Review Article

Skin Cancer and Its Treatment: Novel Treatment Approaches with Emphasis on Nanotechnology

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The life expectancy in the Western world is increasing for a long time, which is the courtesy of a higher life standard, a more thorough hygiene, and, of course, the progress of modern medicine. Nevertheless, one of the illnesses that still proves to be a great challenge regardless of the recent advancements in medicine is cancer. Skin cancer is, according to the World Health Organization, the most common malignancy for the white population. The beginning of the paper offers a brief overview of the latest available information concerning epidemiology, aetiology, diagnostics, and treatment options for skin cancer, whereas the rest of the article deals with modern approaches to skin cancer treatment, highlighting recent development of nanotechnology based treatment approaches. Among these, we focus especially on the newest nanotechnological approaches combined with chemotherapy, a field which specialises in target specificity, drug release control, and real time monitoring with the goal being to diminish unwanted side effects and their severity, achieving a cheaper treatment and a generally more efficient chemotherapy. The field of nanotechnology is a rapidly developing one, judging by already approved clinical studies or by new theranostic agents that combine both the therapeutic and diagnostic modalities.

1. Introduction

Despite the past two decades' advancements, cancer treatment remains a challenge and a motivation for many researchers worldwide. New treatment possibilities are constantly arising and show promise in improving treatment effectiveness, survival rates, and the patient quality of life, while at the same time decreasing unwanted side effects.

This article is an overview of various types of skin cancer, their characteristics, prevalence, and currently used treatment methods, including modern nanotechnology based methods. The latter are constantly improving our treatment possibilities by taking advantage of the specific properties of nanoparticles as carriers and more efficient targeting of the specific properties of cancer cells. We conclude with several prospects of the future in skin cancer treatment.

2. About Skin Cancer

Skin cancer is the most common malignant disease found particularly in Caucasians [1]. More than a million new cases

are reported worldwide each year. The various types of skin cancer are named after the cells they originate from and their clinical behaviour. The most common types are basal cell carcinoma (BCC), squamous cell carcinoma (SCC) (together referred to as nonmelanocytic skin cancers (NMSC)), and malignant melanoma (MM) [2].

2.1. Nonmelanocytic Skin Cancer. NMSC is the most common malignancy found in humans. Each year 2-3 million new cases are reported worldwide, 1.3 million of those are found in the USA only [3]. In Europe, Canada, the USA, and Australia the incidence is increasing by 3–8% per year [4]. The incidence rate is thought to double in the next 30 years [5]. The most important etiological factors include UV light, ionizing radiation, and certain chemical carcinogens. A more detailed overview is shown in Table 1.

BCC represents 80–85% of all NMSC, which makes it the most common skin cancer type. In the USA, 30% of all newly diagnosed cancers are BCC [4]. Worldwide, the incidence

TABLE 1: Important risk factors in skin cancer.

Factor	Description	Incidence	LIT
BCC			
Ultraviolet light	Increased incidence of BCC has been noticed in individuals with <i>fair skin</i> , weaker <i>tanning ability</i> , <i>fair hair</i> , <i>blue eyes</i> , <i>older individuals</i> , men, and those with frequent sun exposure.	The incidence changes nearer to the Equator, where the ultraviolet B waves (UVB) are most frequent. Ultraviolet A waves (UVA) also have carcinogenic effects.	[18, 19]
Ionizing radiation	Ionizing radiation causes BCC in humans and animals. The latency period is 20–30 years.	Patients that have been exposed to 1 Gy (gray) of radiation had a greater risk of developing cancer. In individuals that have been exposed to 35 Gy of radiation, the risk was 40x greater compared to the general population.	[20, 21]
Chemical substances	A <i>large majority</i> of chemical carcinogens cause SCC and not BCC. There are exceptions, such as arsenic in people and 3-methylcholanthrene and antramine in rats.	BCC developed 30–40 years after chronic arsenic exposure, as a consequence of contaminated food, water, seafood, and so forth.	[22]
SCC			
<i>Extrinsic factors</i>			
Ultraviolet light	UV light is one of <i>the most important factors</i> . The most common sites of SCC are the head, neck, and the dorsal side of arms. People with type I skin according to <i>Fitzpatrick</i> are particularly at risk.	SCC incidence increases nearer to the Equator. It <i>doubles</i> per 10° latitude towards the Equator.	[11, 12]
Ionizing radiation	Gamma, Grenz, and X-rays are well known carcinogens.	The incidence of cancer due to radiation increases linearly by 5.5% per 1 Sv.	[23]
HPV	HPV infection presents a risk for cervical SCC development, as well as certain genital and skin variants of SCC	Cervical, anal, and oropharyngeal cancers are almost always etiologically connected to a HPV infection. Together with UVA, they are thought to be cocarcinogens for skin cancer.	[24]
Chemical substances	Hydrocarbons, arsenic, and tobacco are well known carcinogens.	Hydrocarbons were important etiological factors in <i>certain professions</i> (e.g., chimney sweeps). Skin lesion development correlates to arsenic exposure.	
<i>Intrinsic factors</i>			
Genodermatoses	Those with Xeroderma Pigmentosum (XP) are more susceptible to UVA radiation, which leads to skin and eye degeneration and the development of skin SCC, BCC, and MM	In individuals with XP, the incidence of cancer before the age of 20 is <i>2000X greater</i> than in the general population.	[25, 26]
Immunosuppression	Chronic immunosuppression (e.g., long-term corticosteroid immunosuppression therapy or posttransplant therapy) increases skin cancer incidence.	(i) In Netherlands and Norway, the incidence in patients after heart or kidney <i>transplant</i> is 65 to 250 <i>times greater</i> . (ii) In the USA 35% of individuals within 10 years of a heart transplant developed some form of skin cancer.	[27–29]
Actinic keratosis (AK)	(i) These lesions are the most common premalignant conditions. (ii) <i>Bowen's disease</i> and <i>Erythroplasia of Queyrat</i> are forms of SCC in situ that can sometimes develop into an invasive form.	They represent one of the most common reasons for a dermatologist visit in the USA. In the USA, AK were present in 55% of fair skinned men and 37% of fair skinned women between the ages of 65 and 74.	[30, 31]
Other skin lesions	SCC often develops in scar tissue (e.g., healed burns). Similarly, it also arises in areas of chronic inflammation, such as ulcers, sinus tracts, and inflammatory dermatoses.	Approximately 1% of skin cancer develops in chronically irritated skin. In 95% it is SCC.	

TABLE 1: Continued.

Factor	Description	Incidence	LIT
<i>Malignant melanoma</i>			
Constitutional factors (race, pigmentation, and genetic predisposition)	(i) Skin type and <i>sunlight</i> are the main factors that influence MM incidence. (ii) The incidence of MM and other types of skin cancer is greater in patients with XP and albinism. (i) The main environmental factor for MM and other skin cancer development is short wavelength UV light present in sunlight. (ii) The prominent effects of UV radiation are pyrimidine dimer formation, DNA base and nucleoprotein crosslinking, and polynucleotide chain disruption.	(i) On average, MM is 3-4 times more common in less pigmented races, compared to more pigmented ones. (ii) <i>The number of melanocytic nevi</i> that a person has on their skin is a good indicator of MM risk.	[32]
Ultraviolet light	Multiple factors were proposed; occupation, diet, smoking, oral contraceptives, endometriosis, Parkinson's disease, TNF inhibitors, and so forth.	Incidence increases <i>nearer to the Equator</i> , where the UVB dose in sunlight is highest. UVA also have carcinogenic effects.	[32, 33]
Other factors		Statistically significant links with the disease have not been found for most factors, with the <i>exception of endometriosis and Parkinson's disease</i> . Correlation with MM has been found there.	[34, 35]

FIGURE 1: Skin types according to Fitzpatrick and Sober [12]. Sun exposed skin: type 1 always reddens and rarely tans; type 2 often reddens and rarely tans; type 3 mildly reddens and gradually tans; type 4 rarely reddens and easily tans; type 5 rarely reddens and easily tans; type 6 never reddens.

increases by 10% per year, mostly in older men, but also in young women [2, 6].

