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Review Article

Skin Cancer: Current Treatments, Limitations and the Role of Polymeric Nano Particles for the Effective Treatment of Skin Cancer

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Abstract

Skin cancer is the commonly and aggregation of the cells in one part of the skin. It is enhanced form the cells that line up along the membrane that separates the superficial layer of the skin from deep layer. The current treatment of the skin cancer includes Topical chemotherapy, surgical excision, Mohs micrographic surgery, radiation therapy, Photodynamic therapy. The limitation of skin cancer is Skin irritation at the site of treated place, Changes in the skin colour or dark pigmentation. Where nano particles is used for the delivery of a controlled and sustained dosage of a skin cancer drug through the skin over a period of time. The polymeric nano particles offers various advantages over the skin cancer increased solubility, sustain release, penetrability, specific site of action. Hence this article discusses about the pathology current treatments, limitations and role of the polymeric nano particles on skin cancer.

INTRODUCTION

Cancer this name denotes the one of the most major public health cause in the world the cancer occurred by the persistent injury in tissue, host environment relation. It appears the basal cell skin cancer arises from DNA mutation in basaloid cells in the upper layer of the skin. Many of these cancers seem to be controllable but compromised may leads to the growth of the tumours. For the squamous cell carcinoma it tumour arises from the epidermis. Where there is the alteration in the gene or immune surveillance system that controls it, these skin cancer start grow where this gene is altered by the UV radiation. Where skin is same as all body tissues, is made up of cells. Penetrations across the skin (percutaneous) are limited by the barrier of enormous organized structure of stratum corneum. The skin has the two major layer epidermis and dermis. The epidermis is composed of the keratinocyte which is basically in the form of the brick & mortar shape which is generally used for conceptualize the barrier property of skin which includes merkel cells, melanocytes and Langerhans. This bilayer forms the complete regions of semi crystalline gel and liquid crystal domain. Where the second layer which lies beneath the epidermal layer is dermis which is thicker than epidermis generally 1-4mm.The current treatment of the skin cancer depends upon the size of the tumour and microscopic characteristics of the cancer. Where the various types of the treatment (a) Topical medication, (b) Destruction by electrodessication and curettage, (c) surgical excision, (d) Mohs micrographic surgery, (e) radiation therapy, (f) Photodynamic therapy. In the skin dermis composed of the collagens and elastic fibres. Where nano particles is used for the delivery of a controlled and sustained dosage of a drug through the skin over a period of time. Nano-technology involves the development of carrier's devices or systems sized in 1 to 100 nm range although this limit can be extended up to 1000 mm. This trend is generally based on the unique properties which meet a wide range of application and market needs. The mode of preparation plays the vital role. The polymeric nano particles offer various advantages increased solubility, sustain release, penetrability, specific site of action, and reduced dose for therapeutic action. Many types of polymeric nanoparticles are available synthetic and semisynthetic have been reported in literature in treating cancers. These reviews discuss about the pathology current treatments, limitations and role of the polymeric nano particles on skin cancer.

SKIN CANCER

Skin cancer is a large multifactorial design in which has large genetic component. Skin cancer is one of the most common malignancies in human worldwide and its incidence is increasing

rapidly and it's being reported a growing a one million cases are reported annually [1]. The ultraviolet UV radiation is the major prime factor for the skin carcinogenesis. The study of skin carcinogenesis is of major interest for both scientific researches and also for clinical practices for *In vivo* studies may facilitate the investigation of earlier alteration in the skin and the mechanism involved. This would lead to the development of new treatment strategies for skin cancer [2]. The skin has the major association with aging human cells accumulates with senescent cells with both epidermis and dermis.

Types of skin cancer

The skin cancer includes two type's melanoma skin cancer and non-melanoma skin cancer. Later it was included Basal cell carcinoma and squamous cell carcinoma [3].

Basal cell carcinoma: The basal cell carcinoma is an abnormal growth of tumours on the surface of the skin. In which among the Caucasian population. This would cause open sores red patches and pink growth on the skin surface. Basal cells would grow slowly and could damage the tissues around it in which would spread to a distant area of the tissues.

