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REVIEW ARTICLE

A Review on the Comparison of Vemurafenib and Dabrafenib in the treatment of Melanoma caused by Mutation of Braf

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ABSTRACT:

Metastatic melanoma is one of the most aggressive forms of skin cancer. The mortality rate of this cancer is high .Almost 60% of the melanomas are due to the mutation of BRAF gene. BRAF V600E mutations has been implicated in melanoma genesis by different mechanisms. It occurs due to the improper regulation of the activation of downstream MEK (mitogen activated protein kinase enzyme)/ERK (extra cellular signal related kinase) effectors. In order to overcome the increasing rate of this disease a comparative study has been performed between two ERK/MEK inhibitors namely vemurafenib and dabrafenib and also to understand the relative efficacy and toxicity effect between these two therapeutic modalities.

KEYWORDS: Metastasis, Melanoma, BRAF.

INTRODUCTION:

Metastatic melanoma is an aggressive form of cancer but it's uncommon among the other types of cancer. The World Health Organization mentioned that its incidence seems to be increasing faster. Nearly 50% of the melanomas are due to activation of BRAF mutations .This mutation in melanoma occurs 90% at the codon 600 and among these over 90% of this kind of mutations occurs in the single nucleotide mutation which leads to the substitution of glutamic acid for valine[1] (BRAFV600E: nucleotide 1799 T>A, codon GTG >GAG). BRAFV600K mutation is the next most occurring mutation. The findings indicate that BRAF mutated melanomas arises in early life at low cumulative Ultraviolet doses, but high cumulations of UV doses are required for the melanoma which is occurring without BRAF mutation.

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BRAF mutations are common in melanomas on the trunk in both cohorts. This is due to the fact that BRAF mutated melanoma is decreased in highly sun exposed sites. The increase of melanoma also arises through other mechanisms but only in the presence of high cumulative dose of UV. These mutations have been shown to harbor KIT mutations.[2]

Melanoma has historically had a poor prognosis because of lack of responsiveness to traditional chemotherapies. BRAF leads to challenging but promising focus for the development of novel targeted therapy.

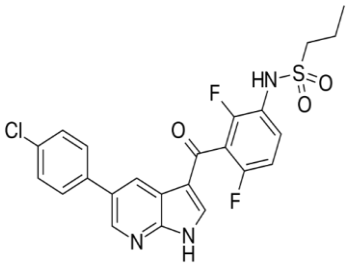
BRAF:

BRAF a part of RAF which is regulated by binding with RAS gene. BRAF-66% in melanoma. It is low in other types of cancer like lung cancer and colorectal cancer. The differing percentages to cause cancer in melanoma compared with other types is due to the lowering proportions of V600E mutations that affect the kinase domain of the protein.

BRAF encodes a serine /threonine protein kinase that is the downstream effectors protein of kras and activates the MAPK signal transduction pathway involved in the regulation of cell proliferation and survival .Upon activation BRAF phosphorylates downstream mediators MEK1 and MEK2 which subsequently activate ERK1 and ERK2 involved in the regulation of growth regulating proteins such as c-JUN and ELK1 Activating mutations in BRAF lead to increased kinase activity.[1]

Function:
BRAF belongs to the family of RAF. It is responsible for cell growth, differentiation and secretion.

Treatment:
Vemurafenib:
Oral Tablet: 240mg
Structure:



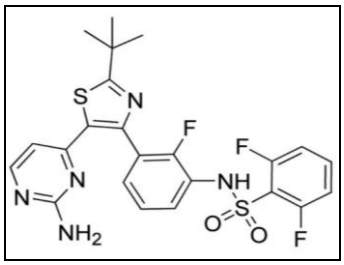
Mechanism of action:
Vemurafenib inhibits oncogenic BRAF by binding to V600E which renders the protein inactive inhibiting downstream proliferation and signaling ultimately leading to cancer cell apoptosis [3]

ADR:
Dermatologic: Alopecia (36% to 45%), Papilloma of skin (21% to 30%), Photosensitivity (33% to 49%), Pruritus (23% to 30%), Rash (37% to 52%)
Gastrointestinal: Nausea (35% to 37%)
Musculoskeletal: Arthralgia (53% to 67%)
Other: Fatigue (38% to 54%)[4]

Resistance:
The three main mechanisms of vemurafenib are:
There is an alternative survival pathway, where there is an over expression on the cell surface protein PDGFRB
BRAF pathway gets reactivated when there is a mutation in oncogene NRAS. Stromal cell secretion of hepatocyte growth factor (HGF).[5] Labeled Indications: Treatment of unresectable or metastatic melanoma in patients with a BRAFV600E mutation (as detected by an approved test).

