The Impact of Molecular Testing on Treatment of Cancer of Unknown Primary Origin

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The preponderance of data support the accuracy of molecular assay diagnoses in about 80% to 90% of patients with known advanced primary cancers and in patients with cancer of unknown primary origin.

Cancer of unknown primary origin (CUP) is a common (accounting for about 3% of all advanced cancers annually) heterogeneous clinical pathologic syndrome defined as the presence of cancer without a clinically detectable anatomical primary site of origin.[1] The CUP syndrome has been recognized for decades; the majority of patients have small, clinically undetectable primary sites, as has been proven by autopsy series.[1,2] Recently, using evolving and new diagnostic technologies, we have attained the ability to accurately determine the tissue of origin in most patients with CUP.[3-20]

The clinical biology of CUP remains a puzzle. The mechanism by which a very small clinically undetectable primary site can metastasize and produce larger clinically demonstrable metastases is unknown. Perhaps detailed genomic analysis of these cancers may eventually explain this syndrome. Nonetheless, these occult primary tumors usually metastasize to the same sites as those of patients with carcinomas of known primary origin, and they respond similarly to the standard therapies used for their counterparts with easily recognized primary tumor sites. Favorable subsets of patients with CUP have been recognized for years, based upon standard clinical and pathologic features. These subsets represent about 20% of all CUP patients.[1] Most of these patients have occult, clinically undetectable primary tumors, but with rather typical metastatic patterns and histologies, allowing presumptive diagnoses and specific therapy. On the other hand, about 80% of all CUP patients, most with adenocarcinomas, have metastatic tumors that are very difficult to treat specifically, since the tissue of origin is unknown. Therefore, broad-spectrum empiric chemotherapy has been the standard approach for most patients for the last 30 years.[1]

Perspectives on the Current Management of CUP

Now that it has become possible to diagnose the tissue of origin accurately in the majority of patients with CUP, management of these patients has shifted from a standard empiric broad-spectrum chemotherapeutic approach to a more personalized site-specific treatment. Therapy for CUP, once the tissue of origin has been accurately diagnosed, should be similar to that used for other patients with known advanced primary cancers. Treatment for many patients with solid tumors has improved substantially in recent years, and it has become relatively site-specific and variable for different cancers. In many of these patients with known advanced cancers (breast, lung, ovary, colorectal, kidney, others), a wide variety of sequential treatments can produce good control of the cancer, often for many months or years. Therefore, knowledge of the tissue of origin in CUP is critical for many patients. Specific genetic aberrations have been noted that are actionable or druggable by various commercially available agents and/or other potentially useful drugs now being evaluated in clinical trials. The stakes are much higher now than previously in accurately determining the tissue of origin in CUP patients, given that doing so often enables us to then tailor treatment to the individual patient, rather than initially administering the same cytotoxic treatment to all patients.

In the last several years, improvements in the number and accuracy of immunohistochemistry (IHC) stains and the emergence of gene expression profiling assays have enabled us to make an accurate tissue-of-origin diagnosis in the majority of CUP patients. Standard pathology (histology and IHC) is an accepted time-honored approach in the diagnosis of CUP, but gene expression profiling has only been recently evaluated. Three critical questions concerning use of gene expression profiling assays in the diagnosis of CUP are: (1) Are these assays accurate in predicting the tissue of origin in patients with both known and unknown primary cancers? (2) Do the assays complement and compare
Cancer of unknown primary (CUP) is a clinicopathologic syndrome representing many types of advanced cancers with clinically undetectable anatomical primary sites.

