REVIEW ARTICLE

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Current state of melanoma treatment – from conventional therapies to nanotechnology and beyond

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Abstract

Introduction and Objective. Melanoma is recognized as the most aggressive type of skin cancer, and its global incidence is rising. Early detection of melanoma is crucial, as it allows for curative surgical removal with clear margins based on the tumour's depth. However, managing advanced melanoma, particularly cases with metastasis, remains a significant clinical challenge, often leading to fatal outcomes. The aim of the review is to highlight the current knowledge of melanoma treatment strategies, with a focus on both conventional therapies and recent advancements, including immunotherapy and nanotechnology-based approaches.

Review Methods. The literature review made use of databases including PubMed and Google Scholar, with the sources ranging from 2017–2024. Key words included primarily 'melanoma', 'melanoma treatment' and 'melanoma therapy'. Peer-reviewed articles were included, both reviews and original research papers involving cell lines, animal models, and patient cohorts.

Brief description of the state of knowledge. Treatment such as radiotherapy and chemotherapy face such challenges as resistance, leading to melanoma recurrence and progression, along with side-effects. Recent advancements focus on more targeted and personalised treatments. Targeted therapies and immunotherapies, particularly with immune checkpoint inhibitors, have shown considerable potential, although they also come with limitations. Hence, innovative approaches, including the use of nanotechnology and combination therapies, are being developed to further enhance melanoma treatment.

Summary. The significant metastatic capacity of melanoma, the poor prognosis associated with its advanced stages, and the limitations of conventional therapies, emphasise the need for novel treatment strategies.

Key words

melanoma, melanoma treatment, conventional therapies, targeted therapy, immunotherapy, nanotechnology

INTRODUCTION AND OBJECTIVE

Melanoma, a malignancy arising in pigment-producing cells–melanocytes, is the most aggressive form of skin cancer, and its incidence has been increasing worldwide [1–3]. The cancer can arise in different anatomical sites, most commonly in the skin (cutaneous melanoma), but also in the eye (uveal melanoma) [4], mucosal membranes [5], or even the central nervous system [6]. The review focuses on cutaneous melanoma, which causes approximately 55,500 deaths annually [1].

Malignant melanoma of the skin can be caused by a variety of exogenous and endogenous risk factors, with ultraviolet (UV) radiation and sunburns being the primary exogenous factors leading to the development of this and other skin cancers [1]. Factors like ageing further increase this risk, as prolonged UV exposure leads to an accumulation of mutations due to weakened DNA repair mechanisms and changes in cell division [7]. Considering the genetic factors, several germline mutations in genes such as *CDKN2A* (the most common alterations), *CDK4, MITF, TERT* or *MC1R*, have been linked to a higher likelihood of developing familial cutaneous melanoma [8, 9]. Regarding somatic mutations status, cutaneous melanoma can be classified into four subtypes: B-Raf proto-oncogene serine/threonine kinase (*BRAF*) mutant (~40–60% of cases); neuroblastoma RAS viral oncogene homolog, proto-oncogene GTPase (*NRAS*) mutant (~24% of cases); neurofibromin 1 (*NF1*) mutant; and triple wild-type for *BRAF*, *NRAS*, and *NF1* mutations [10, 11].

Melanoma is also classified using the tumour–nodes–metastasis (TNM) staging system to identify different stages of the disease: localised (stage I–II), node-positive (stage III), and advanced or metastatic (stage IV). The current classification system is based on the American Joint Committee on Cancer (AJCC), 8th Edition [12, 13]. Key factors for staging and evaluating recurrence risk include tumour thickness (Breslow depth), ulceration, mitotic rate, microsatellite and in-transit lesions, lymph node involvement, and the presence of distant metastases. Most cases of cutaneous melanoma are diagnosed at a localised stage and are effectively treated through surgical removal with sufficient margins [14].

Therapeutic efficacy for more advanced melanoma, especially in cases where tumour has already metastasized,

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remains a significant clinical challenge [15]. Nevertheless, melanoma, considered among the most resistant cancers to traditional treatments like chemotherapy, radiation therapy, and early targeted therapies, has experienced dramatic improvements in clinical and therapeutic approaches over the past decade. These improvements are driven by advancements in cancer cell biology, immunology and the development of nanotechnology [16, 17]. When treated with combination immunotherapy, about 50% of patients with metastatic melanoma survive for five years following diagnosis [18]. Additionally, more than one-third of patients continue to survive after several years on combination BRAF/MAPK kinase (MEK) targeted therapy [19] or single-agent PD-1 blockade [20]. Despite the treatment advances, there remains a need for further therapeutic options for patients who are resistant to the targeted and immune treatments.

