based on the clinical history and detailed physical examination, and the tissue of the altered areas is biopsied and sent for confirmation of the diagnosis through histopathological examination.

TREATMENT

The Brazilian Society of Dermatology (SBD) emphasizes that all cases of skin cancer must be diagnosed and treated early, including those with low lethality, which can cause mutilating or disfiguring lesions in exposed areas of the body, causing suffering to patients.

Treatments for skin cancer are different. The following are described in the literature: surgical excision, curettage, electrocoagulation, cryosurgery with liquid nitrogen, 5% imiquimod cream, topical 5-fluoracil, radiotherapy, chemotherapy, photodynamic therapy, etc.

In these situations, topical medications represent an alternative in the treatment of cutaneous neoplasms. Among them, immunomodulators stand out, especially imiquimod.

IMMUNOMODULATORS

Modern immune therapy involves the use of immunomodulators. These are drugs that can exacerbate or reduce the immune response, for topical and/or systemic use, for the treatment of diseases caused by hypersensitivity or immunodeficiencies. They are divided into two basic groups: immunostimulators, which lead to an increase in innate and adaptive immunity, and immunosuppressants, which decrease the activity of the immune system (LIMA, 2004).

In the context of oncology, the use of immunomodulation is limited to some

specific types of cancer. Only three diseases have approved treatments, they are: non-small cell lung cancer, skin cancer and kidney cancer (clear cell).

This group of drugs includes the imidazoquinolines, the group to which imiquimod belongs, which are agonists of Toll-like receptors (TLR) 7 and 8, these drugs are being widely used in dermatology and other areas as modifiers of the immune response (LIMA, 2007).

The Ministry of Health (MS) through Technical Note N° 134/2012 (updated in 2015) defines the active ingredient: Imiquimod. Trade names: Aldara®, Ixium®, Modik®, Imoxy®, Imiquimode®. Reference drug: Ixium® (BRASIL, 2015). Therapy with 5% imiquimod has been used successfully in Brazil for the treatment of several dermatological conditions, including basal cell carcinoma, Bowen's disease, molluscum contagiosum and viral warts (FESTA NETO, 2002).

Unlike most immunomodulators that have the function of inhibiting the immune response, imiquimod promotes its activation. It acts by modifying the biological response by inducing cytokines, causing the immune system to recognize tumor cells as antigens, eradicating them (MELO, 2015).

In addition, imiquimod enhances the production of interferon, which has an antiviral, antiproliferative and antiangiogenic effect. It also stimulates Langerhans cells, the main antigen-presenting cells of the epidermis, to migrate to the lymph nodes and activate the production of T cells (SHUMACK, 2002).

The literature shows the cure rate of superficial BCC with the use of imiquimod ranging from 78.4% to 90%, and the rapid response with treatment is a predictor of long-term efficacy (OZOLINS, 2010).

It must be noted that the success of

imiquimod therapy depends in part on the willingness and ability of the patient or caregiver to follow the treatment regimen for the required period. This includes proper application of the cream to the area to be treated. Lesions that are outside the field of vision, for example, on the back, may present a difficulty in application if the patient is not assisted during treatment. Patients may be more likely to prematurely discontinue therapy if they are unwilling to tolerate uncomfortable skin reactions.

DISCUSSION

This topic presents the main results of studies concerning the topical treatment of skin cancer with an immunomodulator. A total of 18 articles were found using the descriptors in the aforementioned databases, of which seven met the inclusion criteria and were selected for analysis.

Table 1 shows the studies carried out from 2002 to 2018 and published in national journals.

FINAL CONSIDERATIONS

It was intended with this literary narrative to update relevant knowledge, based on scientific evidence, about treatment with topical immunomodulator in skin cancer.

In view of the above, it is concluded that surgical excision remains the first-line treatment for skin cancer, with a higher cure rate than other therapeutic modalities.

However, imiquimod may be useful when surgery is contraindicated, for patients who may be able to follow this therapy and tolerate possible adverse skin reactions.

In clinical practice, in addition to being based on oncological and dermatological procedures, one must take into account the patient's acceptance of the proposed treatment, type of recovery, financial costs, location of the scar, histological type of lesion and life expectancy (WULKAN, 2015).

Thus, it is believed that less invasive approaches have had good results with dermatological procedures, which reflects the importance of integrating skin cancer control action.

