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The Therapeutic Benefits of Biodegradable, Drug-Encapsulated, Polymer-Based Nanoparticles in the Targeted Treatment of Different Skin Cancers

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Abstract:

Skin cancer affects one in five Americans, with approximately 9,500 people in the US diagnosed with skin cancer every single day. Skin cancer, like many other cancers, is often treated with chemotherapy, radiation therapy, or surgical resection, all of which are often accompanied by harsh side effects and long-term recovery. In recent years, the use of biodegradable nanoparticles to deliver chemotherapeutic drugs in situ (at the site of tumors) has been a novel therapy to provide more targeted treatment and reduce the vast side effects that accompany chemotherapy, by utilizing fewer drugs and increasing the efficiency of the drugs used. While nanoparticle therapy has been explored through the lens of treating different skin cancers, the purpose of this paper is to discuss the benefits and limitations of various types of nanoparticles in the treatment of different skin cancers and varying stages.

1. INTRODUCTION

According to the American Academy of Dermatology Association, an estimated 9,500 people in the US are diagnosed with skin cancer every day.[1] The three most common types of skin cancer are melanoma, basal cell carcinoma, and squamous cell carcinoma. Less common skin cancers include Merkel cell carcinoma, Sebaceous gland carcinoma, and Kaposi sarcoma.[2] Skin cancer is a public health issue while skin cancer experts do not currently recommend screenings for most people, they do recommend that individuals bring up any noticeable changes to their skin to their primary care physician or dermatologist, as early detection is key to treating skin cancer and preventing its spread.[3]

There is a surge in public health efforts to educate the average person on the risks and signs of skin cancer, this is evident in the rise of social media toolkits that share statistics on skin cancer, facts about the dangers of ultraviolet radiation, and recommendations for what types of changes one should bring up with a physician. This is especially crucial as approximately 90% of non-melanoma skin cancers, and 85% of cases of melanoma, are associated with exposure to ultraviolet radiation. While exposure to ultraviolet rays (from the sunlight or indoor tanning beds) is the primary cause of skin cancer, what many people do not know is that it is the most preventable cause of skin cancer, further indicating the importance of public health education.[4] However, there is still work to be done in health education. According to a survey from the Centers for Disease Control and Prevention, about 50% of all adults and 65% of white adults ages 18-29 reported experiencing sunburn in the span of one year, highlighting the fact that sun protection measures are still not being observed.[5]

Skin cancer, like many other malignancies, is commonly managed with chemotherapy, radiation therapy, or surgical resection-- all of which can result in significant side effects and prolonged recovery periods. In recent years, biodegradable nanoparticles have emerged as a novel method for delivering chemotherapeutic agents directly to tumor sites (in situ), offering a more targeted approach that enhances drug efficiency while minimizing systemic toxicity. Although nanoparticle-based therapies have been investigated for various types of skin cancer, this paper, a narrative review of medical literature, aims to evaluate the advantages and limitations of different nanoparticle formulations across distinct cancer types and stages.

2. EPIDEMIOLOGY

2.1. Prevalence of Dermatological Cancers

Skin cancers are often categorized as melanoma skin cancer or nonmelanoma skin cancer. Approximately 2-3 million nonmelanoma skin cancers and 132,000 melanoma skin cancers are diagnosed globally each year, according to the World Health Organization. 1 in 3 cancers diagnosed is a form of skin cancer and according to Skin Cancer Foundation Statistics, 1 in 5 Americans will develop skin cancer in their lifetime.[6]

2.2. Health Disparities in Skin Cancer Diagnoses

Research has shown the importance of early detection on the prognosis of skin cancer diagnoses, indicating the value of having access to routine primary care where patients can bring up changes they noticed in their skin.[7] Health disparities exist in a variety of patient populations, particularly ethnic minorities, people of low socioeconomic status, rural-residing patients who have limited access to primary care physicians and dermatologists, the elderly population, and uninsured patients.[8]