The primary aim of this review is to discuss the current knowledge on the treatment of malignant cutaneous melanoma, and to summarise both the advantages and limitations of conventional therapies, targeted- and immunotherapies. The use of nanoparticles in melanoma treatment (with their major advantages and limitations) is also summarised. Additionally, other emerging therapies are mentioned.

REVIEW METHODS

Source publications were searched using electronic databases such as PubMed and Google Scholar. The inclusion criteria were based on peer review original articles and review papers published between 2017–2014. Previously published articles were excluded unless they presented historical perspectives or important findings. The recommendations of the NCCN, EORTC and ESMO organisations were also used to find information (URL: https://www.nccn.org/; https://www.eortc.org/; https://www.esmo.org). Key words included primarily 'melanoma', 'melanoma treatment' and 'melanoma therapy'. For further search, the combination of words: 'surgery', 'radiotherapy', 'chemotherapy', 'targeted therapy', 'immunotherapy', 'nanotechnology', 'nanoparticles', 'photodynamic therapy', 'photothermal therapy' and 'PROTACs' with the word 'melanoma' was used.

STATE OF KNOWLEDGE

Conventional therapies. Surgical intervention is typically the first-line treatment for early-stage melanoma and remains a valuable option for localised disease. For suspected melanocytic lesions, an excisional biopsy that includes the entire lesion with a margin of 1–3 mm is considered the standard diagnostic procedure. It is worth emphasising that any suspected lesion as a surgical specimen needs to be returned for histopathological analysis. Partial biopsies or punch biopsies are not recommended, since they may lead to a spread of melanoma cells, and as a consequence, also mortality risk [21]. Hence, they are only performed under certain circumstances. For instance, partial biopsies may be indicated for larger lesions located in areas such as the head, neck, hands, feet, anterior legs, or genitalia [22]. The subsequent course of treatment is determined by the results of the histopathological examination.

Guidelines from the National Comprehensive Cancer Network (NCCN), the European Organisation for Research and Treatment of Cancer (EORTC), and the European Society for Medical Oncology (ESMO), all provide similar recommendations for surgical excision margins in the treatment of primary cutaneous melanoma, based on the Breslow thickness. For melanoma *in situ,* all three organisations recommend margins of 5–10 mm, with consideration for narrower margins in sensitive areas such as the face, where Mohs micrographic surgery may be used. For melanomas ≤1 mm in thickness, a 1 cm margin is generally recommended. For melanomas measuring 1–2 mm, the guidelines suggest a margin of 1–2 cm. In cases of melanoma between 2–4 mm, a margin of 2 cm is preferred, and this is consistent for melanomas >4 mm. These recommendations aim to ensure complete tumour removal (URL: https://www.nccn.org/; https://www.eortc.org/; https://www.esmo.org/; accessed: September, 2024).

Sentinel lymph node biopsy (SLNB) is a critical procedure for staging and prognostic evaluation in melanoma patients, particularly those with higher-risk tumours. The decision to perform SLNB depends primarily on the Breslow thickness of the melanoma and additional histopathological features. Generally, SLNB is recommended for melanomas with a Breslow thickness of 0.8 mm or bigger, or for those less than 0.8 mm that exhibit high-risk characteristics, such as ulceration or a high mitotic rate. In these cases, SLNB helps determine if there has been microscopic metastasis to regional lymph nodes, which is not detectable through clinical examination or imaging. In particular, SLNB is not usually recommended for melanomas thinner than <0.8 mm unless there are high-risk features, such as ulceration or tumour regression, which could increase the potential for nodal involvement and a positive deep margin are present, SLNB may still be considered.

For thicker melanomas (≥1 mm), SLNB is strongly recommended, as the risk of sentinel lymph node metastasis increases significantly with tumour thickness. Other histopathological indicators influencing the decision to perform SLNB include tumour ulceration, high mitotic index, and lymphovascular invasion, all of which are associated with a higher likelihood of lymphatic spread. Moreover, SLNB should be conducted in patients with intermediate to thick melanomas (1.0–4.0 mm and above), as this procedure can provide crucial staging information and guide further management, such as the need for adjuvant therapy. The presence of microscopic metastasis in sentinel lymph nodes is an important prognostic marker that significantly impacts long-term outcomes and survival rates [23, 24].

