

Metastatic melanoma: New paradigms of treatment and new toxicities

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1. Introduction

Metastatic melanoma was historically designated the “drug killer cancer” because for decades no drug had demonstrated any benefit in terms of overall survival (OS) for patients with metastatic melanoma. This situation has radically changed over the last 2 years. Melanoma appears today as a “pilot” disease for which the most innovative therapeutic strategies have demonstrated significant efficacy. The two strategies are immunotherapy on the one hand and targeted therapy on the other. These two significant breakthroughs led to the authorisation in the United States (US) and in Europe of two drugs: the anti-BRAF agent vemurafenib and the anti-CTLA-4 monoclonal antibody ipilimumab. More recently, two additional targeted agents, dabrafenib and trametinib, were authorised in the US. Moreover, the field continues to improve with the exciting development of new drugs following these two new approaches.

2. Immunotherapy: anti-CTLA-4 and anti-PD-1

The anti-CTLA-4 monoclonal antibody ipilimumab was the first drug ever to demonstrate a significant OS benefit in the context of a randomised phase III trial [1]. This pivotal trial showed that ipilimumab at the dose of 3 mg/kg, alone or in combination with a peptidic vaccine and compared with vaccination alone, prolonged the survival of patients with pre-treated metastatic melanoma. Median OS of patients was around 10 months with ipilimumab versus 6.4 months with the vaccination. A second pivotal trial evaluated ipilimumab at 10 mg/kg, combined with the standard chemotherapy dacarbazine (DTIC), compared with dacarbazine alone in first-line treatment. The ipilimumab-containing arm demonstrated a significant survival benefit compared with dacarbazine alone (HR = 0.72; $P < 0.001$) with a median OS of 11.2 months versus 9.1 [2]. This trial did not suggest that the

combination of DTIC with ipilimumab added any benefit, but rather added toxicity, especially in terms of hepatotoxicity.

Clinical results with ipilimumab are characterised by low objective response rates, usually below 20%, but frequent long-term responses. Responses are often delayed, being observed after at least 4 months following initiation of therapy, and can even occur after an initial tumour progression or the appearance of new lesions.

As expected for a new mechanism of action, blocking CTLA-4 is associated with a new spectrum of adverse events. These are frequent, occurring in 40% of the patients and are mostly immune-related, as expected for an immunostimulatory agent. The most frequent side effects are skin rashes, diarrhoea and colitis resembling Crohn's disease, hypophysitis and hepatitis. Adverse effects usually resolve spontaneously or after steroid therapy. High-dose steroids have to be prescribed in cases of severe immune-related adverse events; rarely, stronger immunosuppressive agents, such as anti-TNF-alpha (infliximab), can be needed.

Challenging questions remain to be answered to optimise the efficacy of this new treatment. Indeed, the survival benefit concerns few patients, and we currently lack predictive clinical or biological markers of response. Furthermore, the two pivotal trials have explored two different doses, 3 or 10 mg/kg, and two schedules of follow-up treatment designs. Thus, the optimal administration schedule is still unknown.

Programmed death-1 receptor (PD1) and its ligand (PD-L1) are new, highly promising targets in immunotherapy. PD1 protein is another immune checkpoint expressed on many T cells in response to inflammation. The engagement of PD1 on the lymphocyte surface by one of its ligands, PD-L1, that can be expressed on melanoma cells, delivers inhibitory signals resulting in T-cell function down-regulation [3].

In contrast to CTLA-4/CD28 interaction that down-regulates T-cell activation in lymphoid organs during naïve T-cell

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priming, PD-1/PDL-1 interaction mostly contributes to exhaustion of T cells in peripheral tissues afterwards. Reactivation of T cells that are already present on tumour sites is thus an alternative and potentially complementary strategy to improve cancer immunosurveillance.

Very compelling results of phase I trials evaluating two anti-PD1 antibodies nivolumab and lambrolizumab were recently published [4,5]. Various dose and schedule regimens were evaluated in phase I trials. Response rates were around 30–40% for both antibodies, with the vast majority of responding patients still in response after median follow-up durations of more than 1 year. The safety profiles of these new anti-PD-1 agents seem tolerable, with 10–12% of grade 3 or 4 adverse events, usually manageable except in rare cases of severe pneumonitis.

