Cancer Treatment Reviews 39 (2013) 305–312

Contents lists available at SciVerse ScienceDirect

Cancer Treatment Reviews

journal homepage: www.elsevierhealth.com/journals/ctrv

Hot Topic

Is combination therapy the next step to overcome resistance and reduce toxicities in melanoma?

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ARTICLE INFO

Article history:
Received 6 September 2012
Received in revised form 8 October 2012
Accepted 9 October 2012

Keywords:
Vemurafenib
Melanoma
Drug resistance
Toxicity
Squamous cell carcinoma
Combination therapy

ABSTRACT

In the last few years, several drugs targeting signalling proteins critical for melanoma entered clinical evaluation. In 2011 vemurafenib (Zelboraf®, F. Hoffman-La Roche Ltd.) was approved for BRAF V600-positive melanoma and showed high overall response rates (48–53%). However recent results from a phase II clinical trial also showed that the median duration of response was 6.7 months and median progression free survival was 6.8 months with tumour relapse. Resistance to targeted agents is quite common and understanding of the underlying molecular mechanisms might predict response or failure. The knowledge of the mechanisms involved in intrinsic and acquired resistance to mutated BRAF is increasing swiftly. Subsequently the elucidation of these mechanisms resulted in the development of rational combination therapies to overcome toxicity and resistance. These combination therapies will be discussed.

Introduction

Vemurafenib (Zelboraf®, F. Hoffman-La Roche Ltd.) has recently been approved as monotherapy for BRAF V600E mutation-positive metastatic melanoma. For a long time dacarbazine was the standard of care with an overall response rate (ORR) of only 15–20% and no improvement in overall survival.[1] New treatment is clearly needed since the median survival of these patients is less than 1 year.[2] After the discovery of activating mutations in the serine/threonine kinase BRAF, found in approximately 50–70%[3,4] of all melanomas, the possibilities for targeted therapy were investigated. This led to the approval of BRAF inhibitor (BRAFi) vemurafenib by the FDA in 2011.[5] All clinical trials confirmed high overall response rates (48–53%)[5–7] and in a phase III clinical trial vemurafenib showed, as compared to dacarbazine, both improved progression-free (PFS) and overall survival (OS) in patients with metastatic melanoma with the BRAF V600E mutation.[5] However recent results from a phase II trial showed that after a response duration of 6.7 months some patients show tumour relapse due to mechanisms that are not fully understood.[7] In addition approximately 25% of the patients develop hyperproliferative skin lesions and some even cutaneous squamous cell carcinoma (CSCC). Now investigators focus on the diverse pathways of vemurafenib resistance (and toxicity), because this might lead to new strategies to overcome or delay resistance and prolong responses.

In this paper we discuss the recent developments concerning BRAF signalling in melanoma pathogenesis and the development of possible combination therapies to overcome resistance and to reduce toxicity.

Vemurafenib has shown to benefit patients with BRAF V600E activating mutation in clinical trials as monotherapy. During the escalation phase of a phase I clinical trial[6] the recommended phase II dose was determined at 960 mg twice-daily (BID). In the extension phase, treatment with vemurafenib resulted in complete or partial tumour regression in the majority of patients (81%, 26 patients). In a phase II study[7], vemurafenib treatment was effective (ORR: 53%) and no severe or life threatening toxic effects occurred. However a large number of patients (26%) developed CSCC or keratoacanthoma (KA). Dose reductions were needed in 45% of the patients and dose interruptions were needed in 64% of the patients. The median OS was 15.9 months. In a phase III clinical trial[5], comparing vemurafenib to dacarbazine, vemurafenib therapy was associated with a longer median OS of 13.2 months compared to

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http://dx.doi.org/10.1016/j.ctrv.2012.10.006

9.6 months in the dacarbazine arm. The latest update on this study shows a 12-month OS of 55% for vemurafenib and 43% for dacarbazine.[8] Even though the responses are high, the duration of response has been limited due to development of resistance. The development of tumour resistance to single-targeted agents appears inevitable and given the high responses it is of pivotal importance to identify alternative therapies that overcome this problem.

Targeting BRAF: mechanism of action of vemurafenib

To understand the pathways that underlie resistance and toxicity, it is important to understand the mechanism of action of the drug. In 2002 researchers from the Sanger Institute found that a certain RAF kinase in the mitogen-activated protein kinase (MAPK) pathway, BRAF kinase, was mutated in approximately 8% of a cohort of 923 tumours and cancer cell lines.[4] BRAF mutations appeared most common in melanomas (60%), papillary thyroid, low malignant potential ovarian and colorectal cancers.[4] Melanomas that harbour the BRAF V600E mutation constitutively activate the MAPK pathway. Vemurafenib was then developed as a potent kinase inhibitor with specificity for the BRAF V600E mutation within cancer cells.[9–11]