If surgery cannot be performed due to medical inoperability, particularly in certain melanoma types, such as mucosal melanoma, lentiginous melanoma, or uveal melanoma, radiation therapy (RT) may be considered, despite melanoma being a relatively radioresistant tumour. RT treatment may also be adjuvant, and thus be used after surgery in cases when there is a high risk of melanoma recurrence. Occasionally, after surgery, radiation therapy is also administered to the region where lymph nodes were removed, especially when a significant number of nodes were affected by cancer. The goal is also to reduce the likelihood of the cancer returning and the distant spread of melanoma cells. Importantly, RT may be employed to alleviate symptoms resulting from the metastasis of melanoma to other organs, such as the brain or bones.

This form of treatment, aimed at symptoms' management, is referred to as palliative therapy. While palliative radiation is not intended to eradicate cancer, it can potentially reduce tumour size or temporarily slow its progression, aiding in the control of certain symptoms [25].

Another conventional therapy, which is also not devoid of disadvantages due to its limited effectiveness, toxicity, side-effects, and the problem of developing resistance mechanisms, is chemotherapy that employs cytotoxic drugs to kill melanoma cells that have spread beyond the skin. These drugs may be administered either intravenously or orally. In melanoma treatment, commonly used chemotherapeutics include dacarbazine, temozolomide, nab-paclitaxel, paclitaxel, cisplatin, and carboplatin. They are used alone or in combination, e.g. carboplatin with paclitaxel, though the efficacy of drug combinations versus single-agent therapy still remains uncertain, and in some cases can increase side-effects [26].

Advancements beyond conventional therapies – targeted therapy and immunotherapy. Over the past decade, there has been significant progress in treating patients with unresectable or metastatic melanoma. Somatic mutations are the primary focus of current melanoma treatments since they are specific to the tumour and provide actionable targets for therapy. Treatment of malignant melanomas includes advancements in molecular therapies that focus on inhibiting the mitogen-activated protein (MAP) kinase (MAPK) pathways, specifically targeting the oncogenic B-Raf proto-oncogene serine/threonine kinase (BRAF) and dual-specificity kinase (MEK) signalling, as well as in immune checkpoint inhibitors that target the programmed death-1 (PD-1) and cytotoxic T-lymphocyte antigen 4 (CTLA-4) receptors [27]. The major targeted therapies and immunotherapies, both in pre-clinical and clinical trials, are presented in Figure 1.

Almost 50% of cutaneous melanomas have a genetic mutation that causes a change at position 600 in the *BRAF* proto-oncogene, serine/threonine encoding kinase [29]. BRAF kinase is a crucial component of the mitogen-activated protein kinase (MAPK) pathway, which controls essential cellular processes, such as proliferation, differentiation, migration, and apoptosis. The most common abnormalities in the BRAF gene, accounting for about 90%, are the resulting $BRAF^{V600E}$ and $BRAF^{V600K}$ mutations. The discovery of the BRAF mutation's role in melanoma led to the development of targeted BRAF inhibitors (Tab. 1), including vemurafenib; the first targeted drug for melanoma) [30], dabrafenib [31], and encorafenib [32]. Within a decade of the identification of the BRAF oncogene, vemurafenib and dabrafenib received the approval

