Targeted therapy in melanoma – the role of BRAF, RAS and KIT mutations

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Melanoma today is considered as a spectrum of melanocytic malignancies characterised by clinical and molecular features, including targetable mutations in several kinases such as BRAF or c-KIT. The successful development of therapies targeting these mutations has resulted in new specific treatment options. These include vemurafenib, dabrafenib, trametinib, imatinib and other kinase inhibitors that are selected when the respective mutation is present.

The BRAF inhibitor vemurafenib has resulted in improved survival in patients with BRAF-mutated advanced melanoma. Dabrafenib has shown similar efficacy. The MEK inhibitor trametinib also improved overall survival. In addition, the MEK inhibitor MEK 162 was investigated in a phase II clinical trial and showed promising efficacy in terms of response rate and progression-free survival (PFS) in NRAS-mutated melanomas. After this first success in the treatment of advanced melanoma, there is expectation that combinations of kinase inhibitors will additionally improve overall survival rates and PFS in advanced melanoma.

1. Introduction

Melanoma is the most common lethal cutaneous malignancy. It arises from melanocytes that have their origin in the neural crest. The genetic events and their relationship to the complex interaction with the microenvironment transforming normal melanocytes into melanoma are under intensive investigation.

2. Molecular dissection of melanoma

In the last decade melanoma was dissected into several molecular subgroups on the basis of genomic alterations, including mutations, deletions and amplifications, in addition to clinical features. These subgroups include BRAF, NRAS and KIT mutated melanomas.

First, up to 50% of melanomas derived from the skin without chronic sun damage (intermittently exposed to ultraviolet (UV)) contain mutations in the gene encoding the serine–threonine protein kinase BRAF. BRAF together with ARAF and CRAF activates a second protein known as mitogen-activated protein kinase kinase (MEK), which in turn activates extracellular signal-regulated kinase (ERK).

Second, 20% of melanomas present with RAS mutations. Most of the NRAS mutated melanomas are superficial, spreading melanomas (intermittently exposed to UV). However, NRAS seems also to be involved in melanomas deriving from giant congenital nevi. A recently published model for congenital nevi [1] used a melanoma mouse model overexpressing NRAS under the control of a tyrosinase promoter in combination with loss of INK4a. The phenotype of these mice closely resembles giant congenital nevi. In this model, haplo-insufficiency of the transcription factor SOX10 prevented melanoma formation.

Finally, minor percentages have activating mutations in the KIT gene, most common in mucosal melanomas derived from the genital regions [2,3] or mutations in GNA11 or GNAQ genes in uveal melanomas [4,5]. Some of the targetable mutations in the KIT gene are also found in acral and other mucosal (for example, penile or anal) melanomas but with lower frequency. The KIT receptor protein tyrosine kinase is a transmembrane protein consisting of extracellular and intracellular domains. Most KIT mutations are located in exon 11, which codes for the juxtamembrane domain, and in exon 13, which codes for a kinase domain.

Recently, deep exome sequencing shed further light on the genomic landscape of melanoma [6,7]. Both publications impressively demonstrated that UV light is responsible for most mutations in melanomas derived from UV-exposed skin.

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Hodis et al. reported that more than 80% of all non-silent coding mutations are UVB-dependent. Similar observations were also reported by Krauthammer et al. In addition, both papers provide evidence that RAC1 might be another driver mutation for melanoma in addition to BRAF and NRAS. RAC1 is a member of the Rho family of GPTases and therefore shares some features with the RAS oncogenes. Interestingly these investigations also identified deactivating mutations in phosphatases. These molecules might contribute as a feedback mechanism during the activation of signalling pathways, and defects in their function may contribute to tumour initiation and progression. Obviously there are many genetic alterations in melanoma. It will be crucial to identify driver mutations that are promising targets for therapy in this huge landscape of genetic alterations. These genetic alterations are definitely not restricted to exomes. There are also relevant mutations in non-coding DNA sequences such as promoter regions. Huang et al. described two independent mutations in the promoter of telomerase reverse transcriptase (TERT) [8]. Keeping these data in mind, we can expect many more surprising discoveries using these powerful techniques in the near future.

