Original Article

Circulating tumor DNA use in a community oncology practice

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Contributions: (I) Conception and design: All authors; (II) Administrative support: MF Xavier, CL Costantini; (III) Provision of study materials or patients: MF Xavier, CL Costantini; (IV) Collection and assembly of data: ED Chamberlain; (V) Data analysis and interpretation: All authors; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

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Background: This retrospective single center study aimed to describe circulating tumor DNA (ctDNA) comprehensive genomic profiling (CGP) utilization in a community practice for patients with advanced solid tumors.

Methods: All patients were included who were seen at the Scripps Hillcrest Oncology Clinic (San Diego, CA, USA) between September 2016 to March 2018 who had ctDNA assay testing performed. In this cohort, all ctDNA testing was performed to aid therapeutic decision making with wide variety in both the type of advanced solid tumor, as well as the line of therapy.

Results: Of the assays performed in the 41 patients included in this review, 42% of therapeutic actions following ctDNA assay results were influenced by the ctDNA result, including initiation of the corresponding Federal Drug Administration (FDA) approved therapy, placement on clinical trial, and initiation of off label-targeted options. In addition, CGP results guided clinicians away from futile or harmful treatments, such as EGFR inhibition in colorectal cancer patients with discovered *KRAS* mutations. No additional prognostic or therapeutic information was gathered in one quarter of patients for which ctDNA was drawn. Furthermore, discovered genomic alterations by ctDNA testing did not influence therapeutic action in 58% of cases.

Conclusions: These results highlight the conundrum that having additional information regarding an individual's tumor biology does not yet translate into meaningful targeted therapy in the majority of cases. Further studies are needed regarding ctDNA utilization to help guide community oncologists who will continue to face the choice between targeted therapy, immunotherapy, and cytotoxic chemotherapy as science advances.

Keywords: Circulating tumor DNA (ctDNA); comprehensive genomic profiling (CGP); community/health; advanced solid tumors

Submitted Dec 29, 2018. Accepted for publication Mar 12, 2019.
doi: 10.21037/tcr.2019.03.15
View this article at: http://dx.doi.org/10.21037/tcr.2019.03.15

Introduction

Comprehensive genomic profiling (CGP) is routinely incorporated into the treatment and management for patients with advanced solid tumors with guideline support from several organizations (1-3). Traditionally, CGP has been performed on tissue obtained from invasive biopsies in patients with advanced tumors. However, a tissue approach to CGP has its limitations including acquisition of tumor specimen, inability to profile cancer in real time, time to results, and time to treatment. A recent study in newly diagnosed advanced lung cancer treated in the community showed that despite recommendations for CGP, less than 8% of patients were tested for all the guideline recommended genes (4).

CGP utilizing cell-free circulating tumor DNA (ctDNA) has emerged as an alternative to tissue biopsy. ctDNA CGP has shown to have high concordance with tissue CGP, and patients with ctDNA detected therapeutically targetable alterations who are treated with targeted therapy have

similar clinical outcomes as those treated based on tissue CGP results (5,6). Additionally, ctDNA CGP has been shown to overcome barriers associated with inter and intra tumor heterogeneity (7). There are currently more than twelve ctDNA assays available with variable supporting evidence in some types of advanced cancer. Two of the most widely used ctDNA assays in community oncology practices include Guardant360® and FoundationOne®Liquid. Both Guardant360 and FoundationOneLiquid have received Breakthrough Device (formerly Expedited Access Pathway program) designation by the Federal Drug Administration (FDA), with FDA approval still pending. Though the FDA has yet to approve either assay, both are widely used in oncology practice.

The majority of clinical data has described the incorporation of ctDNA into the treatment for patients with advanced solid tumors treated in academic centers. It is known that the majority of cancer patients are treated in the community setting. Harnessing the information gained from ctDNA CGP has the potential to provide significant positive impact for the care of patients in the community setting where, unfortunately, there is limited data on its utilization. Here we aimed to describe a single center experience with ctDNA CGP to better understand and elucidate how this technology is being utilized in the community setting.

This retrospective single center study aimed to describe the clinical characteristics of patients with advanced solid tumors, defined as stage IIIB or higher, who underwent ctDNA analysis in a community oncology practice, to describe the prevalence of mutations identified and available therapeutic options according to the mutation, and to delineate the clinical action taken following the results of ctDNA analysis.