Dabrafenib:
Oral Capsule: 50 mg, 75 mg

Structure:



Mechanism of action:
Dabrafenib inhibits the MAPK pathway in BRAF V600E melanoma cells leading to decreased proliferation.

Most common adverse reactions (>=20%) for dabrafenib are hyperkeratosis, headache, pyrexia, arthralgia, papilloma, alopecia, and palmar-plantar erythrodysesthesia syndrome.

Indication: Dabrafenib was given for patients who had unresectable or metastatic melanoma with BRAF V600E mutation.

Labelled indications:
Melanoma (metastatic or unresectable): Treatment of unresectable or metastatic melanoma in patients with a BRAF V600E mutation (single agent therapy) or in patients with BRAF V600E or BRAF V600K mutations (in combination with trametinib); confirm BRAF V600E or BRAF V600K mutation status with an approved test prior to treatment.

Non-small cell lung cancer (metastatic): Treatment of metastatic non-small cell lung cancer (NSCLC) in patients with BRAF V600E mutation as detected by an approved test (in combination with trametinib).

Limitations of use: Not indicated for treatment of patients with wild-type BRAF melanoma or wild-type

BRAF NSCLC.ADME:
Dabrafenib is metabolized hepatically. CYP2C8 and CYP3A4 acts as a mediator for the bio transformation process. Then it is further oxidized by CYP3A4 to form carboxydabrafenib and it is excreted in bile and urine. Then it undergoes decarboxylation to form desmethyl - dabrafenib which is reabsorbed from the gut .It is then further metabolized by CYP3A4 to oxidative metabolites.

Renal excretion of this accounts for less than 20% But the major route of excretion is through fecal .Dabrafenib should be taken only in empty stomach[6], [7]

Vemurafenib Vs Dabrafenib:
Vemurafenib and dabrafenib are indicated for patients with non-resectable or metastatic melanoma associated with the BRAF V600E mutation. The MEK inhibitor trametinib is also indicated for melanoma associated with BRAF V600E or V600K mutations. Since 2014 trametinib has also been registered for use in combination with dabrafenib for the treatment of patients with BRAF (V600E) or BRAF (V600K) melanoma.[8]

Vemurafenib and dabrafenib prolong both progression-free survival and overall survival of melanoma patients and are therefore promising options for patients with tumours that arise from a BRAF V600 mutation.[9]

Treatment with vemurafenib:
Vemurafenib is an oral, highly selective and competitive drug with the BRAFV600E mutation, . Used at the dose of 960mg orally twice daily, it is the first-line of treatment for patients with this mutation in metastatic melanoma.it can present several adverse events, such as arthralgia, rash, fatigue, alopecia, photosensitivity, squamous cell carcinomas and keratoacanthomas[10]

Vemurafenib seems to be more nephrotoxic than dabrafenib. This renal toxicity seems to be more prevalent among male patients with melanoma.The mode of injury seems to be tubular interstitial injury. There is a need to monitor renal function and electrolyte levels in all patients who receive these drugs.[11]

Treatment with Dabrafenib:
Dabrafenib is an oral, selective drug administered orally at 150mg dose twice daily. The most common adverse events are: hyperkeratosis, headache, pyrexia, arthralgia and cutaneous papillomas.[10]

In patients with metastatic melanoma, combined therapy with dabrafenib and trametinib increases progression-free survival compared with treatment with dabrafenib alone. Compared with treatment with vemurafenib (which provides median progression-free survival of 7.3 months), combined therapy with dabrafenib and trametinib provides improved progression-free survival (median survival is 11.4 months)[9] Both drugs have achieved an increase in the rates of progression-free and overall survival in stage III clinical trials compared with conventional chemotherapy in patients with BRAF-mutated metastatic melanoma.[13]

Resistance developed during the treatment:
Many patients develop resistance to ERK signaling inhibitors, due to compensatory mechanisms such as EGFR over expression or an adaptive transcriptional response. The other mechanisms that can confer resistance to treatment include increased activity of the PI3K/AKT/mTOR pathway and up regulation of the ERK signaling pathway.[9]

Many patients develop resistance, which is associated with survival of 6–7 months. The majority of the resistance mechanisms are due to the reactivation of the MAP kinase pathway.[13]

The combination of BRAF and MEK inhibitors when (dabrafenib and trametinib), compared with BRAF inhibitors as monotherapy, delays the resistance and reduces the occurrence of hyper proliferative skin lesions.[13]