Squamous cell carcinoma: Squamous cell carcinoma in which occurs due to uncontrollable growth of an abnormal cell on the upper surface of the skin known as (epidermis) [4]. It occurs like the scaly crusty bleeding scars on the surface of the skin. It occurs on the all the surface of the skin like neck scalp arms and legs (American Academy of Dermatology). The main source of the squamous cell carcinoma is ultraviolet radiation [5].

Melanoma: Melanoma is the dangerous form of skin cancer. In which the unrepaired DNA damage to the normal skin cells in which would triggers mutations. This mutation would rapidly multiply and forms tumours. Melanoma is responsible for all cancer-related mortalities and morbidity. Non –melanoma skin cancer which has more aggressive factors with which would cause significant disfiguration like scalp peeling on the surface of the skin physically and also affects the patients psychologically. The main causative factor of the squamous cell carcinoma and basal cell carcinoma is the ultraviolet radiation [6].

Actinic keratosis (AK): Actinic keratosis is a precancerous patch of thick scaly or crusty on the skin. This is mainly due to the damage exposure of the ultraviolet radiation. This is common in the fair toned people. It is a precancerous. If we leave it leads to the formation of squamous cell carcinoma. They often occur on the most sun-exposed areas like neck face scalps hands arms.

They usually look likes thick scaly or crusty surface looks like rough in fact. An actinic keratosis lesion may range between 2 to 6 millimetres and can grow to certain diameters [7].

PATHOPHYSIOLOGY OF SKIN CANCER

Skin is the largest organ with immune function and covers 16% of the body represents an intrinsic activity of the immune cell and non –immune cells and molecules that are interrelated [8].

ULTRAVIOLET RADIATIONS (UVR)

UV Radiation that can damage DNA and create mutagenesis in which several genes are involved in the skin cancer. Sunlight is the continuous spectrum of electromagnetic radiation which is divided into three major spectra of wavelength ultraviolet visible and infrared [9]. In which UVR is classified in according to wavelength UVA (315-400nm) UV B (280-315nm) UV C (100-280nm) UV Range is the most significant spectrum of sunlight which would cause photo aging skin cancer 65%-90% of melanoma occurs due to the Ultraviolet radiation. Ultraviolet UV radiation causes inflammation immune change photo aging and DNA damage that promotes cellular senescence and carcinogenesis. Ultra-violet radiations are the one of the main prime etiologic factors for the occurrence of skin cancer. Ultra violet radiation B (280-315nm) is main radiation resource of forming skin cancer in which alters the normal state of life by inducing the variety of mutagenic and cytotoxic lesions which damages DNA by producing cyclobutane pyrimidine dimmers. Ultra violet B radiations have only 1% of solar energy. It has the highly active component of a solar radiation which would produce modification in DNA. It has been found that the formation and the alteration in skin cancer are developed at the molecular level. The ultraviolet radiations in which would produces the wide range of molecules in the skin, in which would produces Reactive oxygen species which would affect DNA \RNA and transcriptional targets [10]. Tβhe formation of dimers in which cellular damage and causes alteration (UVR and skin cancer). Pro-inflammatory cytokines and environmental stress also can induce (Mitogen-activated protein kinase) MAPK P38 cascade in the epidermis in which leads to the formation of the skin cancer [11]. The cancer incidence rate seems to be the higher rate in fair skin peoples than the darker skin peoples. UVR is crucial in the prevention of skin cancer. UVR creates p53 tumour suppressor genes which involve in the DNA damage. UV β rays which would also damage the DNA and causes the inflammatory responses and causes tumor. The change in the lifestyles and higher exposures of sunlight due to the outdoor activities is also the major factor for skin cancer. Due to the exposure of UVR the skin wrinkles skin aging losses of skin elasticity are happens [12]. Actinic keratosis which caused by the chronic exposure to ultra violet radiations. The squamous cell carcinoma and basal cell carcinoma are developed with pain full sunlight exposure [13]. Hence exposure to sunlight (UVR) on the child wood wound also causes the skin cancer.