People who get skin cancer show typical signs of chronic sun damage, for example, collagenosis, irregular pigmentation, wrinkling of the skin, telangiectasia of the skin, and solar keratosis on sun exposed areas. Superficial BCC is of a red, slightly wrinkled, and scaled appearance with small ulcerations on the most exposed areas. They can be round or oval shaped with a poor defined border. The centre can be uniformly fibrotic. A superficial BCC can clinically appear as subacute or chronic dermatitis [7].

The other type of NMSC is SCC, which represents 15–20% of all NMSC, whose growth exhibits local destructiveness and surrounding tissue invasion, and also causes death more frequently than BCC [4]. Its incidence is increasing, though the increasing rate varies geographically [8]. The risk factors that lead to SCC development can be divided into extrinsic (UVA, ionizing radiation, human papilloma virus (HPV), and chemical substances) and intrinsic (genodermatoses, immunosuppression, preexisting skin lesion, and preexisting actinic keratosis). Further details can be found in Table 1.

2.2. Malignant Melanoma. Skin melanocytes are cells that produce the skin pigment melanin, and MM affects them specifically. Its incidence is still on the rise in areas with light skinned population that is overly exposed to sun radiation. Only Australia, with an incidence of 50–60/100000, reports a slowly declining trend since 2005 [9]. In Europe the incidence of this kind of skin cancer is 10–20/100000 inhabitants, while the USA stands at 20–30/100000. Slovenian incidence has, in the year 2012, been 23,1/100000 in the male population and 23,8/100000 in the female population. Thus, the yearly incidence of new diagnoses for Slovenia alone is about 700 new patients [10].

Even with MM representing a mere 4% of newly discovered cancers, it takes the sixth place as the most common female and seventh as the most common male cancer in Slovenia. In the rest of the world, the MM is more common in males than in females.

According to a 2010 research, 13200 [4] new cases of MM are found annually, whereby the incidence in the Caucasian population is sixteen times greater than in Afro-Americans and ten times greater than in Latin-Americans [4]. The most prominent etiological factors are constitutional factors, UV light, and other factors [11] (Table 1).

MM is most often developed in skin melanocytes, which are intermittently exposed to the sun radiation. Development from the retinal, anogenital, and the gastrointestinal tract is rarer. There are multiple MM risk factors.

Skin Type. The risk depends on the skin type. The highest is in people with light skin (1 in 40), while it is considerably lower

in dark skinned people (1 in 1000) or Latin-Americans (1 in 200). The type of developed MM also depends on skin type, with dark skinned individuals; the acral lentiginous type, which usually presents itself on hands or soles of the feet, is the most common. In Caucasians, there are six distinguished skin types, and the highest risk is in individuals of skin types I and II. A depiction of said types can be seen in Figure 1.

Sun Radiation. MM and NMSC risk depends on both skin type and UV exposal. Both UVA and UVB of natural or artificial origin are cancerogenic. While the UV rays induce the desired tanning and vitamin D production, they also have a mutagenic effect and depress the immune system. [2]. The most important risk factor is the so-called intermittent sun exposure, as well as the childhood and adolescence sun exposure. The weaker risk factor is a chronic or professional exposure, except in head and neck MM. Other risk factors are also connected to the UV exposure; the number of newly formed naevi (see below for further details), sunburns, and presence of actinic keratosis are statistically linked to a higher risk for this type of cancer.

Naevi. Along with the skin type and UV exposure, the number of atypical (dysplastic) naevi also contributes to an increased risk. Characterized as such are naevi bigger than 6 mm in diameter, with uneven shape and colour. If we count more than 50 atypical naevi in a single individual, the state is called atypical naevi syndrome. This state increases MM risk fivefold. Even in people with multiple atypical naevi, MM most commonly develops in formerly unaltered skin; therefore the removal of unsuspecting dysplastic naevi is not advisable [2].

Age. MM incidence increases with age, while the average patient age is 62 years. It has to be pointed out nevertheless that MM is still one of the most common cancers in young adults as well [10].

Gender. In most countries, the male population is more susceptible for MM than the female. Life risk for men is 1,5 times higher than that of women. Slovenian incidence of MM is higher in women than in men [10].

Immunosuppression. Immunosuppression is a MM risk factor, which also decreases the patient survival [13].

Formerly Removed MM. In patients with MM, the risk for new MM is 3–7% [13].

Family History. 5–10% of MM appears in the “high-risk” families. Two or more close relatives with MM mean increased

risk. Alongside MM, these families are also more susceptible for pancreatic cancer, mesothelioma, and retinal melanoma. Familial form of MM is connected to low and high penetrance genes. The most commonly known low penetrance gene is MC1R. Thus far, the high penetrance genes are *CDK4*, *CDKN2A*, *POT1*, *TERT*, and *BAP1*. The *CDKN2A* mutation is discovered in 2% of the MM patients, making it most commonly connected to the disease.

MM has to be always on our differential diagnosis list when a pigmented skin lesion or a long-standing stable nevus starts to change colour, shape, or size. Seen can be a change of colour, bigger radius, uneven borders, and sometimes bleeding, itching, and pain in the lesion [14]. These criteria are nicely presented in the mnemonic ABCDE (asymmetry, border, colour, dimension, and evolution).

2.3. Skin Cancer Diagnostics. Skin cancer diagnosis begins with a dermatological examination, medical history, dermoscopy, and surgical biopsy with pathohistological biopsy. Dermoscopy is a noninvasive method, where we use a lens (a lens system) and a strong light source, which enables us to distinguish typical skin cancer skin changes. With both MM and NMSC, one confirms the diagnosis of a suspect lesion with skin biopsy and a pathohistological examination. The biopsy includes an excision of 2–5 mm of healthy skin and is performed either using punch or shave biopsy. Further therapy is decided based on the anatomical site and size of the tumour.

3. Current Therapeutic Approaches in Treating Skin Cancer

3.1. Surgery

NMSC. There are many treatment options for the NMSC. The most appropriate is surgery through a radical excision. If the tumour of less than 2 mm in diameter is excised with a border of 4 mm of healthy skin, the recurrence is present in only 5% of cases [15, 16]. For superficial tumours, a 2–3 mm border is sufficient [17]. The excision must be as deep as the hypodermis.

Whenever a radical excision is not an option due to an unfavourable cosmetic defect or accompanying disease, one of the following treatment options may be used. Cryotherapy, curettage and electrodesiccation, radiotherapy, topical application of 5-fluorouracil or imiquimod, electrodesiccation with curettage, and diathermia are the appropriate treatment options for superficial BCC and Bowen's disease of the thorax and limbs. Of course, in such cases the patient should always be warned of a higher recurrence risk. Radical excision is the treatment of choice in case of a recurrence [16].

