CLINICAL VIGNETTE

A Patient with Melanoma and Another with Hairy Cell Leukemia Walk into a Pharmacy….

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A 79-year-old male was referred to hematology clinic in 2006 for evaluation of pancytopenia. He was otherwise healthy with no significant past medical history and on no medications at the time. A bone marrow biopsy confirmed a diagnosis of hairy cell leukemia (HCL). Given the severity of his pancytopenia, therapy was initiated with a course of 2-CDA (cladribine). He achieved a complete response with normalization of his blood counts. In 2010 (roughly four years later), his counts again fell, and marrow evaluation confirmed recurrence. He received a second course of 2-CDA, and again had normalization of his counts. He did well for roughly three years, but by July of 2013, he had worrisome pancytopenia, so he was treated with a course of rituximab. His counts did improve, but by November of 2014, they were falling.

Third-line therapy for recurrent hairy cell leukemia is far from well-established, and the reality of the challenge was becoming quite stressful for the patient and his physician. We were contemplating another course of rituximab with the understanding that the likelihood of a durable response was very small. Soon after the visit, I attended the annual UCLA research conference in Lake Arrowhead. I walked into the discussion on new phase I trials about five minutes late, and my ears perked up when the discussant mentioned a new trial of combined B-RAF and MEK inhibition for multiple malignant conditions that are known to harbor a BRAF mutation, including refractory hairy cell leukemia.

The patient was in the phase I clinic a few days later and enrolled on this trial. Within two months on therapy, his blood counts showed significant improvement and a repeat marrow biopsy showed no evidence of hairy cell leukemia.

This case serves as an example of the metaphorical holy grail in oncology: understand the driving mutation of a malignant process, then targeting that pathway with a medication that inhibits that driver. Until fairly recently, we have not had the technology to really understand the true drivers of most malignancies at the molecular level. This ignorance has led us to treat diseases that seem clinically similar with the same therapeutic approach, which clearly has not achieved acceptable results. Perhaps the first example of how to clinically disparate processes can be driven by the same mutation was seen in the finding that gastrointestinal stromal tumors (GIST) and chronic myeloid leukemia (CML) have very similar instigating molecular anomalies and thus can both effectively be treated with the same targeted therapy, imatinib.

It has been known for years that roughly 50% of melanoma cases harbor a mutation in the BRAF pathway. This mutation affects the RAS/RAF/MEK/MAPK signaling pathway. This information has been exploited therapeutically with the introduction first of the BRAF inhibitor vemurafenib and, even more potently, by the combined blockade of BRAF and MEK pathways with the combination of dabrafenib and trametinib.[1] This strategy has been one part of a revolution in the treatment of metastatic melanoma.

The success in melanoma has led to excitement that other malignancies driven by BRAF might also be effectively treated with a similar strategy. Despite having no clinical similarity, it turns out hairy cell leukemia is perhaps the best example of a BRAF-driven process. This was first reported by an Italian group, which set out to better understand the genetics underlying hairy cell leukemia in 2011 in

the New England Journal of Medicine.[2] They started with an index patient and completely profiled the genome of the malignant cells, which uncovered five missense mutations including a heterozygous mutation in BRAF that results in the BRAF V600E variant protein. They then looked for this mutation in another 47 patients with classic hairy cell leukemia and found the same mutation in every one of these patients. The mutation was present in 100% of their population of patients with hairy cell leukemia. Equally fascinating is that they then sequenced the malignant cells of 195 patients with clinically similar indolent lymphoproliferative disorders, and none of them had the BRAF mutation. In their conclusion, they point out this data "may have implications for the pathogenesis, diagnosis and targeted therapy of HCL."

These data led the investigators of the current phase I trial to include hairy cell leukemia, a fairly obscure malignancy, in their study. This has had an immediate positive impact on our patient, who has attained a response to therapy that was very unlikely with any currently available modalities. Perhaps more importantly, this case serves as a paradigm of a logical way to focus our strategy in cancer research, which has been the model employed at UCLA for decades.

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