**Probing the unknown in cancer of unknown primary: which way is the right way?**

Cancer of unknown primary (CUP) is defined as biopsy-proven presence of metastases in the absence of an identifiable primary tumour despite a standardised diagnostic work-up. This heterogeneous clinical entity is not rare, as it makes up 3%–5% of newly diagnosed malignant tumours annually and ranks as the sixth cause of cancer death in developed societies [1]. The diagnosis of CUP is considered as a challenging clinical situation because it creates considerable anxiety to the patient and forbids administration of primary-specific modern anticancer therapies that include targeted agents. The most important breakthrough in the rational management of CUP patients was the identification of distinct clinicopathologic subgroups [2]. Patients with isolated axillary nodal adenocarcinoma, squamous carcinomatous involvement of cervical or inguinal lymph nodes, males with midline nodal carcinoma, women with serous papillary peritoneal carcinomatosis and patients with high-grade carcinomas bearing neuroendocrine features belong to the 'favourable risk' CUP cohort. These patients should receive tailored treatment similar to that applied for various metastatic tumours of known primary (breast cancer, head/neck cancer or anal cancer, germ-cell tumour, ovarian cancer, etc) and often enjoy long-term disease control. Disappointingly, ∼80% of CUP patients harbour high-volume metastatic deposits in numerous, often peculiar organ sites in viscera, bones and soft tissues. These belong to the 'poor-risk CUP' cohort, which is considered by many investigators as the 'genuine' CUP entity. Poor-risk CUP is characterised by regression or dormancy of the primary tumour, early systemic spread, aggressive biology, resistance to therapy and dismal patient outcome, with most succumbing to the disease within a year from diagnosis [3]. Prognosticators that would either predict length of survival or benefit from cytotoxic and targeted therapeutic agents would be highly desirable, as they would allow tailoring therapy to the patients’ needs. Potentially, more toxic therapy would be considered for those likely to benefit from it with substantial survival prospects, while patients with poor life expectancy and low likelihood for response would be managed with low-toxicity palliative therapy or best supportive care.

In this issue of the journal, Kodaira et al. [4] report on a retrospective cohort of 58 CUP patients managed with combination chemotherapy. Reported response rate is 34% and median overall survival unexpectedly high at 16.7 months. Among studied parameters, poor performance status (PS), low serum albumin and presence of pleural/bone/liver metastases were found prognostic for survival on univariate analysis, while on multivariate regression, only poor PS and bony deposits retained prognostic significance for dismal outcome. How do we interpret these data in the context of accumulated evidence from other CUP series and how original are they?

The strengths of the retrospective analysis stem from the fact that all patients had been meticulously worked up for the missing primary, adequately studied for tissue of origin by means of immunohistochemistry and appropriately staged with imaging/endoscopic tests. They were also uniformly treated with paclitaxel/carboplatin chemotherapy, a regimen of broad-range compounds considered as standard for the management of poor-risk CUP patients. Poor PS and bony metastases not related to occult prostate cancer predicted for a disappointing 37% probability of survival at 1 year. Similar conclusions have already been published by other investigators who reported poor PS and bony deposits among others as ominous prognostic factors on univariate analysis, though only PS persisted as prognostically significant in multivariate analysis [5, 6]. Consequently, the study’s conclusions may not be original but provide additional support and validation for existing prognostic models.

On the other hand, the study has weaknesses that probably account for the rather optimistic quoted median survival. Several biases indicating selection of patients exist. First, only patients fit enough to tolerate a rather dose-intensive regimen of paclitaxel at 200 mg/m² and carboplatin at an area under the curve of 6 mg/ml × min were a priori included in the analysis. Indeed, 84.5% of patients had an Eastern Cooperative Oncology Group PS of zero to one. Secondly, patients seemed to have poor-risk CUP with rather ‘favourable’ features: half had well-differentiated tumours and only 11 harboured liver deposits, a metastatic niche with ominous ramifications for fitness, biochemical reserves and survival. Most importantly, the ‘poor-risk’ population was not so, as it was infected by patients belonging to favourable CUP subgroups. In fact, five patients had squamous cell nodal CUP and 11 serous papillary peritoneal carcinomatosis, cases known to respond to taxane/platinum combinations and faring well in the long term [2, 7]. Indeed, the 34% remission rate in this series was probably driven by the response rates of squamous CUP and peritoneal CUP patients (50% and 63.7%, respectively). This probably is the case for the median survival of 16.7 months, which should also be viewed with caution as the median follow-up time of the study patients was hardly 12 months.