MM. Local treatment of MM consists of a radical excision of the skin tumour or the biopsy site. It consists of a healthy skin border as well as the tumour. The area of the border depends on the thickness of the tumour and extends to the deep fascia. The recommended radical excision border widths are shown in Table 2. Such skin defects are usually primarily sutured, but if this is impossible, a skin graft is used [17].

TABLE 2: Breslow's depth.

Breslow tumour thickness	Recommended excision margin
<1 mm	1 cm
1–2 mm	1–2 cm
2–4 mm	2 cm
>4 mm	2 cm

The tumour is classified using the Breslow classification, which depends on the tumour depth and sorts the tumour into one of the five stages. Stage I means that the tumour cells have infiltrated up to 0,75 mm, stage II 0,76–1,5 mm, stage III 1,51–2,25 mm, stage IV 2,26–3,0 mm, and stage V deeper than 3,0 mm [36].

Metastases are discovered in about 20% of all MM patients. Based on the histopathological examination, clinicians decide on the possible sentinel node biopsy in the MM patients. This procedure is used for discovering of metastases that are clinically (palpation, ultrasound, and cytological puncture) invisible, due to an insufficient tumour mass. The removed sentinel node is inspected by a pathologist. Further MM treatment depends on the test results [37].

Clinically apparent regional lymph node metastases, discovered by palpation or ultrasound, are confirmed by a thin needle aspiration biopsy, followed by a cytological analysis of the gathered material. In case of a positive result (a metastatic node), a therapeutical dissection is immediately performed. Therapeutical dissection is a radical metastatic node removal in the individual nodal regions.

3.2. "Basic" Pharmacological Therapy

NMSC. Although the golden standard for NMSC is a surgical excision, the treatment of choice for the Bowen's disease is a local, topically applied 5-fluorouracil. Imiquimod and 5-fluorouracil can also be used for the treatment of superficial BCC (except for the nodular form). Morbidity and mortality have been significantly decreased by newer drugs that regulate some key cell receptors (i.e., 5-fluorouracil) and the immune response. Imiquimod (which does not affect the mortality) and interferons (i.e., IFN- α 2b) are some of these. For systemic therapy, especially for MM, dacarbazine, temozolomide, or carboplatin/paclitaxel are also used [2].

Vismodegib is the first oral selective inhibitor of the Hedgehog signal pathway (HPI, Hedgehog Pathway Inhibitor). It binds selectively to the transmembrane smoothened protein (encoded by the *SMO* gene), where it inhibits the hedgehog signalling pathway, which also inhibits tumour growth. Two clinical studies were performed, namely, ERIVANCE BCC and STEVIE, where vismodegib was used in patients with advanced or metastatic BCC, some of which were also Gorlin syndrome patients [38].

MM. There have been no novel approaches in systemic metastatic MM treatment. Dimethyl triazeno imidazole carboxamide (DTIC, analogue temozolomide) is the only recommended monotherapy, though it was only effective in rare patients. In case of a lack of response to the DTIC

therapy, a cisplatin (or its analogues) combined with other cytostatic drugs (carboplatin, nitrourea, taxanes, vindesine, and vinblastine) may be effective. Unfortunately, this comes at a cost of more unwanted side effects, while the prognosis remains unchanged [2].

3.3. Targeted Therapy

3.3.1. BRAF and MEK. The discovery that up to 66% of MM harbour activating mutations in serine/threonine-protein kinase (BRAF), which results in a constitutively active kinase leading to unregulated growth and proliferation, has led to the development of different targeted therapies, as well as affecting the general diagnostic approach in patients with metastatic diseases. Hence, the testing for BRAF mutations should therefore be considered in all patients with metastatic disease, either by polymerase chain reaction (PCR) or immunohistochemistry (IHC) [39].

Highly selective BRAFV600 inhibitors such as vemurafenib and dabrafenib represented a breakthrough in the treatment of metastatic melanoma. Vemurafenib showed and improved response rate and median overall survival when compared to dacarbazine. Dabrafenib improved progress-free survival and median survival in stage IV MM patients, compared to those treated with dacarbazine [39].

The major issue in most patients is the development of resistance, whereas the mitogen-activated protein kinase (MAPK) pathway reactivation appears to play a major role [39]. Mitogen-activated protein kinase (MEK) is a serine/tyrosine/threonine kinase, which is an important part of the MAPK pathway. One key strategy has been the simultaneous inhibition of both BRAF and MAPK pathways, which is based on data from preclinical studies that have shown that dual BRAF and MEK inhibition increases apoptosis and delays the onset of resistance compared to BRAF inhibitors alone [39]. Furthermore, a common mechanism of resistance to BRAF inhibitors is reactivation of the MAPK pathway. For this reason, it was hypothesized that BRAF inhibitors combined with MEK inhibitors would potentially overcome such resistance. It has been shown that the combination has improved response rates, led to improvements in progression-free survival, and increased the overall survival with manageable toxicity [39].

Previous attempts at targeting mitogen-activated protein kinase kinase (MEK) were limited by toxicity and limited antitumor ability. Newer MEK inhibitors (selumetinib, trametinib, cobimetinib, and binimetinib) have shown promise and have been developed along with BRAF inhibitors as a part of a combination therapeutic strategy [39].

As monotherapy, trametinib showed a survival advantage compared with conventional chemotherapy. Binimetinib has shown similar clinical efficacy in BRAF-mutant melanoma and activity in NRAS-mutant melanoma. Selumetinib has shown an improvement in progress-free survival when compared to chemotherapy. However, the overall response rates are lower than BRAF targeting therapies. Therefore MEK inhibitors are used as part of a combination therapy of BRAF mutated diseases [39].

3.3.2. Type III Transmembrane Receptor Tyrosine Kinase. Certain acral and mucosal subtypes of MM appear to show type III transmembrane receptor tyrosine kinase (KIT) activating mutations. A study in 2011 has shown that imatinib treatment is promising, particularly in patients with an exon 11 or 13 mutation [40]. Nilotinib has also been shown to be effective in patients who were intolerant, or whose disease has progressed after imatinib therapy, as well as those with brain metastases [41]. KIT therapy is still being refined but presents a possible treatment option for selected subsets of patients [39].

3.4. Immunotherapy

3.4.1. Interleukin 2. In the 90s there was a breakthrough in the field of MM treatment. Following the therapies based on DNA-damaging agents, the newest treatment option for MM was immunotherapy in form of IL-2 [42]. It is a protein the size of 15,5 kDa and one of the first extensively described and characterized cytokines. Its mode of action is the binding with a receptor consisting of 3 subunits (IL-2R α , IL-2R β , and IL-2R γ). The combination of these activated the proliferation of T, B, and NK cells, which are of vital importance for the homeostasis of the immune system. In 1998 the FDA approved the use of it as a therapeutic option. The drawback of such a therapy is numerous unwanted side effects (inflammatory response, nausea, diarrhoea, etc.) as well as low response rate [42].

3.4.2. Interferon. Interferons have been, in the past thirty years, among the plethora of drugs, tested for the treatment of MM, both in randomised and nonrandomised studies. Of all the adjuvant options, the IFN- α therapy has proved the most efficient and has since been adopted as part of the standard treatment. It has a broad spectrum of positive effects on the immune system and can aid the removal of the melanoma cells, which might have remained after the operation. It also exhibits an antitumor activity in metastatic diseases [37].

