Targeted therapy in the era of immunotherapy

Grant McArthur, MB, BD, PhD, FRACP, Head, Cancer Therapeutics Program, and Director, Melanoma and Skin Service, Peter MacCallum Cancer Centre, University of Melbourne, Australia

At the Canadian Melanoma Conference, Dr. McArthur discussed the prospects of achieving long-term disease control in melanoma through a better understanding of the adaptation that occurs following administration of targeted therapies.

The development of resistance is the major clinical dilemma in targeted therapies. The problem in targeted therapy, well illustrated in the trial of cobimetinib vs placebo in combination with vemurafenib,[1] is that, although the addition of a MEK inhibitor to a BRAF inhibitor improves progression-free survival (PFS) quite substantially, the curve continues an apparently inevitable descent towards progression and therefore resistance, except in certain subsets of patients. The current challenge with targeted therapies is achieving long-term disease control, which Dr. McArthur considers possible if new targets can be identified.

He presented a mechanistic view of what happens following treatment of a patient with targeted therapy. When treatment with a BRAF inhibitor or a combined BRAF/MEK inhibitor is initiated, there is a rapid reduction and then a rebound phenomenon with phosphorylation of ERK. Within 1 to 3 weeks, a number of adaptations occur in cell cycle and metabolism, as well as at the epigenetic, phenotypic and immune level. Understanding this early adaptation is key to finding opportunities to enhance cell kill and achieve sustained control of the disease with targeted therapies—waiting until resistance develops is too late. "It becomes that whack-a-mole phenomenon I'm sure you've all heard presented, where you plug one gap in a signalling network and another one opens up," said Dr. McArthur.

CLINICAL DATA TO SUPPORT EARLY INTERVENTION

The phase 1 BRIM7 trial showed that adding a MEK inhibitor (cobimetinib) to a BRAF inhibitor (vemurafenib) up front, rather than waiting for resistance to develop, dramatically increased PFS, from 2.8 months to 13.8 months, and tripled 3-year survival (from 11% to 37%). "The study design did not allow for definitive conclusions," Dr. McArthur cautioned, "but provides a strong vote in favour of upfront optimal therapy."

As part of the BRIM7 study, researchers looked at positron emission tomography (PET) scans of patients with stage IV disease, taken 15 days and 43 days after treatment initiation. They found that if PET scan at 15 days showed complete metabolic response (CMR), there was outstanding PFS and overall survival (OS). If CMR took longer to achieve, PFS and OS stabilized briefly, compared to those who never achieved CMR, but then fell. "There is something about the early rapidity of response that I think is worth studying to develop new treatment approaches," observed Dr. McArthur.

His group is now investigating 3 areas in early adaptations: the cell cycle, metabolic adaptation (which PET scans suggest is important), and immune adaptation.

Cycle cell adaptation

There are 2 major regulators of the cell cycle in melanoma, the pRB and p53 tumour suppressors. Viral oncoproteins are known to transform cells through inactivation of pRB and p53. Mutations or deletions of p53 are seen in less than 10% of melanomas, as Dr. Watson presented at the Canadian Melanoma Conference; there is in fact upregulated expression of the p53 inhibitors, MDM2 and MDM4. When MDM4 is high, there is degradation of p53. pRB is even more rarely deleted in melanoma, but is closely regulated by the RAS/RAF, MEK/ERK pathway through CDK4. In programmed death receptor 1 (PD-1) resistance, Dr. Ribas showed that JAK-STAT signalling pathways are important and appear to be involved in resistance to BRAF inhibitors. BRAF, when activated, turns off pRB and allows cell cycle progression. "The way we've been thinking about overcoming the development of resistance is to turn pRB on to stop cells dividing. You can do that through CDK4 inhibitors: we now have 3 approved CDK4 inhibitors for estrogen receptor (ER) positive breast cancer," noted Dr. McArthur.

