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Tumour Review

Cancer of Unknown Primary origin in the genomic era: Elucidating the dark box of cancer

Panagiota Economopoulou [a], Giannis Mountzios [b], Nicholas Pavlidis [c], George Pentheroudakis [c,*]

[a] Medical Oncology Unit, 2nd Department of Internal Medicine, Propaideutic, Attikon University Hospital, Haidari, Greece
[b] Medical Oncology Dpt, University of Athens School of Medicine, Athens, Greece
[c] Medical School, University of Ioannina, Greece

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ABSTRACT

Cancer of Unknown Primary (CUP) comprises a heterogeneous disease group with diagnosis of metastatic malignancy in the absence of an identifiable primary site after diagnostic work up. CUP may either resemble a specific primary tumor site sharing common clinicopathological characteristics and prognosis, or present as a distinct disease entity with undifferentiated pathological features, usually bearing dismal prognosis. Diagnosis and management have traditionally been based on clinicopathological characteristics and therapeutic strategies have been mainly empirical. In the last decade, the advent of massive gene sequencing and the advances in genomic technologies have shed light on the genomic landscape of CUP. Several gene panel tests are currently commercially available and are used in an effort to correlate the genomic characteristics of a specific CUP tumor to those of a known primary tumor, guiding thus therapeutic management. Nevertheless, these efforts are hampered by the rarity of CUP and the inability to validate the results of such tests due to the paucity of randomized clinical trials. In the current work, we provide an overview of CUP with emphasis on the impact of the genome sequencing technologies on diagnosis and management of these tumors. We also discuss potential implications of genomics for the future treatment of CUP and address the challenges of the implementation of these therapeutic strategies in routine clinical practice.

Introduction

Cancer of Unknown Primary (CUP) comprises a heterogeneous group of patients with cytological or pathologic diagnosis of metastatic malignancy in the absence of an identifiable primary site after a standardized diagnostic work up [1]. There is poor consensus on the extent of the diagnostic evaluation necessary. CUP accounts for approximately 3% of all malignancies, although there is a high variability among the series due to difficulty in defining CUP [2].

Historically, CUP has been associated with a poor prognosis [3] and patients are traditionally offered non-selective, empirical treatment [4–5]. However, in the last two decades, the ability to identify the occult primary site or tissue of origin has greatly improved. The diagnosis of CUP was initially made when advanced imaging techniques suggested the absence of a primary tumor. This was followed by standard pathological approaches that combined morphology and immunohistochemical (IHC) studies in order to subclassify CUP into specific subgroups [6]. Recently, molecular profiling methods, including DNA microarrays, quantitative reverse transcriptase PCR (qRT-PCR) and microRNAs have been used to evaluate the tissue of origin (ToO) in metastatic samples [7]. Identification of ToO might help customize therapy to the putative primary and therefore improve clinical outcome.

Although initially thought to represent a disease entity with a distinct biological signature, there is now increasing evidence that CUP represents a group of heterogeneous, unrelated site-specific tumors which happen to share the property of having a primary site that escapes detection [8]. As our view of CUP has evolved through the development of new techniques, our understanding of biology has become more personalized. The future of patients with CUP is based on understanding the primary site of origin and, most importantly, the molecular complexities driving the neoplastic process in each individual patient. Furthermore, as genomic characterization of CUP is refined, the assigned "unknown" term is being challenged (see Fig. 1).

In this review, we summarize diagnostic challenges in CUP, with emphasis on molecular profiling assays and their impact on management of this unique disease entity.

* Corresponding author.

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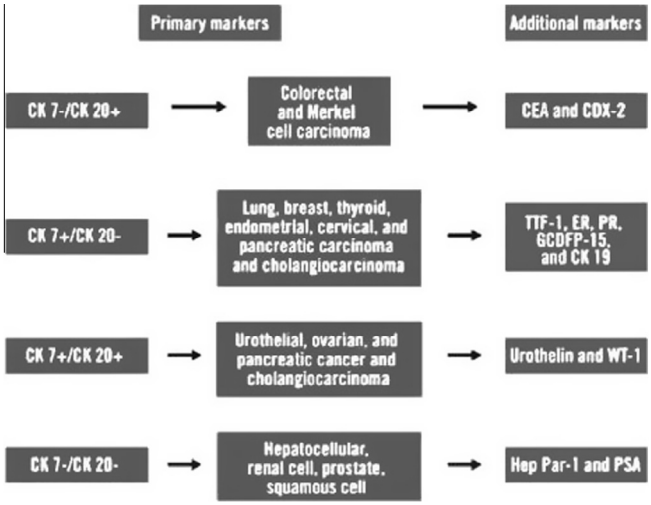

Fig. 1. Immunohistochemical algorithm for CUP. Reproduced with permission from ESMO Clinical Practice Guidelines. Ann Oncol 2011;22(Suppl. 6):vi64–8.

