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Current Trends in Pharmacy and Pharmaceutical Chemistry

Journal homepage: https://www.ctppc.org/

Review Article

Metastatic melanomas: Treatment overview

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ARTICLE INFO

Article history:
Received 20-09-2021
Accepted 29-09-2021
Available online 16-11-2021

Keywords:
Metastatic melanomas
Immune therapies
Combination therapies
Bio-chemotherapies
Targeted therapies.

ABSTRACT

Melanomas especially metastatic melanoma chemotherapeutic treatment has been discussed in the review article. The recent advancement in the chemotherapy being Immunotherapy targeted therapy, combination therapy, targeted therapy, combination therapies and biochemotherpies all of which have been discussed in this review article.

1. Introduction

Melanomas have been fatal and incidences have been rising since past 30 years. Malignancy currently ranks as the fifth and sixth most common cancer in men and women in USA.[1] Melanoma has high incidences in young and been fatal in significant years of potential life lost productivity. One quarter to one third patient of all patients with melanoma experience reoccurrence and development to more advanced stage diseases. About 1 million melanoma survivors are living in US. Melanoma represents 4% of cancer it is responsible for 80% of skin cancer deaths. Early diagnosis of melanoma can lead to cure but historically the prognosis of patient with metastatic disease is poor.[2] The medium rates had been less than 1 year and overall 5 year mortality nearly 90%. Ipilimuab was introduced in 2011, no single drug or combination of drugs demonstrated a significant effect on overall survival T-cells & tissues.[3] OS in patients with metabolic melanoma with advancement in research on tumour biology & immunology has led to the development of new targeted and immunotherapeutic agents that may sustain and afford progression free survival (PFS) & overall survival in patients with melanoma.[4]

2. Review

2.1. Immunotherapy and melanoma

It is complex mechanism between immunologic environment and tumours, dynamic and difficult to understand however it is still important to understand functionality and efficacy and immunotherapeutic agents.[5] With advancement in understanding the role of various mechanism mediated by cancer cells to evade immune detection has gained pivotal attention of cancer chemotherapy to develop targeted molecules capable of manipulating the microenvironment in favor of an anti tumour immune response.[6] Thus the agents/ drugs which increase immune response and specificity with tolerability and low adverse drug profile are more preferred. These agents include the first of it being approved at high dose

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https://doi.org/10.18231/j.ctppc.2021.013

interleukin (IL-2) for advanced metastatic melanoma.[7]

2.1.1. MOA of Immunomodulators

These have been described in individual section but for convenience the mechanism of action is being summarized as follows:

The products of individual's human tumors gene mutations are recognized foreign antigens. However many of tumors are mistakenly identified as self by host immune system and helps cancer cells to escape from immune detection and allowing tumors to survive and grow: these escape from immune control is now viewed as hall mark of cancer progression and its cause.[8]

Some patients with cancer show an adaptive immune response specifically directed against antigenic proteins expressed in there tumors. These are summarized here, that T-cells secretes cytokines, which in turn generate acute inflammation that proceeds to expansion of cytotoxic T cells, tissues destruction at potential control or even elimination of malignancy. T-cell function is hampered in cancer because the tumor in lieu contains suppressive elements, including regulatory T cells and myeloid derived suppressor cells also the tumor milieu exerts suppressor activity on soluble factors such as IL-6, IL-10 vascular endothelial growth factor (VEGF) and transforming growth factor β and ligands for co-inhibitory receptors or checkpoint molecules which include cytotoxic T lymphocytes associated antigen-4 (CTLA-4) and programmed cell death protein-1 (PD-1) contribute to down modulation of CD8+ and CD4+ effector cell function making these receptors logical targets for drugs such as ipilimumab act as anti CTLA-4 monoclonal antibodies and nivotumab and lamberolizumab (anti-PD-1 monoclonal antibodies). Melanoma cells have been found to express high levels of programmed cell death ligand 1 (PD-1), (B7-H1) protein, a ligand for PD-1 receptor.[9,10]

2.2. Targeted therapy in melanoma[11,12]

It is now being assumed that melanoma has a complex connection with molecular observations in genes that alter critical signal pathways controlling cells proliferation, differentiations and death. It has been observed that about 50% of melanoma contain mutations that activates RAS/RAF/MEK/ERK (mitogen activated protein kinase pathway, making it a prime therapeutic target). These are some mutations in BRAF in cutaneous melanoma particularly those without chronic sun damage which include.