BRAF is the second kinase in the cascade consisting of RAS, RAF, MEK (mitogen-activated protein kinase) and ERK (extracellular signalling-regulated kinase [MAPK] kinase) (Fig. 1). It is long known that signal transduction through this pathway is involved in proliferation, invasion and drug resistance of various cancer types. The MAPK pathway is one of the key regulators of cell cycle progression and is commonly activated in human tumours. In normal cells activation of receptor tyrosine kinase (RTK) stimulates phosphorylation of guanine exchange factor (GEF), including SOS1/SOS2, that activate RAS. Activated RAS binds to activated RAF which subsequently leads to phosphorylation of MEK. Finally MEK phosphorylates ERK which enters the nucleus. By inhibiting ERK signalling in a V600 BRAF-selective manner, with a BRAFi such as vemurafenib, cell proliferation is inhibited.[12]

Vemurafenib only inhibits the ERK pathway and cell proliferation in tumours with mutant BRAF. In tumours and normal cells with wild-type BRAF vemurafenib causes paradoxical activation of the pathway which will be discussed in the toxicity and resistance part. However vemurafenib only reactivates the pathway when there is upstream RAS or RTK (receptor tyrosine kinase) activity (Fig. 2). Since vemurafenib is a very specific inhibitor of ERK signalling this underlies its broad therapeutic index in V600E mutated melanoma.

Toxicity and resistance

Mechanisms of toxicity

Vemurafenib has shown remarkable results in clinical trials conducted so far. However approximately 25% of the patients develop hyperproliferative skin lesions and some even CSCC. These cutaneous side effects disappeared after drug withdrawal. An explanation for this can be found in the finding that selective BRAFi can suppress the RAF/MEK/ERK pathway in tumour cells that harbour a BRAF-mutation, but can activate this same pathway in tumour cells with a mutation in the KRAS gene, which possesses a wild type BRAF gene.[13–16] In normal cells activation of the BRAF/MEK/ERK pathway promotes cell growth, but excessive activation is associated with cancer. Signal activation through RAS enzymes is low when BRAF is mutated, so ERK signalling is predominantly

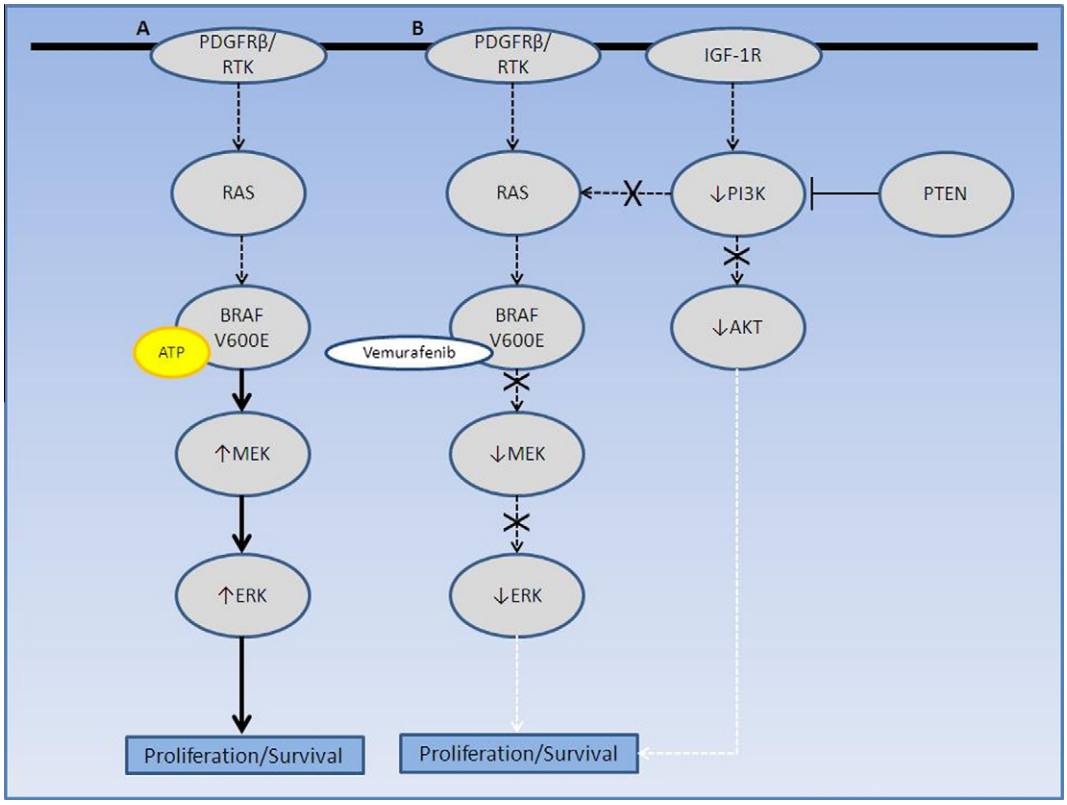

Fig. 1. Mechanism of action of vemurafenib in vemurafenib-sensitive cells. Mutated BRAF V600E causes excessive signalling in the RAS/RAF/MEK/ERK pathway, leading to increased MEK and ERK. (A) Hyperactivation of the pathway leads to excessive proliferation and subsequently to tumour growth. (B) When treated with a BRAF inhibitor such as vemurafenib, the pathway is inhibited, leading to tumour shrinkage. Additionally PTEN normally inhibits the PI3K pathway thus proliferation and cell survival through this pathway is inhibited also. RTK, receptor tyrosine kinase; PDGFRβ, beta-type platelet derived growth factor.