ESMO Open Cancer Horizons

How I treat cancers of unknown primary

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Despite the progress in cancer diagnostics and therapeutics where the use of gene expression profiling has elucidated underlying molecular mechanisms, cancer of unknown primary (CUP) still remains an unexplored area. Being a heterogeneous, often aggressive disease, it poses a significant clinical challenge. The overall worldwide incidence is 3%–5% with the majority of patients presenting with extensive metastatic deposits, ranking relatively high among causes of death attributed to neoplasms. Although thorough clinical examination, laboratory tests, radiology examinations and detailed pathology analysis are performed, the primary site may not be identified.[1]

Patients with CUP have clinical and radiological findings compatible with metastatic disease in the presence of a cytological or pathological diagnosis of malignancy. Efforts should be made for obtaining a rather generous amount of tumour specimen in order to proceed with the pathology examination. The pathology report should contain morphology review and immunohistochemistry studies in order to confirm malignant diagnosis and exclude melanomas, sarcomas, lymphomas and germ cell tumours. After establishing epithelial histology, staining for CK7 and CK20 may limit the differential diagnosis to few possible sites of tumour origin. Targeted, judicious application of additional immunohistochemical markers (CEA, PSA, CDX-2, TTF-1, ER, PR, AFP, β-HG, PLAP, HMB45) may further enhance the diagnostic output and should be applied according to the patient' s clinical, radiology and pathology data. Most commonly, CUPs are poorly or moderately differentiated carcinomas or adenocarcinomas, less often squamous cell carcinomas, carcinomas with neuroendocrine differentiation, undifferentiated neoplasms. It is vital to not miss a diagnosis of curable malignancies such as germ cell tumours or lymphomas especially when poorly differentiated/undifferentiated histology is present.[2 3]

Apart from meticulous pathology review, all patients should undergo thorough physical examination, basic blood and biochemistry analyses and chest/abdominopelvic CT scans. In cases of female patients, bilateral digital mammography should not be omitted in order to exclude a possible occult breast cancer. Serum tumour markers are often elevated in a non-specific manner in patients with CUP, consequently their measurement offers no diagnostic or prognostic assistance. Exceptions are determination of serum PSA in male patients with bone metastasis so as to exclude occult metastatic prostate cancer, germ cell tumour markers (AFP, bHCG) in patients with midline disease, serum AFP in liver-dominant disease so as to exclude hepatocellular cancer. Endoscopies, additional biomarkers and radiological examinations should be sign, symptom or laboratory orientated.[4] The role of PET/CT remains to be fully evaluated in large-scale prospective studies. Currently, as it is more effective in detecting additional metastases rather than the hidden primary, it should be used when radical therapy is contemplated for localised CUP: cervical head/neck adenopathies, axillary adenopathy and single metastatic lesions.[5 6] Regarding serum tumour markers, it is of note that the evaluation of the most commonly used lacks any prognostic or diagnostic assistance since a non-specific overexpression is present in many CUP cases.

On the completion of investigations, patients can be classified into specific clinicopathological prognostic subgroups. Good performance status and non-elevated serum LDH are favourable prognostic (median overall survival of 12 months) whereas poor performance status and elevated LDH are poor prognosticators.[7] One of the most significant clinical advances in CUP was the realisation that patients with CUP can be broadly classified in favourable risk CUP subsets (20% of patients) versus poor risk CUP subsets (80% of patients). Classification in these specific clinicopathological subsets is based on pathology, imaging and clinical criteria. In essence, patients with favourable risk CUP subsets seem to harbour tumours equivalent, in terms of biology and outcome, to those of metastatic counterparts of known primaries and fare better in terms of medium-term

prognosis with primary-specific therapy.[4] Those favourable CUP subsets include:

- Poorly differentiated carcinoma with midline nodal distribution (extragonadal germ cell syndrome).
- Women with papillary adenocarcinoma of peritoneal cavity.
- Women with adenocarcinoma involving only axillary lymph nodes.
- Squamous cell carcinoma involving cervical lymph nodes.
- Neuroendocrine carcinomas.
- Men with blastic bone adenocarcinomatous metastases and elevated PSA.
- Adenocarcinoma with a colon-profile (CK 20+, CK 7-, CDX 2+)
- Isolated inguinal adenopathy (squamous carcinoma).
- Patients with a single, small, potentially resectable tumour.

On the other hand, patients with poor-risk CUP have a dismal prognosis. These are essentially patients with high-volume visceral metastases of unknown primary (liver, lung, bone, brain, peritoneum) and may be the patients truly harbouring a peculiar clinical entity with distinct biology.[4] In these cases, the use of platinum-based doublet regimens aims at prolongation of survival with palliation of symptoms and better quality of life, if possible. Platinums are combined with new-generation compounds such as taxanes or gemcitabine based on studies where the use of doublet chemotherapy is more effective than platinum monotherapy. The use of triplets can result in excessive toxicity, and it not advised.[8 9] In addition, over the last few years, immunotherapy has gained approval for a series of cancer types with promising results. Although PD-1 antibody pembrolizumab has been Food and Drug Administration-approved for all cancers that are microsatellite instability (MSI) deficient, it still remains unclear whether immunotherapy has potential in CUP cases.[10] Specific predictive biomarkers at this point are missing while they seem to be inconsistent across several tumour types. We recently advocated a CUP-specific prognostic classifier that takes into account the CUP clinicopathological subgroup, presence of leucocytosis at baseline and performance status in order to classify patients with CUP to good risk (median overall survival (OS) 36 months), intermediate risk (median OS 12 months) and poor risk (median OS 6 months), (figure 1).[11]