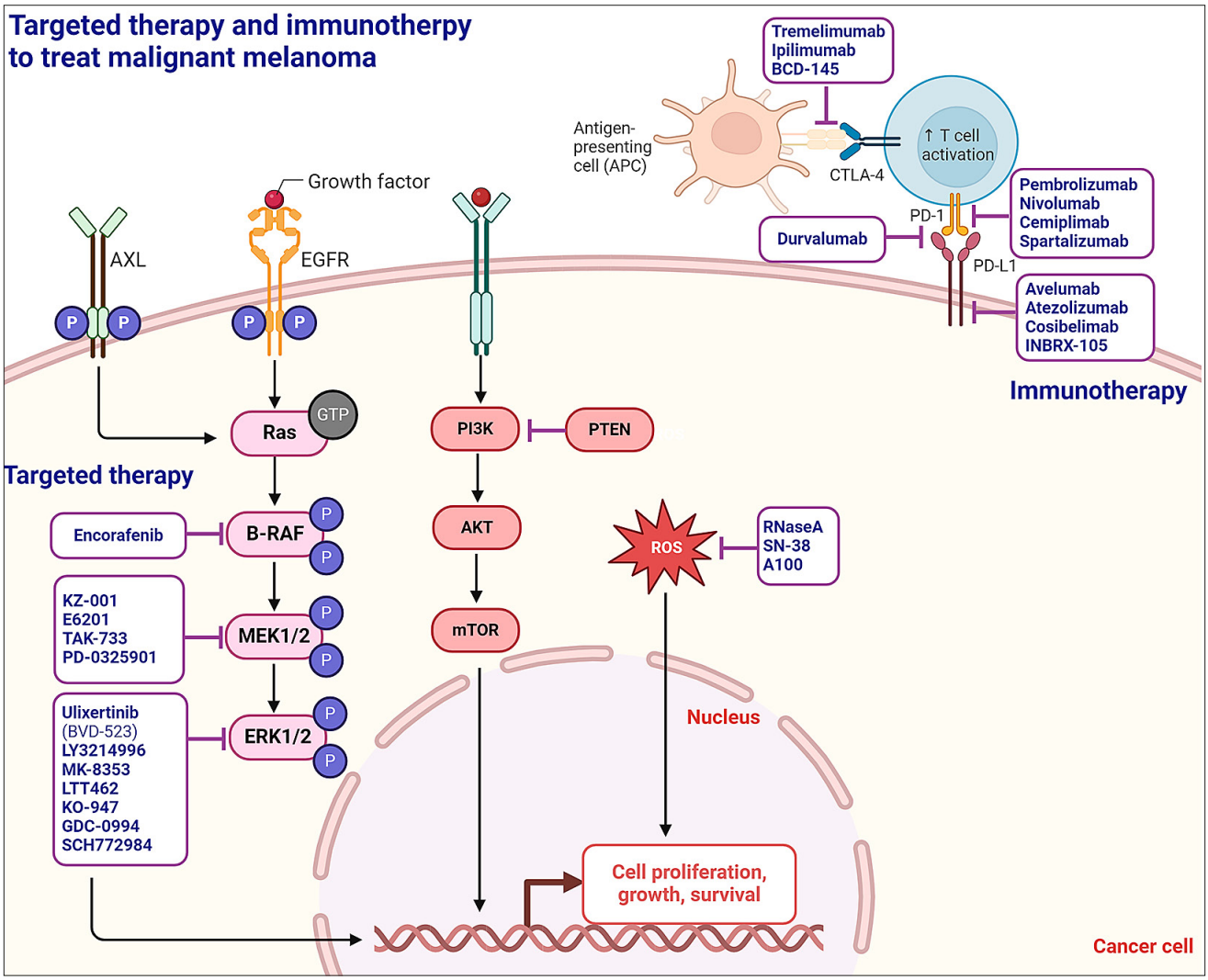

Figure 1. Schematic representation of targeted therapies and immunotherapies in pre-clinical and clinical trials. Adapted with modifications from: [28]. Created in BioRender

Table 1. The most common targeted therapies and immunotherapies used for melanoma treatment