	TITLE	TYPE OF RESEARCH	METHODOLOGY	RESULTS	CONCLUSION
1	Analyze hindsight of conduct for carcinoma basal cell and spinocellular in head and neck (WULKAN, 2015)	Study retrospective	were analyzed 69 patients (51 women and 18 men) with average age of 59.4 years and that presented CBC or CEC treated by surgery with freezing of injury in intraoperative, cryotherapy or Imiquimod 5% per six weeks with 36 months of follow-up.	The kind of reconstruction more frequent was the closure primary (71%). THE tumor recurrence in cases operated was from 4%. Cryotherapy and use of Imiquimod 5% caused six cases of reactions light places with more recurrence descriptive in treatment of superficial CBC (28%).	CBC don't superficial and carcinoma spinocellular must be treaties surgically. The CBC superficial can be treated with cryotherapy and use of Imiquimod 5% with less complications and best result aesthetic.
2	Extensive carcinoma basal cell responsive to Imiquimod: follow-up of 36 months (MELO, 2015)	report of case report of	sex patient female, white, 69 years old, presenting plaque injury erythematous scaly crusty (12x10cm) there are more of 20 years. Diagnosed with superficial CBC multicentric in lumbar region, but refused treatment surgical. held five applications weekly of Imiquimod 5% for eight weeks.	clinical cure and histological without relapses until publication date of the study (36 months later), with great result aesthetic and few adverse effects. the patient comes being accompanied quarterly no relapses, completing three years without injury.	The results clinicians and histological were excellent, with total regression of the injury.
3	immunotherapy topical in treatment of carcinoma basal cell periocular (MACEDO, 2009) topical in	Report of case	Patient of sex male, 57 years old, presenting nodule lesion-ulcerative (10 mm) in medial corner of left eye there seven years, accompanied by episodes of bleeding. Biopsy: BCC nodular. used imiquimod cream 5% five times a week by 16 weeks.	THE use topic do anatomy-pathological revealed absence of neoplasm in tissue examined. There are no signs of relapse after twelve months of follow-up. Side effect observed: conjunctivitis mild reaction.	THE use topic do imiquimod 5% in cream for the treatment of carcinomas basal cell have shown themselves effective. This immunomodulator overlaps in in relation to others therapies conservative like interferon and the interleukins intralesional.

4	lentigo malignant in face: one challenge in conduct (GOMES, 2017)	Report of case	sex patient female, 70 years, presented there five years stain brownish in lower eyelid of right eye. Biopsy incisional and examination immunohistochemistry: malignant lentigo. opted for surgery with wide margin. used imiquimod like therapy adjuvant after surgical excision.	dermoscopy it was observed regression of pigmentation and clinical cure in area no excised.	highlights Good results cosmetics and the low morbidity, however they are associated with a higher rate of recurrence. need for realization of studies comparatives that guide the best conduct in these cases, Looking to effectiveness of treatment and the result aesthetic/functional satisfactory.
5	lentigo malignant treated with imiquimod topic: the value gives dermoscopy at the monitoring clinical (COAST, 2011)	Report of case	Reaction female, 82 years old, white, multiple comorbidities. had injury in the malar region right started two years ago. Biopsy: lentigo malignant. It was chosen by the use of imiquimod 5% cream with daily application.	Reaction inflammatory intense and progressive, from so that the treatment was interrupted at 31st day. after two months, the clinical aspects and dermoscopic pointed to the resolution of lesion. Follows in follow-up regular clinic,	Reaction inflammatory alternatives, like the imiquimod, are valid for patients with refusal to procedure surgical and comorbidities important. there is no consensus about the criteria of cure. like the Continuation...

6	remission of malignant lentigo extensive after treatment with imiquimod (PIAZZA, 2009) remission of malignant lentigo	Report of case	Patient of 87 years, sex female, white, multiple comorbidities. presented large area of hyperpigmentation on the left side of the face with two years of evolution. Biopsy: melanoma evil of intra-epithelial. excised if the injury and proceeded to a local grafting. THE component of upper eyelid has not been removed, because the patient does not accepted the realization of procedure. after a few months, she returns presenting LM on the eyelid upper, injuries applicants in graft and clinically, a compatible injury with CBC in the corner inner eye. she performed treatment with imiquimod 5%, prescribed five Times a week, for 12 weeks.	complete clinical and histological remission of LM and BCC. The patient was followed up for three years and there were no signs of recurrence. The patient died of acute myeloid leukemia at 91 years of age.	the imiquimod seems to be a good indication for treatment of LM, mainly, in patients aged advanced or clinical status committed. It works by preventing the progression for Lentigo Malignant melanoma and is an option in treatment of metastases skin of melanoma.
7	Treatment topic of carcinoma basal cell superficial and nodular hair imiquimod 5% cream: observation of 10 cases (PARTY NETO, 2002)	Study retrospective	Were selected 10 sick (7 women and 3 men), white, CBC carriers who refused, as first option, the treatment surgical of your tumors. At applications with Imiquimod were daily, and the mean number of treatment days was 23.	all the sick responded to medication with disappearance of injuries and are followed every two or three months, until moment of publication without relapse of the frame (13 to 15 months after).	the imiquimod topic in treatment of CBC not yet must be used as a routine before being rated by studies multicentric and protocols well structured, mainly in the follow-up of these patients for a longer time. The drug can, in particular situations, replace a surgical treatment in a conservative manner and with aesthetic results. favorable.

Table 1 - Studies carried out from 2002 to 2018 and published in national journals.

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