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Use of comprehensive genomic profiling to direct point-of-care management of patients with gynecologic cancers

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HIGHLIGHTS

- Few effective standard options available for patients with refractory disease
- Identification of genomic alterations can inform treatment decisions.
- Point-of-care management using this approach is feasible.
- A molecular tumor board (MTB) is an important component of point-of-care management.
- Implementation barriers of MTB-based therapeutic recommendations are discussed.

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ABSTRACT

Objective. To determine the feasibility and clinical utility of using comprehensive genomic profiling (CGP) in the course of clinical care to identify clinically relevant tumor genomic alterations for patients with either rare or refractory gynecologic cancers to facilitate point-of-care management. Use of an expert, multidisciplinary, institutional molecular tumor board (MTB) assessment is discussed regarding input on putative targeted options for individualized therapy.

Methods. A prospective clinical trial is ongoing. We report on the initial 69 patients with gynecologic cancers that were either rare or refractory to standard therapy. CGP was performed by Foundation Medicine, Inc. Genomic alterations were reviewed by members of an MTB. Consensus recommendations on genomically targeted, FDA-approved, on- and off-label therapies and clinical trials were sent to the treating physician, and decisions and outcomes were assessed.

Results. Study outcomes were available for 64 patients. The mean number of genes altered per tumor was 4.97 (median = 4; range, 1–26), and the average turnaround time from testing laboratory report to generation of formal recommendations was approximately three weeks. Evaluation of genomic and clinical data by the MTB led to generation of targeted treatment options in all 64 patients, and the percentage of patients for whom one or more of these recommendations were implemented by the treating physician was 39%. Sixty-four percent of the patients receiving targeted therapy based on a CGP result experienced radiologic response or showed evidence of clinical benefit or stable disease.

Conclusion. These data suggest that an institutional MTB is a feasible venue for reviewing tumor genomic profiling results and generating clinical recommendations. These data also support the need for further studies and guidelines on clinical decision making with greater availability of broad genomically based diagnostics.

1. Introduction

In 2015, the estimated number of cases of gynecologic cancer, including ovarian, endometrial, cervical, vaginal, and vulvar cancers,

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occurring in the United States was approximately 98,000 with over 30,000 deaths [1]. Several factors contribute to this high mortality rate: the majority of ovarian cancers are diagnosed at an advanced stage and most advanced endometrial cancers recur following initial standard of care therapy. Furthermore, standard therapy options are very limited in patients with ovarian or endometrial cancer that is recurrent or refractory to initial therapy [2,3]. Thus, novel treatment options, but especially targeted therapies for the treatment of advanced gynecologic cancers, represent a major unmet need.

It is becoming increasingly clear that both ovarian and uterine cancers are highly heterogeneous diseases with respect to prognosis, sensitivity to standard cytotoxic therapy, tumor histology, and the underlying molecular characteristics of the tumor. Clinicopathologic and molecular studies of epithelial ovarian cancers (EOCs) have provided the basis for simplifying the classification of these tumors into two categories that provide insight into the mode of tumorigenesis: type I (including low-grade serous, endometrioid, mucinous and clear cell cancers) and type II (including high-grade serous tumors) [4,5]. On a genomic level, mutations in potential oncogenic driver genes such as *KRAS* are much more commonly observed in type I compared with type II EOCs [4]. In addition, genomic alterations in other regulators of the mitogen-activated protein kinase (MAPK) pathway (e.g., *BRAF*), receptor tyrosine kinases (e.g., *ERBB2*), and loss-of-function mutations in *PTEN* also occur at a higher frequency in type I tumors [5–7]. Regarding type II EOCs, high-grade serous ovarian cancer is characterized by a nearly ubiquitous presence of mutations in *TP53*, a relatively high rate of defects in *BRCA1/2*, and a higher burden of genomic alterations, which are rarely seen in type I tumors [5,8–21]. Importantly, both DNA- and RNA-based next-generation sequencing (NGS) technologies are providing the basis for a rapid expansion of our understanding of the spectrum of molecular alterations occurring within ovarian cancers and their potential impact on malignant behavior. For example, studies involving the extensive characterization of the transcriptome of high-grade serous ovarian cancer, as well as the exomes of both newly diagnosed and chemoresistant, recurrent high-grade serous ovarian cancer have been reported [9,22,23], and some of these data are available online through The Cancer Genome Atlas (TCGA) project.

