Case Report

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Increased Somatic Mutations with Large Panel Next Generation Sequencing (NGS) in Deficient MMR (dMMR) Tumors: An Illustrative Case Report

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Abstract

Large panel Next-Generation Sequencing (NGS) of tumors or circulating cell-free (cf) DNA is commonly used when cancer progression occurs after standard therapies. Such NGS is done in order to evaluate the tumor for the presence of somatic genomic alterations in one or more of hundreds of genes with the hope of identifying a targetable or actionable molecular abnormality.

For colorectal cancer, routinely testing for tumor deficiency of expression of one of several mismatch repair genes (dMMR) is recommended for nearly all cases and commonly done using immunohistochemistry (IHC). Recently the FDA granted accelerated approval for checkpoint inhibitor use in any solid tumors demonstrating dMMR and routine testing for MMR expression in non-colorectal cancers is therefore anticipated. Also, dMMR tumors typically show more potentially actionable somatic driver mutations than are seen for proficient MMR tumors (pMMR), when NGS of the tumor tissue or circulating cf DNA is preformed.

Here, a Lynch syndrome patient is reported whose colon cancer demonstrated 70 somatic alterations. After a prolonged response to PD1 inhibitor therapy, a liquid biopsy again showed many mutations in the tumor circulating cf DNA. The very high BRCA2 Mutation Allelic Frequency (MAF) reported suggested a potential benefit from PARP inhibitor therapy in this patient.

This case illustrates that because patients with dMMR tumors characteristically demonstrate many mutations currently identified by NGS, patients with dMMR (or MSI-H) tumors might particularly benefit from NGS of their tumors in order to identify molecular actionable abnormalities that might respond to a highly targeted therapy. As patients with dMMR tumors live longer through checkpoint inhibitor therapy use it might also be anticipated that real-time NGS of their tumors could identify actionable molecular abnormalities acquired during the time they receive the checkpoint inhibitor.

Keywords: Next generation sequencing; Mismatch repair

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Case Report

GG is a 37 y/o man who underwent a right hemicolectomy for a pT3N1b colonic adenocarcinoma in 9-2010. His mother, maternal grandfather, a maternal uncle and a maternal cousin had each been diagnosed previously with colon cancer. Germline testing identified a deleterious MSH2 mutation (1303delA MSH2) (Myriad Genetics, Salt Lake City, Utah, 84108).

He completed adjuvant FOLFOX chemotherapy in 3-2011. In 9-2014 he underwent removal of recurrent disease in four mesenteric lymph nodes. In 11-2014 biopsy of one of numerous liver lesions confirmed progressive metastatic disease and treatment with FOLFOXIRI/bevacizumab resulted in radiographic improvement [1,2].

Although there was no progression on FOLFOXIRI/bevacizumab,

he requested NGS of his primary tumor that had been removed in 2010. A single somatic alteration or multiple somatic alterations in a single gene was seen in 70 genes (Memorial Hospital for Cancer and Allied Diseases, MSKCC, Department of Pathology, 1275 York Ave, NewYork/NY 10065).

He received immunotherapy with the checkpoint inhibitor Durvalumab. After an initial response there was radiographic progression in 7-2016. In 10-2016 he started therapy with carcinoembryonic T cell biospecific antibody (TCB)/Atezolizumab, but in 1-2017 scanning again demonstrated progression and he then started therapy with FOLFOX/bevacizumab. With further progression in 3-2017, the checkpoint inhibitor Pembrolizumab was added. In 9-2017 he was admitted with peritonitis and completed a course of antibiotics with apparent resolution of the peritonitis.

In 8-2017 Liquid biopsy circulating cf DNA demonstrated a somatic alteration in a single gene or multiple somatic alterations in a single gene in 42 genes. Among these, there was a BRCA2 T3033fs alteration identified in roughly 83.2% of the tumor circulating cf DNA. The PARP inhibitor Olaparib was recommended (Guardant Health, Redwood City, CA 94063).

Discussion

On May 23, 2017 the FDA granted accelerated approval for the treatment of all patients with unresectable or metastatic solid tumors demonstrating MSI-H or dMMR. For treatment of solid tumors, the FDA approval represented the first time that a drug's approval was based on a biomarker rather than a tissue of origin. The approval was based on the results of five clinical trials that involved 149 patients with a total of 15 cancer types. The complete or partial response rate was 39.6%. Among 78% of the responding patients, the response lasted for 6 months or longer [3].

Even before the FDA approval, testing CRCs for dMMR (or MSI-H) was recommended for nearly all patients with CRC [2]. Such testing for dMMR is typically done using IHC. With the FDA approval, it would seem reasonable that all patients with nearly all metastatic solid tumors be tested for dMMR (or MSI-H), regardless of the tissue of origin, particularly once progression had occurred on standard therapies.

dMMR (or MSI-H) tumors characteristically harbor far more potential driver events than those with normal MMR expression (proficient or pMMR). For example, in an analysis of 100,000 human cancer genomes, the authors reported "the vast majority of MSI-High samples also had high tumor mutational burden (TMB) (83%) and 97% had TMB >/= 10 mutations/Mb [4].

Since NGS sequencing of dMMR tumors would be expected to result in many genetic alterations and therefore a high probability of identifying potentially effective targeted therapies, patients with dMMR tumors would appear to be among the most likely patients to benefit from NGS of their tumors. Whether tumors with actionable driver somatic mutations identified in the setting of dMMR tumors are as likely to respond to the targeted agent as are patients with tumors harboring those alterations without dMMR remains to be clarified through clinical trials.

The identification of a high MAF for the altered BRCA2 seen in GG's liquid biopsy underscores the potential benefit of NGS of tissue or liquid biopsies in patients with dMMR tumors. GG's germline testing did not identify a germline BRCA2 deleterious mutation. However, the high MAF seen for BRCA2 cf DNA suggests Loss of Heterozygosity (LOH) in his tumor. Thus, while his colorectal cancer was not secondary to a germline mutation in BRCA2, PARP inhibitor therapy is currently FDA approved for patients with BRCA-derived ovarian cancers [5]. Like GG, such patients have LOH and a presumed resulting lack of normal BRCA expression in their tumors, as the basis for the observed PARP inhibitor therapy benefit. The same BRCA alteration had been noted in the tumor tissue NGS, although the MAF was not reported. Further studies are needed to determine if additional actionable somatic driver mutations might be acquired during the time that patients benefit from checkpoint inhibitor therapy and therefore such patients might be encouraged to undergo "real-time" NGS after progression on checkpoint inhibitors.

In summary, mixed results have been reported regarding whether large panel NGS of solid tumors will result in identifying enough tumors harboring actionable abnormalities that such testing should be routine for all patients with solid tumors who have exhausted standard therapies. Given the very high TMB seen in dMMR tumors, patients with these tumors in particular might be offered and benefit from NGS testing of their tumors, with the hope of identifying an actionable molecular abnormality.

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