3. Breakthrough with kinase inhibitor therapy in melanoma subgroups

The best-validated targeted drugs in melanoma are the selective BRAF inhibitors vemurafenib (PLX4032, Zelboraf™) and dabrafenib (GSK2118436, Tafinlar™) as well as the LGX818 (Novartis) compound [9] that appears to have the highest affinity for the catalytic domain of the kinase. All of them are relatively selective for their intended target V600E BRAF, with little cross-reactivity for wild-type BRAF and CRAF [10,11]. A few other kinases are inhibited with 10- to 100-fold of the concentration needed to inhibit V600 BRAF. These molecules selectively inhibit the growth of cells that harbour a V600 BRAF mutation. In phase I clinical trials, where patients were selectively enrolled on the basis of the presence of a tumour $BRAF^{V600E}$ or $BRAF^{V600K}$ mutation, vemurafenib and dabrafenib both demonstrated evidence of tumour regression early in the course of therapy in the majority of patients [11–13]. Subsequent phase II and III trials designed to evaluate overall disease control and survival in comparison with standard chemotherapy have documented the durability of response in larger cohorts. In a phase II trial, vemurafenib produced objective responses in 53% of 132 patients with metastatic melanoma harbouring a $BRAF^{V600E}$ or $BRAF^{V600K}$ mutation [14,15]. The median duration of response was 6.7 months. In a phase III trial with single-agent dacarbazine as the control arm, overall survival (OS) was significantly improved amongst 337 patients with $BRAF^{V600E}$ mutant metastatic melanoma receiving vemurafenib compared with 338 patients who received dacarbazine (hazard ratio (HR) 0·37; 95% confidence interval (CI): 0.26–0.55; $P < 0.001$) [16]. Progression-free survival (PFS) was also significantly improved (hazard ratio 0.26; 95% CI: 0.20–0.33; $P < 0·001$) and the response rate was superior in the vemurafenib arm (48% objective response rate versus 5%; $P < 0·001$). The benefit of vemurafenib was maintained in an updated overall survival (OS) analysis with approximately 10 months median follow-up, as demon-

strated by the median OS with vemurafenib of 13.2 months compared with 9.6 months with dacarbazine and a hazard ratio (HR) for death of 0.62 (95% CI 0.49–0.77) in favour of vemurafenib [17]. These data led to approval of vemurafenib in the United States (US), European community and Switzerland. Dabrafenib was compared with dacarbazine (random ratio 3:1) in a phase III trial in patients with previously untreated stage IV or unresectable stage III melanoma harbouring the BRAFV600 mutation. Median PFS was 5.1 months for dabrafenib (187 patients) and 2.7 months for dacarbazine (63 patients), with an HR of 0.30 (95% CI: 0.18–0.51; $P < 0.0001$) [18]. This drug was recently approved by the Food and Drug Administration (FDA) in the US.

In summary, vemurafenib and dabrafenib have both demonstrated impressive clinical efficacy with response rates in the region of 50% in V600 BRAF mutated advanced melanoma [11,12,19]. Although the response duration is highly variable, as shown by these phase II and phase III trials, these results are a breakthrough in melanoma treatment.

Furthermore, multiple *in vitro* studies have demonstrated that mutated BRAF signalling is mediated via MEK and ERK [20]. Thus, selective MEK inhibitors have also shown efficacy in patients with BRAF mutant metastatic melanoma. Selumetinib was the first allosteric, selective MEK inhibitor to be evaluated in a phase II clinical trial in patients with metastatic melanoma [21]. This agent produced an objective response rate in patients with BRAF mutant tumours, whereas no response was observed in wild-type tumours, reinforcing the importance of selecting a specific patient population. The addition of selumetinib to dacarbazine has resulted in prolonged PFS in BRAF mutated metastatic melanoma [22] and was the first agent to show clinical activity in uveal melanoma when compared to temozolomide [23]. Trametinib is another, orally available selective inhibitor of MEK1 and MEK2. It demonstrated a reasonable objective response rate and an improved survival compared to chemotherapy in BRAF mutant melanoma. The median PFS was close to 5 months using the MEK inhibitor in comparison to 1.5 months in the chemotherapy group. After 6 months, there was an improvement in the overall survival rate in the trametinib group of 81% (versus 67% in the chemotherapy group). Trametinib (Mekinist™) was recently approved by the FDA for the treatment of patients with unresectable or metastatic melanoma with BRAF V600E or V600K mutation.