3.4.3. Cytotoxic T-Lymphocyte-Associated Protein 4. Breakthroughs in immunotherapy have also enabled the use of T-cell activation regulation by blocking cytotoxic lymphocyte associated antigen-4 (CTLA-4) in MM therapy. Ipilimumab is a human IgG1 monoclonal antibody that demonstrated an improvement in overall survival through this mechanism even in patients with advanced MM [39, 43].

3.4.4. Programmed Death 1. Clinical benefit has also been seen in programmed death 1 (PD-1) blocking antibodies. Pembrolizumab and nivolumab are antibodies, used in the treatment of distant melanoma metastases. Nivolumab has successfully increased overall survival and one- and two-year survival rates when compared to dacarbazine and ipilimumab. It appears to be very well tolerated, with mild and manageable unwanted side effects such as rash, diarrhoea, and pruritus [39].

Pembrolizumab is a humanized anti-PD-1 IgG4 antibody that has also demonstrated a clinical benefit in patients with advanced MM. It also appears to be well tolerated with few

unwanted side effects. PD-1 pathway inhibiting drugs also show promise in haematological malignancies [39].

Clinically, both CTLA-4 and PD-1 directed monotherapies have proven benefit in advanced MM. Additionally, in preclinical mouse models, the combination of CTLA-4 and PD-1 blockade appeared to be synergistic, leading to the clinical development of this combination. The combination demonstrated increased toxicity, although most seems to be treatable and reversible with prompt intervention [39].

3.5. Adoptive Cell Immunotherapy (ACT). ACT refers to the process of administering autologous or allogenic tumour-reactive T or NK cells to patients with the intent of achieving tumour regression. This process occurs through the isolation of lymphocytes with high affinity for tumour antigens, which can be selected *ex vivo*, stimulated, expanded, and infused back into the patient and represents an area of great promise in the treatment of metastatic MM. It has been shown that numerous antigen-specific T cells can be isolated from excised tumours in MM. The limitations of this approach are the potential logistical and technical hurdles from patient selection, tumour resection, and expansion of adequate numbers of viable tumour infiltrating lymphocyte (TIL) cultures. To address some of these, novel strategies, such as genetically modified T cells, are being developed [39].

4. Preventive Approaches in Skin Cancer Treatment

Regular check-ups for former patients of skin cancer should include active searching for tumour recurrences and also for newly acquired tumours and MM, for which they are more susceptible. These check-ups should offer an opportunity for treating actinic keratosis. Bleeding, ulcerating, or changing lesion biopsies should be performed at the same time. Primary care physicians should aim to discover malignancies at an early stage, when they are still small and easily treated. Preventive measures should be built around the most important etiological factor, namely, sunlight. Exposure to the latter should be reduced, in children and adults alike. Children should avoid unnecessary exposure to sunlight, if they must, then times before 10.00 and past 14.00 are most appropriate. Parents should be reminded of UV radiation hazards (sunburns) and also of chronic sun exposure manifestations, such as wrinkled and thickened skin, irregular pigmentations, actinic keratosis, and tumours. Covering the sun exposed skin is advisable at all times. Sunscreens protect from UVA and UVB radiation. They are proven to protect from actinic keratosis, but not necessarily from BCC. Also, they partially protect from sunburns, though this can mislead the user with regard to the received sun radiation. It has been noticed that many MM patients show suboptimal levels of vitamin D at diagnosis and that people with higher vitamin D levels have a lower MM-related mortality. The links and causality between the two, however, have not yet been established [17, 44].

5. Nanotechnological Methods

5.1. Nanomaterials and Their Attributes. For the treatment of skin cancer, many different types of nanoparticles have been

studied. Some of these are liposomes, dendrimers, polymerosomes, carbon-based nanoparticles, inorganic nanoparticles, and protein-based nanoparticles [45]. Some of these will be presented and further discussed in the following chapters. Also, a brief overview of all mentioned nanotechnological approaches in treating skin cancer can be seen in Figure 2.

Nanosystems can be made from different materials (organic, inorganic) which determine their properties. Recently there have been quite a few studies discussing the different new possibilities of combining pharmacological agents and diagnostic procedures [46, 47]. Some common properties of nanosystems include their size ranging from 1 to 100 nm, design through methodologies that exhibit fundamental control over the physical and chemical attributes of molecular-scale structures, as well their possible combination to form larger structures [48–50]. Some of the other characteristics that emphasize the wide range of their possible use in medicine are related to the fact that the delivery systems based on these structures can be found on different polymeric structures that possess hydrophobic and/or hydrophilic components. This in turn helps to solve the problem of solubility and delivery of highly hydrophobic anticancer drugs via the bloodstream [51]. We know that conventional drug delivery systems (DDSs) are often accompanied by systemic unwanted side effects that are mainly attributable to their nonspecific biodistribution and uncontrollable drug release characteristics. However, functionalized nanomaterials can increase the target specificity as well as the uptake and selective accumulation near a tumour due to the enhanced permeability and retention (EPR) effect [52, 53]. This in turn leads to lower drug doses and fewer unwanted side effects on healthy tissues [54, 55]. These systems can, because of their size, circumvent filtration through the kidneys and therefore stay longer in the bloodstream. With specific adjustments (e.g., PEGylation) their half time can also be increased. Another benefit is that because of their high capacity, it could be possible to use drug carriers with more than one drug in combination therapy. Furthermore, drugs are, as stated previously, with the help of these carriers protected from a wide range of factors (physical and chemical changes in the body, pH changes, ionic strength, etc.), the premature decomposition due to enzymatic activity, or activation of the immune system [48, 56, 57].

5.2. Methods to Achieve Controlled Drug Release. The release of the drug from the carrier can be controlled via external or internal stimuli [58, 59]. The release is mediated by changes in pH (lower in a biochemically more active tumour), temperature (higher in the tumour), redox potential, biological macromolecules (enzymes, glucose, antigens, etc.), light, magnetic field, ultrasound, and a combination of these stimuli [60, 61]. Useful diagnostic modalities are MRI with T1 and/or T2 sensitive agents, fluorescein markers, and radionuclides [56, 57].

5.2.1. Endothelium Targeting. Current nanoparticle aided drug delivery is at its most useful in solid tumour therapy [62, 63]. Molecular biology methodology allows us to uncover

FIGURE 2: Graphically depicted properties and methods of nanotechnology in skin cancer treatment.

potential targets within tumour vasculature, such as integrins, which have a role in angiogenesis [64, 65]. Integrins bind to the tripeptide Arg-Gly-Asp (RGD) inclusive sequences and have been included into a cyclic nanopptide RGD-4C, which binds to integrins $\alpha_5\beta_3$ in $\alpha_5\beta_1$ without any cross-reactivity with thrombocyte integrins and other ubiquitous receptors [66]. Coupling RGD-4C with doxorubicin increases the latter's chemotherapeutic efficacy, which grants a decreased hepatotoxicity and cardiotoxicity [67]. Other binding sequences also exist, such as histidine-tryptophan-glycine-phenylalanine (HWGF), which actively binds to matrilal metalloproteinases 2 and 9, which enhances adenoviral tropism for big blood vessel endothelial and smooth muscle cells [68]. Another such molecule is the NGR hexapeptide, which binds to N angiogenic endothelial cell peptidases [66]. Coupling doxorubicin and melphalan with TNF- α increases the chemoreactivity of chemotherapeutics against murine tumours eight- to tenfold [69]. Another antiangiogenic solid tumour treatment approach uses a synthetic $\alpha_5\beta_3$ analogue with the intention of targeted delivery of therapeutic genes complexed with cation nanoparticles in tumour endothelial cells [70]. A similar approach is used for location specific MR imaging with $\alpha_5\beta_3$ targeted paramagnetic nanoparticles, which can discover early tumour angiogenesis [66, 71].