2.3. Demographic Risk Factors for Skin Cancer

Risk factors for skin cancer also affect groups of individuals with specific characteristics. According to the Centers for Disease Control and Prevention, these characteristics include those with a lighter natural skin color, as the skin is more sensitive to sunlight and burns easily, those with blue or green eyes or blonde or red hair, individuals with certain types of, or a large number of moles on their skin, those with a family history of skin cancer, and older-aged individuals.[9]

2.4. Classification and Characteristics

Melanoma is characterized by an abnormal mole as it can develop within the mole or appear suddenly as a dark spot on the skin and is known as one of the most serious types of skin cancer because it tends to spread.[10]

Nonmelanoma skin cancers include Basal cell carcinoma (BCC) and Squamous cell carcinoma (SCC). Basal cell carcinoma is characterized by a flesh-colored, round-shaped growth, pink patch of skin, or pearl-like bump on the skin. It is common on the head, neck, and arms, but can form anywhere on the body and is also often found on the chest, abdomen, and on legs. BCC can grow deep and penetrate the nerves and bones, causing further damage. It does not usually spread.[10]

Squamous cell carcinoma is characterized by scaly patches and often appears as a firm, red-colored bump or sore that often heals and reopens, making it highly metastatic in that it can quickly spread through the blood or lymphatic system. Early diagnosis is crucial to prevent it from growing deep into the skin and spreading to other areas of the body.[10]

Other skin cancers include Merkel cell carcinoma (MCC) and Sebaceous gland carcinoma (SGC). Merkel cell carcinoma is characterized by a sore-looking scar, it grows quickly (becomes noticeably bigger in a few weeks), is often pink, red or purple, is not painful to the touch, and often develops on the head or neck where sun exposure is most intense. Over 97% of individuals who develop this form of carcinoma are older than 50. It is often mistaken as an insect bite, cyst, pimple, or sore.[10]

Sebaceous gland carcinoma is characterized by cancer in the sebaceous glands. While sebaceous glands are on most areas of our skin, the area around the eyes has the greatest number of sebaceous glands, which is why this form of cancer is often found on or around the eyelids. While most growths are benign, if this type of cancer spreads, it is often deadly.[10]

3. PATHOGENESIS

3.1. Pathogenesis of Melanoma

Melanomas tend to have two phases of growth: a radial and a vertical growth phase. The radial growth phase is when malignant cells grow radially in the epidermis layer of the skin. As time progresses, malignant melanoma cells begin to grow vertically, invading the dermis layer and developing the ability to metastasize throughout the body.[11]

3.2. Pathogenesis of Basal Cell Carcinoma

Basal cell carcinoma is often a result of direct DNA damage from ultraviolet radiation (where short-wavelength UV-B photons damage DNA and RNA with what are referred to as “UV-signature” C-T

and tandem CC-TT transitions, or indirect DNA damage through reactive oxygen species (as melanin absorbs longer-wavelength, UV-A photons). It has also been shown that ultraviolet exposure can cause suppression of the cutaneous immune system by impairing the body's natural immune surveillance of skin cancer. There is also a genetic component in the development of Basal cell carcinoma, with 70% of people with sporadic BCC exhibiting a mutation in the PTCH1 gene. The mutation in this gene is associated with immature pluripotent cells associated with the hair follicle and are thought to be cells of origin from which BCC arises.[12]

3.3. Pathogenesis of Squamous Cell Carcinoma

The pathogenesis of cutaneous squamous cell carcinoma arises from a multistep process involving not only ultraviolet radiation but also mutations in genes such as TP53, CDKN2A, NOTCH1, NOTCH2, EGFR, and TERT. There are also several molecular pathways, such as RAS/RAF/MEK/ERK and PI3K/AKT/mTOR that play a role in the pathogenesis of this form of skin cancer.[13]

3.4. Pathogenesis of Other Skin Cancers

Merkel cell carcinoma (MCC) is an aggressive neuroendocrine skin cancer that follows two distinct etiologies, one viral and one nonviral. Approximately 60% of cases of MCC are caused by clonal integration of Merkel cell polyomavirus DNA in the tumor genome, in addition to the persistent expression of viral T-antigens. The second cause is UV damage over time, leading to highly mutated genomes and resulting in a nonviral form of MCC.