Uterine cancer includes endometrial carcinoma and the relatively rare uterine sarcomas, including leiomyosarcoma and carcinosarcoma [24,25]. The histological subtypes of endometrial adenocarcinoma include endometrioid, clear cell, serous, mucinous, and mixed-cell carcinoma histologies [26]. Endometrial cancers have been classically categorized into two prognostic groups on the basis of overall tumor characteristics and patient metabolic and endocrine-related risk factors [7,27]. More recent detailed genomic profiling of endometrioid and serous endometrial carcinomas by the TCGA and other groups have led to the molecular reclassification of endometrial carcinoma into four discrete molecular subgroups with different genomic landscapes, resulting in a molecular classification scheme that is distinct from the overlaying histological classification [28,29].

Despite the usefulness of these classification schemes in characterizing ovarian and endometrial cancers, the current standards of care for the treatment of these diseases are primarily based on morphological/histological subtype, tumor stage, and tumor grade, with few effective standard options available for patients with refractory or recurrent disease [2,3]. However, recent technological advancements in tumor genomic sequencing have made it possible to use the new molecular taxonomy of cancer available through large research databases, such as the TCGA. In this precision medicine approach, identified and potentially "actionable" genomic alterations can inform treatment decisions for individual patients in the setting of routine clinical care, particularly in cases where conventional cancer assessments and treatments are suboptimal. Nevertheless, the feasibility and clinical utility of such an approach is still unclear.

Here, we report results for the initial cohort of patients with gynecologic cancers enrolled in an ongoing comprehensive, prospective genomic profiling protocol at the Rutgers Cancer Institute of New Jersey (CINJ). The main goal of the study was to investigate the rate of putative actionable molecular alterations of this set of tumors. Of particular interest was to determine the feasibility and the impact of point-of-care testing of tumor somatic molecular alterations on decisions related to subsequent therapy in this cohort of "real-time" patients with rare or refractory gynecologic cancers.

2. Methods

2.1. Study participants

An initial subgroup of 67 patients with gynecologic cancers were enrolled onto an institutional review-board approved, prospective study trial at the Rutgers CINJ from 2013 through 2015 for the genomic profiling of patients with rare or refractory cancers. Two additional patients were presented retrospectively to the tumor board off protocol and are also included here. Detailed results for the first 100 patients enrolled in the parent study observing various tumor types have been previously reported [30]. Our analysis of patients with gynecologic cancers consisted predominantly of those with ovarian or uterine cancers that were rare and/or refractory to prior therapy. A small number of patients with advanced vaginal or cervical cancers were also included. Inclusion criteria included: Age ≥ 1 year (allowing for inclusion of pediatric patients), prior confirmed diagnosis of rare cancer or cancer with a poor prognosis with standard therapy, and available tumor tissue sample.

2.2. Genomic profiling through comprehensive genomic profiling

Tumor specimens were evaluated by histologic examination of hematoxylin and eosin stained sections. Formalin-fixed, paraffin-embedded tumor specimens from patients in this trial underwent hybrid capture-based comprehensive genomic profiling (CGP) in a Clinical Laboratory Improvement Amendments (CLIA)-approved, New York State accredited commercial laboratory (Foundation Medicine, Inc, Cambridge, MA) [31]. Sequencing initially included the entire coding regions of 236 cancer-related genes as well as 47 introns of 19 genes involved in fusions. Later in the study, the panel was expanded to include 315 cancer-related genes as well as introns of 28 genes involved in fusions. The specific assay version used was determined by the date of patient enrollment in the study. All classes of genomic alterations were assessed: DNA single-base mutations (i.e., single-nucleotide variants, including missense, or nonsense mutations leading to the insertion of a different amino acid or a stop codon, respectively), small DNA insertions or deletions, copy number alterations, and gene rearrangements.

2.3. Molecular Tumor Board (MTB) assessment

The MTB team consisted of experts from various disciplines including medical oncologists, surgical oncologists, pathologists, clinical trialists, systems biologists, genetic counselors, and biomedical research scientists. Team discussions of CGP results of individual patients within the context of patient-, disease-, and treatment-related factors focused on refining diagnosis, gaining additional insight into the natural history of the disease, and tailoring therapy for each patient. Consensus recommendations regarding clinical trials and on- and off-label FDA-approved therapeutic approaches were sent in a formal letter to the treating physician. Clinical recommendations included targeted therapies based on each patient's tumor genomic profile, applicable clinical trials, as well as guidance related to the need for serial biopsy and germline testing. Targeted therapies included FDA-approved, on- or off-label targeted therapies, cytotoxic agents, or radiation therapy for patients with tumors characterized by DNA repair pathway defects. The proportion of study participants receiving therapy consistent with the consensus recommendations and patient outcomes was determined through