Martin et al[3] (*Int J Cancer* 2018) showed that inhibition of CDK overcomes cell cycle adaptation to BRAF or MEK inhibitors. In tissue culture, the triple combination flat-lines growth of these cells. The same effect is seen with in vivo xenograft tumours. Research is also finding (in new unpublished data) that CDK4 inhibitors activate p53, which may provide added benefit. Sheppard and Foo (unpublished) find that mutation of p53 correlates with resistance to palbociclib. CDK4 inhibition leads to a marked reduction in expression of MDM4, which leads to accumulation of p53.

CDK4 is in clinical trials, and despite it not yet being clinically validated, Dr. McArthur is conducting experiments to develop melanoma cells resistant to CDK4 inhibitors and see if that could be overcome. The small-molecule screen showed 2 different melanoma cell lines resistant to CDK4 inhibitors, and in clinical trials these cells were seen to be more sensitive to an epigenetic modifier drug—an inhibitor of PRMT5 (protein arginine methyltransferase) that also increases p53 levels by reducing MDM4.

"Everything leads back to the pathway," stressed Dr. McArthur. PRMT5 inhibitors can overcome resistance to CDK4, and there are new targets regulating p53 that might be combined with BRAF and MEK inhibitors to control disease. The multifactorial mechanism of action may, when these concepts move into the clinic (GSK's PRMT5 inhibitor is currently the first to enter human clinical trials), identify targets that can overcome cell cycle adaptation and prevent the emergence of resistance.

Metabolic adaptation

Many pathways impinge on cancer metabolism. BRAF potently upregulates metabolism in melanoma cells as it regulates glucose transport. Treatment with a BRAF inhibitor switches that around: cells become dependent on alternative mechanisms for generating energy, which is why there is such marked uptake of fludeoxyglucose (FDG) on a PET scan of metastatic melanoma lesions. Conducting a screen to make the BRAF inhibitor work better, researchers looked at cell viability and glycolysis measured by lactate production, to see if glycolysis could be turned off more effectively. The screen identified new targets in proteins involved in mRNA transport, one of which is a kinase, and therefore a potentially druggable target that might make BRAF and BRAF/MEK inhibitors work better. Dr. McArthur is now in the early stages of developing a small-molecule inhibitor of this kinase, called UHMK1.

Dr. McArthur considers UHMK1 an especially interesting kinase because it binds RNA, is involved in cell cycle progression, and is involved in synaptic plasticity of neurons. "It allows them to adapt in different situations: there are in fact single nucleotide polymorphisms (SNPs) in this kinase gene that predispose to schizophrenia. It has an interesting role in neurobiology, plasticity and adaptation," he noted. With its ability to overcome the oxidative phosphorylation seen with BRAF inhibitors and prevent accumulation of these proteins, UHMK1 kinase inhibition may be able to overcome adaptation.

During adaptation, a switch to mitochondrial metabolism occurs that is at least partly mediated by UHMK1, providing a potential drug target to overcome early adaptation. "These are early days," cautioned Dr. McArthur, "but we think we now have a multifaceted functioning target for which we could develop a small molecule in order to overcome this metabolic adaptation."

Immune adaptation

Immune adaptation is more immediately clinically attractive because there are already drugs that can be used to help improve long-term disease control. Treatment with BRAF inhibitors produces a number of changes in melanoma cells. There is not only increased expression of differentiation antigens, but also a reduction in various immunosuppressive factors. Richard Scolyer and James Wilmott reported that early treatment biopsies show an influx of CD8-positive T cells into tumours that is lost at progression.[4] This establishes that immune adaptation occurs early on in treatment with a BRAF inhibitor. The hypothesis is that this mechanism might provide an opportunity to enhance response to BRAF inhibitors.

Two phase 3 trials are underway to add antibodies to PD-1 or its ligand (PD-L1) to BRAF inhibitors. One, which has nearly completed recruitment, is adding an anti-PD-L1 to a BRAF/MEK inhibitor. With 500 patients, the study is adequately powered to give an idea of OS, as well as PFS. "That's important, because really what we're talking about now is the hypothesis of long-term disease control—that's what we're shooting for now in melanoma," concluded Dr. McArthur.

References

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