CURRENT SKIN CANCER TREATMENT

Different approaches are used to treat the different type of skin cancer. Fairly most of the skin cancers and pre-cancers can be cured with minor surgeries during the initial stage itself [14]. The skin cancer treatments are

Surgical procedure

Surgical procedures in which the tumours are later forms as a cancer are identified and removed by means of surgery.

Mohs surgery

The surgeon removes the thin layer of the skin. The Mohs surgery which has been done with small part of the healthy tissue is removed with cancer cells. Mohs surgeries which carried out mainly for the squamous cell carcinoma and basal cell carcinoma [15]. Mohs surgery is possible effective treatment and leaves

small scars and also reduces the additional treatment after the surgeries.

Cryosurgery

The cryosurgery is also known as the (cryotherapy) in which use of the drugs with the surgical procedure. By use of the extreme cold which has been produced by liquid nitrogen and argon gas used to kill the abnormal tissue or cancer cell growth. The liquid nitrogen is the nitrogen in the liquid state at an extremely low temperature [16], Which has the ability to freeze the living tissue in which can able to hold or it can kill cancer cells. Cryosurgery which is used to treat the external tumour's in the skin. For the external tumour's treatment, the liquid nitrogen is applied directly to the cancer cells by the cotton swab spraying device. And it also used treat the tumors inside the body (internal tumours inside the bone. By using cyclopropane an instrument which is placed in contact with the tumor the internal tumors can be treated with liquid nitrogen. By using the sonogram or MRI the cyclopropane would be monitors the freezing of the cells, which should not affect the healthy cells [17]. The cryosurgery is used to treat various cancers and cancerous precancerous or noncancerous conditions. In addition to prostate and liver cancer cryosurgery is the effective treatment for the retinoblastoma and pre-cancerous stage of the both squamous cell carcinoma and basal cell carcinoma pre-cancerous skin growth known as the actinic keratosis. Cryosurgery is also used to treat some types of low-grade cancerous and non-cancerous tumor growth in the bone [18].

Cryosurgery reduces the risk of joint damage when compared with other extensive surgeries

Side effects due to cryosurgery: Cryosurgery may cause swelling and scarring loss of hair in the treated place if nerves are damaged it leads to the loss of sensation and causes loss of pigmentation of the nearby bone. Cryosurgery may lead to fractures in which destruction tissues during the treatment. But these effects may not be seen for sometimes after the initial time [19].

CHEMOTHERAPY

Chemotherapy (chemo) is a type of a treatment that includes medication or combination of medication to treat cancer [20]. Chemotherapy is a systemic therapy. In which drug may affect the entire body. Chemotherapy may affect rapidly growing cancer cells and also affects the healthy cells grows rapidly. Chemo may be used to shrink or reduce the tumor that causing pain or pressure. The main aim of the chemotherapy is to prevent or to slow down the spreading and growth of cancer cells [21]. Chemotherapy is mostly given in combined medication only sometimes it would give alone. Chemotherapy drugs given by orally, creams, or intravenous [22]. The drugs used for skin cancer is shown in Table 1

Side effects due to chemotherapy

The chemotherapy is a systemic therapy in which would affects the entire body. It works by killing cancers cells also the healthy cells. The side effects depend on the amount of the dose given to the patients and other side effects are (a) Increased sensitivity to the sunlight, (b) Discoloration of the skin or scaring, (c) Increased risk of infection (Due to less count of WBC), (d) Easy bruising or bleeding (Due to less count of platelets), (e) Fatigue or dizziness (Due to less count of RBC), (f) Alopecia (Hair loss), (g) Loss in appetite, (h) Dryness in the edges of the nails, (i) Diarrheal and constipation, (j) Nausea and vomiting . These side effects would go away once if treatment is finished. These side effects are caused by the chemotherapy are manageable [27].

Table 1: Chemotherapy drugs used for skin cancer.

