Disease kinetics for decision-making in advanced melanoma: a call for scenario-driven strategy trials

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In the past 5 years, the treatment of metastatic melanoma has changed from almost no effective treatment to the use of targeted and immune therapies with proven improvements in survival. The time has now come to define the optimal drug combinations, sequence of treatment, and drug regimens (intermittent *vs* continuous dosing) in the treatment of patients with metastatic melanoma. In view of the prevalence of advanced melanoma, finite resources, and the heterogeneity of disease characteristics, not all possibilities can be tested in therapeutic trials starting from an unselected population of patients with metastatic melanoma. In practice, clinicians rely on a few clinically derived signals, especially dynamic signals, to categorise patients into scenarios, from fast disease kinetics to slow disease kinetics, which drive clinicians' therapeutic decision making. The realistic goals of therapy are different in each scenario. We recommend that these scenarios are incorporated into clinical trials as either patient inclusion criteria or stratification factors. This approach is not only feasible but is also the only way to generate evidence for more effective and individualised treatment strategies for patients with metastatic melanoma.

Lancet Oncol 2015; 16: e522–26

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Introduction

In the past 5 years, several drugs have shown clinical significance in the treatment of patients with metastatic melanoma—namely, two molecularly targeted drugs (a BRAF inhibitor[1] and a MEK inhibitor[2]), two immune checkpoint inhibitors (CTLA-4 antibody[3] and PD-1 antibody[4,5]), and two combinational therapies (a BRAF inhibitor plus a MEK inhibitor,[6,7] and an anti-CTLA-4 antibody plus an anti-PD-1 antibody[8]). Yet, most patients will still succumb to their disease. Since the number of patients is finite, it is not possible to design trials that compare all existing treatment options, including optimal combinations, sequencing, and intermittent versus continuous dosing. Additionally, owing to the introduction of these drugs into widespread clinical use over a very short period of time, there has been little time to generate effective treatment strategies that are adapted to the many specific clinical situations with which clinicians are faced.

Clinicians are expected to make strategic decisions regarding treatment options by the use of predictive markers and evidence from rigorous clinical trials. However, predictive markers in advanced melanoma are not robust and are neither sensitive nor specific.[9–11] At present, evidence-based practice is impeded by clinical trials that oversimplify patient disease characteristics and the landscape of treatment options, only testing one drug against another, and only in stereotypical cases. In particular, phase 3 trials for melanoma are not sufficiently large, nor do their inclusion criteria cover the entire range of metastatic melanoma, to provide insights into the effectiveness of therapy in real-world subgroups.

In this Personal View, we define clinically derived signals that could be used to categorise patients into three scenarios mainly on the basis of disease kinetics. We recommend the incorporation of these scenarios into the design of clinical trials to generate a base of evidence for more effective and individualised treatment strategies for patients with advanced melanoma.

Use of clinically derived signals to define different disease scenarios

Clinicians who treat patients with advanced melanoma are consciously or unconsciously using clinically derived signals from the observation of their patients and of the behaviour of their metastatic disease. These signals have not yet been adequately defined to use as a basis for the inclusion, exclusion, or stratification of patients in therapeutic trials, but they are the major driver of clinicians' therapeutic decisions when selecting a trial to be proposed to a patient or when selecting approved therapies. These signals can be separated into two categories: instantaneous signals, and dynamic signals that require time to characterise correctly.

Instantaneous signals can be thought of as a photograph of the disease at a given moment in time. They include variables such as the presence of brain metastases, the presence of a tumour metastasis in a potentially life-threatening location, the radiological assessment of tumour burden, serum lactate dehydrogenase (LDH) levels,[9] and the performance status of the patient.[12,13] These instantaneous signals are often used as inclusion, exclusion, or stratification factors in the enrolment of patients for clinical trials.

By contrast, dynamic signals are analogous to a motion picture and need a time period to record the clinical course of the disease. These signals give more information regarding the patient's progress and possible outcome than instantaneous signals do, just as the next scene of a film can be predicted from the previous scene but not from a photograph. An assessment of the dynamic signals needs at least two consecutive measures of the same signal. They are regarded as important decision-making variables by most clinicians and are known as disease kinetics, disease progression, disease tempo, or disease aggressiveness, as mentioned in algorithms and guidelines.[14–16] These dynamic signals can be assessed before treatment (ie, pretreatment disease kinetics) or during treatment (ie, kinetics under treatment).