The poor outcome that has been observed for poor-risk CUP patients has inevitably led to the application of molecular profiler assays in order to (a) biologically identify the tumour's origin (pick the tissue of origin strategy) or (b) to apply targeted therapy according to identified driver mutations (pick the target strategy). The evidence for effectiveness of both strategies in improving patient outcome remains inconclusive to date.[12 13] It is suggested that after inconclusive extensive pathology and clinical investigation, a molecular profiler assay can be used for biological assignment of a primary tissue of origin,

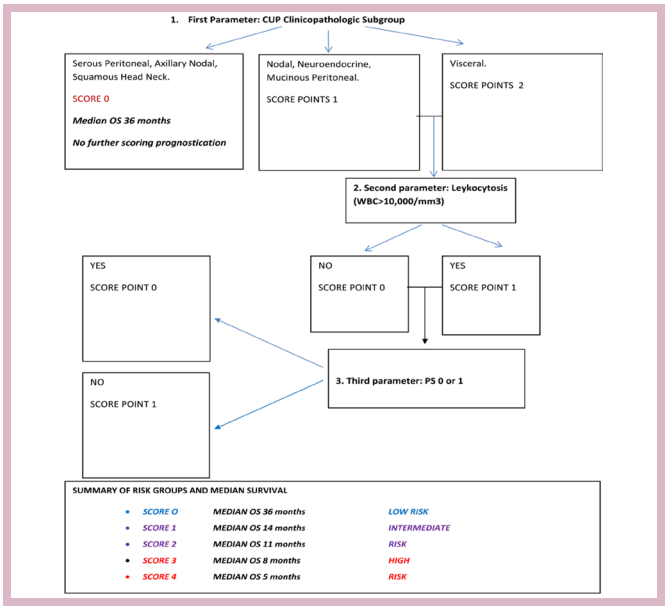

Figure 1 Prognosticator scheme for all patients with CUP. CUP, cancer of unknown primary; WBC, white cell count.

followed by patient management with primary-tailored therapy. This may be especially helpful in cases where a site of origin clinicopathologically analogous to responsive tumours is revealed. In particular, a large prospective non-randomised phase II clinical trial of 252 patients suggested improved survival of patients with CUP when site-specific therapy is applied determined by a gene expression profile assay.[14] However, until the randomised phase III GEFCAPI-04 trial results become available, no high-level evidence is available in order to establish improved CUP patient outcome from the pick the tissue of origin strategy.

On the other hand, providing tumour-agnostic therapy according to molecular alterations identified in patient's tumour has also been investigated (pick the target strategy). The randomised controlled phase II clinical trial SHIVA identified targetable alterations in 195 patients after screening 741 patients with any tumour type. Patients were then assigned to receive matched targeted therapy or investigators choice chemotherapy, the study failing to show improvement of progression free survival, the primary trial endpoint.[15] Ongoing trials (NCI-MATCH, MOSCATO) using NGS tools in order to identify targetable molecular aberrations in solid tumours may shed light to the question of actionability and clinical effectiveness of therapeutic modulation of driver mutations in a tumour-agnostic context. The ultimate question to be addressed in CUP is whether it is a metastatic disease from a primary that simply cannot be identified or rather a distinct prometastatic molecular disease with a common tissue-transcending signature. Needless to say, most research regarding the molecular features of CUP is based on single biopsies, thus not reflecting tumour heterogeneity and evolution. Liquid biopsies are very

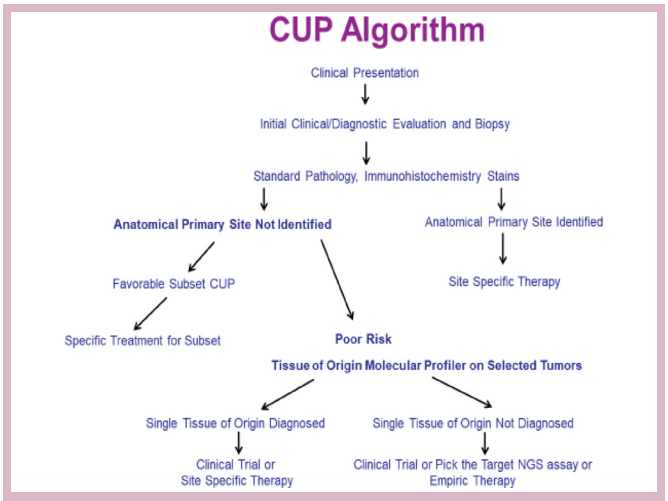

Figure 2 Proposed algorithm for cancer of unknown primary (CUP) diagnosis and management.

attractive tools in cancer diagnosis and therapeutics and need to be further evaluated in CUP large scale studies.

To conclude, CUP is a distinct clinical entity, patients diagnosed have a poor outcome apart from a minority of them who fall into favourable risk subsets. For the wide majority of the patients, extensive visceral disease, chemoresistance and short overall survival constitute an unmet need in everyday clinical practice. Molecular classifier assays may be used in poor-risk CUP in order to further investigate the possible primary origin or identify a targetable molecular aberration. Such assays, when implemented, should be coupled to clinical trial or prospective registry settings, in order to generate evidence in the near future for or against their clinical utility. A proposed algorithm for treating CUP is provided (figure 2). Elucidating the underlying molecular driving mechanisms of CUP and establishing specific prognostic and predictive biomarkers will ultimately improve patient outcomes through improved therapy stratification.

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