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Targeted Next-Generation Sequencing for the Management of Patients Diagnosed With a Cancer of Unknown Primary

The Oncologist

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- The authors present the findings of a retrospective study assessing the clinical utility of targeted next-generation sequencing (NGS) in the diagnosis of cancers of unknown primary (CUPs). The clinical picture and NGS results suggested the likely primary tumor in 15% of cases. Molecularly guided therapeutic options were identified for just over half the patients tested, impacting treatment choice in approximately 30% of these patients.
- In patients with CUP, NGS testing does not contribute significantly to the identification of the primary cancer site. However, it does impact the selection of therapy in this population.

– Sarah Fenton, MD

Oncology

Written by F. Anthony Greco MD

Cancer of unknown primary (CUP) is a clinical pathologic syndrome of about 30 different metastatic cancers arising from clinically undetectable/occult anatomical primary sites proven by hundreds of autopsies and other data. The mechanism explaining how occult primaries produce detectable metastasis is an enigma, but it is likely to have a genetic/epigenetic basis. The occult primary is the shared feature of all cancers in this syndrome. However, aggregate data now support that the clinical behavior/biology of CUP and the response to site-directed therapies and outcome, once the tissue of origin (ToO) is diagnosed, are similar to known primary metastatic cancers. The inability in the past to diagnose the ToO was a major hurdle hindering the management of patients according to their specific type of cancer. CUP was often considered a single cancer type, and the ToO remained unknown/rarely suspected in most patients; empiric chemotherapy was, at that time, and even currently, considered by some as standard. The approach to CUP has evolved, and the difference compared with known primary cancers is the size of the primaries.

The diagnosis of the ToO is now possible in about 90% to 95% of patients despite not finding an anatomical primary site by the combination of clinical features, standard pathology including immunohistochemistry (IHC), and, if necessary, a molecular cancer classifier assay (MCCA) such as the 92-gene RT-PCR assay. The cancers in CUP can now largely be identified, and the syndrome is no longer as heterogeneous. Next-generation sequencing (NGS) can be useful, as it is with known metastatic cancers.

As noted by Fusco et al, NGS findings may rarely provide insight as to the ToO/possible primary in the appropriate clinical and pathologic context, and this is even more common/robust/accurate with an MCCA. ToO diagnosis is critical for precision therapy for each patient, recognizing that some cancers are more treatable/responsive than others. NGS findings may also be important and are best interpreted once the cellular context/ToO is known. With this knowledge, therapy should be site-specific, similar to metastatic cancers with known primaries. Clinical studies often did not attempt to diagnose the ToO and accrued different cancer types with varying biology and expected responses to various therapies but all considered as "one cancer type. Randomized studies which used an MCCA were flawed by: 1) skewed patient accrual with the majority having relatively unresponsive ToOs (physician reluctance with suspected responsive cancer types); and 2) older protocol designs without recently improved therapies for many ToOs, including targeted drugs and immunotherapy. Sweeping conclusions are not valid regarding these studies. Reported data and studies in progress show improved outcomes for selected responsive ToOs, including several CUP subsets (colorectal, renal, breast, melanoma, germ cell, lung, neuroendocrine, and others). For now, poorly responsive ToOs, including CUP/subsets (pancreaticobiliary, most advanced squamous cancers, sarcomas, others) do not benefit more than with empiric chemotherapy.

NGS tissue/blood findings in CUP have been reported several times but represent a large cauldron of many specific cancer types. One would expect to see many genetic alterations, very similar to NGS findings in known metastatic cancers. There are several overlapping genetic alterations in many cancer types, although a few are more common in certain cancers than others. It is not surprising that some patients respond to targeted drugs or immunotherapy based on NGS findings, although there is no convincing evidence of an improved outcome for most patients. It seems misguided to obtain NGS data initially in all patients without an attempt to diagnose the ToO, which is required to properly interpret NGS findings and plan optimal therapy for each patient. NGS findings alone will often suggest an initial therapy that is not indicated for that specific patient or will be suboptimal. For example, NGS may show a HER-2/neu alteration but the ToO determined by IHC and an MCCA is renal cell carcinoma. Without a ToO, a clinical trial of a HER-2/neu inhibitor or empiric chemotherapy would be inappropriate initially rather than site-specific therapy for CUP/renal subset.

Hopefully, in the future, NGS platforms may provide critical pathogenetic data—yet to be fully discovered—for each patient's tumor for optimal, perhaps curative therapy regardless of the ToO. Except for rare agnostic findings such as microsatellite instability-high, high tumor mutational burden (recently debated), and NTRK fusions, NGS now adds little to determine initial therapy for CUP without a ToO diagnosis. The ongoing CUPSICO randomized prospective phase II study requires NGS prior to empiric chemotherapy with an accrual goal of nearly 800 patients. Those with stable/objective responses are randomly assigned 3:1 to targeted therapy if the target is found or to immunotherapy as "maintenance" versus continued empiric chemotherapy. Only a minority of the patients will have an actionable alteration to receive targeted therapy or immunotherapy, which explains the 800 accrual goal. There will likely be an improvement in progression-free/overall survival since many have responsive cancers and a proportion has highly actionable findings. However, no attempt to determine the ToO initially is illogical, and the results may delay future studies to ultimately and definitively establish the value of initial precision therapy for each patient. Randomized studies in unselected CUP involve about 30 different metastatic cancers and are impossible, irrational designs, although results may be positive or negative depending on the cancer types accrued, which remain unknown. Large prospective phase II studies with site-specific therapy for responsive ToOs subsets (colorectal, renal, lung, breast, germ cell, GE junction/gastric, others) and comparisons of survivals to historical patients with the same known cancers who received similar therapy should be able to settle the issue rather quickly and would supplement the studies supporting this approach, as reported in small numbers with CUP/colorectal subset (now a favorable subset as mentioned by Fusco et al) and the CUP/renal subset.

Abstract

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BACKGROUND

Cancer of unknown primary (CUP) comprises a heterogeneous collection of malignancies that are typically associated with a poor prognosis and a lack of effective treatment options. We retrospectively evaluated the clinical utility of targeted next-generation sequencing (NGS) among CUP patients to assist with diagnosis and identify opportunities for molecularly guided therapy.

PATIENTS AND METHODS

Patients with a CUP at Moffitt Cancer Center who underwent NGS between January 1, 2014 and December 31, 2019, were eligible for study inclusion. Next-generation sequencing results were assessed to determine the frequency of clinically actionable molecular alterations, and chart reviews were performed to ascertain the number of patients receiving molecularly guided therapy.

RESULTS

Ninety-five CUP patients were identified for analysis. Next-generation sequencing testing identified options for molecularly guided therapy for 55% (n = 52) of patients. Among patients with molecularly guided therapy options, 33% (n = 17) were prescribed a molecularly guided therapy. The median overall survival for those receiving molecularly guided therapy was 23.6 months. Among the evaluable patients, the median duration of treatment for CUP patients (n = 7) receiving molecular-guided therapy as a first-line therapy was 39 weeks. The median duration of treatment for CUP patients (n = 8) treated with molecularly guided therapy in the second- or later-line setting was 13 weeks. Next-generation sequencing results were found to be suggestive of a likely primary tumor type for 15% (n = 14) of patients.

CONCLUSION

Next-generation sequencing results enabled the identification of treatment options in a majority of patients and assisted with the identification of a likely primary tumor type in a clinically meaningful subset of patients.

Additional Info

Article Citation

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Evaluation of Targeted Next-Generation Sequencing for the Management of Patients Diagnosed With a Cancer of Unknown Primary

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