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A Challenging Task: Identifying Patients with Cancer of Unknown Primary (CUP) According to the Molecular Tumor Board Perspective

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Abstract

Background

CUPID is an ongoing prospective phase II trial (NCT06490172) comparing molecularly guided therapy versus standard chemotherapy in patients newly diagnosed with metastatic cancer of unknown primary (CUP).

Materials and Methods

Patients with an unfavorable CUP diagnosis, as defined by the European Society of Medical Oncology (ESMO) guidelines, underwent tumor molecular profiling and were discussed in a molecular tumor board (MTB). Patients with actionable alterations were assigned to molecularly guided reference histopathology and clinical second opinion up to central eligibility review (MTB). Patients without actionable alterations were randomized to standard of care (SOC) or to a primary tissue-sparing arm.

Results

As of 15 April 2026, 628 patients had screened screening and 166 (26.1%) were screen failed. Screen fails were due to technical reasons (n = 109), failure to meet inclusion and exclusion criteria (n = 54), and other reasons (n = 3). Of the 166 screen failures, 25 (15.1%) were due to CUP diagnosis not meeting ESMO-defined molecular profiling criteria, and 141 (84.9%) were due to other reasons identified by the MTB. These cases were classified as unfavorable CUP by the MTB, underscoring the importance of molecular profiling and MTB discussion for accurate CUP characterization in routine practice.

Conclusion

Patients with CUPID-like histopathologic challenges with unstructured screening and international clinical trial and the difficulties in diagnosing unfavorable CUP. Recombination of molecular profiling and MTB review with clinical second opinion in CUPID illustrates a feasible, tissue-sparing strategy to address these challenges and improve diagnostic pathology and clinical CUP algorithms.

Implications for Practice

A high unmet need exists for improved management of cancer of unknown primary (CUP), particularly for patients with unfavorable CUP. The CUPID trial illustrates a feasible, tissue-sparing approach to molecular profiling and molecular tumor board review that addresses this challenge for in the ongoing CUPID2 trial, which compares treatments guided by molecular profiling versus standard chemotherapy in patients with unfavorable CUP. Integration of molecular profiling and molecular tumor board review into clinical second opinion workflows may improve diagnostic accuracy and the interpretation of the ESMO CUP criteria and support more consistent, tissue-sparing, and molecularly informed management of CUP.

Introduction

Cancer of unknown primary (CUP) is defined as a histologically confirmed metastatic cancer for which a standard diagnostic workup fails to identify a definitive site of origin.[1, 2] The incidence of CUP has declined over the past decades, from approximately 3% of all cancer diagnoses in Europe to a single-digit percentage in recent years, reflecting improvements in diagnostic technologies, the implementation of pathology-based CUP algorithms, and the increasing use of molecular profiling.[3] Despite this decline, CUP remains a challenging diagnostic entity with a heterogeneous clinical presentation and poor outcomes.[4, 5]

The CUP guidelines of the European Society of Medical Oncology (ESMO) place a strong emphasis on the diagnostic workup to identify tissue of origin and to distinguish favorable from unfavorable CUP.[6] Favorable CUP includes cancer of unknown primary with a single metastatic site (PET) staining, an in-depth medical history, and thorough physical examination and basic blood work. Unfavorable CUP requires more extensive diagnostic evaluation, including immunohistochemistry (IHC) and molecular profiling. Although the ESMO guidelines provide a structured framework for the clinical and IHC pictures of metastases, detailed tests are required, namely tissue-of-origin molecular profiling, to refine the diagnosis and guide treatment. Molecular profiling can identify actionable alterations, provide prognostic or predictive information, and support cancer prognosis and diagnosis in rare cases with metastases suggestive of primary tumors of known origin.[7] However, the ESMO guidelines do not specify how to integrate molecular profiling into the diagnostic workup, nor do they define the clinical significance of molecular profiling results. Thus, the ESMO guidelines do not address the clinical significance of primary tumor, a CUP diagnosis is unfavorable.

Although the ESMO guidelines, the CUPID guidelines, and the CUPISCO study (NCT02779751) "favorable" CUP subsets, which include approximately 15%-20% of patients,[8], there are not universally accepted. Many CUP patients with unfavorable CUP diagnoses have metastases and are highly suggestive of a CUP of unknown primary, but they do not meet the ESMO-defined established treatment criteria for the putative site of origin,[9, 10] or metastases are amenable to local therapy, such as surgery or radiotherapy, but the primary site is not known. These patients with unfavorable CUP have a worse clinical outcome than those with favorable CUP and are given the recommended empiric chemotherapy (platinum-based combinations) by ESMO guidelines.[11] Whereas the primary site of origin is known in favorable CUP, the ESMO guidelines do not specify how to treat patients with unfavorable CUP or the clinical significance of a specific site of origin. The ESMO guidelines do not specify how to treat patients with unfavorable CUP, but they do recommend empiric chemotherapy (6,7-9). Although site-specific various treatments have been discussed as a potential approach for unfavorable CUP, there is no consensus on the optimal approach.[12] Molecular profiling studies in unfavorable CUP have shown that the tissue-of-origin molecular profiling primary predictions, followed by systemic treatment tailored to the putative primary, was not superior to standard empiric chemotherapy.[13, 14]