Drug	Mechanism	Reference
5-Fluorouracil	Blocks enzyme synthesis of pyrimidine thymine.	[23]
Capecitabine	Inhibits the synthesis of ThMP active form of thymine required for the de novo synthesis of DNA.	[24]
Diclofenac	Inhibition of prostaglandin through COX.	[25]
Topotecan	Topoisomerase I moves torsional strain in DNA by inducing reverse single-strand break.	[26]

TOPICAL IMMUNOTHERAPY

Topical immunotherapy involves a daily application of a special cream for up to several weeks as a treatment for pre-cancerous and skin cancer lesions [28]. The cream stimulates the own body's own immune system to protect and destroy skin cancer. Immunotherapy is cancer treatment that uses body's immune system to attack cancer cells. It stimulates the immune system to produce interferon's to attack the cancerous and pre-cancerous cells. This treatment is used in the most initial stage of skin [29], and which is made up of white blood cells, organs, tissues, and lymph nodes and this treatment is applicable for the large difficult lesions [30], and it is inexpensive and rate cure is not far good as compared to the surgeries.

Types of immunotherapy

Different types of immunotherapy are used to treat skin cancer

Monoclonal antibodies: In which the drug is designed to bind to the specific part target in the body .Which would cause immune response to fight against cancer and another type of monoclonal antibodies is the mark, cancer cells it is more easier to immune system to find and destroy the skin cancer. It is also known targeted therapy [31].

Adoptive cell transfer: Is a treatment which boosts T cells to fight against cancer .T cells type of white blood cells and it is the part of the immune system. The researcher would take T cells from the tumor. They then isolate the T cells that are most active against your cancer or modify genes in them to make them find cancer and destroy cancer cells [32].

Cytokines: The protein s which is made up of your body's cells, which plays an important role in the normal immune response and in the immune system to respond against the cancer cells. There are two types of cytokines they are Interferons and Interleukins [33].

Vaccines treatments: Which works against cancer by

boosting your immune system responses to cancer treatment? Treatment vaccine is different from the one that prevents cancer.

DRUGS USED AND SIDE EFFECTS

Imiquimod. (aldara) a drug used. The each type cancer would cause different side effects. It depends upon the how healthy you before the cancer treatment and it depends upon how much doses which have given to you and these are the most common side effects are (a) Pneumonitis (Inflammation in lungs leads to difficulty in breathing, (b) Swelling, (c) Colitis, (d) Skin rashes, (e) Muscles and joint aches, (f) Pancreatitis, (g) Heart palpitation, (h) Hepatitis [34].

RADIATION THERAPY

Radiation therapy uses high energy radiation to shrink the tumor size and to kill cancer spreading cells by using strong rays like x-rays gamma rays and charged particles rays and the rays are which used more precisely towards the tumors and which is given precisely to avoid the damage of other healthy tissues and normal cells. The radiation given would be focused from the outside of the body or skin and it is focused by the electron beam radiation .a beam of an electron that does not goes deeper in the skin, which avoids the side effects to other organs. The three type's radiation therapies are given to skin cancer patients. They are (a) External-Beam Radiation therapy, (b) Internal-Beam Radiation therapy, (c) Systemic-Beam Radiation therapy [35].

External-beam radiation therapy

In which the radiations would be relieved from the machines to an outside of the body and beam size of ray towards the skin cancer affected place would be adjusted using an accelerator or software known as the lilac [36].

Internal Radiation Therapy

This is also known as brachytherapy allows a higher dose of radiation to a small region that might be possible with the external radiation material known as the implant. Its main is to protect the internal organs from the damage heat produced by the radiations. The radioactive isotopes are used. In which they place an implant closer to the tumor. The damage caused is less while compared to the external beam radiation therapy [37].

Systemic Radiation Therapy

The radioactive substance that is swallowed or receives an injection of a radioactive substance such radioactive iodine would bound to the monoclonal antibodies. This system is not improved a lot the clinical trials are going on.

Side effects

(a) Skin irritation at the site of treated place, (b) Changes in the skin colour or dark pigmentation (c) Hair loss in the area being treated. Damage saliva making glands and teeth while treating near the structures due to this problem only radiation therapy is not used in the younger peoples.