1. *BRAV600E:* Mutations occurs due to substitution of glutamic acid for valine at amino acid 600 in gene coding serine-threonine protein kinases BRAFV600E.
2. *BRAFV600K:* Substituting lysine for valine which is 5% to 6%.
3. *NRAS:* It is less common 10 to 20% and mutually exclusive as it involves NRAS gene bound in melanoma of skin that has not been chronically exposed to sun.
4. *KIT Genetic Observations:* Upstream tyrosine kinase like KIT genetic observations are less common. They occurs mainly in melanoma arising all mucosa acute skin and skin with sun induced damage but least occurs or observed in melanomas of skin without chronic sun exposure.[13]
5. *PI3K/PTEN/AKT Abberations:*These are also observed with less frequency.[14]

2.3. Evolution and chemotherapy of metastatic melanoma and treatment

1. *Dacarbazine and IL-2:* They were only approved agents FDA in treatment of metastatic melanoma. In 1975, dacarbazine was approved IL-2 has been approved recently.[15]
2. *Temozolomide:*It is orally active alkylating agent a derivative of dacarbazine with comparable pharmalogical and pharmacokinetic profile as compared to 13dacarbazine. It is used to commonly in therapy of melanoma in lieu of intravenous dacarbazine.[16,17]

2.3.1. Other agents[18]

These includes nitrogenous (carmusteine, lomusteine and fotemusteine) platinum analogues (cisplatin and carboplatin) vinca alkaloids (vinblastine, vincristine) and taxanes (paclitaxel and docetaxel)

1. *Fotemustine:* It was first drug to show efficacy in brain metastasis. This agent is also under study for intraheptic artery chemoembolization in patient with isolated liver metastasis for primary oveal melanoma.[19]
2. *Cisplatin and Carboplatin:*[20,21] They demonstrated moderate activity as single agent with response ranging from 15 to 20%.
3. *Paclitaxel:*[22] It is used as a single agent or in combination with other antitumor agent in patient with metastatic melanoma. Formulation of paclitaxel are also available such as nab-paclitaxel particle are found to be well tolerated and can be used as single agent in metastatic melanoma. Nab — paclitaxel is more advantages over paclitaxel which include lower rate of allergic reaction.

2.4. Combination chemotherapies

For the unresponsive cases of metastatic melanomas mostly combination therapies are used and adopted some of them are over viewed in this section. Generally, combination

therapy includes one or two agents given treat these malignancies.

1. *Carboplatin & Nab-paclitaxel:* This has been used in patient with metastatic melanoma and to elevate the RR and Median OS.[23]
2. *Dartmouth Regimen:* It is a combination of cisplatin, dacarbazine, carmusteine, tamoxifen it had substantial RR of 54% and was used in 1980s and 1990s.[24]
3. *Triple Drug Combination:* Cisplatin, vinblastine and dacarbazine for metastatic melanoma. The treatment has several AES with gastrointestinal and hematological toxicities.[25]
4. *Cisplatin, vinblastine, dacarbazine and Interferon- α (IFN-α):* The modification in cisplatin, vinblastine, and dacarbazine regimen was included with interferon-α and IFN-α to develop bio-chemotherapy regimen. Compared to dacarbazine the combination regimen overall good response however these regimen fail to extend survival significantly and are associated with higher toxicities.[26]
5. *Angiogenesis inhibitors:* Their role is being explored in metastatic melanoma. Angiogenesis is formation of new blood vessel in process of tumour growth and metastatic propagation which is fundamental event. VEGF pathways has pivotal role & its key regulators also play pivotal role in angiogenesis.[27] In melanoma there in substantial evidence that VEGF is important in growth factor for capillaries in metastasis. In metastatic melanomas that increase serum contraction of VEGF with tumors progression and survival, moreover transcriptional up- regulation of VEGF has been reported as an important escape mechanism of melanomas cells are exposed to conventional agent such as dacarbazine.[28]
   Bevacizumab: It is recobinant humanized murine anti-VEGF antibody. In phase 2 studies when bevacizumab was combined with angiogenesis inhibitors. Bevacizumab when combined with temozolomide or nab-paclitaxel and carboplatin in patients with stage IV melanoma showed promising activity.[29]

2.5. *Biochemotherapy*[30]

When chemotherapy is, combined with IL-2 or IFN-α it is referred to as biochemotherapy. IL-2 was approved by FDA for treatment of malignant melanoma in 1985 and 1993. It is also approved for use an adjuvant therapy for early-stage melanoma. IFN-α showed modest benefits.