Despite these two distinct etiologies, both the viral and nonviral forms of MCC are similar in terms of their presentation, prognosis, and their response to different therapies. Both forms have high proliferation rates and elevated levels of cell-cycle-dependent genes (from the inactivation of RB and p53, common tumor suppressors). MCC is also accompanied by a strong MYC signature due to MCL activation (either by the virus or simply from gene amplification) and is often associated with attenuated neuroendocrine differentiation due to the ATOH1 transcription factor.[14]

Ocular sebaceous carcinoma arises from the eyelash or eyelids and is associated with actinic keratosis or Bowen disease, suggesting that this form of cancer originates from pre-existing intraepidermal neoplasia (a condition where abnormal cells are located on the surface of organ lining tissues) or ultraviolet radiation.[15]

4. CURRENT TREATMENTS

4.1. Radiation Therapy

Radiation therapy is the use of radiation to treat tumors.[16] Advantages of radiation therapy include the death of large amounts of cancer cells, the ability to reduce the size of tumors thereby relieving mass effect, or the effect of a large tumor pushing on organs, or simply reducing the size of tumors to make them easier to be resected surgically. Radiation therapy can also stimulate an immune response against a tumor and is useful in cases where organ preservation is key. These advantages are especially relevant in the case of treating skin cancer with regards to minimizing the loss of skin in the process.[16]

Disadvantages of radiation therapy include damage to the surrounding tissues, and the inability to kill tumor cells that cannot be seen on imaging scans (such as cancers that are near lymph codes or metastatic cancers that have spread throughout the body). Other disadvantages include poor wound healing and complications, and inconvenience concerning the timing and frequency of radiation sessions required.[16]

4.2. Chemotherapy

Chemotherapy is the development of antitumor drugs to treat either hematologic or solid tumors.[16] Chemotherapy, alongside other systemic therapies such as hormone, antibody, and immune-modulator therapies, is often prescribed alongside radiation therapy to kill a larger number of cancer cells throughout the body. Compared to surgery, chemotherapy also makes it possible to kill microscopic diseases at the edge of tumors that are not visible to surgeons.

Disadvantages of chemotherapy include its inability to deliver systemic therapy, especially in patients who are on blood-thinning medications or have certain health conditions such as kidney or liver failure and heart disease. Consequently, chemotherapy is associated with extensive systemic toxicities as the

therapy travels throughout the body and also affects normal, healthy tissue. Chemotherapy also results in the uneven takedown of cancer cells compared to radiation therapy.[16]

4.3. Surgical Resection

Surgical treatment involves the cauterization or physical resection of tumors.[16] Advantages of surgical intervention include the direct removal of a large volume of a tumor, and treating tumors that cannot be treated with radiation therapy (such as areas treated previously) or chemotherapy. Surgical resection also makes it possible to further analyze the tissue sample to inform treatment options (dermatopathology). Surgical resection is often less time-consuming as surgeries are typically performed over the course of a day, compared to radiation and chemotherapy treatments that might be required on a daily, weekly, or monthly basis over longer periods.[16]

4.4. A Novel Approach: Nanotechnology

In recent years, there has been a rise in the use of nanotechnology in medicine. Specifically, the targeted treatment of cancers with biodegradable, polymer-based nanoparticles that encapsulate chemotherapeutic drugs, and deliver them in-situ, instead of systemically, to attack cancer cells and reduce the systemic side effects associated with traditional chemotherapy more accurately.[17]

