The Practical Oncologist

Why is BRAF V600E mutation testing required prior to vemurafenib therapy?

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This is Jeffrey Weber, I am a medical oncologist and the director of the Donald A. Adam Comprehensive Melanoma Research Center at the Moffitt Cancer Center in Tampa, Florida. I am a melanoma researcher, interested specifically in the immunotherapy and targeted therapy of melanoma. Among the FAQs that we are often asked or the frequently asked questions are the query of "Why is the BRAF V600E mutation testing required prior to vemurafenib therapy?" And the answer to that question is very straightforward. Vemurafenib is a small molecule or a drug that clearly has activity at inhibiting a molecule that we call BRAF or B-R-A-F. BRAF is a molecule that exists in a cascade and the cascade goes from RAS to RAF to MEK to ERK and it is a signal transduction cascade where in the cell, a substance that may bind to the outside of a melanoma cell triggers a signal which then triggers another protein, which then triggers another protein, in sort of like a waterfall or a cascade. And when there is a mutation, which happens about 40-50% of the time in patients with melanoma, when there is a mutation in that BRAF gene, the cell essentially becomes addicted to the BRAF product and you get what we call constitutive expression and activation of the melanoma cells and the melanoma cells will continue to grow and grow and proliferate and become malignant. When vemurafenib is used it specifically blocks the mutated BRAF gene, and it should, and many in cases, in fact well over 50% of the cases will cause the tumor to stop growing and shrink. In other words, it is a very effective drug against melanomas in which you have the BRAF mutation. Paradoxically, if the cell, the melanoma cell, does not have the BRAF mutation, if it is what we call wild-type, it has been found that you get a paradoxical activation of this cascade and the cells might actually grow faster and proliferate. Therefore, the last things you want to do is to give a patient who does not have the BRAF mutation; that is, has a normal BRAF gene making a normal BRAF protein in their melanoma cells, the drug vemurafenib because it actually will have the reverse effect, it will actually make that melanoma cell grow and that of course we do not want. Therefore, the biomarker for the effectiveness of vemurafenib is the presence of the BRAF V600E mutation, so that is why you always want to make sure that you know that if you are going to get vemurafenib and you have melanoma, that your melanoma expresses the V600 mutation.

I thank you very much for your attention.