PHOTODYNAMIC THERAPY (PDT)

Photodynamic therapy PDT is the treatment that uses a special type of drug known as the photosensitizing agents along with the light source to kill the cancer cells the drugs only works after the certain kind of lights only [38]. PDT also was known as the photo chemotherapy, phototherapy and photo-radiation therapy. PDT harness the energy of light to damage or destroy the targeted tissue of cancer cells. A sensitizer absorbs energy directly from the light source and transferred to the molecular oxygen. The singlet oxygen in which is a cytotoxic agent reacts with the cellular components to cause the damage of cancer cells.

Side Effects

(a) Pain experienced during treatment, (b) Erythema, (c) Burning stinging experience, (d) Skin infection, (e) Peeling and blistering, (f) Swelling and Redness.

POLYMERIC NANOPARTICLES FOR THE TREATMENT OF SKIN CANCER

Nano particulate delivery systems, such as those based on poly (alkyl cyanoacrylate) polymers, have been studied extensively for many years as a potential means for drug delivery and targeting. These polymeric nanoparticles offer several advantages such as increased solubility, sustain release, penetrability, specific site of action, and reduced dose for therapeutic action. Many types of polymeric nanoparticles including both synthetic and semisynthetic have been reported in literature in treating various diseases including cancers. The nano particles is generally defined as solid, colloidal particles in the range between 10-1000nm. The term polymeric nano particle is collective term which is given for any type of polymer nano particle, but for specific type's nano-spheres and nano-capsules. Polymers are high molecular weight compound of many repeating subunits called monomers which is connected by the covalent bonds. Nano particles made of natural polymers i.e. chitosan, synthetic biodegradable polymer (poly (lactide-co-glycolide)) and non-degradable polymer i.e. poly-acrylates. To give the effective treatment the nano particles are used. The main advantages of the nano particle are deep entrance to cell and organelles, generally it's small with high surface volume ratio. However, very less reported have been published their potential use in treating skin cancers.

In the year 2000, Paul et al., (2000) have studied the potential sustained release by using the biodegradable nanoparticles loaded 5-Fluorouracil.They prepared the nanoparticle using four different bio-degradable polymer loaded 5-fluorouracil in three different concentration of drug and three different concentration of polymers. They found that by washing particles using re-suspension and centrifugation with ultrasound protocol resulted in dislodge the majority of the drug, incorporation efficiency and low level of strongly entrapped drug. By increasing the 5-fluorouracil before polymer addition increased the loading of the drug. They evaluated the drug release form nano particles using the Franz cell diffusion, results in the initial burst effect followed by a slower release phase nearly 24. They got good release rate nearly 66% by the preparation with poly (lactide-co-glycolide) of their 5-FU over this period. They have concluded that 5-fu loaded nanoparticle might be readily added into hydrogel-based delivery system to give sustained drug release for the treatment of the trans-epithelial drug-delivery.

Apart from this study no study till date reported the potential

use of these polymeric nanoparticles despite their tremendous advantages in treating skin carcinomas.

CONCLUSION

The dermal application of the drugs has ease in application. Drug delivery as well as risk assessment depends crucially on the ability of such carriers to overcome the skin barriers and reach deeper layer of the tissue. In this regarding Nano-particles especially polymeric nano-particle will offer various advantages such as solubility, sustain release, penetrability, specific site of action, and reduced dose for therapeutic action in treating skin cancer. However except few studies, no studies till date have been explained the potential benefits polymeric nano particles treating skin cancer. Hence, future studies may concentrate on this nano particles for the potential use of the polymeric nano-particles treating skin cancer.

CONFLICT OF INTEREST STATEMENT

The authors declare that there are no conflicts of interest involved in this study. The authors alone are responsible for the content and writing of the paper.

AUTHOR'S CONTRIBUTION

Vinoth Kumar G and Raahulan S was the lead author and synthesized the literature. Raahulan S was involved in drafting the paper. Karri VVSR provided conceptual input, design and critical revision of the manuscript. All authors read and approved the final paper.

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