INTERVIEW

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Case discussion

An 88-year-old patient with BRAF V600K mutation-positive recurrent melanoma

DR GONZALEZ: This gentleman with recurrent scalp melanoma after surgery eventually developed in-transit metastases in the cervical lymph nodes and was referred to our center. He had limited treatment options. His tumor was initially determined to be BRAF wild-type with a cobas® test. However, I would recommend that oncologists perform alternative confirmatory tests to determine whether a patient's tumor harbors a BRAF mutation.

We did so in this case and ascertained that the tumor did in fact harbor a BRAF V600K mutation. Once we determined that he had BRAF mutation-positive disease, the probability of getting the tumor under control was high.

He was initially enrolled on a trial of vemurafenib for atypical mutations that we're conducting specifically for patients with non-V600E mutations to confirm that the response rate is similar to that seen in patients with V600E mutations. He achieved a partial response, but his disease eventually progressed on vemurafenib, at which point we transferred him to a trial of combination therapy with vemurafenib and GDC-0973, a MEK inhibitor (NCT01271803), on which he achieved a complete response. He is currently faring well.

DR LOVE: What side effects did he experience on vemurafenib alone?

DR GONZALEZ: He had a long history of sun exposure, and he developed multiple squamous cell carcinomas. We excised multiple lesions at his weekly hospital visits. That's a well-established side effect of vemurafenib, occurring in 20% to 25% of patients. This is believed to be due to paradoxical activation of the MAPK pathway in the cutaneous lesions (Su 2012).

Interestingly, the addition of GDC-0973 to vemurafenib resolved the skin toxicities because of the MEK blockade, and he has not had subsequent squamous cell cancer. This is one of the reasons I prefer therapy with the combination of BRAF and MEK inhibitors.

However, the ultraviolet A (UVA) light-induced photosensitivity caused by the BRAF inhibitor is not necessarily diminished by the addition of a MEK inhibitor. It can be extremely severe. Patients need to protect themselves from the sun because blistering burns can develop. These UVA sunburns can penetrate through car windows, and sunscreens are not particularly effective. Patients need to cover up properly.

This patient hasn't experienced any significant toxicity with combination vemurafenib/GDC-0973 except for a bit of fatigue. He continues to experience photosensitivity with the combination therapy.

Track 5

DR LOVE: Would you discuss the mechanism of action of the investigational oncolytic immunotherapeutic agent talimogene laherparepvec in melanoma?

DR GONZALEZ: It's an interesting agent. We were involved in the early-phase studies of talimogene laherparepvec. It's a herpes simplex virus type 1 engineered to express GM-CSF and activate an antitumor immune response. The patient must have an injectable tumor, but it doesn't need to be limited to in-transit metastases. Theoretically, you can inject it into a lymph node, but the tumor must be injectable.

Of note, local and systemic responses have been seen with this agent. The Phase III OPTiM trial is ongoing and the results will be reported soon (Andtbacka 2013). (Editor's note: Subsequent to this interview the initial results of this study were presented [2.1].)

Tracks 10-11

Case discussion

A 42-year-old patient with BRAF wild-type metastatic melanoma experiences a complete response to high-dose IL-2

2.1

OPTiM: A Phase III Trial of Talimogene Laherparepvec (T-VEC) versus Subcutaneous GM-CSF for Unresectable Stage IIIB/C and IV Melanoma

Efficacy	T-VEC (n = 295)	GM-CSF (n = 141)	Unadjusted odds ratio	*p*-value
Durable response rate	16.3%	2.1%	8.9	<0.0001
Time to treatment failure	8.2 mo	2.9 mo	0.42	<0.0001
Select adverse events (all grades)	**T-VEC** (n = 292)		**GM-CSF** (n = 127)	
Fatigue	50.3%		36.2%	
Chills	48.6%		8.7%	
Pyrexia	42.8%		8.7%	
Influenza-like illness	30.5%		15.0%	
Injection site pain	27.7%		6.3%	
Vomiting	21.2%		9.4%	
Cellulitis (Grade 3 or 4)	2.1%		<1%	

Andtbacka RH et al. *Proc ASCO* 2013;**Abstract LBA9008**.

DR GONZALEZ: Given his diagnosis, the patient's treatment options were limited to immune therapy, of which the 2 current choices are high-dose IL-2 or ipilimumab. This patient received high-dose IL-2. He achieved a complete response and is now out a number of years and faring well.

DR LOVE: A number of attempts have been made to predict who fares well with high-dose IL-2 and other therapies, but it's difficult to identify a factor. One such preliminary report was on the correlation of NRAS mutations with clinical response to high-dose IL-2 in about 100 patients with advanced melanoma (Joseph 2012). What are your thoughts?

DR GONZALEZ: NRAS is another mutation that we look for in patients with melanoma. Some preliminary evidence has indicated that patients with NRAS mutations may respond better to immunotherapy.

NRAS mutations are interesting because they occur in approximately 20% of patients with melanoma. About 50% of patients with melanoma harbor the BRAF mutation, and if we add another 20% with NRAS mutations, which are activating both the parallel AKT pathway and the MAP kinase pathway, we can potentially target that mutation too. Those patients might respond to MEK inhibitors specifically, and other agents are available. We have pan-RAF inhibitors — BRAF is one of the RAFs, but another one called CRAF is also activated in melanoma along with NRAS. So this gene might be blocked in the same way that the BRAF gene is. That's an interesting potential new target in melanoma. ■

SELECT PUBLICATIONS

Joseph RW et al. **Correlation of NRAS mutations with clinical response to high-dose IL-2 in patients with advanced melanoma.** *J Immunother* 2012;35(1):66-72.

Su F et al. **RAS mutations in cutaneous squamous-cell carcinomas in patients treated with BRAF inhibitors.** *N Engl J Med* 2012;366(3):207-15.