Figure 1. The CUPID2 trial design. CUPID2 compares molecularly guided therapy versus standard chemotherapy in patients with unfavorable cancer of unknown primary (CUP). Patients with unfavorable CUP undergo molecular profiling and molecular tumor board review, followed by randomization to molecularly guided therapy or empiric chemotherapy. Molecular profiling results are reviewed by a clinical second opinion panel, which includes a reference histopathologist and a clinical second opinion panel. Patients with actionable alterations are assigned to molecularly guided therapy, while those without actionable alterations are randomized to standard of care (SOC) or to a primary tissue-sparing arm. Abbreviations: CUP, cancer of unknown primary; ESCO-MTB, European Cooperative Oncology Group performance status; IHC, immunohistochemistry; MTB, molecular tumor board; NGS, next-generation sequencing; PD-L1, programmed death-ligand 1; SOC, standard of care.

The CUPISCO trial (Fig. 1) compared empiric targeted platinum with unfavorable CUP, an molecularly guided therapy versus empiric chemotherapy in patients with unfavorable CUP. Patients with CUP with favorable prognosis subtypes, squamous cell carcinoma, and adenocarcinoma of the peritoneal cavity, lymph nodes, or retroperitoneum were excluded. The primary endpoint was the difference between the two treatment arms in progression-free survival (PFS). Although the molecularly guided therapy arm had numerically higher PFS, the difference was not statistically significant (HR = 0.85, 95% CI: 0.69-1.05, p = 0.13

objective [9], we have therefore developed specific diagnostic algorithms and recommendations using radiology and pathological criteria for lung (Fig. 2) and cholangiocellular carcinoma (Fig. 3), as well as cancer of mammary origin (breast; supplemental online Fig. 6), salivary gland cancer (supplemental online Fig. 7), renal cell carcinoma (supplemental online Fig. 8), and serous carcinoma (supplemental online Fig. 9) in a CUP scenario. These algorithms consist of suggested modifications to the existing ESMO guidelines. On the one hand, they could improve the ability to efficiently select patients with "true" CUP in future CUP trials. On the other hand, they should characterize patients with "false" CUP, who might benefit from treatment according to the identified respective tumor entity, which was hopefully administered in patients screen failed for CUPISCO. The algorithms will obviously need to be tested for their feasibility and practicability in future CUP trials, although by the very nature of CUP, the accuracy of diagnostic decisions will never be properly cross-validated.

(III) Cases Not Compatible with CUP Because of Noncarcinoma Histology in Central Review

Soft tissue tumors that show positivity for cytokeratins can represent a pitfall and easily be misinterpreted as carcinoma, especially as these types of neoplasms are extraordinarily rare. Helpful in the diagnostic workup is the clinical presentation with age, location of the lesions, and a basic pathology workup using pan-cytokeratin, S100, smooth muscle actin, desmin, and CD34. A lack of cytokeratin staining should question a diagnosis of carcinoma and lead to the consideration of a noncarcinoma entity such as melanoma, lymphoma, or mesenchymal neoplasms.

Conclusion

Revision of CUP diagnoses by central eligibility review helped to identify the primary cancer in many cases. This could be achieved by the scrutiny of second assessment itself and by additional clinical tests and central IHC workup, which proved particularly helpful to identify rare entities overlooked by primary pathologists. Having implemented and enforced the central eligibility review by both reference pathology and a clinical eligibility team from the very start of the CUPSICO trial, we truly believe in the integrity of our study cohort as a "true" CUP cohort. Having initially underestimated the uncertainties of CUP diagnosis, the study team pushed early on to formalize the decision process and to educate investigators.

Beyond the CUPISCO trial itself, its eligibility process has demonstrated that even when adhering to a centralized process and following established guidelines [3], the diagnosis of CUP, being a diagnosis of exclusion, remains challenging [9, 10, 30, 31]. CUP ESMO guidelines [3] were designed to guide real-world treatment decisions and not to define unfavorable CUP as a target population for clinical trials. The CUPISCO trial shows a need for additional detailed consensus diagnostic guidelines for CUP trials to allow harmonization of study populations and spare trial eligibility teams the burden of turning down patients after prolonged screening processes. The current trial also shows that the correct diagnosis of CUP is a multidisciplinary effort between oncologists, pathologists, and radiologists.

When ordering diagnostic tests in patients with suspected CUP, oncologists and pathologists should balance ordering too few versus too many tests. Concerns of overdiagnosing are reinforced by two recent randomized CUP trials, which showed no benefit of gene expression profiling-based site-specific treatment versus standard platinum-based chemotherapy [11, 12]. The implementation of diagnostic algorithms could aid a more efficient histopathology workup, as the tissue is often limited, and assist in making timely diagnoses without over-burdening the patient.

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