Methods

IRB approval was obtained for retrospective review of all patients seen at the Scripps Hillcrest Oncology Clinic (San Diego, California, USA) between September 2016 to March 2018 who had ctDNA assay testing performed as ordered by their primary oncologist. The ctDNA assay utilized was Guardant360 (8). This review comprises patient cases from three medical oncologists. CtDNA results were defined as "clinically actionable" if the identification of the mutation was associated with an FDA approved therapy, an off-label therapy, or a targeted therapy clinical trial. Mutations identified comprise four major classes of alterations, including single nucleotide variants, indels, amplifications, and gene fusions. Therapeutic action taken following ctDNA assay result was recorded in a binary fashion, either as treatment choice was influenced or not influenced based on ctDNA result. Patients with targetable mutations who were subsequently treated with an FDA approved therapy, clinical trial, or off-label treatment were categorized as patients whose treatment choice was influenced by ctDNA results. Patients with identified mutations by ctDNA assay though whom were subsequently treated with non-targeted therapy, immunotherapy, supportive care only, or died were categorized as patients whose treatment choice was not influenced by ctDNA results.

Results

Forty-one patients with advanced cancer diagnoses underwent ctDNA analysis during the study period (*Table 1*). Of these, 68% were female and 32% were male. Twelve percent of patients were between the ages of 30 to 49 years, 41% were age 50 to 69 years, and 46% were age 70 to 89 years at the time of ctDNA collection. Cancer type varied, with the majority of patients having been diagnosed with lung cancer (44%) followed by colorectal cancer (20%) and breast cancer (10%). CtDNA assays were used at the time of diagnosis in 22% of patients, at the time of decision for second-line therapy in 29% of patients, at the time of third-line therapy in 24% of patients, and at the time of fourth-line therapy or greater in 24% of patients. In all patients, assays were drawn to aid in therapeutic decision making.

Median turn-around time for ctDNA results was nine days from sample collection to results report. Clinically actionable mutations were detected in 31 of the 41 patients (76%). In 3 patients (7%), ctDNA detected mutations were present but either were variants of uncertain significance or were not clinically actionable as defined in the study methods. No ctDNA alterations were detected in 7 patients (17%, *Table 2*). Of the 97 mutations identified across 34 patients' circulating tumor DNA, 5 mutations are linked to FDA approved therapy, 46 with clinical trials, and 46 with off label therapeutic targeted agents (*Table 3*). Assay results influenced the treating physician's treatment choice in 42% of the cases with identified mutations (*Table 4*). Two of 34 patients found to have tumor DNA mutations underwent treatment with FDA approved therapy, 5 went on to clinical trial based on the identified mutations, 2 received off-label treatment, 7 received immunotherapy, 9 received chemotherapy, and 9 did not receive further

Table 1 Characteristics of 41 patients who underwent clinical ctDNA testing during the study period

Variables	N (%)
Sex	
Female	28 [68]
Male	13 [32]
Age	
30–49 years	5 [12]
50–69 years	17 [41]
70–89 years	19 [46]
Cancer type	
Breast	4 [10]
Lung	18 [44]
Endometrial	2 [5]
Cholangiocarcinoma	1 [2]
LMS	1 [2]
Pancreatic	2 [5]
CRC	8 [20]
Mesothelioma	1 [2]
PNET	1 [2]
CUP	1 [2]
Other	2 [5]
Clinical status at ctDNA collection	
New diagnosis	9 [22]
Second line	12 [29]
Third line	10 [24]
≥ Fourth line	10 [24]

ctDNA, circulating tumor DNA; LMS, leiomyosarcoma; CRC, colorectal cancer; PNET, pancreatic neuroendocrine tumor; CUP, cancer of unknown primary.

Table 2 ctDNA results in 41 patients

ctDNA assay	Patients, n=41, (%)
Average turnaround time, days	9
Actionable mutation detected	31 [76]
Mutation(s) present but no therapeutic option or VUS	3 [7]
No mutation(s) detected	7 [17]

ctDNA, circulating tumor DNA; VUS, variant of unknown significance.

Table 3 Therapeutic options for 97 clinically actionable mutations detected in 31 patients

Therapeutic option, based on mutation	Mutations, n=97, (%)
FDA approved therapy	5 [5]
Clinical trial	46 [47]
Off label	46 [47]

FDA, Federal Drug Administration.

Table 4 Therapeutic action following ctDNA assay result

Therapeutic option based on mutation	Patients, n=31, (%)
Treatment choice influenced by ctDNA result	13 [42]
Treatment choice not influenced by ctDNA result	18 [58]

ctDNA, circulating tumor DNA.