Other methods include selective targeting of blood and lymphatic vessels with peptide covered quantum dots [72] and also with NGR covered liposomes for tumour blood vessel closure [73].

Other important endothelial targets for therapeutic drug delivery include cell adhesion molecules (CAMs) (e.g., ICAM-1 and PECAM-1). Anti-CAM nanoparticles can deliver compounds to pulmonary and heart endothelium in vivo [66, 74].

5.2.2. pH Controlled Drug Release. Some human tissues have, under certain conditions such as cancer or inflammation, a lower pH than healthy tissues [75, 76]. These pH differences are a useable stimulus for property modulation of certain materials, which can be used for specific reactions, such as controlled drug release [77].

An example of this principle is mesoporous silica nanoparticles (MSNP), which can, in intravenous use, release the incorporated drug before they reach the target area. This is an undesired effect, since the potentially toxic drugs damage healthy cells before they reach the cancer cells. Difference in pH can be used as a release stimulus, because the pores present in silica nanoparticles can be blocked by pH sensitive functional groups and hence can be unblocked when pH reaches a low enough value [78, 79]. For this, we use different classes of pH sensitive molecules, which efficiently close the pores [78, 79].

5.2.3. Temperature Controlled Drug Release. Heat is another stimulus that can be used for triggered release of molecules from MSNP [80, 81]. Temperature of many tumours is slightly higher than normal body temperature. With this

phenomenon in mind, we can use temperature responsive polymers as the pores' plugs [82, 83]. A commonly used temperature responsive polymer is poly(N-isopropylacrylamide) (PNIPAM) [84]. Volume of the said polymer can change in water, at the so-called low critical solution temperature (LCST) [85]. Below this temperature, the PNIPAM chains are hydrated and hence extended. This can, in connection with MSNPs, prevent the drug release from the pores. At the temperatures above the LCST, PNIPAM chains dehydrate, which causes them to contract, and release the drug held within [86]. Pure PNIPAM is usually not used in such drug delivery, because its LCST is about 32°C, which is, in light of the higher normal body temperature, inappropriate, because it would keep the pores open at all times. We can, however, raise the LCST by copolymerization with other monomers (acrylamide, or N-isopropylmethacrylamide) [87, 88] to about 37°C [89, 90]. By using this copolymerized PNIPAM, one can raise the releasing temperature to above 37°C. Higher temperatures can also be achieved by external stimulation, for example, magnetic field, or light, which interact with the inorganic nanoparticles included in or bound to the MSNP. An interesting use of this principle is a combination of iron oxide nanoparticles and PNIPAM. Exposing the said system to an outer electromagnetic field causes a raise in the local temperature around the nanoparticles, which subsequently leads to a phase transformation of PNIPAM, which enables the release of the drug [91].

5.2.4. Redox Potential Control. Intracellular and extracellular environments of living tissues exhibit different redox potentials. Due to a 100–1000-fold increase of glutathione (GSH) levels within tumour cells compared to the extracellular levels, a natural redox potential may occur [86]. These potential differences can be used for triggering the drug release from nanoparticles within the cancer cells (inside trigger). Here, similarly to the pH system, a redox responsive system was devised, where a variety of nanoplasts may be used. Particles used for this purpose include CdS [92], Fe₃O₄ [93], or gold nanoparticles [94], but also MSNP, covalently bound to biomolecules. The typical redox responsive plug-MSNP bond is a disulphide one [95]. Due to high intracellular GSH concentration, the disulphide bridge dissolves, which causes the emergence of two thiol groups on the targeted tumour site, because GSH acts as a reducing agent [95]. Low blood reducing agent levels allow for the disulphide connections to remain intact.

5.2.5. Biomechanical Triggering. Biocompatible and bioactive molecules are, due to their responsiveness to bodily stimuli, frequently used for controlled drug release. The most often used biomolecules are bioenzymes (e.g., β -D-galactosidase [96]), glucose, antigens, and aptamer targets [97]. Enzyme responsive nanogates are, due to anomalous elevation of enzymatic activity in certain unhealthy tissues, a feasible option for MSNP pore closure.

5.2.6. Optic Tuning. Light can be, thanks to its specific physical properties, used as a trigger for releasing encapsulated molecules from micro- and nanosystems. It is possible,

within the MSNP frame, to successfully include light sensitive molecules, which gives us a light-responsive drug delivery system. The light-responsive MSNP state modulation can be reversible or irreversible, which is usually dependent on the manner of chromophore bonding to MSNPs. The photochromic nanoparticle component isomerisation is usually followed by heat or visible reversion. Light, used as the stimulant, has usually a wavelength of 300–400 nm, while we use visible light ($\lambda > 400$ nm) in order to achieve reversion. The reversible pore plugging and unplugging offers some distinct advantages, because it enables the possibility of using complex drug releasing mechanisms [66].

5.2.7. Magnetic Activation. Magnetic nanoparticles (MNPs), sized 10–100 nm, which are responsive to a magnetic field, are used as multimodal drug delivery systems, based on their superparamagnetic properties [98, 99]. Materials, used most often, are iron oxide nanoparticles (IONP) [100, 101]. They are used in two main forms, namely, magnetite (Fe₃O₄) and its oxidised metabolite, maghemite (γ -Fe₂O₃) [102]. The magnetic field is created using strong permanent magnets, usually of the neodymium kind. In order to localize the nanoparticles in the target tissue, one must focus the magnetic field on a specific area to which the IONP (with the incorporated drug) are drawn [103, 104]. The power and location of the magnetic field are adaptable, which means that we may control the nanoparticle accumulation, which lessens the unwanted cytotoxic effects on healthy tissues [105]. The magnetic field gradient is dependent on local resistance (caused by blood flow and depth of the targeted site), which makes these nanoparticles more efficient in areas with less blood flow, and closer to the surface. IONP are, in general, coated with hydrophobic polymers, which makes them less susceptible to opsonization, which, in turn, prolongs the circulation time and secures the binding surface for drug molecules, or specific target ligands [106]. MSNP in combination with magnetic nanoparticles represent a promising alternative drug delivery method, one which is advantageous due to its high capacity, target specificity, and magnetic properties that are useful in targeting and controlled drug release [91].

5.3. Common Nanoparticulate Systems

5.3.1. Liposomes. Liposomes are phospholipid vesicles ranging in size mostly from 50 to 100 nm. Their membrane is double layered, quite similar to biological ones, with an internal aqueous phase [107]. Liposomes can be divided according to their size and number of layers into multi-, oligo-, or unilamellar [108]. The aqueous core can be used for the encapsulation of water soluble drugs, whereas the lipid membrane can act as a carrier for hydrophobic and amphiphilic compounds [108]. To avoid the reticuloendothelial system (RES) after intravenous injection special PEGylated liposomes have been developed (sometimes called "stealth liposomes"), which reduce the clearance of the active compound and prolong the circulation half time. Other positive features of liposomes are very good circulation, penetration, and diffusion qualities [107, 108]. The surface of the vesicles can be bound with ligands or polymers,

which extensively increases their specificity for drug delivery. Research has already shown that liposomes gather close to tumour vessels in the interstitial fluid. There are currently a few different types of liposomes used as drug carriers for anticancer therapy. One of these therapies is also the treatment of MM [109, 110].