Another weak point of the paper is the small sample size. This logically means that the multivariate analysis examines too many parameters on the basis of too few events and is thus not robust enough. Finally, the author statement that PS and bony spread can be used for selection of therapy is misguided. As they did not analyse for correlations with treatment response or toxicity, there
is no evidence to link prognostic information from the authors’ model to predictive information for benefit from therapy. Consequently, it is not known if the two parameters predict for patient prognosis irrespective of therapy administered (prognostic factor) or whether they predict for benefit from therapy (predictive factor). Previously published data indicate that PS and bony metastases are prognostic, rather than predictive factors [8, 9].

Since this series does not provide us with breakthrough data, the major questions remain. What are the unmet needs of patients with poor-risk CUP and which should be the modern approach for tailoring treatment? To answer the first question, reliable prognostication is needed but ultimately its impact will depend on availability of effective therapy, targeted or cytotoxic, that will improve patient survival. Widely employed chemotherapeutic regimens for fit patients with poor-risk CUP, such as platinum/taxane or platinum/gemcitabine combinations occasionally provide symptom palliation but fail to prolong survival beyond the median 12-month survival benchmark. Combinations of chemotherapy with targeted agents, such as bevacizumab or epidermal growth factor receptor tyrosine kinase inhibitors, were applied blindly in an unselected patient population and failed to substantially alter the dismal outcome of these patients [10]. Accordingly, in the absence of effective therapies which should be the modern approach for improving our armamentarium and managing CUP patients?

To answer the latter question, we should set our queries and priorities straight. First, we need to identify the pool of patients with genuine CUP: tumours that probably preserve a genetic signature from the cryptic tissue of origin but also possess a distinct gene signature, responsible for dormancy of the primary and systemic spread [3]. This second signature could emerge either in the primary site or in one of the metastatic deposits. It is likely that such a genuine CUP cohort is a subgroup of patients currently diagnosed with poor-risk CUP.

Secondly, we need to decide on how to use the powerful microarray platforms that screen the expression of multiple genes in each tumour sample [11, 12]. Should we compare the multigene expression of a CUP case with that of primary tumours in order to biologically classify CUP? In such a strategy, this would be followed by administration of therapy specific for the ‘biological’ primary tissue, i.e. 5-fluorouracil-based chemotherapy and bevacizumab for a CUP classified as ‘colon cancer’. Alternatively, should we prefer to study the multigene expression of CUP tumours in order to identify a ‘CUP-specific prometastatic’ signature? The latter would necessitate genome-wide profiling and implementation of the microarray technology differently from currently licenced applications. This would result in administration of therapy targeting the ‘CUP-specific’ molecular aberrations. Of course, one cannot exclude the coexistence of both ‘primary-specific’ and ‘CUP-specific’ signatures and that modulation of both is superior in improving patient survival.

Whatever the strategy opted for by clinical investigators, one fact stands out. Only prospective trials that will randomly assign patients to empircic chemotherapy versus microarray-based assignment of primary tissue and primary-specific therapy will definitely show if microarray technology, apart from assigning a primary, really meets its goal: to improve patient survival. Preliminary epidemiological data indicate that CUP, even when biologically classified to a primary tumour group, behaves differently from the parent tumour in terms of response to therapy and disease course [3, 13]. If this is true, therapy tailored to the primary tissue of origin may fail to result in disease control similar to that seen for patients with equivalent overt tumours. In parallel, a translational research programme should be focused to highlighting the pathophysiology of CUP and identifying the prometastatic CUP-specific molecular phenotype. If this exists, it should also be targeted. Disappointingly, up to date, the powerful microarray platforms have not been used for the latter assignment. Until we know which way is the right way, it is only logical to explore both ways.

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