- *Multiple drug regimen:*[31] Biochemotherapy regimens with multiple drug was used clinically, it showed improved response rates but failed to show higher OS in large clinical trials. This drug includes dacarbazine, tamoxifen, cisplatin, vinblastine, carmustine and temozolomide along with combinations of closes of IL-2 and IFN-α.
  When used IL-2 biochemotherapy advises reduced doses of IL-2 to make it safer with combinations. It also produces substantially more constitutional, hemodynamic and hematologic AES.[32]

2.5.1. *Immune checkpoint inhibitors*[33]

CTLA-4 inhibitors (cytotoxic T-lymphocyte associated antigen-4, PD-1 (programmed cell death protein-1), PDL-1 (programmed cell death ligand-1), RAS/RAF/MEK/EKK pathway, KIT inhibitors are some of the immune checkpoints. Inhibition of these checkpoints may eventually inhibit certain events in the immune system causing antitumorogenic and anticancer activity.

2.5.1.1. CTLA-4 inhibitors[34]. Some of the CTLA-4 inhibitors include ipilimumab and tremilimumab.

1. *Ipilimumab:* Substantial attention has received T-activating drug discovery. Result of which include ipilimumab a T-cell activating agent used for advanced melanoma. It acts as CTLA-4 inhibitors and a monoclonal antibody. It prevents down regulation of T-cell activation, allowing sustained immune response to tumor antigens on malignant melanocytes. When exposed to antigen presenting cell (APCs), T-cell activation requires co-stimulatory signals. Tumor associated antigens are presented by major histocompability complex I and II on specialized AFCs bind to the cell receptors. Second cell required for T-cell activation occurs when 137 molecules on APC bind to CD2A receptors. In absence of second signal T- cell become allergic and fail to mount a full immune response. T-cell that do receive both signals become activated able to proliferates and targets tumors. Shortly after T-cell activation CTLA-4 is up-regulated, competitively inhibiting the binding of 137 molecules to D28 and halting T-cell activation and proliferation.[35]

   It was approved by FDA in March 2011. Significant consequences of the T-cell activation and proliferation resulting from treatment with ipilimumab are the development of immune mediated AEs.
2. *Tremelimumab:* Is another CTLA-4 antibody response in approximately 10% of the patients in phase 1 and phase 2 trials but similar to ipilimumab but the phase 3 trial failed to show significant effect. It has not been approved by FDA.[36]

2.5.2. *PD1 and PD-L1*[37]

PD-1 and PD-L1 pathway has gained much importance for the discovery of PD-1 and PD-L1 inhibitors. It has significant role in tumor induced immunosuppression in melanoma and is an and in another malignant malignancies

PD-1 is immune inhibitory receptor in CD28 family. The interaction of PD-1 with the ligand PD-L1 (also known as B7-H1) inhibits T-cell proliferation survival and effector functions (cytotoxicity and cytokine release). This induces apoptosis of tumor specific T-cell promotes of CD4+ T-cell into immunosuppressive regulatory T-cell and increases resistance pf tumor cell ti CTL attack.

1. *Nivolumab:*[38] It is inhibitor of PD-1 receptor and a fully human IG-4 antibody. This agent was evaluated in patients with unresponding metastatic solid tumors. It was found to be active in patient with melanoma renal cell cancer and non small cell lung cancer. CTLA-4 and PD-1 play complementary role in regulating immunity. In clinical trials nivolumab was found to be effective 1 year survival.
2. *Pembrolizumb:*[39] It is highly selective humanized IG-4-K isotype monoclonal antibody active against PD-1. It received the break through designation from FDA based on the observations in clinical trials.
3. *MPDL3280A:* Human monoclonal antibody anti-PD-L1 that blocks the binding of PD-L1 to PD-1 and B7-1. In clinical trials MPDL3280A as monotherapy was well tolerated and associated with dweable responses.
4. *BMS-966559:* It is fully human IG-4 PD-L1 antibody which was evaluated in phase 1 trials and was found to be successful.
5. In conclusion PD-1 receptor blocks show higher response rates than ipilimumab, higher tolerability and less grade 3 and 4 adverse effects thus making it promising therapy for metasatic melanomas.