The advance in cationic liposomes has led to a successful delivery of siRNA [109, 111]. Theranostic liposomes have also been developed, which can be equipped with an array of different nanoparticles as well as an active compound. Some are used in anticancer therapy with a special vitamin E based coating called D- α -tocopherol polyethylene glycol succinate (TPGS). Liposomes can be modified to include magnetic elements, which allow for real time monitoring or for the entrapment of gasses and drugs [45].

Liposomes filled with doxorubicin, cisplatin, oxaliplatin, camptothecin, and other drugs have reached higher cytotoxicity and decreased adverse effects, due to targeted release [45]. According to a study conducted by Fang et al. [112], flexible liposomes increased aminolevulinic acid penetrance better than lysosomes, though both increased penetrance in comparison to the control treatment. Niosomes (nonionic surfactant vesicles) filled with 5-fluorouracil produced an eightfold increase in cytotoxicity, compared to an aqueous solution [45].

5.3.2. Solid Lipid Nanoparticles. Solid lipid nanoparticles (SLNs) were presented in 1990 as an alternative to liposomes, emulsion, and polymeric nanoparticles as drug carriers. They are very stable and therefore provide protection from degradation of the drug as well as enable easy control over drug release [113, 114]. Organic solvents are not required for their development. They are biodegradable, biocompatible and very rarely toxic. Furthermore, their production and sterilization are not profoundly difficult. It has been shown that with the use of these nanoparticles the in vitro and in vivo efficacy of the drug docetaxel in colorectal cancer and MM has increased [45].

5.3.3. Polymeric Mycelia and Nanospheres. Polymeric mycelia are structures that consist of two or more polymeric chains with varying degrees of hydrophobicity [115, 116]. Mycelia spontaneously converge into a characteristic (mycelial) structure, which consist of a centre and a shell with different properties. The hydrophobic parts form the centre, which decreases their exposure to an aqueous environment, while the hydrophilic parts form the shell that remain in contact with the aqueous environment, thereby stabilizing the centre [117]. The usual size of pharmaceutically useful mycelia is 10–80 nm. Since they are smaller in size than liposomes they have a shorter circulation time and are more inclined to enter tumours, due to the EPR effect [118]. Drugs with low solubility can be transported in the hydrophobic centre, while the hydrophilic shell offers sterical protection to the mycelium, which reduces systemic toxicity. Its usefulness can be improved with the inclusion of ligands into the shell (e.g., antibodies, peptides, nucleic acid aptamers, carbohydrates, and other molecules) [117].

Polymeric mycelia are usually more stable in the blood-stream than liposomes and other surface mycelia [118]. They can be used to deliver two or more active ingredients in combined therapy, due to their considerable size. Paramagnetic metals, like gadolinium or manganese that are often used as contrast agents, can be inserted into the mycelia. As such, they can also be used in imaging [119, 120].

Polymeric nanospheres are insoluble colloid nano- or microparticles with a polymeric centre, about 10–1000 nm in size. They are usually used as pH sensitive pharmaceutical delivery systems and are administered per os [45].

5.3.4. Dendrimers. Dendrimers are unimolecular monodisperse synthetic polymers that possess a layered structure and are sized below 15 nm. They consist of a core, made of repeating units and various terminal groups, that determine their 3D structure [121, 122]. They can be made to deliver hydrophilic or hydrophobic pharmaceuticals, nucleic acids, and imaging contrasts, due to their well-defined size, molecular mass, monodispersity, multivalency, the number of available internal compartments, high level of branching, and many functional groups on the surface [121]. Dendrimer targeted ligands are capable of specific targeting and tumour elimination [122, 123]. These ligands include oligosaccharides, polysaccharides, oligopeptides, semiunsaturated fatty acids, folates, and tumour associated antigens. The downside to dendrimers is the difficulty to release the pharmaceutical in a controlled manner. New developments in dendrimer and polymeric chemistry have produced a new type of molecule, called dendronized polymers [124]. Dendronized polymers are linear polymers that carry dendrons on every repeated unit and have an increased circulation time, which is advantageous for drug delivery. A drug can also be bound to a degradable link that can be used to control the release of the drug [125–127].

5.3.5. Nanotubes. Carbon nanotubes are carbon allotropes, composed of one or more coaxial sheaths of graphite only a few atom layers thick and folded into cylinders [128]. They can be single-walled or multiwalled and exhibit extraordinary physical, photochemical, and electrochemical properties [128, 129]. Being semiconductors, they are often used as biosensors [130, 131]. They can also be used as drug transporters or as a basis for tissue regeneration [132]. Single wall carbon fibre nanotubes (SWCNT) that are capable of tumour targeting are synthesized by covalently binding several copies of tumour specific monoclonal antibodies, radiating ion chelates and fluorescent probes to the tubes [132]. This system can then be filled with molecules of an antitumor drug. Since this does not require covalent bonding, the antibodies capability to bind to tumour cells is not impaired by a greater quantity of the drug [133]. They can be used to carry gadolinium atoms, which is useful in MRI imaging of tumours. They can also be equipped with agonists or antagonists to various receptors on their surface, which can be used to treat the tumour [45].

5.3.6. Mesoporous Nanoparticles Based on Silica. Mesoporous silica is an effective drug transporter. In comparison to

common organic transporters, they have a variable particle size, a different morphology, an even and adjustable pore size, high chemical and mechanical stability, a large surface, pore volume, a great drug transporting capacity, and simple surface functionality [45, 101, 134–136].

5.3.7. Quantum Dots. Quantum dots are colloid fluorescent semiconductive nanocrystals with a size of 2–10 nm. They have a broad absorption spectrum and a symmetrical and narrow emission, usually in the visible spectrum near the infrared area [137]. The central core of the quantum dots usually consists of a combination of elements of the II–VI groups (e.g., zinc, cadmium, selenium, and tellurium), or the III–V groups (e.g., arsenic and phosphorus) of the periodic table, enveloped by a sheath of ZnS [137, 138]. By changing the size and composition, we can control the emission spectrum and quantum results. They are suitable for high-intensity, long-term, multitarget bioimaging applications, due to their photostability [137–140].

We can select a specific colour of emission of a quantum dot. In order to detect MM, however, we have to create a hydrophilic surface and attach a ligand that can be used to detect the tumour [141]. These ligands can be antibodies, peptides, smaller molecules, or inhibitors [141, 142].

Biocompatibility can be increased by adding silicon or other biocompatible polymer sheaths, which also decreases their toxicity.

5.3.8. Gold Nanoparticles. Gold nanoparticles are metal nanoparticles that can be formed into various geometric structures, such as nanospheres, nanocages, and nanorods of 1–150 nm in size [143]. These particles show a combination of physical, chemical, optical, and electronic properties that are not found in other biomedical nanomaterials and are applicable in gene delivery, as contrasting agents and as part of drug delivery systems [144, 145]. The advantages of gold nanoparticles lie in the simple synthesis of various particle sizes, confirmed biocompatibility, and the capability to conjugate with other biomolecules without changing their biological properties [146, 147]. Particles under 50 nm can pass the blood-brain barrier. They are also nontoxic and biocompatible, as they do not induce an allergic or immune response of any kind [45].

5.3.9. Superparamagnetic Ferrous Oxide Nanoparticles and Thermal Therapy. These are nanoparticles composed of ferrous oxide, covered with a sheath, that enables stability, prevents agglomeration, and enables other functions (e.g., targeting, binding of active ingredients) [100, 101]. They can very effectively be synthesized by decomposing iron precursors while being immersed in oleic acid. These particles, however, are hydrophobic and need further manipulation to achieve hydrophilicity [148].