Drug/compound	Treatment type: targeted therapy (TT) immunotherapy (IT)	Mechanism of action	Advantages	Limitations	Reference
Vemurafenib	TT	Inhibition of mutated $BRAF^{V600E/V600K}$	Rapid response, effective in patients with mutated *BRAF*, improved survival	Limited to *BRAF*-mutant melanoma; resistance develops; photosensitivity or rash may occur	[35]
Dabrafenib	TT	Inhibition of mutated $BRAF^{V600E/V600K}$	Good tolerance, effective in patients with mutated *BRAF*, improved survival	Limited to *BRAF*-mutant melanoma; resistance develops	[31]
Trametinib (in combination with dabrafenib)	TT	Inhibition of MEK1//2	Can enhance efficacy of BRAF V600E or V600K inhibitors, targets downstream signalling	Side-effects, e.g., rash, gastrointestinal issues	[36]
Cobimetinib	TT	Inhibition of MEK1//2	Improves response rates and progression-free survival; synergistic with BRAF inhibitors	Increased toxicity when combined with vemurafenib	[37]
Palbociclib	TT	Inhibition of CDK4/6	Targets cell cycle regulation, potential use also in combination therapy	Potential for resistance; more data on efficacy still needed	[38]
Pembrolizumab	IT	Inhibition of PD-1/PD-L1 interaction (immune checkpoint inhibitor)	Durable response, prolongs progression-free and overall survival	Immune-related adverse effects; variable response rates	[39]
Nivolumab	IT	Inhibition of PD-1/PD-L1 interaction (immune checkpoint inhibitor)	Improved overall survival	Immune-related adverse effects	[40]
Ipilimumab	IT	Inhibition of CTLA-4 to enhance T-cell activation	Can induce long-lasting responses	Significant immune-related adverse effects	[41]
Talimogene laherparepvec (T-vec)	IT (oncolytic immunotherapy)	Direct tumour targeting with immune activation	Higher durable response rate, potential to enhance immune response	Side-effects related to virus infusion; limited availability	[42]
Lifileucel	IT (adoptive cell therapy)	Uses autologous tumour-infiltrating lymphocytes (TILs) to attack melanoma cells	Offers a personalised treatment approach by expanding patients' own immune cells	Potential for immune-related adverse effects; complex, labour-intensive process	[43]

of the Food and Drug Administration (FDA) and were widely used. Combining these BRAF inhibitors with mitogen-activated protein kinase kinase (MEK) inhibitors, such as cobimetinib, trametinib [19], and binimetinib, has further enhanced treatment outcomes, increasing response rates and overall survival while reducing side-effect [19,33]. Despite these advances, clinical relapse due to acquired resistance is almost inevitable in patients receiving combined BRAF and MEK inhibitors. This resistance arises from a variety of mechanisms, making it challenging to prevent or manage effectively. Such mechanisms include, for instance, *BRAF* splice variants that form dimers, *BRAF* amplification, reactivation of extracellular signal-regulated kinase (ERK) signalling through *MEK1/2* mutations, among others [34].

Another protein of interest in the case of melanoma targeting is neuroblastoma RAS viral oncogene homolog, proto-oncogene GTPase (*NRAS*). Approximately 20–30% of *NRAS* mutations are encountered in cutaneous melanoma [27]. Interestingly, melanoma exhibits *NRAS* mutations more frequently than other genes from the RAS family, namely, *KRAS* or *HRAS*. Mutations of the latter two are typically more prevalent in other forms of cancer. The most common mutations in the *NRAS* gene in melanoma include resulting $NRAS^{Q61R}$, $NRAS^{Q61L}$, and $NRAS^{Q61K}$. In both experimental and clinical contexts, various treatments aimed at disrupting oncogenic signalling pathways activated by NRAS have been thoroughly investigated. However, so far, no targeted therapies have been approved for NRAS-mutant melanoma, and most patients are treated with immune checkpoint inhibitors (ICIs). However, patients who do not respond, or develop resistance, have limited alternatives. Targeting RAS proteins, including NRAS, is challenging, and while progress has been made with KRAS inhibitors, equivalent treatments for NRAS mutations are still lacking [44]. Selective MEK inhibitors offered novel treatment options by blocking growth and triggering cell death in both *NRAS*- and *BRAF*-mutant melanoma cell lines. Pre-clinical models indicate that both *NRAS*- and *BRAF*-mutated melanoma cells respond to MEK inhibition. Unfortunately, nearly 80% of patients finally develop resistance to both BRAF and MEK inhibitors over time [45].

Advances in cancer immunotherapy, particularly through checkpoint inhibitors targeting cytotoxic T-lymphocyte antigen 4 (CTLA-4) and programmed death 1 (PD-1) protein, have revolutionised melanoma treatment. CTLA-4 is a negative regulator of T-cell activation in lymphoid tissues, while PD-1 protein is involved in promoting T-cell exhaustion in the tumour microenvironment. Pioneered by Allison and Honjo, who were awarded the Nobel Prize in Physiology or Medicine in 2018 [46,47], these therapies have changed the standard of care for melanoma and other solid tumours. Combined therapy with ipilimumab – the first significant immune checkpoint inhibitor (approved in 2011), and nivolumab which target the PD-1 protein, shows a 53% response rate [48], significantly improving survival compared to earlier monotherapies with ipilimumab only, which had a 10% response rate. However, the immune-mediated side-effects are more common with combination treatments. However, they can be managed [49]. In 2022, nivolumab was also paired with relatlimab, which blocks the lymphocyte-