The primary resistance to BRAF inhibitor treatment is the amplification of the CCND1 gene (encoding cyclin D1), 92 and stromal expression of hepatocyte growth factor, 93.[14]

Comparative treatment with Dabrafenib and vemurafenib:
Evidences have proved that patients with previously untreated BRAF Val600Glu or Val600Lys mutant unresectable or metastatic melanoma who were treated with the combination of dabrafenib and trametinib had significantly longer overall and progression-free survival than those treated with vemurafenib alone in a COMBI-v trail. From the patient's perspective, which integrates not only survival advantage but also disease-associated and adverse-event-associated symptoms, treatment with the combination of a BRAF inhibitor plus a MEK inhibitor (dabrafenib plus trametinib) adds a clear benefit over monotherapy with the BRAF inhibitor vemurafenib and supports the combination therapy as standard of care in this population.[15]

Combination of dabrafenib and trametinib is found to be cost effective than vemurafenib monotherapy.The cost effectiveness in this combination therapy is required to achieve the clinically promising treatment.[16]

This combination treatment also shows the overall survival when compared with vemurafenib monotherapy for the patients who suffered from BRAF V600E or V600K mutation without increased overall toxicity. Hence our study shows that first line use of this combination therapy (BRAF and MEK inhibitors) resulted in higher response rates and longer duration of response and delayed resistance which shows the overall survival benefit.[16]

Secondary resistance and paradoxical activation of the MAPK pathway that occur with BRAF-inhibitor monotherapy, which translate into rapid tumor relapses

and emergence of skin cancers, respectively, were both improved by the combination therapy.

A decreased ejection fraction was more frequent with the combination therapy than with vemurafenib (8% vs. 0%), and this side effect has been observed previously with single-agent MEK inhibitors[12]

Dabrafenib and vemurafenib are both selective type I BRAF inhibitors, with proven efficacy in BRAFV600 metastatic melanoma. Unlike dabrafenib, which is more selective for BRAFV600E than wild-type RAF kinases, vemurafenib has similar potency for CRAF, wild-type BRAF, and BRAFV600E. [14]

Toxicities of the drug:

Generally the usage of BRAF inhibitors may lead to the development of some conditions like cutaneous toxicities such as rashes, photosensitivity, alopecia, palmoplantar erythrodysesthesia, and proliferative skin lesions, including keratoacanthomas (KAs) and cutaneous squamous cell carcinomas (cuSCCs).[17]

Toxicity is the main difference between dabrafenib and vemurafenib The effects like Cutaneous toxicities, including rash, hyperkeratosis, cuSCC, and cutaneous keratoacanthoma, occur with both drugs, but this occurs very less in the dabrafenib trials when compared to vemurafenib.[19]

Photosensitivity (related to the chemical structure of the molecule and UVA exposure rather than RAF inhibition) and hepatitis occur for the patients treating with vemurafenib but not with dabrafenib. But pyrexia occurs more frequently and severely with dabrafenib than vemurafenib.[19]

The toxicity profile of dabrafenib was manageable and generally similar to that of vemurafenib with the exception of pyrexia in 6% of patients and lower incidence of SCC (11%). Tumor shrinkage was observed in nine of 10 patients with melanoma and previously untreated brain metastases[19]

Another BRAF inhibitor, LGX818, is a new drug is also in development[20] Initial data from a phase I trial (n = 54) says that it is active, and this drug may have a more favorable toxicity profile when compared to vemurafenib or dabrafenib, with photosensitivity and pyrexia reported in less than 10% of patients, and cuSCC in less than 5%[18]

Use of combined therapy:

The onset of resistance is delayed in the combination of a BRAF and MEK inhibitor and increased apoptosis compared with BRAF inhibitor monotherapy[20] The aim of combined treatment was to (I) circumvent or delay the acquired resistance which occurs due to reactivation of the MAPK pathway and (ii) to reduce the toxicities which occurs in the case of monotherapy, especially the cutaneous toxicity from BRAF inhibitors that occur due to paradoxical activation of the MAPK pathway in BRAF wild-type keratinocytes[20]

Dabrafenib is also used in patients with BRAFV600E and BRAFV600K mutated metastatic melanoma, including those with brain metastases.[14]

With other combinations:

Immunotherapy with both drugs:

Combination of BRAF inhibitors with immunotherapy is considered to be safe and effective, given differences in their modes of action and toxicity profiles. BRAF inhibition leads to increased expression of melanoma differentiation antigens and an influx of tumor-infiltrating lymphocytes.[14]

A trial of vemurafenib with the immunotherapy like ipilimumab has commenced.[14]