There is now ample evidence to treat patients based upon a tissue-of-origin diagnosis made by an oncologist and pathologist. Results of a large prospective single-arm study provide support for the clinical usefulness of a molecular assay in this setting; improved survival was seen in CUP patients treated with site-specific therapy informed by a molecular assay tissue-of-origin diagnosis.[21] A single diagnosis was rendered in 98% of those patients, and 194 patients received site-specific treatment. Median patient survival compared favorably to that of 396 historical control patients (12.5 months vs 9.1 months, respectively). Any control group, regardless of the clinical trial methodology, is unlikely to be ideal in this setting because patients with CUP represent a heterogeneous group consisting of about 30 different primary tumor types, many of which are relatively insensitive or resistant to most forms of chemotherapy, including standard empiric therapies for CUP. The survival of more than half of patients with molecularly diagnosed responsive tumors (colorectal, breast, ovary, kidney, prostate, bladder, non–small-cell lung, germ cell, poorly differentiated neuroendocrine, lymphoma, and small-cell lung cancer) was significantly longer (13.4 months vs 7.6 months; \( P = .04 \)) than the survival of patients with less responsive tumors (pancreas, biliary tract, gastroesophageal, liver, melanoma, sarcoma, cervix, endometrium, mesothelioma, skin, thyroid, head and neck, and adrenal). In general, the survival of molecularly diagnosed subsets mirrored the survival of known advanced cancers of the same type. Other retrospective[14,15] and prospective[13,16] studies show that gene expression profiling of the biopsy specimen provides a relatively accurate diagnosis of the tissue of origin and therefore allows a more customized approach to each patient, rather than broad-spectrum empiric therapy.

In CUP patients the primary site is not clinically detectable, and a tissue of origin must be determined by the nature of the metastatic cells in the biopsy specimen, as assessed via the appropriate use of classic histology, IHC stains, and a molecular profiling assay. Site-specific and molecularly targeted therapies continue to improve for several types of advanced solid tumors. It is also logical to apply these treatments to CUP patients diagnosed with specific cancer types. Patients diagnosed with more responsive tumor types will benefit most from discovery of their tissue of origin; however, a sizable minority of patients, although accurately diagnosed, currently will not benefit much from site-directed therapy, since useful therapy for their tumor type is only marginally effective or not yet available.
How I Approach a Patient With Possible CUP

Based on all of the accumulated knowledge about CUP, my approach to a patient with possible CUP begins with a detailed history, physical examination, and review of the biopsy histology, followed by a reasonable search for the anatomical primary tumor site.\[1,14,15\] If a primary tumor site is found, CUP is no longer a consideration, and treatment proceeds in a standard fashion. If the primary site remains occult, I next determine whether the patient has a favorable clinicopathologic subset of CUP. These well-documented subsets are treated with site-specific regimens, and in some, the tissue of origin may also be definitively determined by IHC and/or gene expression profile assays.

The majority of CUP patients (80%) do not fit into a recognized favorable subset.\[1\] For these patients, I talk with the pathologist about the histology of the biopsy and clinical details, particularly the metastatic sites and the amount of biopsy material available. A selected IHC evaluation is appropriate,\[1,3,14,15\] and in the minority of patients, the tumor staining patterns are highly suggestive/diagnostic of a single tissue of origin. A gene expression profile assay is indicated in patients without a single-tissue-of-origin diagnosis by IHC, and a diagnosis is ultimately established in the majority of patients.\[13-16\] If possible, additional IHC staining not initially performed should be done in an attempt to confirm the molecular diagnosis.\[16\] Further genetic analysis may also be performed, searching for actionable abnormalities for the given IHC test and/or molecular diagnoses, such as subtypes of breast cancer (human epidermal growth factor receptor 2/neu \[HER2/neu\]), lung cancer (epidermal growth factor receptor \[EGFR\] mutation, ALK and ROS1 rearrangements), colorectal cancer (KRAS mutation), melanoma (BRAF mutation), gastroesophageal junction cancer (HER2/neu), etc. Site-specific therapy with a standard clinical guideline regimen is planned for each patient diagnosed with a single tissue of origin, and empiric chemotherapy is reserved for the small minority of patients with an uncertain tissue of origin.

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References:

REFERENCES


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