BRAF V600K-Mutant Cutaneous Melanoma

Subjects: Allergy
Contributor: Gianluca Avallone

BRAF is a serine/threonine protein kinase that, activating MAPK and ERK signalling, is involved in cell proliferation. About 50% of melanomas harbour a BRAF mutation. Of these 50%, 10% have a V600K mutation. Recent findings have underlined how melanoma V600K seems to be less dependent on the ERK/MAPK pathway, with a higher expression of PI3KB and a strong inhibition of multiple antiapoptotic pathways. Both target therapy with BRAF inhibitors + MEK inhibitors and immunotherapy with anti-checkpoint blockades are effective in melanoma V600K, although no sufficient evidence can currently support a formal recommendation for first line treatment choice in IIIC unresectable/IV stage patients.

cutaneous melanoma | BRAF mutation | BRAF V600K | target therapy | immunotherapy

1. Introduction

Target therapies with BRAF/MEK inhibitors have been demonstrated to improve overall survival (OS) and progression free survival (PFS) in metastatic cutaneous melanoma, reaching almost 50% of metastatic patients, due to the high BRAF mutation's incidence rate, with a very tolerable toxicity profile for patients [1]. Almost 50% of cutaneous melanomas harbour a BRAF mutation [2]. Multiple rare V600 mutations have been described in melanoma (V600D/V600R), although evidence is very limited in terms of clinical characteristics and benefits from target therapy with BRAF/MEK inhibitors [3].

2. Epidemiology

Melanoma BRAF V600K at least accounts for 10% of all BRAF mutated melanomas, being the second more common genotype after V600E [2]. HBRAF mutation seems to be more frequent in the Caucasian population, with a higher incidence of V600K mutated melanomas. In Kaori Sakaizawa et al., only 20–30% of melanomas were BRAF mutated and less than 5% were V600K, suggesting that the difference is attributable to the lower incidence of non-chronic sun damage melanoma among Asians [4].

3. BRAF Mutation Testing

BRAF mutation testing is routine and it is mandatory for all patients with advanced melanoma, due to its impact on therapeutic decision making [5]. In the last years, several techniques have been developed, including immunohistochemistry (IHC), Sanger sequencing and Next Generation Sequencing (NGS) [5]. IHC has a good profile in terms of sensitivity and specificity, but is not able to detect other V600 mutations, such as V600K [5][6].

Mostly, IHC is indicated as a screening test in specific contexts and needs to be confirmed afterwards by NGS or a PCR- based approach [5].

Liquid biopsy is arising as a promising technique for detecting BRAF mutation and for monitoring tumour response to therapy [7].

4. Clinical and Dermatological Features

V600K melanomas have shown to have clinical and dermatological peculiarities from others V600 mutated melanomas. In a multivariate analysis on 308 Australian patients, the melanoma V600K subgroup demonstrated a higher prevalence of patients with older age and objectively appreciable chronic sun-damaged (CSD) skin at dermatological examination, compared to melanoma V600E [8]. The most common primary site for melanoma was the trunk for both genotypes (V600E 38% vs. 41% V600K), although in melanoma V600K the head and neck regions were more frequently affected (33% V600K vs. 11% V600E, respectively) [8]. No differences were found between the proportion of occult melanoma in the two subgroups [8]. In melanoma V600K, the disease-free interval from diagnosis of primary melanoma to the first distant metastasis appeared to be shorter (17.4 months) compared to V600E melanoma (39.2 months), with no significant differences in terms of survival [8]. NGS analysis of 446 melanomas confirmed the higher incidence of V600K mutation in male gender, old age (>60 years) and primary tumour of head, neck, or upper back, with a history of chronic sun exposure and damage. No difference was found between the cutaneous melanomas and metastatic melanomas of unknown origin [9].

5. Biological Identity of Melanoma V600K

As for V600E, BRAF V600K mutation in melanoma promotes a strong activation of the MAPK and ERK pathway, stimulating cell survival and proliferation [10]. Recent preclinical studies have suggested how, biologically, melanoma V600K has its own peculiar features. In 2017 Yuanyuan Li et al. detected how in V600K melanoma the KIT expression gene and c-KIT protein were up-regulated compared to melanoma V600E. Although the significance is unclear, c-Kit is involved in melanogenesis and it may also contribute to melanoma progression and proliferation. Additionally, mir-222 was downregulated and it is implicated in the expression of the KIT gene as an inhibitor, altering metabolic signals [10]. In V600K melanoma, many pro-apoptotic regulators were downregulated as Caspase-7, Bid and Bak, suggesting another mechanism of escape of V600K tumours from apoptosis and promoting cell survival [10]. Melanoma V600K was associated with a lower expression of dual-specificity phosphatase (DUSP6), a transcriptional target of the ERK pathway involved in feedback regulation and reflective of ERK activation, whereas PIK3B expression was higher, as well as tumour mutational load [11]. ERK is a transcriptional factor downline of MAPK signalling that incites a strong stimulus on cell proliferation. PI3KB is part of the PI3K-AKT pathway: when overexpressed, it inhibits apoptosis, promoting cell survival [11]. However, an analysis of molecular expression of high-CSD melanoma, which is known to be correlated with BRAF V600K, has outlined an increment in NF-1 and TP53 mutations, as well as an increase in tumour mutational load compared to

melanoma V600E [11]. Research on melanoma has shown how PFS and OS showed either a strong trend or significantly better outcomes as TMB (tumour mutational burden) increased when treated with immunotherapy [12].

6. Therapeutic Effects of BRAF/MEK Inhibitors and Immunotherapy on Melanoma V600K

Recently, the RELATIVITY-047 (relatlimab + nivolumab vs. single agent nivolumab) trial has demonstrated a strong advantage in PFS of the combination of anti-LAG3 + anti PD-1 on single agent anti PD-1, with an excellent toxicity profile, promising to be the future first line of treatment for metastatic melanoma. Although no clinical outcomes for melanoma V600K were reported, no difference in terms of PFS were found between melanoma WT and BRAF mutated melanoma, suggesting that BRAF mutated melanoma patients could also benefit from it [13].

7. Conclusions

To date, the literature has shown that melanoma V600K has its own biological features, which should not be overlooked. However, further investigation on V600K melanoma is needed. Melanoma V600K represents a specific subgroup of cutaneous melanoma, with a high prevalence among Caucasian, male and elderly patients, often with a history of CSD. Melanoma V600K has been demonstrated to be significantly more aggressive and rapid in progression than melanoma V600E with inclusive or partial data in terms of OS and PFS after receiving either one of the principal therapies approved for unresectable/metastatic melanoma (immunotherapy (PD/PDL-1 agent, CTLA4 agent) or BRAFi ± MEKi). Both target and immunotherapy seem to be effective for V600K melanoma, although no gold standard has been identified yet. Future studies should clarify which therapeutic strategy may be more effective for this specific patient subgroup. In addition, prognostic factors on treatment response could be usefully investigated.

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