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Methotrexate in the Treatment of Non-Melanoma Skin Cancers

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ABSTRACT

Background: There are three types of non-melanoma skin cancer (NMSC): basal (BCC), keratoacanthoma (KA), and cutaneous squamous cell carcinoma (cSCC). These three malignancies account for 99 percent of all tumors in this category. Because it slows DNA synthesis in quickly proliferating cells, methotrexate (MTX) is an effective treatment for tumors that are fast developing. To prevent the production of the purine nucleotide thymidine, it inhibits the development of tetrahydrofolate by binding to the dihydrofolate reductase.

Objective: To assess the efficacy and safety of MTX in the treatment of NMSCs.

Conclusion: When used as a less intrusive and less expensive treatment for NMSCs, MTX has the potential to be a very effective and safe alternative treatment, especially in patients who are elderly or have other medical conditions.

Keywords: Non-melanoma skin cancers (NMSCs), Methotrexate (MTX).

INTRODUCTION

By far the most common malignancies are those that do not spread to the lymph nodes or bones. NMSCs with basal cell carcinoma (BCC) and squamous cell carcinoma (SCC) as their primary tumours account for 70% and 25% of all NMSCs, respectively. Skin cancer, on the other hand, can develop from any of the cells in the skin, and both basal cell carcinoma and squamous cell carcinoma have excellent prognosis when detected in their early stages, despite the fact that their behaviour, development, and metastatic capabilities differ from each other [(1)].

Epidemiology:

BCC had a negligible impact on the mortality rate of NMSCs. According to the American Cancer Society, 1 in 14,000,000 people will develop metastatic BCC, and 2 in 14,000,000 people will die from locally advanced BCC. It's safe to assume, then, that the mortality rate will be 0.02 per 10,000.

In contrast, SCC has a variable metastatic rate of 0.1–9.9 percent and is responsible for roughly 75 percent of all NMSC-related fatalities [(1, 2)].

Clinical presentation:

In terms of aggression, BCC is the least aggressive NMSCs because it contains cells that are similar in appearance to epidermal basal cells. Despite the ability to locally infiltrate, tissue damage, recurrence, and a limited capability for metastasis, the cancer has spread throughout the body. BCC displays a modest level of malignancy. Age, sex, hereditary history like Fitzpatrick skin types I and II, Gorlin–Goltz syndrome, and immune status are all individual risk factors for BCC [(1)].

Squamous cell carcinoma is an abnormal proliferation of invasive squamous cells and can progress. SCC also has a high risk of recurrence, which is determined by the size of the tumor, the degree of histological differentiation, the depth of the lesion, the presence of perineural invasion, and the patient's immune system [(3)].

Pathogenesis of NMSCs:

Different factors, including UV radiation, human papillomavirus (HPV), arsenic compounds, X-rays and other chemical products all play an important role in the development of NMSCs and actinic keratosis (AKs) (figure 1) [(2)]

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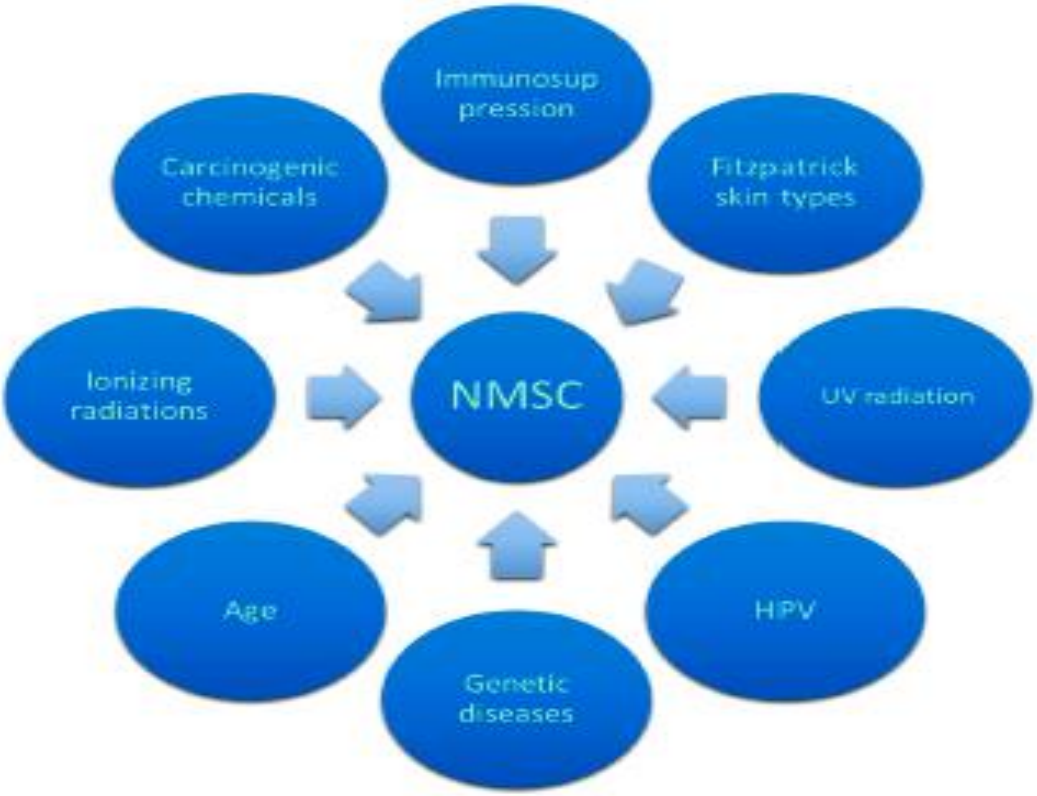

