A Longitudinal Study to Monitor Cancer Treatment and Progression Using Circulating, Cell-Free DNA

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Abstract

Urine and ovarian cancers are the fourth and fifth, respectively, most common cancers in women and are estimated to account for nearly 25,000 deaths in the US annually. The use of circulating, cell-free DNA (cfDNA) to monitor disease burden during and post treatment has implications for effectively treating this disease. Collection and sequencing of cfDNA over time would allow assessment of tumor burden by detecting cfDNA mutations from a minimally invasive blood draw to ascertain tumor presence and aid in defining treatment strategies. We performed a pilot study to retrospectively study the cfDNA isolated from 11 women with gynecological cancers. Each had undergone tumor resection and the tumor was sequenced to determine its mutational profile. Tumor mutation allele frequencies of mutations detectable between 10% and 1% were determined by LoFreq. The cfDNA was collected and extracted at a minimum of two time points ranging from 7 to 64 months apart. Samples were sequenced using next generation sequencing technologies to determine mutations pasted in the germline. We observed a correlation between tumor-specific mutation frequency in the cfDNA and survivability. In 9 of 11 women, no neoplasms were identified in the patient and all 11 were in remission of disease (3). In 2 of 11 women, while the frequency of the primary tumor mutation in the first time point was less than 1%, a resurgence of the mutation(s) detected in the primary tumor was observed at the second time point, with mutant allele frequencies ranging from 5% - 75%. This increase in mutation frequency corresponded to morbidity or mortality.

This study demonstrates the use of cfDNA in amplicon-based sequencing assays to assess tumor burden in a minimally invasive manner in the research setting. Such techniques will be important in reducing the labor involved with gynecological cancers.

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