Clinical evaluation-diagnostic and prognostic challenges

CUP presents as a metastatic tumor and even after extensive clinical and pathologic investigation, the primary site is suggested in only a minority of cases. However, in 75% of cases an occult primary is found post-mortem [9]; therefore, in the majority of CUP cases current methods often fail to detect the primary site (see Fig. 2).

The evaluation of presumed CUP should be focused and stepwise. Although diagnostic algorithm strategies depend on clinical presentation, overall diagnostic approach should include initial clinical evaluation and biopsy, additional work-up directed by clinicopathological characteristics to identify specific subgroups, immunochemistry and gene profiling to predict the ToO and guide site-specific treatment. The minimal standard work-up includes a complete history and thorough physical examination, basic blood and biochemical tests, urinalysis, fecal occult blood testing and focused imaging [6]. Even in the setting of molecular assays, imaging can play an integral role in the multidisciplinary diagnostic evaluation of patients with CUP. In the absence of contraindications, a baseline i.v. contrast computed tomography of the chest, abdomen and pelvis is the standard of care in all CUP patients [4]. Women should undergo a mammography and vaginal ultrasound and men should have a serum prostate-specific antigen determination. If mammography and ultrasound of the breasts are negative in a woman with adenocarcinoma and isolated axillary lymphadenopathy, magnetic resonance imaging (MRI) of the breasts is useful in detecting an occult breast tumor. In the absence of a breast mass in MRI, it is unlikely that a tumor will be found at mastectomy [10]. Specific organ endoscopy should be restricted to patients with symptoms or suggestive pathology or imaging (see Table 1).

The role of positron emission tomography (PET)–CT in management of CUP is unclear. Several studies have found that PET/CT identifies more primary sites (24–44%) compared to CT or MRI (20–27%) [11–13]. In one of those studies, patients' prognosis could be assessed based on the extent of disease without the need for identification of the primary tumor [13]. However, due to lack of large randomized studies assessing the utility and cost-effectiveness of PET scan, its use is not currently recommended for routine screening [4]. PET/CT scan is warranted in selected cases, such as patients with squamous lymphadenopathy of the head and neck (cervical carcinoma of unknown primary site) [14–15]. In these patients, it is more sensitive in detecting the primary tumor than CT scan or MRI [16]. Furthermore, it may help guide the biopsy and facilitate irradiation planning and surveillance. PET/CT scan is also a valuable imaging modality in patients with a single site of metastatic disease, to determine the extent of disease if locoregional therapy with a curative intent is planned [17].

Although serum tumor markers in CUP are generally not considered to be diagnostic, a panel of tumor markers is used in the initial work-up, because they are easily available and can direct differential diagnosis in combination with other clinicopathologic parameters. In certain cases, they are particularly useful in

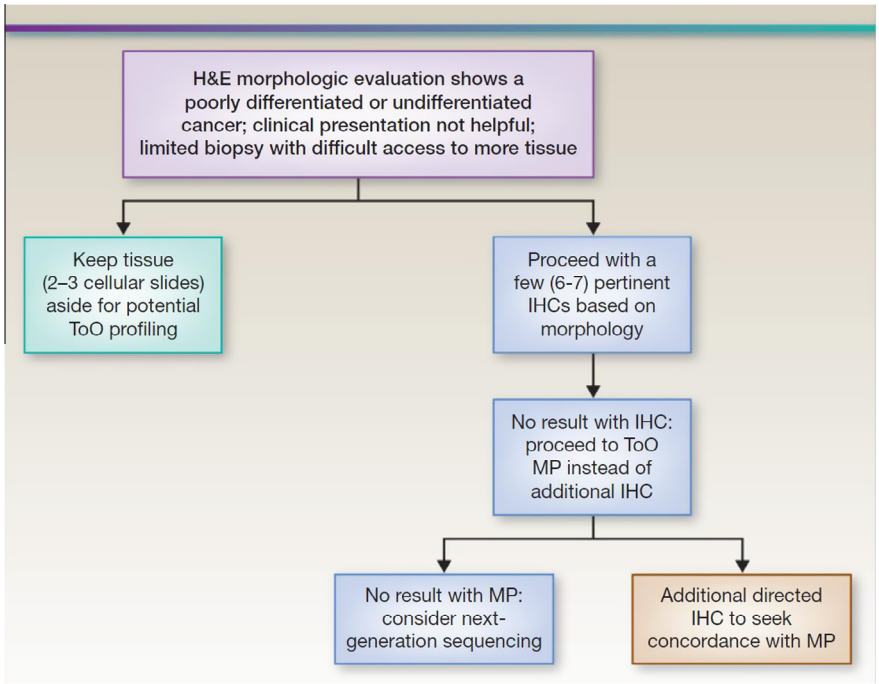

Fig. 2. Suggested algorithm for the use of Tissue-of-origin molecular platforms. Reproduced with permission from Clin Cancer Res 2013;19:4027–33.