Figure (1): The pathogenesis of non-melanoma skin cancers (NMSCs) is complicated by a number of factors. UV stands for ultraviolet; HPV is for Human Papilloma Virus [(2)].

Methotrexate in the treatment of non-melanoma skin cancers

Non-melanoma skin cancers are becoming more common among Caucasian people over the world. NMSC lesions can be recognized by dermatologists, rheumatologists, gastroenterologists, and primary care physicians, with dermatologists treating the majority of them [(3)].

Second primary NMSCs are common despite first surgical treatment being curative. Skin pigmentation and sun exposure are major risk factors for NMSCs. NMSCs are more common when medications that speed up the phototoxic process are used [(4)].

Methotrexate and thiopurines are two examples of drugs referred to as "photosensitizers." Biologic therapy does not have this side effect. This led to frequent monitoring of people after solid organ transplantation after immunosuppression, which is also thought to increase the incidence of NMSCs in particular squamous cell carcinoma [(5)]. Methotrexate use was observed to be associated with an increased risk of second NMSCs by in individuals with RA or IBD who used the drug [(4)].

Squamous cell carcinoma is a serious health issue because of the rise in its incidence and the possibility of it spreading. Surgery is an option for those who have SCC that has spread to other parts of their bodies. Surgery may occasionally result in unacceptable morpho-functional consequences due to SCC's common location in the facial region. These patients may be treated with radiation or systemic or intra-arterial chemotherapy as a last resort. Therefore, the use of intralesional medicines as 5-FU or interferon α -2b have been described [(3)].

Patients with infiltrating SCC may benefit from intralesional methotrexate (MTX-il) neoadjuvant surgery because it reduces tumour size, reduces surgery-related morbidity, and produces improved functional and cosmetic outcomes [(4)]. Pre-surgical MTX-il infiltration to reduce the size of the SCC was investigated by **Salido-Vallejo *et al.*** [(4)] in clinical practice and the results showed that neoadjuvant MTX-il reduced the pre-surgical size of SCC lesions and coupled their subsequent surgery.

Keratoacanthoma (KA) is a fast-developing cutaneous tumor derived from the hair follicle. On the clinical and histological level, KA is quite similar to SCC, which occurs frequently in elderly persons who live in sun-exposed areas [(5)]. Although, it is possible that KA will take a long time to involute naturally, it is also possible that it could continue to expand throughout that time, culminating in the impingement of critical structures. Furthermore, SCC that has been misdiagnosed as a KA has the potential for metastasis. As a result, early intervention can expedite the healing process, prevent functional loss, and improve overall cosmesis [(6)].

Radiation therapy, a systemic oral retinoid, and intralesional infusion of 5-Fluorouracil (5-FU),

methotrexate, or interferon α -2a have all been described as effective treatments for ovarian carcinoma. A surgical excision, on the other hand, continues to be the treatment of choice for the vast majority of KA cases. When a large or strategically located lesion is removed surgically, it may result in functional and cosmetic problems for the individual [6].

The face and the scalp were the most commonly affected areas in one study, with 74 percent (twenty eight from total thirty eight) of KA lesions being found there. Patients over the age of 65 or those suffering from concurrent conditions are not viable candidates for surgical intervention. It's for this reason why non-surgical treatments are preferred when possible. For example, intralesional MTX can be used to treat acne without the need for surgery, which is an example of a non-surgical therapeutic strategy. The use of an intralesional MTX for the treatment of KA has been described by **Della Valle and Milani** [7].

MTX is an effective treatment for tumors that are quickly growing due to its ability to stop DNA synthesis in dividing cells. To stop the creation of tetrahydrofolate and prevent the synthesis of thymidine, MTX, a folic acid derivative, binds to dihydrofolate reductase [8]. Slow-growing lesions may not respond well to intralesional chemotherapy; for example, a KA treated with an intralesional 5-FU after only 16 weeks exhibited no response. There are alternative treatment options available when intralesional chemotherapy fails to eradicate the non-proliferating KA [6].

By delivering powerful chemotherapy drugs like MTX locally, intralesional injections can avoid systemic toxicity [8]. MTX-treated patients with renal insufficiency developed pancytopenia, according to **Yoo and Kim** [6]. As a result, patients receiving intralesional MTX should have a baseline test and a follow-up test.