The combination of these kinase inhibitors clearly shows further encouraging data. The combination treatment with dabrafenib and trametinib was analysed with different dosages in 247 BRAF V600 mutated melanoma patients. Median PFS was significantly improved at 9.4 months for the patients treated with 150 mg dabrafenib twice daily and 2 mg trametinib daily, as compared with 5.8 months for the patients treated with dabrafenib alone (HR for progression or death, 0.39; 95%CI, 0.25–0.62; $P < 0.001$). The rate of complete or partial response in the combination group was 76% (compared with 54% with monotherapy ($P = 0.03$) [24]. In other words, the combination of BRAF and MEK inhibitors results in an increased response rate and prolonged PFS [24]. Today, there are several phase III clinical trials that compare the response rates and the PFS in BRAF mutated patients for mono-

therapy with a BRAF inhibitor versus combination of BRAF and MEK inhibitors.

Lito et al. have investigated the ERK-dependent feedback mechanism during BRAF inhibition using a selective inhibitor. They could clearly show that a BRAF inhibitor blocks RAF monomers, resulting in RAF dimer formation. These dimer feedback mechanisms are decreased. The addition of a MEK inhibitor can overcome this problem and enhance the inhibition of the pathway and antitumour efficacy [25].

In vitro investigations using NRAS mutant melanoma cell lines have suggested that MEK inhibitors may be useful in this genetic background. A recent clinical trial using the MEK1/2 inhibitor MEK 162 in a phase II clinical trial has confirmed that advanced NRAS mutant metastatic melanoma can be successfully treated in patients. A response rate of approximately 25% was found, with a PFS similar to that observed using MEK inhibitors in BRAF mutant metastatic disease [26]. Other MEK inhibitors have been investigated in NRAS mutated melanomas with some promising results.

Until recently, most clinical trials investigating immunomodulation, chemotherapy or targeted therapy have excluded patients with brain metastasis due to concerns about drug penetration through the blood–brain barrier and symptoms such as intracranial bleeding resulting in life-threatening consequences. Lately, the urgent need for medical treatment of this patient population led to a trend change. There are recent data [27] using the anti-CTLA-4 antibody ipilimumab at a dose of 10 mg/kg every 3 weeks for four cycles in melanoma patients with brain metastasis, with a response rate of 16% in asymptomatic and 5% in symptomatic patients. A recently reported trial [13] on dabrafenib in asymptomatic patients with BRAF-mutated melanoma and at least one measurable brain metastasis between 5 mm and 40 mm in diameter has further demonstrated clinical activity. Moreover, in a pilot study [28] of 24 symptomatic, very advanced melanoma patients with brain metastasis and harbouring a BRAF V600 mutation were treated safely and effectively with vemurafenib, improving patients' performance status and quality of life. Further clinical trials – including combined therapies with other inhibitors, with immunotherapy and with stereotactic radiosurgery – are needed in the near future.

Both BRAF and MEK inhibitors have a very peculiar side-effect profile. As recently reported, BRAF inhibitors are characterised by activating germline mutations of RAS and lead to cutaneous side effects recently defined as RASopathic [29]. They involve both epidermis and adnexa and include inflammatory disorders such as maculopapular exanthema, follicular rash or pruritus, hair and nail changes, as well as keratinocytic proliferations such as keratosis pilaris, palmoplantar hyperkeratosis, acanthopapilloma, keratoacanthoma and squamous-cell carcinoma [30]. Melanocytic disorders and proliferations have also been observed. In particular, vemurafenib causes an important UVA-dependent phototoxicity [31] that needs adequate UV protection. Dabrafenib, on the other hand, does not seem to cause phototoxicity reactions [30]. Its most common adverse events include skin-related toxic effects, fever, fatigue, arthralgia, and headache [18].

