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BRAF Inhibitors and Control of Mutant BRAF Effects

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Abstract

BRAF is a serine/threonine kinase from the RAF kinase family that has a regulatory role in the activation of MAPK/extracellular-signal-regulated kinase (ERK) signaling pathway. Excessive activation of this pathway plays an oncogenic role in a variety of human malignancies. Mutant BRAF inhibitors have molecular targeted activity, and immunomodulatory effects on the tumor microenvironment. The use of BRAF inhibitors is effective in preventing disease progression. However, drug-resistance emerges from paradoxical hyperactivation of mitogen-activated extracellular signal regulated kinase (MEK), the signaling molecule immediately downstream of BRAF pathway.

Abbreviations: ERK: Extracellular-Signal-Regulated kinase; HCL: Hairy Cell Leukemia; ORR: Overall Response Rate; LVSD: Left Ventricular Systolic Dysfunction; SCC: Squamous Cell Carcinomas; AES: Adverse Events

Introduction

BRAF is a serine/threonine kinase from the RAF kinase family. It is encoded by the BRAF gene located on chromosome 7 at 7q34 position. BRAF gene has a regulatory role in the activation of MAPK/extracellular-signal-regulated kinase (ERK) signaling pathway. Excessive activation of this pathway by a variety of receptors leads to uncontrolled cell proliferation, differentiation and survival. It plays an oncogenic role in a variety of human malignancies [1].

Approximately 43 mutations have been identified in exons 11 and 15 of the BRAF gene and are associated with a variety of human malignancies. The most common of which is BRAF V600E mutation, which is caused by adenine (A) and thymine (T) exchange at position 1799 on exon 15 resulting in the change of amino acid 600 in the protein sequence from valine to glutamate. This will lead to constant activity of the downstream kinases, independently of the extracellular signals, and increased cell proliferation [1]. BRAFV600E mutation is recurrent in various solid tumors, including cutaneous melanoma, lung, ovarian, bladder, thyroid, prostatic cancers, cholangiocarcinoma and sarcoma/GIST. In hematological malignancies, BRAF V600E has been defined as a genetic lesion in almost all cases of classic hairy cell leukemia (HCL). The possibility of mutations in exon 11 (F468C, D449E) should be excluded in HCL with absence of BRAF gene (BRAFWT) mutation [2]. BRAF V600E mutation is not detected in other B-cell malignancies, including SMZL, HCL-v, mantle cell lymphoma and Waldenstrom macroglobulinemia [1].

BRAF inhibitors and control of mutant BRAF effects

Mutant BRAF inhibitors (v-Raf murine sarcoma viral oncogene homolog B) represent a key example of targeted therapy used in a genetically defined patient population [3]. BRAF inhibitors include vemurafenib, dabrafenib and encorafenib. They have molecular targeted activity, and immunomodulatory effects on the tumor microenvironment, leading to increased tumor recognition by the immune system, and anti tumor T cell responses [4]. The use of BRAF inhibitors halts the continuation of the pathway and is effective in preventing disease progression. The clinical efficacy of BRAF kinase inhibitors has been reported in melanoma. They also offer a new therapeutic opportunity for the treatment of BRAF V600E refractory HCL [1]. BRAF inhibitors efficacy has been reported in basket trials on diverse non-melanoma BRAF-mutant cancers. The overall response rates (ORR) in these tumors are generally lower than those observed in melanoma. In metastatic colorectal cancer (mCRC), for example, the ORR to BRAF inhibitors and combined inhibitors of BRAF/MEK is much lower [3].

BRAF inhibitors and malignant melanoma

BRAF inhibitors monotherapy in malignant melanoma

BRAF inhibitors vemurafenib and, subsequently, dabrafenib

and encorafenib have been approved for use in patients with BRAF mutant melanoma. Their use as monotherapy in advanced melanoma brought a significant increase in progression-free and overall survival. However, approximately 50% of patients developed acquired resistance, even in patients whose disease was initially sensitive to these drugs [5]. In some cases of melanoma, responses to BRAF inhibitors monotherapy have been noted despite disease progression on a prior course of treatment with different BRAF inhibitor. This raises the question of the mechanism by which the different inhibitors against the same targets may show distinct clinical activity on a patient-by-patient basis [3].

Combined BRAF and MEK inhibition in malignant melanoma

The majority of drug-resistance to BRAF inhibitors results from paradoxical hyperactivation of mitogen-activated extracellular signal regulated kinase (MEK), the signaling molecule immediately downstream of BRAF pathway [5]. Alternatively, escaping drug response to BRAF inhibitor induced cytotoxicity has also been attributed to other mechanisms independent of the MAPK-pathway re-activation [6]. Malignant melanoma carrying an activating V600 BRAF mutation exhibits robust initial responses to treatment with combination of BRAF inhibitors and MEK inhibitors, with greater than 50% ORR in pivotal trials [3]. Concomitant inhibition of BRAF and MEK brings about more prolonged disease control [5], delays the emergence of drug resistance, and is associated with prolonged progression-free and overall survival when compared with BRAF inhibitors monotherapy [5].