Pretreatment disease kinetics

Two successive measures of total tumour burden while the patient is not undergoing any treatment (ideally, two assessments within 4–12 weeks before treatment) provide an objective measure of disease kinetics[17] and, in our view, is one of the most useful assessments to assist clinical decision making. However, the worsening of a patient's performance status or an increase in concentration of serological markers (ie, LDH) over a short period of time might also be useful.[10] Dynamic signals are sometimes inferred from instantaneous signals when no previous documentation is available. For example, a high tumour burden is usually regarded as an indicator of fast disease tempo and thus disease aggressiveness. However, a high tumour burden alone does not necessarily equate to fast disease tempo, or a low tumour load to slow disease tempo. A high tumour burden might occur in a patient with slowly progressing melanoma who has not been restaged for a prolonged period of time; by contrast, tumour load can be low in a patient with rapidly progressing melanoma when metastatic disease first manifests itself immediately after resection of high-risk regional disease or after a long period of indolence.

Kinetics under treatment

The early changes of disease characteristics and kinetics after treatment has begun are important dynamic signals to assess disease progression, to which clinicians intuitively assign a high importance. If a patient's disease is clearly progressing within the first few months of treatment with either BRAF inhibitor alone or with a combination of BRAF and MEK inhibitors, then he or she is unlikely to benefit from the same treatment at any time thereafter. However, the situation with immunotherapy is more complex than the situation with BRAF and MEK inhibitors. A small minority of patients whose disease has progressed within the first 12 weeks of anti-PD-1 therapy will benefit from the same treatment if it is continued.[4,5,18] However, with anti-CTLA-4 therapy, absence of an obvious treatment response in the short term (within 12–16 weeks) can still result in durable disease control or treatment response, although the percentage of patients who benefit after initial progression is low.[3]

The different scenarios in advanced melanoma

In practice, clinicians use clinically derived signals with a particular emphasis on dynamic signals. These signals are interpreted by the clinician as a scenario that drives a pragmatic decision regarding the ideal treatment strategy.

Initial scenarios

Most newly diagnosed patients with distant metastatic melanoma can be simplified into three scenarios.

In fast disease kinetics (ie, immediate danger), the first objective is to preserve life and relieve symptoms in the short term. The ideal strategy is to use a fast-acting treatment with the highest possible response rate with acceptance of high toxicity. Long-term survival is only a secondary, although less realistic, objective.

In intermediate disease kinetics (ie, non-immediate danger), the first objective is to prolong survival. The ideal strategy is to start with the treatment that will give the highest chance of a prolonged survival (3–5 years), and the strategy is altered depending on the result of treatment and toxicities.

In slow disease kinetics, the first objective is to prolong survival with the best possible quality of life. The current strategy is to start with treatments such as surgery, radiosurgery, or any straightforward treatments that have low toxicity, low morbidity, and some potential to preserve long-term survival. This conservative approach might change soon and if new treatments can really improve 5-year survival, or even lead to a cure when they are given very early on, in these patients with low-aggressiveness disease. In this case, toxicity would no longer be a concern.

Adjustment of scenarios with treatment

In everyday clinical practice, decisions regarding treatment and assessments of the benefit of a treatment often use signals other than classical outcomes used in clinical trials, such as objective response (by Response Evaluation Criteria in Solid Tumors) or progression-free survival. For clinicians, the assessment of treatment effectiveness can be simplified into two dominant scenarios.

In the first scenario, where the patient benefits from treatment, the benefit can be interpreted as obvious or just relative to what was expected from the natural kinetics of the disease. The perception of benefit is a multifactorial integration of subjective factors, and the patient might be interpreted as deriving benefit even if some evidence of disease progression exists. In this scenario, the same treatment will be continued unless a much better treatment is available (ie, a treatment that can improve response, quality of life, toxicity, and survival).

In the second scenario, the patient is not benefiting from treatment or is likely to lose benefit quickly. The definition of loss of benefit is a clear worsening of dynamic signals during treatment, such as a rapid increase in most pre-existing metastases, including the development of new metastases with or without life-threatening implications. Such a worsening of dynamic signals might be accompanied by a loss in performance status or increased disease-related symptoms. Of note, the development of a single new metastasis or slow progression of a subset of pre-existing metastases alone is not an absolute indicator of loss of treatment benefit. However, if a loss of benefit is observed, the strategy is changed as soon as possible if another treatment strategy exists.