5. Nanoparticles for the Targeted Treatment of Skin Cancer

Treating skin cancer with nanoparticles is an emerging field of research. Drug-encapsulating nanoparticles can be modified in many ways to enhance their specificity in targeting tumor sites, but also in their ability to disintegrate tumors. Nanoparticles can be composed of a variety of materials such as vesicular carriers (phospholipids), other lipids, polymers or polymeric micelles, nanofibers, or metallic components. Their size, charge, shape, molecular weight, elasticity, and surface chemistry (such as the conjugation of targeting compounds) can be easily engineered, as well as their formulation. Drug solubility, pH, viscosity, hydration level, and concentration levels can also be adjusted as needed, based on the type of cancer being treated or a patient's specific needs.[17]

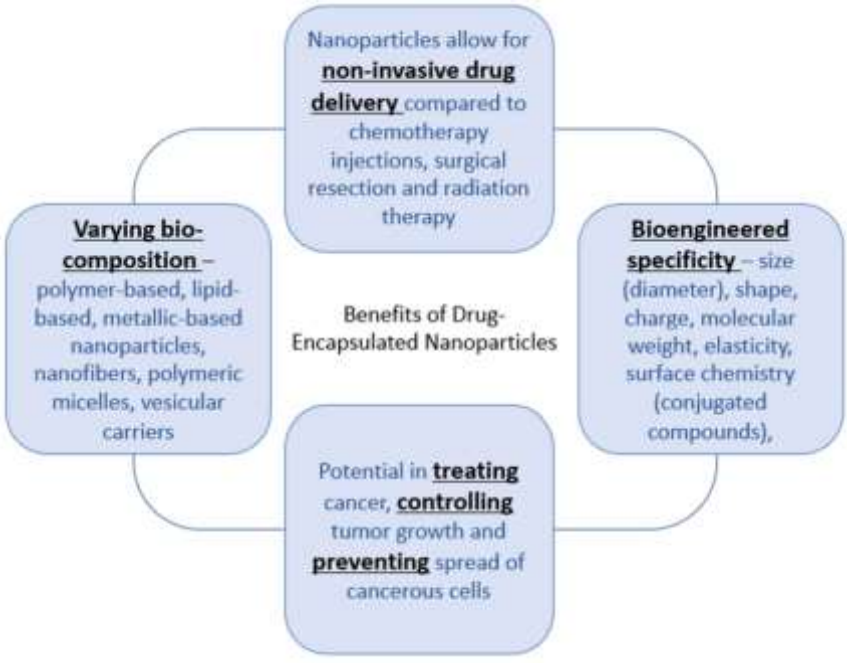

Figure 1. *Benefits of Utilizing Drug-Encapsulated Nanoparticles. A graphical representation of the benefits of using nanoparticles as drug carriers. These benefits include 1) non-invasive drug delivery, 2) bioengineered specificity to target treatment to different cancers and patient needs, 3) the ability to treat, control and prevent disease, and 4) varying composition of nanoparticles to tackle different types of diseases.*

5.1. Composition of Nanoparticles

Nanoparticles for the treatment of skin cancer tend to be categorized into three groups: 1) lipid-based nanoparticles, 2) inorganic nanoparticles, and 3) polymer-based nanoparticles. Lipid-based nanoparticles include solid lipid nanoparticles, niosomes, cubosomes, and liposomes. Inorganic

nanoparticles include mesoporous silica nanoparticles, gold nanoparticles, silver nanoparticles, and carbon-based nanoparticles or nanotubes. Polymer-based nanoparticles include polymeric nanoparticles, polymeric micelles, dendrimers, and polymersomes.[18]

5.2. Topical vs. Systemic Treatment

Nanoparticles can be administered topically (trans-dermally or via the hair follicles) or systemically (such as via injection into the bloodstream). Nanoparticles can be applied topically to the surface of the skin and in the proximity of hair follicles, where they accumulate in furrows and penetrate the skin in the opposite direction of hair growth.[19]

Nanoparticles, in the form of a topical ointment (nanoparticulate paclitaxel ointment), have shown potential in treating not only skin cancers but also preventing metastasis as shown by reduced tumor diameter and retraction away from the basement membrane.[20] This is due to the taxane present in Paclitaxel, which inhibits cell growth by blocking mitosis by interfering with microtubule movement.[18]