2.5.3. RAS/RAF/MEK/ERK pathway targeted therapies[21,40]

This pathway is being targeted for many therapies and tested in clinic. BRAF is the most common mutated protein kinase in human cancers.

1. *BRAF:* it is most potent mutated protein kinase in human cancer.[41]
2. *Vemurafenib:* it was developed as a potent BRAF inhibitor. Somatic mutation in BRAF a serine-threonine kinases as present in 40% to 60% of metasatic melanomas. Most of mutations occurs at 600^{th} amino acid position where in valine is substituted the V600E mutation.[40]
3. *Sorafenib:* It is non selective BRAF inhibitor and shows better results in melanomas.[21]
4. *Dabrafenib:*[42] It is an agent active against BRAF and in May 2013 was approved for treatment of patients with BRAF V600E mutation positive occurestable or metasatic melanoma. Vemurafeninb has a serious adverse effect of cutaneous squamous cell carcinoma (CuSCCs) and rash not seen with dabrafenib. It also has adverse effect of ceratoacanthoma which is also least seen with dabrafenib. Dabrafenib is found to be quite effective in treatment of intracanal metastasis.
5. *Trametinib:*[43] In preclinical models, mutations of BRAFs were associated with enhanced sensitivity to MEK inhibition: pharmacological MEK blockade was found to completely abrogate tumor growth in BRAF, mutant-positive xenografts. Trametinib a potent and highly selective MEK1/2 inhibitor received FDA approval on May 29, 2013 for the first line treatment of patients with unrespectable or metasatic melanoma harboring a BRAF V600E/K mutation (Currently trametinib is not indicated for patients who have received previous BRAF inhibitor therapy).
   Although coetaneous toxic effects mainly papulopustular rash were noted in 87% of patients, no cuSCC was observed during trametinib treatment. Other less common but potentially significant toxic effects observed with MEK inhibition by trametinib included a decreases in cardiac ejection fraction or ventricular dysfunction and visual problem (i.e. retinal pigment epithelial detachment or retinal vein occlusion), and interstitial lung disease.
6. *Dabrafenib/trametinib combination therapy*[44–46] Resistance to therapy with BRAF kinase inhibition develops quickly, typically within 6 to 7 months of therapy initiation. To address this tissue and potentially delay the developments of resistance to treatment and to minimize toxic effects associated with BRAF inhibition, combination therapy with dabrafenib and trametinib has been investigated. The combination received accelerated FDA approval in January 2014 for use in the treatment of patients with unresectable metastatic melanoma with a BRAF V600K mutation. Approval was based on the results of a phase 2 study in which 162 patients were randomly assigned in a 1:1:1 manner to receive 150 mg of dabrafenib twice daily plus either 1 or 2 mg of trametinib daily (150/2 mg or 150/1 mg). Proliferative skin lesions including cuSCC papillomas and hyperkeratosis which are commonly seen with BRAF inhibition mono therapies were less frequently observed (the cuSCC incidence was 19% with dabrafenib immunotherapy vs. 7% with combination therapy).

2.5.4. KIT Inhibitors[47–50]

Somatic mutations in KIT occur infrequently in patients with melanoma with 2% to 3% incidences KIT mutations are most frequent in mucosal melanoma subtypes and are rarely reported in coetaneous melanomas particularly those associated with intermittent ultraviolet exposure. Mutations of c-kit in melanomas are variable and only select KIT alterations are truly oncogenic and indicative of an effective therapeutic target.

3. Conclusion

With the advent of newer therapies, the survival rate has been improved in metastatic melanomas. Further exploration of biochemical pathways for the rate determining enzymes that may be inhibited to develop anticancer agents against metastatic melanomas must be explored and also much explored to develop the above agents. The molecular biology principles in consideration with oncology, pharmacology and medicinal chemistry have led to the development of these agents.

4. Source of Funding

None.

5. Conflict of Interest

None.

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Cite this article: Nerkar AG. Metastatic melanomas: Treatment overview. *Curr Trends Pharm Pharm Chem* 2021;3(4):50-55.