Whole-Exome Sequencing of Metastatic Cancer


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Genomic Profiling
Building a Continuum From Knowledge to Care

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The greater availability and reduced cost of next-generation sequencing has allowed some major academic cancer centers to integrate genomic profiling into clinical practice. In principle, prospective genomic profiling has the potential to inform treatment decisions, identify patients for relevant clinical trials, and trigger additional exploratory studies.

In this issue of JAMA Oncology, Beltran and colleagues’ reported the experience of the prospective whole-exome sequencing (WES) for patients with advanced cancers in the setting of routine practice at an academic institute. Although prescreening may have been required, it is remarkable that, in a cohort of 97 patients predominantly composed of those with prostate (51%) and bladder cancers (21%), more than 90% had adequate biopsies of the metastases for WES. All somatic alterations were listed in reports to patients by relevance to treatment or cancer biology; 92% of patients had “clinically or biologically informative” alterations, although it is not clear how many patients actually had alterations considered to be “clinically actionable” with an investigational or commercially available agent. Notably, less than 5% of patients received therapies recommended on the basis of the genomic analysis, in part as a result of issues with drug availability. The application of WES was highlighted in 2 examples, including immediate utility to a patient with urethral cancer who received trastuzumab and paclitaxel on the basis of HER2 amplification and achieved a complete remission.

In the other example, WES was used retrospectively to investigate the molecular basis of an exceptional response to cisplatin and docetaxel combination therapy in a patient with advanced prostate cancer. Genomic interrogation revealed a somatic hemizygous deletion of the FANCA gene and a germline missense variant in the other allele. Because FANCA is a member of the Fanconi anemia core complex critical to DNA crosslink repair, the biallelic alterations provided a plausible explanation for sensitivity to platinum. Impressively, FANCA-modified cell lines and patient-derived xenografts (PDX) were generated for functional testing.

Fanconi anemia pathway gene alterations are well known in platinum-sensitive tumors such as ovarian cancer but are under-recognized in prostate cancer. The finding here highlighted the power of WES in revealing rare genomic events that are otherwise unsuspected. However, it should be noted that the specific FANCA genotype alone may not fully explain the dramatic response in this patient. Indeed, the functional loss of FANCA variant S1088F appeared to be partial, and the PDX response to cisplatin alone was modest (growth inhibition). To optimize the value of this anecdotal clinical finding, additional studies in PDX...
Whole-exome sequencing of metastatic cancer

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