Combined treatment with vemurafenib:

Studies showed that some patients developed panniculitis predominantly on the upper and lower extremities 10 days after the initiation of combined treatment with cobimetinib and vemurafenib for metastatic melanoma, These cutaneous nodules disappeared during cobimetinib intermissions and it recurred when the molecule was resumed. Recurrence of cutaneous nodules was observed after initiation of trametinib combined with dabrafenib, and resolved once again with trametinib discontinuation.[21] We believe that clinicians should be aware of this cutaneous adverse event in patients treated with combined therapy, which can lead to unfounded BRAF inhibitor treatment discontinuation[22]

From the literature studies, it is known that there is a variation in the baseline LDH level in COMBI-v and coBRIM.COMBI-v had slightly slowly proportion of patients with elevated LDH than coBRIM [23]

The potassium channel inhibitor TRAM-34 is considered as highly effective in combination with vemurafenib. This combination leads to enhance the apoptosis and cell viability was decreased. The combination vemurafenib/TRAM-34 was also effective in vemurafenib-resistant cells, since it makes the acquired resistance to overcome. Vemurafenib decreased ERK phosphorylation, suppressed antiapoptotic Mcl-1 and enhanced proapoptotic Puma and Bim.The particular importance for vemurafenib and its combination with TRAM-34. is that the ROS

represents an initial and independent apoptosis pathway in melanoma cells.[24]

Vemurafenib shows higher RR than the drug dacarbazine (57% vs. 9%) and also that nearly all vemurafenib-treated patients obtained at least some reduction in tumor burden.[19]

Combined treatment with dabrafenib:

The appropriate selection of systemic therapy for metastatic melanoma is the combination therapy with dabrafenib and trametinib revealed that long-term survival and durable responses are associated with good prognostic features at baseline, including factors related to low-volume disease. However, such baseline factors are classically considered a reason to choose front-line immunotherapy. The need to develop specific predictive molecular markers for each therapy is very important. Another issue related to this treatment is the determination of the optimal sequence of administered therapeutic agents, since it remains unknown if treating patients with ipilimumab and nivolumab followed by dabrafenib and trametinib is more effective than treatment with dabrafenib and trametinib followed by ipilimumab and nivolumab.[25]

BRAF inhibitors used for other complications:

Treatment of V600E BRAF-mutant lung adeno carcinomas with dabrafenib is under evaluation in a phase 2 trial, and could represent another milestone in individualized therapy for lung cancer patients.[26]

Combination therapy of cetuximab and vemurafenib is used for refractory BRAF (V600E) mutant metastatic colorectal carcinoma[28]

Advantage of dabrafenib over vemurafenib:

Recent advances in melanoma therapy with inhibitors of the BRAF/MEK/ERK signaling cascade helped to treat the metastatic patients. These are highly effective in the metastatic disease in spite of displaying different side effects. Recent studies showed that a leukopenia patient with BRAF V600E-mutated stage IV melanoma who was treated with the BRAF inhibitor vemurafenib had an immediate therapeutic switch to a different BRAF inhibitor called 'dabrafenib', which had no negative influence on the leukocyte count. It showed a differential influence of different BRAF inhibitors namely vemurafnib and dabrafenib on patients' leukocytes despite similar clinical efficacy in melanoma.[29]

Though both the drugs vemurafenib and dabrafenib have comparable clinical efficacy, Vemurafenib decreases the peripheral leukocyte count in patients and it also alters CD4 + T cell phenotype and function. Thus, selective BRAFi can significantly affect patients' peripheral lymphocyte populations.[27]

From literature studies, we observed that clinically available inhibitors of BRAF (vemurafenib and dabrafenib) or MEK (trametinib) exert potent antileukemic activity in patient's hairy cell leukemia cells in vitro; dabrafenib seems more effective at inducing apoptosis than vemurafenib even in hairy cell leukemia cells from patients relapsing after vemurafenib; and further the bone marrow microenvironment antagonizes both MEK-ERK dephosphorylation and apoptosis induced by BRAF inhibitors. Finally, by showing that dabrafenib is less affected than vemurafenib by such a protective stromal effect and that the latter is further reduced by using the combined therapy of BRAF and MEK inhibition (dabrafenib + trametinib), we offer viable strategies to inform the clinical use of BRAF and MEK inhibitors in hairy cell leukemia and exert potent antileukemic activity.[30]

CONCLUSION:

Thus we conclude that the drug Dabrafenib shows the safety and better efficacy and it also has lower toxic effect when compared to vemurafenib.

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