Adverse events of BRAF inhibitors

In spite of the potent anti-cancer effects of combined BRAF and MEK inhibition, they are increasingly recognized to be associated with adverse cardiovascular effects including hypertension, left ventricular dysfunction, venous thromboembolism, atrial arrhythmia, and electrocardiographic QT interval prolongation. The underlying mechanisms by which left ventricular systolic dysfunction (LVSD) occurs in association with combined BRAF inhibitor and MEK inhibitor have not been extensively studied. It is expected that disruption of the MAPK pathway could lead to a change in the physiological cardioprotective mechanisms and affect apoptosis, remodeling, and hypertrophy, ultimately leading to LVSD [5].

Plenty of cutaneous findings have also been developed in patients treated with BRAF inhibitors. The most frequently reported cutaneous findings in a study on a group of 33 patients are photosensitivity, warts, actinic keratosis, and cutaneous squamous cell carcinomas (SCC). All these findings were seen with greater frequency and earlier in patients taking vemurafenib. They may be directly related to the therapeutic mechanism of the drug. The important role of RAS mutations has been highlighted in the pathogenesis of SCC and kerato-acanthomas developing in patients taking vemurafenib. The relation between combined BRAF inhibitor and MEK inhibitor and these skin lesions is not well defined. These lesions developed in the presence of BRAF inhibition with and without MEK inhibition in one study [7]. However, another study showed reduced incidence of skin tumors induced by BRAF inhibitor in those receiving BRAF inhibitor and MEK inhibitor combination therapy [5]. Close dermatologic support with frequent full body skin exams is recommended in patients treated with BRAF inhibitors to ensure early identification of non-melanoma skin cancer. Further studies are still needed to provide multiple avenues regarding the molecular biology of these dermatological phenomena [7].

Other reported adverse events (AES) and serious AES in clinical trials and ongoing clinical practice, are ocular toxicity including central retinopathy and retinal vein occlusion, elevation of AST, ALT, and serum bilirubin [8]. A recent report presents a BRAF-mutated non–small cell lung cancer patient who was treated with combined BRAF/MEK inhibition (dabrafenib and trametinib) and experienced 2 unusual AES—Sweet syndrome and MEK-associated retinopathy. The patient responded to steroid treatment and was able to continue BRAF/MEK inhibition through a coordinated multidisciplinary approach [9]. All of these AES or serious AES require careful monitoring and control of risk factors [8].

Conclusion

Further studies are still needed to know why different BRAF inhibitors may show distinct clinical activity on a patient-by-patient basis.

References

1. Ahmadzadeh A, Shahrabi S, Jaseb K, Norozi F, Shahjahani M, et al. (2014) BRAF mutation in hairy cell leukemia. Oncol Rev 8(2): 253.
2. Troussard X, Maître E, Cornet E (2022) Hairy cell leukemia 2022: Update on diagnosis, risk-stratification, and treatment. Am J Hematol 97(2): 226-236.
3. Ng TSC, Hu H, Kronister S, Lee C, Li R, et al. (2022) Overcoming differential tumor penetration of BRAF inhibitors using computationally guided combination therapy. Sci Adv 8(17): 1-16.
4. Peelay Z, Patil VM, Menon N, Noronha V, Parekh D, et al. (2022) Real world analysis of BRAF inhibitors in patients with solid tumors positive for BRAF V600E mutation: A retrospective observational study. Cancer Research, Statistics, and Treatment 5(3): 581-584.
5. Glen C, Tan YY, Waterston A, Evans TRJ, Jones RJ, et al. (2022) Cardiovascular toxicity of BRAF and MEK inhibitors. JACC: CardioOncology 4(1): 1–18.
6. Arozarena I, Wellbrock C (2017) Overcoming resistance to BRAF inhibitors. Ann Transl Med 5(19): 387-399.
7. Mattei PL, Alora-Palli MB, Kraft S, Lawrence DP, Flaherty KT (2013) Cutaneous effects of BRAF inhibitor therapy: a case series. Annals of Oncology 24(2): 530–537.

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8. Troussard X, Maître E, Cornet E (2022) Hairy cell leukemia 2022: Update on diagnosis, risk-stratification, and treatment. Am J Hematol 97(2): 226–236.

9. Maniar R, Gallitano SM, Sameera Husain, Moazami G, Weiss MJ, et al. (2023) Unusual adverse events in a patient with BRAF-mutated non–small cell lung cancer treated with BRAF/MEK inhibition J Natl Compr Canc Netw 21(3): 232–234.

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