Table 5 Therapeutic action following ctDNA result

Therapeutic action taken following assay result	Patients, n=34, (%)
FDA approved therapy	2 [6]
Clinical trial	5 [12]
Off label	2 [6]
Treated with non-targeted therapy	9 [26]
Immunotherapy	7 [21]
Other (palliative care, death, result intended for future use, lost to follow-up)	9 [26]

FDA, Federal Drug Administration; ctDNA, circulating tumor DNA.

treatment. These 9 patients either proceeded to hospice, died, were lost to follow-up, or assay results were saved for future use following progression or intolerance to the current line of treatment (*Table 5*).

Discussion

We practice in a unique time in the field of oncology. Knowledge surrounding genetic alterations has increased and tumor genomic sequencing has become more common in standard practice. Mutational analyses performed in advanced solid tumors confer prognostic and therapeutic information in many cases. Liquid biopsies offer a less invasive means of obtaining tumor genomic information,

yet, the current use of ctDNA varies widely. This retrospective review describes its use in one community oncology practice.

In this cohort, all ctDNA testing was performed in patients with advanced solid tumors to aid in therapeutic decision making with wide variety in both the type of advanced solid tumor, as well as the line of therapy. Of the assays performed in the 41 patients included in this review, all 41 assays were performed in effort to aid therapeutic decision making in patients with advanced solid tumors. No assay was performed for treatment monitoring, cancer screening, or residual disease detection. Accordingly, 42% of therapeutic actions following ctDNA assay results were influenced by the ctDNA result, including placement on FDA approved therapy, clinical trial, and off label-targeted options. In addition, mutational results guided clinicians away from futile or harmful treatments, such as EGFR inhibition in colorectal patients with discovered *KRAS* mutations.

Despite the intention to gain prognostic and or therapeutic information from these assays, no further information was gathered in one quarter of patients for which ctDNA was drawn. Furthermore, of those patients with discovered mutations, therapeutic action was not influenced by findings from ctDNA analysis in 58% of cases. Rather, these patients proceeded with chemotherapy, immunotherapy, hospice, or died, further highlighting the conundrum that having additional information regarding an individual's tumor biology does not yet translate into meaningful targeted therapy in the majority of cases. One explanation may be related to the lack of clinical and safety data regarding the use of targeted therapies in the off-label setting. This is currently being investigated in multiple clinical trials such as the NCI-MATCH (NCT02465060) and TAPUR (NCT02693535) which seek to treat patients with therapies targeted to the genomic changes found by genomic sequencing. Such use of off-label treatment, especially combination treatments never previously tested, is both controversial outside of the context of a clinical-trial and may explain the high percentage of patients found in this series who went on to chemotherapy or immunotherapy rather than targeted treatment despite the discovery of tumor mutations with potential off-label treatment options by ctDNA analysis.

Conclusions

This study was performed retrospectively at a single community oncology practice site and this limits generalizability to community practice sites at large. In one of the first series to describe ctDNA utilization by community oncologists, we demonstrate that utilization of ctDNA in this single community center series identified clinically actionable mutations in 76% of the overall cohort, leading to a therapy change based on ctDNA results in 42% of patients. The ability of ctDNA to detect therapeutically actionable information in a rapid turn-around time has significant clinical implications for the community oncology practitioner. No therapy change was initiated for 58% of patients, including those with on-label findings. The increasing use of targeted therapy offers both clinicians and patients optimism for improvements treatment responses and treatment-related toxicities by the way of individualized cancer treatment. This study demonstrates many patients in the community setting already receive targeted treatment in accordance with the patient's tumor genomics. While this study addresses the utilization of ctDNA by community oncologists, it does not address patient-specific treatment outcomes following the use of targeted therapy. Further studies are needed regarding both ctDNA utilization as well as treatment outcome to help guide community oncologists who will continue to face the choice between targeted therapy, immunotherapy, and cytotoxic chemotherapy as science advances.

Acknowledgments

Funding: None.

Footnote

Conflicts of Interest: VM Raymond, MS, full time employee and shareholder of Guardant Health, Inc. The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This research project was conducted with full compliance of the Scripps IRB & Research Management System. Informed consent was waived due to the retrospective nature of the study.

Open Access Statement: This is an Open Access article

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Cite this article as: Chamberlain ED, Costantini CL, Xavier MF. Circulating tumor DNA use in a community oncology practice. Transl Cancer Res 2019;8(2):552-556. doi: 10.21037/tcr.2019.03.15