These nanoparticles gain a large magnetic momentum in an external magnetic field and are therefore considered as superparamagnetic materials, which makes them interesting for biomedical use [149]. They can be used as a contrast in MRI, since they produce a large quantity of contrast per unit, which means that a small dose of particles is sufficient for the

imaging, which decreases toxicity [150, 151]. These particles are capable of transforming the energy of an external magnetic field into heat, which can be used to treat tumours, since tumour cells are more susceptible to high temperatures than normal human cells [152]. Their surface can be augmented with various functional groups, increasing biocompatibility and biodegradability, which further increases their usefulness. Polymers like cellulose, dextran, PEG, or PLGA that can also be added to the surface increase their biocompatibility and biodegradability [153–155].

In past decades, cancer treatment has been mostly based on chemotherapy, radiation, and/or surgery. Certain additional kinds of therapy, for example, therapeutic hyperthermia, have been to some degree successful but have yet to become a part of the standard variety of therapies [156]. The reason for this lies in the difficulty of an accurate differentiation between normal and cancer tissue, but also in the failure of specific targeting of tumours, as well as insufficient understanding with regard to hyperthermic cytotoxicity [157].

In 1991 Roizin-Towle and Pirro discovered that one can destroy all cells with an appropriate amount of heat. However, compared to normal cells, *in vitro* experiments have not shown any increased sensitivity of tumour cells to heat. This differs in radiotherapy and chemotherapy. The aforementioned authors have shown that, in thermal therapy, one needs to achieve a high enough concentration of active particles (ones that are able to emit heat) in the immediate proximity of the tumour cells [156]. Although there is a noticeable difference *in vivo*, there is still a lack of clinically available technology that would make it possible for the active particles to be accurately applied in the effective proximity of the tumours [157].

Hyperthermia is only effective in treating tumours if certain conditions are met [158, 159]. These are a high enough concentration of nanoparticles in the tumour, which is also considerably higher than that in the surrounding healthy tissue, and a sufficiently high specific absorption particle level that is responsible for a sufficiently high intratumoural amount of applied heat, which must be tolerable for the normal tissues [157].

There are three currently researched methods of therapeutically heating nanoparticles. These are optical laser heating, ultrasound heating of small bubbles, and heating of metal nanoparticles, aided by an alternating magnetic field [159–161]. Naturally, there are pros and cons to each of the aforementioned methods. The optical method is an effective way of heating the particles but is limited by the depth related weakening of the laser. Ultrasound is capable of targeted energy focus, but the delivered energy is not constant because of the different sound velocity in different tissues, and the probe opening is also rather small. Magnetic nanoparticles can be effectively heated at any depth, and they can also be used in diagnostic imaging procedures [157].

Hyperthermia can also be used as a form of adjuvant therapy, because it is well-known that exposure of tumour cells to even a slightly raised temperature increases the sensitivity of these cells for chemotherapy and radiotherapy [162–164]. One of the oldest uses of heat application can be

found in treating intraperitoneal ovary cancer metastases, where a higher effectiveness of certain chemotherapeutics has been proven. However, there are limitations to this method as well, for it is impossible to deliver the same amount of heat to all the metastases [157].

Currently, chemotherapy is only an adjuvant therapy to radiotherapy in solid tumours, because selective delivery of the chemotherapeutics to the tumours is lacking, which could be changed with the usage of localized hyperthermia [160, 161, 165]. In this way, the effectiveness of the chemotherapeutics could be increased, which would allow for a lower dosage of the drug in question, which also means that the toxicity in the nontumour tissue would decrease [157].

The combination of chemotherapeutics and hyperthermia can be adjusted, depending on the type and site of the tumour, also for the dose of the drug, and temperature. Much also depends on the chemotherapeutic in question, because the highest effectiveness of the alkylating agents is achieved at 41.5°C, while some other drugs (like cisplatin) can be effective at lower temperatures as well. Raising the temperature to 2–3°C above the basal level raises the local blood flow in the heated areas during and also for a while after heating, which allows for the accumulation of the chemotherapeutics near the heated areas [157].

Additionally, hyperthermia can improve radiotherapy, because ionizing radiation damages the DNA, while heat damages proteins, responsible for the repair of the former. Moreover, hyperthermia can also destroy cells in the hypoxic areas of the tumours, those that are more resistant to radiation [157].

One can heat the nanoparticles in a variety of ways, such as with dielectric energy losses in a material with low electrical conductivity, losses of energy of the Foucault currents in a material with high electroconductivity, frictional heating induced with physical spinning of an anisotropic magnetic particle, and hysteretic losses in a magnetic material [156]. The first two mechanisms can, however, cause unwanted heating of the normal tissue, which makes them clinically less interesting [156].

Frictional heating is possible because of the physical spinning of an anisotropic magnetic particle in an alternating magnetic field, which leads to energy losses. Such heating may induce mechanical cell damage [157]. Hysteretic energy loss is possible because of an irreversible particle magnetization in an alternating magnetic field [156].

5.4. Nanotechnological Approaches in Treating Skin Cancer.

In the field of MM research there have been many new studies in which researchers tried combining new nanotechnological advances with conventional methods and treatment procedures (chemotherapy, photodynamic therapy, etc.) for developing new potential ways of treatment [166]. For example, the Food and Drug Administration (FDA) has permitted clinical trials for at least two novel nanoparticle based formulations with incorporated antitumor drugs, for example, Doxil (Janssen Biotech, Horsham, PA, USA) and Nab-paclitaxel (Abraxane).

Maria Bernadete R Pierre et al. determined that liposomes can reach the appropriate depth to treat skin cancer

(epidermis, dermis) by transdermal application [167]. In a study that included 26 patients, Bedikian et al. achieved an 31% improvement over metastatic malignant lymphoma, using liposomes with vincristine, compared to the control group [168].

Huber et al. investigated the possibility of using doxorubicin (DOX) filled cationic solid lipid nanoparticles (DOX-SLN) to increase distribution and tumour penetration of DOX. In vivo DOX-SLN iontophoresis was effective in inhibiting tumour growth [169].

Mycelia were used in a small-scale phase 1 study, which showed that patients with MM tolerate NC6004 (Nanoplatin) well [170].

Dendrimers were successfully used in immunotherapy, immunoradiotherapy, and other tumour treatments, among others in MM and SCC. They can also be used for diagnostic imaging of cancer cells (e.g., MRI). Gadolinium dendrimer conjugates were shown to enable selective large-scale targeting and imaging of tumours [45, 171, 172].

A low solubility antitumor compound camptothecin has been loaded into polyvinyl alcohol-functionalized multi-walled nanotubes. The results showed that such a combination could be used to treat breast and skin cancer [173].

Gold nanoparticles can be used to increase cell and tissue sensitivity to therapy and to guide and control surgical procedures. Various active ingredients, including proteins, DNA, and smaller drug molecules, can be bound to the surface of gold nanoparticles, which leads to a therapeutic effect in different kinds of tumours, including MM [174, 175]. They are also excellent markers for biosensors, as they can be detected in many ways, such as optic absorption, fluorescence, and electrical conductivity. Together with reflex microscopy, antibody-bound gold nanoparticles enable highly sensitive cancer imaging [145, 174, 175].