Nanoparticles are more commonly administered systemically, through the bloodstream where they degrade and release chemotherapeutic drugs that target tumor sites. They have been shown to be an effective drug delivery system in terms of enabling anticancer drugs to reach the cancer site to not only treat the tumor but also prevent and control metastasis by encumbering cancer cells, thereby preventing invasion into the basement membrane.[19]

Nanoparticles can also be administered alongside immunotherapeutic or immunostimulatory agents. Bioadhesive polymer-based nanoparticles, coupled with immunostimulating CpG oligodeoxynucleotides for example, have also shown to be useful in treating skin cancers when administered systemically. They are commonly used to treat squamous cell carcinoma in particular, a keratinocyte-derived carcinoma that comprises the most common malignancies.[20]

Due to the minimal side effects and localized treatment that nanoparticle-based therapy provides, the field is gaining much recognition in recent years. A literature review, conducted in 2022, highlights different types of research studies that utilized nanoparticles to treat skin cancers.[21]

5.3. Metallic Nanoparticles

Super paramagnetic nanoparticles such as iron-oxide nanoparticles (encapsulated with doxorubicin and 5-fluorouracil) have been applied topically to melanomas and have led to increased cytotoxicity, enhanced immune cell infiltration, and reduced tumor vascularization (preventing metastasis and thereby decreasing host-tumor interactions). They have also been shown to increase transdermal penetration, reducing the need for conjugation or encapsulation of other compounds, as in the case of polymer or lipid-based nanoparticles.[22]As noted in the paragraph above, nanoparticles can be altered in several ways. Charge, size, shape, and surface chemistry play a role in the nanoparticles' bio distribution in different organs in vivo.[23]

5.4. Polymer-Based Nanoparticles: Anionic vs. Cationic

Charge (such as anionic, negatively charged nanoparticles, or cationic, positively charged nanoparticles) can determine where a nanoparticle is more likely to lodge in vivo. The charge of a nanoparticle can be adjusted with the addition of binding plasma proteins, protein interactions, membrane damage, immune-cell stimulation, and the addition of factors that can make them toxic to immune cells.[24]

One example of the use of polymer-based drug-encapsulated nanoparticles as an alternative to chemotherapy is the use of anionic polylactide-co-glycolic acid polyethylene glycol (PLGA-PEG) based nanoparticles, which offer slow, yet steady, biodegradability in vivo.[25] Another example is cationic poly (ethylene oxide)-modified poly (beta-amino ester) based nanoparticles (PbAE), which are also currently being explored to provide targeted drug delivery to tumor sites, particularly in renal cell carcinomas.[26] PLGA-PEG nanoparticles are anionic, while PbAE-based nanoparticles are cationic in nature.

Research has demonstrated that nanoparticles tend to travel to the kidneys, while positively charged nanoparticles take longer to circulate in the bloodstream[27] and tend to travel to other organs, such as the lungs and spleen in a more concentrated capacity.[28] With regards to skin cancer, studies have shown that positively-charged, cationic nanoparticles exhibit enhanced affinity towards negatively charged pores on the skin, and vice versa, with negatively-charged nanoparticles being attracted towards positively-charged pores on the skin. These nanoparticles can be encapsulated with several chemotherapeutic drugs such as Doxorubicin (Adriamycin), Sorafenib, Epirubicin, Etoposide,

Ifosfamide (Ifex), Carboplatin (Paraplatin), to deliver a concentrated, localized amount of biologic to the tumor site, reducing systemic side effects of larger doses.[29]

5.5. Varying Sizes and Diameters of Polymer-Based Nanoparticles

Size (in terms of nanoparticle diameter) also plays a role in biodistribution.[30] The size of nanoparticles can be altered through the addition of adjuvant or hapten properties, and are useful to control penetration ability, surface area coverage, and clearance of particles through different membranes (such as hair follicles or varying layers of the skin in a transdermal setting), or cellular uptake/phagocytotic methods.[25]

