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From chemotherapy to targeted treatment

R. Dummer*, S. Rozati, N. Eggmann, J. Rinderknecht & S. M. Goldinger

Department of Dermatology, University Hospital Zurich, Zurich, Switzerland

Today, melanoma is considered as a spectrum of melanocytic malignancies that can be characterized by clinical and molecular features, including targetable mutations in several kinases. The successful development of therapies, targeting mutated BRAF (v-raf murine sarcoma viral oncogene homolog B1) or c-KIT (v-kit Hardy-Zuckerman 4 feline sarcoma viral oncogene homolog), has resulted in new treatment options including vemurafenib, imatinib and mitogen-activated protein kinase inhibitors. These molecules are selected if the respective mutation is present. After this first progress in the treatment of advanced melanoma, there is expectation that combinations of kinase inhibitor will additionally improve the overall survival rates and progression-free survival in advanced melanoma.
Key words: biochemotherapy, chemotherapy, kinase inhibitor, melanoma, metastatic melanoma, targeted therapy

introduction

Melanoma is the most common lethal cutaneous malignancy. It is derived from melanocytes originating from 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.

retrospective view of chemotherapy

For decades chemotherapy was the backbone of systemic treatment in cases of distant metastasis. Dacarbacine (DTIC) is still the most used cytotoxic agent in metastatic melanoma and remains the standard first-line treatment in wild-type melanomas [1]. Temozolomide is a chemically related oral drug and therefore convenient for outpatient therapy. It demonstrated efficacy equal to that of DTIC in two phase 3 trials [2] although the difference in overall survival, progression-free survival or overall response rate was not seen between the two arms, despite dose intensification in the EORTC trial [2]. Temozolomide penetrates into the central nervous system (CNS) and may induce regression of CNS metastases. Polychemotherapy containing cisplatin, vindesine and DTIC or the combination of carboplatin and paclitaxel [3] may produce responses in 20–40% of the patients. However, an impact on disease-free or overall survival was never shown in randomized trials, considering that these therapies have substantial persisting toxic effects.

Biochemotherapy, a combination of interleukin-2 (IL-2) and/or interferon-α (IFN-α) with chemotherapeutic agents such as DTIC, cisplatin and vinblastine, has demonstrated a high response rate although it was not translated into improved survival and was associated with an increase in toxicity [4, 5].

molecular dissection of melanoma

In the last decade, melanoma was dissected into several molecular subgroups based on genomic alterations including mutations, deletions and amplifications in addition to clinical features. Up to 50% of melanomas derived from skin without chronic sun damage (intermittently exposed to UV) contain mutations in the gene encoding the serine–threonine protein kinase v-raf murine sarcoma viral oncogene homolog B1 (BRAF). BRAF together with ARAF and CRAF activate a second protein known as mitogen-activated protein kinase kinase (MEK), which in turn activates extracellular signal-regulated kinase (ERK). Additionally, 20% of melanomas present RAS (rat sarcoma) mutations. Finally, a minor percentages have activating mutations in the KIT gene, which are most common in mucosal melanomas derived from the genital regions [6, 7], or mutations in GNA11/ or GNAQ genes in uveal melanomas [8, 9]. Some of the targetable mutations in KIT gene are also found in acral and other mucosal 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 localized to exon 11, which codes for the juxtamembrane domain and exon 13, which codes for a kinase domain.

breakthrough with kinase inhibitor therapy in melanoma subgroups

The best-validated targeted therapies in melanoma are the selective BRAF inhibitors, vemurafenib (PLX4032, Zelboraf™) and dabrafenib (GSK2118436). Both are relatively selective for

*Correspondence to: Dr R. Dummer, Department of Dermatology, University Hospital Zurich, Zurich, Switzerland; E-mail: reinhard.dummer@usz.ch

their intended target, V600E BRAF, with little cross-reactivity for wild-type BRAF and CRAF [10, 11]. Few other kinases are inhibited with 10- to 100-folds of the concentration needed to inhibit V600E BRAF. These agents inhibit selectively the growth of cells that harbor a V600E BRAF mutation. In several clinical trials, vemurafenib and dabrafenib have both demonstrated impressive clinical efficacy with the response rate in the range of 50% in V600E-mutated advanced melanomas [11–13].

Unfortunately, the response duration is highly variable as shown by phase 2 and phase 3 trials. In a phase 2 trial, vemurafenib produced objective responses in 53% of 132 patients with metastatic melanoma harbouring a V600E or V600K mutation [14]. The median duration of response was 6.7 months. In a phase 3 trial, with dacarbazine monotherapy as the control arm, overall survival was significantly improved among the 337 patients with V600E mutant metastatic melanoma compared with the 338 patients who received dacarbazine (hazard ratio 0.37; 95% CI, 0.26 to 0.55; $P < 0.001$) [15], as was the progression-free survival. In addition, the response rate was much better in the vemurafenib arm (48% objective response rate versus 5%; $P < 0.001$). These data led to the approval of vemurafenib in the United States, European community and Switzerland.

The appearance of acanthopapillomas, keratoacanthomas and cutaneous squamous cell carcinomas early in the course of treatment with these kinase inhibitors needs special attention [16, 17]. Furthermore, there are well-documented cases of new primary melanomas that do not present a BRAf V600 mutation [14, 18]. Other more common toxic effects observed with vemurafenib include arthralgia, photosensitivity [14], rash and fatigue. Generally, these toxic effects are mild to moderate in severity and, when severe, can be managed with dose interruption and/or reduction. The most common toxic effects observed with dabrafenib are comparable, except there is no photosensitivity [11].

Multiple *in vitro* studies have demonstrated that mutated BRAF signaling is mediated via MEK and ERK [19]. Thus, selective MEK inhibitors have shown efficacy in patients with BRAF mutant metastatic melanoma. Selumetinib was the first allosteric, selective MEK inhibitor to be evaluated in a phase 2 clinical trial in patients with metastatic melanoma [20]. This agent produced an objective response rate in patients with BRAF mutant tumors but not in wild-type tumors and thus reinforcing the importance of selecting a specific patient populations. In the phase 1 dose escalation clinical trial, GSK1120212 demonstrated an objective response rate of 44% with a median progression-free survival of 7.4 months in patients with BRAF mutant melanoma [21]. This agent is being evaluated in additional phase 2 and phase 3 trials in BRAF mutant melanoma. Other MEK inhibitors are currently investigated in NRAS-mutated melanomas with some promising results. The combination of kinase inhibitors such as concomitant BRAF and MEK inhibitor therapy is definitely a key to the future of development strategies.

The kinase inhibitor imatinib has proven efficacy in patients with advanced melanoma harboring KIT mutations [22]. KIT mutations are found in low frequency (10% or less) in melanomas arising from a mucosal or acral lentiginous surfaces [23]. As the vast majority of patients with metastatic melanoma suffer from primary tumors 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 in KIT or amplification [24]. In a phase 2 trial in which 43 patients with KIT mutations or amplification were enrolled, 23% of patients had objective responses [25]. In both studies, certain mutations in exons 11 and 13 of v-kit Hardy-Zuckerman 4 feline sarcoma viral oncogene homolog (particularly the L576P mutation in exon 11) were associated with the highest response rate. Thus, it appears that sensitivity to KIT inhibition exists in metastatic melanoma [20] 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 focussed on resistance mechanisms and strategies to overcome them [26]. In order to further improve the outcome in this still poor prognosis population, patients should be encouraged to participate in well-designed clinical trials.

disclosure

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