activation gene 3 (LAG-3) encoding protein, showing promise in delaying disease progression and preventing recurrence in advanced cases. Checkpoint blockade has also demonstrated effectiveness in treating brain metastases, with a 57% intracranial response rate [50]. Despite these successes, challenges remain, including resistance mechanisms like *JAK1/2* mutations and the need for biomarkers to predict treatment outcomes [51]. In February 2024, the FDA approved lifileucel for patients with inoperable melanoma resistant to other treatments. Over 30% of patients who did not respond to anti-PD-1 therapy showed a response to tumour-infiltrating lymphocytes (TILs) therapy, with ongoing trials further exploring its potential [43].

Although targeted therapies and immunotherapy have been successful, some patients fail to respond effectively and, as mentioned previously, develop resistance. Hence, there is a need to conduct further research on the long-term effects of new treatments, pursue new treatment options, and explore different combination strategies.

Nanotechnology in melanoma treatment. Recent advances in nanotechnology offer innovative approaches for drug delivery. Nanotechnology enhances the targeting of therapies, improving their effectiveness and reducing side-effects, compared to conventional chemotherapy which can harm healthy cells and diminish the quality of life [52–54]. Nanocarrier drug delivery systems (DDSs) are crucial in this field, using nanoparticles to precisely deliver drugs to targeted areas in the body. This may improve therapeutic outcomes and minimise side-effects by either passively targeting tumours through enhanced permeability and retention or actively targeting specific tumour antigens with conjugated antibodies or peptides [55, 56].

Nanomaterials are increasingly utilised in drug delivery DDSs for cancer treatment, including melanoma. Their size and surface properties allow for targeted delivery to melanoma cells, enhancing drug efficacy while reducing side-effects. Nanomaterials can also prevent drug degradation and extend drug half-life, potentially lowering the drugs' doses [57]. Various nanoparticle types (Tab. 2), such as lipid systems, inorganic nanoparticles, polymeric systems, and natural nanosystems, are being explored for melanoma therapy [17, 58].

Lipid-based DDSs, including liposomes, solid lipid nanoparticles, and nanoemulsions, offer stability and controlled release. Liposomes, for instance, improve drug circulation and efficacy, as seen with paclitaxel and vincristine [68]. They are also being investigated for vaccine development against melanoma [69].

Inorganic nanoparticles, such as silica and gold, provide good biocompatibility and can be used for both imaging and drug delivery; however, they often require additional targeting ligands for effective therapy [70]. Silicon-based materials are also used in imaging for melanoma, offering sensitive and non-invasive diagnostics [71]. Polymeric systems, such as micelles, nanoparticles, and hydrogels, enhance imaging and targeted chemotherapy for melanoma, although they may face issues with stability and toxicity [72, 73]. Natural nanosystems, particularly exosomes, are emerging as versatile DDSs due to their ability to carry biomolecules and target specific cells. They show promise in diagnostic and therapeutic applications for melanoma, although their role in immune evasion and resistance to treatment remains a challenge [70].

Nanotechnology offers promising advancements by enabling the development of more precise and safer DDSs.