Smaller nanoparticles (such as those with a diameter of 100-300nm) tend to lodge in the kidneys and lungs. With regards to skin cancer, research has shown that the optimum particle diameter is 400-700nm for nanoparticle transportation across the hair follicles, due to the natural movement of the hair and the cuticula serving as a pump, allowing similarly sized particles to penetrate the skin.[31]

Nanoparticle size has also been shown to be useful in determining, and controlling, the depth of drug penetration through the different layers of the skin.[32] This is especially useful in the case of targeting cases of metastatic skin cancer, where the cancerous cells invade the deeper layers of the skin, towards the vascular basement membrane such as in the case of Basal cell carcinoma.[33]

5.6. Advantages/Disadvantages of Polymer-Based Nanoparticles

There are a number of advantages and disadvantages of utilizing polymer or lipid-based nanoparticles as noted in the section below.[34]

5.7. Metallic Nanoparticles

In addition to polymer-based nanoparticles, super paramagnetic nanoparticles such as iron-oxide nanoparticles (encapsulated with doxorubicin and 5-fluorouracil) have been applied topically to melanomas and have led to increased cytotoxicity, enhanced immune cell infiltration, and reduced tumor vascularization (preventing metastasis and thereby decreasing host-tumor interactions). They have also been shown to increase transdermal penetration, reducing the need for conjugation or encapsulation of other compounds, as in the case of polymer or lipid-based nanoparticles.[35] There are a number of advantages and disadvantages of utilizing nanoparticles that are composed of different metals.[36]

6. CONCLUSION

6.1. Future Therapies – Detection/Prevention in Addition to Treatment

Despite the extensive literature that exists in the field of nanomedicine, there is still much work to be done concerning utilizing nanomedicine for the prevention of disease, in addition to real-time and long-term treatment therapies. In a study done by researchers in India, poly(lactic-co-glycolide) nanoparticles, encapsulated with apigenin, a dietary flavonoid with anticancer properties, were administered to mice in an attempt to not treat, but rather prevent, skin tumors, particularly those induced by ultraviolet B (UVB) radiation (non-melanoma skin cancers or NMSCs).[37] This research explored the potential that nanoparticles have in acting as not only a chemo-therapeutic delivery agent but also as a chemo-preventive delivery agent to inhibit the formation and progression of skin cancers.

6.2. Timeline of Therapies

Further research should be conducted to determine the ideal or most appropriate timeline for nano-therapies. This would include answering questions, including but not limited to: are certain nanoparticle types more appropriate for acute, short-term treatment, or longer-term, continuous treatment? Is the use of nanoparticles justified for preventive use, or exclusively as a therapy for cancer diagnoses? What kinds of patients (demographics, diagnoses, disease stage) would benefit most from this type of treatment? These are just some of the questions that are currently being discussed in recent literature.[38]

6.3. The Rise of Personalized Medicine

This field also delves into the rise of precision medicine and targeted therapies. Despite the progress that has been made in this field, it is important to note challenges that still exist, especially with regards to personalizing this form of therapy for individual patients which have unique pharmacokinetics and

pharmacogenetics which play a role in how effective, and safe, this therapy would be. Further studies should be done on dosage requirements and standardizing treatment guidelines.

6.4. Closing Remarks

In closing, nanoparticles are promising drug carrier systems that not only improve the solubility of drugs that exhibit poor water solubility but also improve pharmacokinetics by increasing drug-half life, reducing immunogenicity from the host system, increasing bioavailability (and utilization) of drug and reducing drug metabolism (particularly the first-pass effect by preventing premature degradation and metabolism of the drug). Nanoparticles offer the ability to fine-tune the release of therapeutic compounds and allow the delivery of multiple drugs at once while reducing the systemic effects of traditional chemotherapy, proving to be a promising, and novel advancement in the treatment of dermatological cancers.

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