Combined blockade of PD-1 and CTLA-4 has also been explored in a phase I trial in 86 patients, and also gave extremely promising clinical results with tolerable adverse events [6].

Combination of nivolumab and ipilimumab was associated with a 53% rate of treatment-related adverse effects that most frequently corresponded to changes in biological parameters (lipase, transaminase elevation) with no clinical manifestation.

3. The second strategy relies on the use of targeted drugs: anti-BRAF and anti-MEK agents

BRAF and MEK are protein kinases involved in the MAP-kinase pathway that is activated in the vast majority of melanomas due to BRAF, NRAS, MEK and KIT mutations in (respectively) about 50%, 15%, 8% and 3% of the cases [7].

Among BRAF mutations, the most frequent one – accounting for more than 90% of the somatic mutations of this oncogene – results in the V600E amino acid replacement.

Small kinase inhibitors directly targeting the mutated BRAF protein have been developed. The first one, vemurafenib, was recently approved as a first-line treatment for patients with unresectable or metastatic melanoma harbouring the V600E BRAF mutation, based on the results of a randomised phase III trial showing a significant improvement in overall survival with vemurafenib (HR: 0.37, $P < 0.001$) and a median progression-free survival (PFS) of 5.3 months versus 1.6 months (HR: 0.26, $P < 0.001$) with dacarbazine and a high response rate around 50% [8]. Dabrafenib, another BRAF inhibitor, showed similar results in term of PFS and objective response rate (ORR), but could not demonstrate OS benefit because the design of the phase III trial included a cross-over [9].

BRAF inhibitors are usually well tolerated, the most common adverse events being arthralgia (56% of the patients), fatigue (46%) and cutaneous manifestations such as rash (41%), photosensitivity (41% for vemurafenib only) and squamous-cell carcinoma of the keratoacanthoma-type (10–25% of the patients depending on the type of BRAF inhibitor used).

However, two major concerns are associated with all specific BRAF inhibitors evaluated so far. The most challenging is the short median duration of the clinical responses, with most of the patients relapsing in the 4–12 months after initi-

ation of therapy. Numerous distinct resistance mechanisms have been identified that can reactivate the MAPK pathway (ERK-dependent) or use additional proliferation pathways [10].

The second issue when using these agents is that they paradoxically activate the MAPK pathway in cells devoid of BRAF mutation, especially in the presence of an additional somatic event occurring in this pathway, such as a RAS mutation. This explains the appearance of squamous-cell neoplasia (keratoacanthomas and squamous-cell carcinomas) as well as new melanomas in a subpopulation of patients [11].

One strategy to decrease secondary resistance as well as neo-tumourigenesis associated with anti-BRAF monotherapy is to combine it with an inhibitor of MEK1 and MEK2 downstream from BRAF. Indeed, several MEK blockers are in development, and one of them, trametinib, has shown a significantly increased PFS in patients with V600E metastatic melanoma in a phase III randomised trial, and was recently approved by the FDA [12]. Another MEK inhibitor, selumetinib, also demonstrated an improvement in PFS when combined with dacarbazine compared with dacarbazine plus placebo in a randomised phase III trial [13]. Anti-MEK drugs are associated with numerous skin side effects, as are most anticancer targeted agents, but potentially serious adverse events involving the retina and myocardia are rare and mostly reversible.

The most promising approach at present is the combination of BRAF and MEK inhibitors. Indeed, this approach not only seems to give higher response rates and longer PFS but is also associated with a significantly decreased incidence of neo-skin-derived proliferation [14].

4. Conclusion

A revolution in the metastatic melanoma treatment paradigm is going on. We now have several effective weapons via both the immunotherapy and the direct targeted therapy approaches. Our challenges are to optimise the design of treatments in terms of combination and/or sequences and to optimise safety regarding the new adverse events that are occurring.

Conflict of interest statement

Caroline Robert is a consultant for Roche, BMS, Merck, Novartis and GSK.

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