MEK inhibitors can cause papulopustular rashes, xerosis cutis (often associated with fissured finger tips), diarrhoea, nausea, vomiting, fatigue and blurred vision [32]. Moreover, self-limiting retinopathy-like dose-dependent retinal disorders with early onset have been described [33]. Only one of the seven described patients was symptomatic. The retinal disorders were transient and resolved even during continuation of MEK therapy. However, a close monitoring of the retina with a specific mark on sub-retinal exudates is highly recommended. The cutaneous side effects during MEK inhibition are similar to those observed with epithelial growth factor receptor (EGFR) inhibitors [34]. Notably, in a recently conducted trial, cutaneous adverse events were observed in over 85% of the patients [35]. This emphasises the importance of regular dermatological follow-up examinations. Thus, regular skin examination and management by experienced dermatologists, as well as continuous prophylactic photo-protection, including a UVA optimised sun screen, are mandatory.

The combination of BRAF and MEK inhibitors interestingly seems to reduce the common cutaneous side effects [24].

The impressive progress observed with the use of kinase inhibitors is unfortunately limited by the development of resistance that is observed after 6 months on average using BRAF inhibitor monotherapy and after 9–10 months using BRAF–MEK inhibitor combination therapy. There is intensive research ongoing to understand the mechanisms behind this clinically very relevant phenomenon. Most investigations have been performed in vitro [36]. It remains unclear which resistance mechanisms are the most frequent in vivo in humans. A recent study using human melanoma xenografts in a nude mouse model has shown that melanoma cells can transcriptionally up-regulate the BRAF molecule in order to compensate the inhibition by vemurafenib. If vemurafenib is removed from the system, there is an over-stimulation of the pathway resulting in decreased proliferation, probably related to oncogene-driven senescence. As a consequence, resistance can be delayed by pulsed therapy with vemurafenib rather than continuous dosing [37]. This observation is interesting and needs to be further investigated in the clinical setting in the near future.

In contrast to BRAF mutated melanoma, the kinase inhibitor imatinib has proven efficacy in patients with advanced melanoma harbouring KIT mutations [38]. KIT mutations are found at low frequencies ($\leqslant$10%) in melanomas arising from mucosal or acral lentiginous surfaces [39]. As the vast majority of patients with metastatic melanoma suffer from primary tumours on glabrous skin (trunk, extremities, and head/neck), the number of patients in the metastatic setting with mutated KIT is small. Durable responses were observed in 16% of a 51-patient cohort with either mutations or amplifications in KIT [40]. In a phase II trial, in which 43 patients with KIT mutations or amplification were enrolled, 23% of patients had objective responses [41]. In both studies, certain mutations in exon 11 and 13 of c-KIT (particularly L576P mutation in exon 11) were associated with the highest response rate. In addition Nilotinib, a tyrosine kinase inhibitor used in imatinib-resistant chronic myelogenous leukaemia (CML), seems another promising agent in the treatment of KIT mutated metastatic melanoma and is currently under clinical investigation. Thus, sensitivity to KIT inhibition exists in metastatic melanoma [21] but it is confined to a subset of this already small subpopulation of patients.

After decades of standstill, progress in understanding the biology of melanomas has resulted in powerful targeted therapies with impact on progression-free and overall survival. Ongoing research is focused on resistance mechanisms and strategies to overcome them [36]. In order to further improve the outcome in this still poor-prognosis population, patients should be encouraged to participate in well-designed clinical trials.

Conflict of interest statement

Professor Dummer receives research funding from Astra Zeneca, Novartis, Cephalon, Merck Sharp & Dhome, Transgene, Bristol-Myers Squibb, Roche, GlaxoSmithKline, and Bayer, and has a consultant or advisory board relationship with Astra Zeneca, Novartis, Cephalon, Merck Sharp & Dhome, Transgene, Genta, Bayer, Roche, Bristol-Myers Squibb, Glaxo-SmithKline, and Spirig.

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