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Underuse of exon mutational analysis for gastrointestinal stromal tumors

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ABSTRACT

Background: Tyrosine kinase inhibitors (TKI) have become the guideline-recommended therapy for high-risk resected and advanced gastrointestinal stromal tumors (GISTs). Exon mutational analysis (EMA) is used to inform pretherapy response to TKI and may predict overall prognosis. Despite these benefits, EMA remains underused, and its impact on TKI therapy decision-making remains unexplored.

Materials and methods: A retrospective cohort was established from 104 patients receiving treatment for GISTs from 2006 to 2017. Current National Comprehensive Cancer Network guidelines indicate that EMA should be considered for all patients undergoing TKI therapy to identify genotypes that are likely, or unlikely, to respond to treatment. We first tracked guideline-considered EMA use and subsequent impact on treatment decision-making. A questionnaire was then administered to gastrointestinal medical oncologists to assess EMA perception.

Results: Among 104 GIST patients, 54 (52%) received TKI therapy. Of these, only 22 (41%) received EMA. Informed by EMA, treatment decisions included 59% who continued with original TKI therapy, 32% who switched to an alternative TKI, and 9% who discontinued or received no TKI. Although 92% of physicians indicated EMA was a valuable tool, only 62% indicated they used it "frequently" or "always" to inform treatment decisions.

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Conclusions: Less than half of patients receiving TKI therapy for GISTs received EMA at a comprehensive cancer center. Despite this low uptake, when it was performed, EMA guided alternative treatment decision in 41% of patients. Physician survey responses indicated that interventions targeting physician education and an electronic medical record reminder may improve EMA uptake.

Introduction

The identification of actionable mutations in gastrointestinal stromal tumors (GISTs) has improved care and survival through the delivery of targeted therapies, such as tyrosine kinase inhibitors (TKI).[1,2] Approximately 80% of GISTs contain mutations in the KIT proto-oncogene receptor tyrosine kinase (KIT) gene and another 5%-10% in the platelet-derived growth factor receptor α gene, leading to gain-of-function mutations in the associated tyrosine kinase domains.[3] The presence of specific mutations within these genes can help predict whether a tumor harbors a genotype that is likely, or unlikely, to respond to TKI therapy.[4] Personalized treatment decisions are facilitated by the use of genetic information gained from exon mutational analysis (EMA) of the tumor.[5,6] EMA allows a physician to make informed treatment decisions about how to manage TKI treatment, the appropriate dosage to prescribe, the selection of an effective agent,[7] or foregoing TKI in select genotypes.

The National Comprehensive Cancer Network (NCCN) now recommends EMA for surgical resection of high-risk tumors, as defined by the modified NIH criteria,[8] as well as for advanced GIST patients undergoing preoperative TKI.[9] In addition, current guidelines state that any patient considered for medical therapy should also be considered for tumor genotyping.[9] These guidelines recognize that the use of EMA in the treatment of GISTs has prognostic potential to improve the level of care. However, despite the utility of EMA to inform TKI therapy, there remains a relatively low uptake by physicians.[10] Furthermore, it has been demonstrated that TKI therapy is underused in GIST patients in accordance with NCCN guidelines, even after a level I evidence of a proven survival benefit.[11-13] To date, rates of guideline-recommended EMA for patients undergoing TKI therapy at a comprehensive cancer center is currently unknown, as are facilitators and barriers to testing from a physician perspective.

Our overall goal is to better characterize the use of EMA in the care of GIST patients. We hypothesize that guideline-recommended EMA is underused in GIST patients receiving TKI therapy at a comprehensive cancer center. To test this hypothesis, we first quantify appropriate EMA use and overall impact on treatment decision-making. Second, we survey medical oncologists who treat patients with GIST to obtain deeper insights into EMA use and gauge familiarity with current NCCN guidelines. Results will identify reasons for the relative underuse of a clinically efficacious tool with potential for informing treatment, as well as provide insight into increasing dissemination of EMA among the GIST community.

Materials and methods

Ethics and patient population

The Georgetown University Institutional Review Board approved the study design and data collection; informed consent was obtained for the physician survey. A retrospective cohort of 104 patients was established from electronic medical records (EMRs) dating from January 2006 to January 2016 from all patients receiving care for pathologically confirmed GIST at Georgetown Lombardi Comprehensive Cancer Center.

Study variables

Demographic and clinical data were retrieved from EMRs and stored in a REDCap database.[14] Variables collected included patient, tumor, and treatment characteristics. Patient-related variables included age at diagnosis, gender, ethnicity, insurance status, and body mass index (BMI). Tumor-related variables included tumor size, tumor location, mitotic index, and presence of metastasis at diagnosis, allowing for pathological staging and risk stratification. Treatment-related variables included presenting symptoms, timing and use of TKI, perioperative details, use of EMA, and impact of EMA on treatment decisions.

Physician questionnaire

A physician questionnaire was developed to quantitatively probe clinical use of EMA for GIST patients within the MedStar Georgetown Cancer Institute, consisting of 10 hospitals and 13 gastrointestinal medical oncologists who treat GISTs. The questionnaire was deployed in an electronic format using REDCap software to 13 physicians.[14]

To ensure the appropriate physician population, the first item asked about the percentage of GIST patients accounting for total patient population. In addition, physicians were queried about the number of years since completing fellowship, and whether or not they received formal training in clinical genetics.

The survey included four sections with Likert-type scales assessing the frequency of EMA use, discussions with patients, factors triggering EMA use, and overall perception of EMA utility in the treatment of GISTs. Lastly, five clinical scenarios were presented where EMA could potentially be used to inform treatment and the physician made a decision about the appropriate course of action. The full questionnaire can be seen in Supplementary File 1.