Overcoming resistance

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At the Canadian Melanoma Conference, Dr. Ribas provided an in-depth look at resistance to cancer immunotherapy in melanoma and presented strategies under development to counter resistance and produce lasting response.

Response to PD-1 blockade therapy requires that the immune system recognize the cancer, and that the cancer allow itself to be recognized. The tumour has to permit the infiltration of T cells, and the T cells need to reach the tumour. If all of this works, patients respond to anti-PD-1 antibody therapy. However, this combination of factors is difficult to achieve.

In a subset of patients with desmoplastic melanoma, accounting for around 4% of melanomas and related to UV light damage, response to PD-1 blockade has been unexpectedly good. These are very solid tumours, more stroma than tumour; with PD-1 blockade, they can significantly shrink without even noticeable inflammation: "T cells just go in and kill the bad guys. And then the bad guys take away the factors that make the bad stroma, and the bad stroma takes away the mass, and the patient responds," said Dr. Ribas. The overall response rate (ORR) in this group of patients is 70%, and 32% respond completely. Desmoplastic melanomas have a high mutational load, and the top mutated gene is neurofibromin 1 (NF1) in a majority of cases.[1]

Dr. Ribas described a phase 2 clinical trial that just opened, SWOG S1512,[2] to provide PD-1 blockade (pembrolizumab) earlier to patients with resectable or unresectable desmoplastic melanoma, in hopes of preventing the need for potentially disfiguring surgeries. Patients in the trial do not need biopsy confirmation, as long as fine needle aspiration (FNA) cytology has been done.

DISTINGUISHING RESPONDERS AND NONRESPONDERS

Looking at what differentiates responders and nonresponders in all melanomas, the immune system in responders appears ready to go, but the tumour is reactively expressing PD-L1 that stops T cells. Nonresponders tend to be the ones without that preexisting immune response.[3] One reason may be mutational load: the higher it is, the more likely the T cells recognize the tumour. Other reasons are being investigated to understand why some patients respond but then progress, as seen in trials of both ipilimumab and pembrolizumab.[4] These investigations are focusing on the interferon receptor pathway that appears to be involved in both primary and secondary resistance.

In a study of patients who initially responded but then progressed at year 1 or 2, JAK mutations were found in 2 cases, while a third case had a beta-2 microglobulin (B2M) mutation.[5] The role of JAK mutations has been corroborated in other studies.[6] B2M mutation has been explored in both melanoma[7] and lung cancer.[8] Both studies describe the process that leads to the loss of these genes: a deleterious mutation in one allele and loss of a chunk of the other allele means no wild-type protein is being made, which leads to the loss of antigen presentation.

Cancer presenting a mutated antigen from its high mutational load triggers a number of signalling events from T-cell receptor to interferon response genes. The bottleneck of this pathway is in the JAKs—if they do not work, there is a reactive expression of PD-L1 as the tumour protects itself from attack, PD-1 turns off T-cell receptor signalling, and the T cells remain in the invasive margin, as the tumour grows until we give a PD-1–blocking antibody. The loss of B2M impedes cytokine-positive T-cell recognition of the tumour, leading to a loss of sensitivity to PD-1 blockade therapy.

GENETIC CONTRIBUTORS TO RESISTANCE AND RESPONSE

In vivo CRISPR screens of these pathways[9] show that altering certain genes prevents T cells from recognizing the tumour and identifies previously unknown genes that act as positive or negative regulators of JAK genes. Genetic events could therefore be masking nongenetic events that lead to other proteins feeding into the interferon-gamma receptor signalling pathway. Very recent work has identified a major chromatin regulator that determines resistance of tumour cells to T-cell–mediated killing.[10,11]

STRATEGIES TO PREVENT AND OVERCOME RESISTANCE

The most common reason for resistance is the absence of T cells in the tumour. Looking at the different cellular microenvironments involved in melanoma resistance to immune checkpoint therapies, 41% are found to display adaptive immune resistance, and have preexisting T cells and PD-LI expression, while 45% show immunologic ignorance, with no tumour-infiltrating lymphocytes (TILs) and no PD-L1 expression. A smaller number of melanomas fall into the category of tolerance (12%) or intrinsic induction (2%), and are more likely to respond.[12]

In personalized immunotherapy, the idea would be to do a biopsy and, if T cells are present but already blocked by PD-L1, the patient would receive PD-L1–blocking antibodies in an attempt to turn a nonresponsive tumour into a responsive tumour. In addition, anti-CTLA4 (cytotoxic T-lymphocyte associated protein 4) can further activate the immune system, as it increases the frequency of T cells circulating and brings them from the margins into the tumour. This was shown in the Checkmate 067 trial, where patients on a combination of nivolumab and ipilimumab did better than on nivolumab or ipilimumab alone.[13] However, toxicity is a major concern with this strategy. Other combinations are being tried to block PD-1 and indoleamine dioxygenase (IDO), a monomeric oxidoreductase that metabolizes tryptophan to kynurenine and blocks tryptophan's activity in cell division. The ECHO-202 study of the IDO inhibitor epacadostat and pembrolizumab[14] showed an ORR (56%) almost as high as seen with the ipilimumab + nivolumab combination, and much less Grade 3 or 4 toxicity (20% vs 59%).

At the 2017 ASCO conference, a study looked at combining nivolumab with a monoclonal antibody targeting lymphocyte activation gene 3 (LAG3) in patients with metastatic melanoma who were progressing on prior immunotherapy.[15] The researchers identified patients who expressed the LAG3 biomarker and treated this group with a LAG3 inhibitor, achieving a response rate of 20%. This is a type of combination that will be tested in many more situations.

Another strategy to render tumours responsive to immunotherapy is to inject them with something that turns on the immune response and attracts T cells from other places.[16] We hypothesize that an intratumoural injection with an oncolytic virus may increase the antitumour activity of pembrolizumab by attracting CD8+ T cells into the tumour and inducing a systemic immune response to both injected and noninjected metastatic lesions. We used an oncolytic virus called talimogene laherparepvec (TVEC), a herpes simplex virus modified to propagate preferentially in cancer cells. In a phase 1 clinical trial, 21 patients with advanced melanoma first had their tumours injected with this virus and were then given the standard pembrolizumab treatment intravenously. Approximately 62% of patients had an objective response to the treatment; impressively, 33% of study patients had a complete response. A phase 3 trial is currently underway.

The same concept could potentially be used in patients who progress on anti-PD-1 therapy, to reverse the lack of T cells. This strategy is being explored in a clinical trial at SWOG, where patients who progressed on anti-PD-1 therapy receive an injection of TVEC into the tumours.

Still another strategy under investigation is combining BRAF and MEK inhibitors with PD-1 blockade to overcome resistance. BRAF and MEK inhibitors contribute to a transient T-cell response in the tumour, but that is lost over time in the majority of cases, leading to relapse. There are currently 4 phase 1 clinical trials of BRAF inhibitors with

MEK inhibitors and anti-PD-1/L1, and all are showing a high response rate. It remains to be seen whether that response will be durable.

"We are beginning to understand why patients respond or resist these therapies," Dr. Ribas concluded. "It is not an easy field of study, but the more we understand the science, the better we can develop new therapies that overcome present-day limitations and liabilities. Clinical development is showing that moving back and forth from the patient to the lab is enabling continuous improvement in the care of patients."

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