Patients with KA can benefit from intralesional MTX injection, according to the research. It is recommended that intralesional MTX injections be utilized first, followed by initial debulking of the KA, especially in individuals over the age of 65 who have many comorbidities as well as in cosmetically sensitive locations [6].

KA is a quickly growing tumor that might induce local tissue destruction, according to **Yoo and Kim** [6], who studied examples of Korean KA patients treated with intralesional MTX. As a result, early therapeutic intervention is needed. Surgery is the preferred treatment, although non-excisional treatment is preferred if surgery would result in poor cosmesis and a loss of function. They discovered a nearly 91% full response rate in Korean patients treated with intralesional MTX for KA. This straightforward treatment is effective while also posing no significant systemic risks.

Malignancy in humans is most commonly caused by NMSC, which includes non-melanoma skin cancer (NMSC) [9]. NMSCs are mostly keratinocyte tumors (KT). Basal cell carcinoma (BCC) accounts for roughly 80 percent of all occurrences of KT, whilst squamous cell carcinoma is responsible for 20 percent of all cases [10, 11].

As an anti-tumor drug, methotrexate is widely employed in the field of oncology. It works by competitively inhibiting the folic acid reductase enzyme, which is required to supply methyl donor groups for the synthesis of DNA, RNA, and proteins. Thus, by limiting pyrimidine metabolism, dihydrofolic acid can be converted to tetrahydrofolic acid, which prevents the formation of toxic by-products. DNA synthesis is impossible without thymidylic acid, and cell division is halted as a result [12].

MTX is used intralesional for the treatment of KT, however the results have only been reported in a small number of people. The efficacy of intralesional MTX was examined in **Gualdi *et al.*** [12] study on 35 patients with various types of KT and not simply KA. In addition, a number of different therapy approaches were evaluated side by side. Patients above the age of 75 (on average) were included in the study. In high-risk locations including the head and hands and feet, most lesions appeared. It appears that KAs have a high rate of success, as all of the patients who took part in the study saw improvements or were fully recovered. Those with cSCC reacted to therapy to a greater extent than patients with BCC, who did not. A possible explanation for the discrepancy is the mechanism through which MTX distributes its pharmacologic effects.

Rapidly growing tumours like KA and cSCC are more responsive to MTX therapy than slow-growing cancers like BCC because MTX suppresses DNA synthesis during cell replication. Since there are only a few BCC instances included in this analysis, the importance of the BCC data is diminished. Their findings on the relationship between intralesional MTX efficacy and tumor size appear to support this idea. Larger tumors have a higher sensitivity to MTX because they are more likely to proliferate quickly than smaller lesions [12].

A study published in 2019 found that intralesional MTX was highly effective in the treatment of KA (94 percent) [13]. These findings have been confirmed by the **Gualdi *et al.*** [12] investigation. In another study, **Moss and Weber** [14] found that 88% of patients with 157 KAs had their symptoms completely resolved after treatment. There aren't many studies on the effectiveness of MTX in the treatment of cSCC. Furthermore, the majority of them viewed MTX as adjuvant therapy rather than a stand-alone treatment. In 2016, A group led by **Salido-Vallejo *et al.*** [4]. looked at the outcomes of surgical treatment alone versus treatment with intralesional MTX prior to surgery in 43 patients. Within 30 days following the

diagnosis, all surgical operations were completed. The average increase in lesion size was 19% in the first group. Patients who received MTX saw a 23% reduction in the size of their lesions. Furthermore, SCC in the lips responded better than malignancies in other parts of the body [(4)].

As an example, **Sendin and Perez** [(15)] published a study in 2018 detailing the treatment of patients with SCC of the lips 50 days before surgery with two injections of MTX. The tumours' size shrank dramatically (68.18 percent decrease for the minor axis and 57.28 percent for the major).

MTX was again employed as neoadjuvant therapy in all additional investigations on this subject. About half of the patients with cSCC responded well to MTX treatment, according to research by **Gualdi *et al.*** [(12)]. This showed that MTX can be an effective treatment for cancers that are inoperable. Both BCC lesions treated in their study initially exhibited a slight improvement in terms of health. There is only one published study on the use of MTX to treat BCC. One intralesional MTX dose was administered to 11 participants in this research, but no improvement was seen [(16)].

One of the biggest problems with intralesional MTX is that there isn't yet a well-defined treatment strategy. These results imply that weekly doses of at least 25 mg/ml over a 4–6-week period are the most effective, according to **Gualdi *et al.*** [(12)]. After the 6th week of treatment, no patient showed any progress. There was no link identified between the treatment's dose or duration and any negative effects. This treatment's effectiveness does not appear to be influenced by past treatments, immunosuppressive concurrent medicines, or the location of a lesion.

CONCLUSION

In conclusion, when used as a less intrusive and less expensive treatment for NMSCs, MTX has the potential to be a very effective and safe alternative treatment, especially in patients who are elderly or have other medical conditions.

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