Superparamagnetic ferrous oxide thermal therapy can be used as an adjuvant therapy in order to sensitise cancer cells to chemotherapy or radiotherapy. Rao et al. have additionally shown that epirubicin loaded superparamagnetic ferrous oxide particles are also suitable for transdermal skin cancer therapy [176].

5.5. Theranostics: An Inspiring Approach Adjusted to Future Cancer Treatment Needs.

The term theranostics was first used by Funkhouser in 2002 [177]. By definition, theranostics provides a combination of diagnostic and therapeutic capabilities, and as such shows great promise to significantly contribute to the advancement of personalized medicine [46, 56]. Theranostic nanomedicine is an interdisciplinary field, which combines the expertise of genomics, proteomics, metabolomics, biophysics, pharmacology, pharmaceutical technology, and so forth. The main aim is to develop an efficient and safe nanosystem that is composed of a high capacity nanoplatform that can carry therapeutic agents and at the same time include a diagnostic component, hence combining both imaging and therapeutic functions [178, 179]. Release of the therapeutic agent on target site could be spontaneous or specially specified (e.g., influence of external or internal chemical and physical stimuli). Such systems could be guided, followed, and monitored to the point of determining the

pharmacodynamic and pharmacokinetic properties of the drug in real time [47, 178, 179]. Moreover, with the selection of the appropriate nanoplatform, one could bypass certain pharmacokinetic limitations of drugs, which could lead to an easier mode of application and, with regard to the aim of reducing systemic toxicity, improve selectivity of targeting only diseased tissues. Due to all mentioned, this field shows most likely the biggest potential in oncology [166]. A great example of that is the sheer number of published studies and articles. Orecchioni et al., for example, recently reviewed the latest studies about the promising usage of graphene as a nanoplatform in cancer therapy [180]. Furthermore, von Felbert et al. recently published their study about improving the specificity of drug transporters as theranostic agents. They developed a homogenous phototheranostic system which combines optic imaging, photodynamic therapy, and immunotherapy [181]. Last but not least, there were also some newer theranostic advances in treating skin cancer. For example, in the study described by Vannucci et al. [182], they have developed a nanoparticle based on the heavy chain of the human protein ferritin and coated it with melanocyte stimulating hormone (MSH), with which they assured tissue specificity. The as-prepared nanoparticles were also coated with PEG molecules, which prevented their binding to unwanted receptors. They also added the fluorescent dye rhodamine as the diagnostic component [182]. Another example of theranostics in skin cancer treatment has been presented in the study by Ma et al., where they used lipid nanomicelles as the carrier for docetaxel. For the diagnostic monitoring they used fluorescent dye 1,1'-dioctadecyl-3,3,3',3'-tetramethyl indotricarbocyanine iodide (DiR) [183]. Both examples show very promising results that could, in a not that far future, make them applicable also in the clinics.

6. Potential Impact of Nanotechnology on Future Skin Cancer Treatment

Novel treatment approaches, regardless of the disease, are meant to be more efficient, cheaper, and without any sacrifice of patient safety, if not even improving it. To achieve the latter, an ideal treatment should be developed taking into account good patient compliance, a better overall treatment efficiency, a very low possible toxicity, and very high yields of reaching the targeted site in the body per unit mass of the medicine. Nanotechnology based formulations can provide all mentioned. They can be more efficient, since they can be decorated with targeting moieties (e.g., antibodies) [184], and at the same time deliver and release the payload in a controlled manner [185]. Both mentioned leads also to a lowered toxicity, since lower doses are necessary to achieve the same effect [186], as well as the targeting and controlled release only at the targeted site, and renders the toxicity highly localized. The latter is also in direct relation to the high yields of the delivery [187]. Knowing these potential advantages of such formulations, it comes to no surprise that these are heavily researched and that there is a high demand for their uptake into clinical practice as soon proven safe. And indeed, there are at least two already approved nanotechnology based formulations used in cancer treatment. As mentioned

already above, these are Doxil (Janssen Biotech, Horsham, PA, USA), a doxorubicin containing liposome injection, and Nab-paclitaxel (Abraxane), which contains paclitaxel bound to albumin nanoparticles ($2r \approx 130$ nm).

Considering all mentioned in regard of skin cancer treatment, there are some promising (at least research) trends that could well mean significant improvements in the potential treatment outcome for skin cancer patients. Several different forms of novel nanosized formulations have been already developed and are presently in different stages of testing [2, 188, 189]. Among others, various lipid-based particles (e.g., micelles, solid lipid particles) are particularly popular [167–169]. These not only have often the ability to outsmart the host defence of the organism, which for itself leads to improved yields of the payload delivery [190], but at the same time provide different other targeting approaches to improve this yield even more. Carbon nanostructures are still among the most researched types of nanostructures for biomedical applications [191, 192], especially considering the high interest in them for various other applications (e.g., molecular electronics), a vast number of modification approaches are available for them [193, 194], making them interesting candidates for future effective cancer treatment [173].

Finally, we believe that the most promising future treatment approaches lie in the field of theranostics, which combines all the right “ingredients” to meet all the requirements of the ideal treatment approach. As such, several novel treatment solutions in skin cancer were already studied [182, 183].

It is worth noting that, from our perspective, MNPs seem to be among the most promising nanoparticulate agents, especially in the treatment of “hard-to-treat” cancer forms (e.g., MM). Among MNPs, the most commonly used particles are certainly based on iron oxides [100, 101]. The latter were combined with various drugs (e.g., epirubicin) [176] and are on their own capable of being used to induce magnetic hyperthermia [158, 159], and since they are mostly functionalized in order to prevent agglomeration [195], their surface is suitable for anchoring different targeting moieties (e.g., antibodies) [196, 197].

7. Conclusions

New nanotechnological materials appear to be efficient cytostatic delivery systems, capable of tumour targeting and thereby decreasing adverse effects, increasing therapy effectiveness, and increasing the survival of skin cancer patients. New pharmaceuticals combined with improved delivery systems therefore present a developing field that will surely improve skin cancer treatment for patients, by improving either the quality of life or survival of affected patients. Finally, through this development, medical professionals will gain new and accurate diagnostic and effective therapeutic options. The advent of new delivery systems can already be seen in the use of transdermal patches [176].

Abbreviations

BCC: Basal cell carcinoma
SCC: Squamous cell carcinoma

CSC:	Cancer stem cell
CMC:	Circulating melanoma cells
EPR:	Enhanced permeability and retention
HPV:	Human papilloma virus
MM:	Malignant melanoma
UVA:	Ultraviolet A
UVB:	Ultraviolet B
TPGS:	D-Alpha-tocopheryl polyethylene glycol 1000 succinate monoester
EDC:	Electrodessication and curettage
MSNPs:	Mesoporous silica nanoparticles
PCR:	Polymerase chain reaction
ISH:	In situ hybridization
PD:	Programmed death
SWCNT:	Single wall carbon nanotubes
IONP:	Iron oxide nanoparticles magnetic
LCST:	Lower critical solution temperature
KIT:	Type III transmembrane receptor tyrosine kinase
MEK:	Mitogen-activated protein kinase
BRAF:	Serine/threonine-protein kinase
CTLA-4:	Cytotoxic T-lymphocyte-associated protein 4
IL-2:	Interleukin 2.

Disclosure

Kristjan Orthaber, Matevž Pristovnik, and Kristijan Skok share the first authorship.

Competing Interests

All authors state that there is no conflict of interests.

Authors' Contributions

Kristjan Orthaber, Matevž Pristovnik, and Kristijan Skok contributed equally to this work.

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