Table 2. Types of nanoparticles used in melanoma treatment

Nanoparticles types	Key characteristics	Application in melanoma treatment	Advantages	Limitations	Reference
Liposomes	Good stability, controlled drug release, bio-degradability	Drug delivery and vaccine development	Prolong drug half-life and enhance efficacy of those targeting the cell cycle, reduce side- effects of the drugs	Potential for drug leakage, higher cost of production, limited shelf life	[59]
Solid lipid nanoparticles	Stable, solid matrix, protects drug from degradation	Targeted drug delivery, passive targeting via enhanced permeability and retention (EPR) effect	Improve drug stability, controlled release, reduce off-target toxicity	Limited drug loading capacity, gelation tendency, potential for aggregation during storage	[60]
Polymeric nanoparticles	Diverse structures (micelles, nanospheres, hydrogels), biocompatible	Drug delivery, immunotherapy, targeted chemotherapy	Increase drug bio-availability prolong circulation time, enhance tumour targeting	Complex synthesis, potential toxicity, stability issues over time	[61,62]
Gold nanoparticles	Small size, high surface area, good conductivity	Photothermal therapy, drug delivery, combined with immunotherapy	Enable treatment and imaging, targeted delivery with minimal invasiveness	Potential toxicity, challenging large scale production	[63]
Silica nanoparticles	Porous structure, biocompatible, easily modifiable surface	Drug delivery, photodynamic therapy, imaging	Prolongs drug retention time, enhances stability	Long-term toxicity and potential immuno-genicity concerns, challenges in scaling up productions	[64]
Exosomes	Natural nano-vesicles, carry proteins, lipids, nucleic acids	Drug carriers, vaccine development, diagnostic biomarker	Bio-compatibility, cross blood-brain barrier, potential for early detection of melanoma	Risk of immune system interference, low production yield, complex isolation	[65]
Dendrimers	Highly- branched, uniform size, modifiable surface	Drug delivery, gene therapy,	High drug loading capacity, precise control over release, low toxicity	Potential toxicity due to surface charge, high synthesis cost, complicated functionalization	[66]
Magnetic nanoparticles	Magnetic core (usually iron oxide), can be directed using magnetic fields	Hyperthermia therapy (external magnetic field induces localised heating to kill melanoma cells), targeted drug delivery	Allow localised treatment through magnetic field, enable simultaneous therapy and diagnostics (theranostics), minimal invasiveness	Potential for magnetic field-related toxicity, aggregation, and difficulties in precise control over biodistribution	[67]

Nano-encapsulation can enhance the solubility, stability, and bioavailability of melanoma drugs, while also improving tumour targeting and reducing side-effects compared to conventional methods. These advancements suggest that nano DDSs could significantly boost the efficacy of immunotherapies for melanoma. Looking ahead, key challenges include further elucidating the mechanisms that enhance the performance of nanosystems over traditional drug formulations. Despite these challenges, the superior histocompatibility, targeted delivery, and reduced toxicity of nano DDSs, position them as powerful tools in advancing melanoma treatment, especially for metastatic cases.

Photodynamic and photothermal therapies. Photodynamic therapy (PDT) and Photothermal therapy (PTT) have gained attention for their ability to target melanoma cells with precision and minimal invasiveness. PDT uses photosensitizers (PS) and specific light wavelengths to produce reactive oxygen species (ROS), which damage cancer cells [74]. This method has shown potential in various cancers, including melanoma [75]. PTT, on the other hand, relies on PS to generate localised heat, inducing hyperthermia to destroy tumour cells [76]. Emerging nanomaterials, such as gold nanoparticles, enhance effectiveness of PTT in melanoma therapy [77]. The development of dual-function nano-agents is also advancing PDT and PTT as promising treatments [78].

PROteolysis Targeting Chimera (PROTAC) technology in melanoma treatment. As melanoma treatment faces ongoing challenges, PROteolysis Targeting Chimeras (PROTACs) [79–81] present a promising new approach. PROTACs are designed to degrade specific proteins within cells rather than just inhibiting their activity. One notable PROTAC – ARV-825 – targets the BRD4 protein which is involved in cancer progression. ARV-825 recruits BRD4 to an E3 ubiquitin ligase, leading to its targeted degradation. This method offers a potentially more effective treatment compared to conventional inhibitors, especially for melanoma resistant to current therapies [82]. Research assessing the effectiveness, delivery and potential side-effects of such compounds in melanoma is currently ongoing.

SUMMARY

The review synthesises the current knowledge of melanoma treatment, from established methods to emerging innovations. Melanoma, characterised by its aggressive progression and increasing global prevalence, poses substantial treatment challenges, especially in its advanced stages with metastasis. Traditional therapies, including radiotherapy and chemotherapy, often struggle with resistance and severe side-effects, leading to treatment failure and disease recurrence. The advent of targeted therapies and immunotherapies represents a significant advancement which, however, is not without its limitations. Recent developments in nanotechnology and novel combination therapies offer new avenues for more precise and effective treatments, but their side-effects should also be monitored. Therefore, future research needs to focus on refining the newly emerging malignant melanoma treatment strategies, addressing the shortcomings of existing therapies, and exploring such cutting-edge technologies as PROTAC to enhance therapeutic outcomes. Advancing personalised and combinatorial approaches will be key to improving treatment efficacy and patient prognosis in this aggressive cancer type. Multidisciplinary management of this disease is essential.

Declaration of competing interests

The authors declare that they have no competing interests.

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