Molecular guided therapies: a practice-changing step forward in cancer of unknown primary management

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Cancer of unknown primary (CUP) accounts for 2–3% of all metastatic cancers and encompasses a diverse array of metastatic cancers without an identifiable primary after adequate diagnostic evaluations.[1] Traditionally, patients are classified according to their clinicopathological characteristics. A small subset (15–20%) of patients have a constellation of clinical and histological features suggestive of a specific primary site guiding the treatment options. Conversely, most patients (80–85%) present with a metastatic disease that does not fit within this small subset, prompting treatment with broad-spectrum platinum-based empirical chemotherapy.[2] Unfortunately, patients diagnosed with this larger unfavourable subset have poor outcomes, with a median overall survival of a few months and a meagre 1-year overall survival rate of 19%.[2] Such dire outcomes have spurred research on alternative treatment approaches by shifting from the one-size-fits-all treatment options to tailored therapies informed by the suggested tissue of origin or biomarker expression.[3] Following the results of the phase 3 GEFCAPI 04 trial in which site-specific therapies did not yield the expected outcomes, agnostic approaches using therapies guided by molecular features, rather than the tissue of origin, represented the next avenue in CUP research.[4,5]

In *The Lancet*, Alwin Krämer and colleagues report the results of the CUPISCO trial,[6] a prospective randomised, phase 2 trial that evaluated biomarker-driven therapies in patients with unfavourable CUP done at 159 sites in 34 countries outside the USA. There were 326 patients in the molecularly guided therapy (MGT) group and 110 patients in the standard platinum-based chemotherapy group. The median age of participants was 62·0 years (IQR 53·0–69·5), 222 (51%) were men and 214 (49%) women; 323 (74%) participants were White, 43 (10%) Asian, seven (2%) Native American, five (1%) Black, and 57 (13%) of unknown ethnicity. This study marks the first instance in the past decade in which a randomised trial using a tailored approach has shown an improvement in progression-free survival, the primary outcome, for this subset of patients (6·1 months [95% CI 4·7–6·5] in the MGT group *vs* 4·4 months [4·1–5·6] in the chemotherapy group; hazard ratio 0·72, 95% CI 0·56–0·92) compared with standard platinum-based chemotherapy. The analysis of overall survival, a secondary endpoint, was immature but showed a trend for improvement with MGT (14·7 *vs* 11·0 months; HR 0·82, 0·62–1·09). The rates of related adverse events were lower with MGT versus chemotherapy (672·9 *vs* 1286·4 per 100 patient-years), except for serious adverse events (23·2 *vs* 27·2 per 100 patient-years), and there was no evidence of a significant difference in the time to deterioration of quality of life.

It is believed that the CUPISCO trial is the first randomised trial to highlight the relevance of molecular testing in CUP and to show a progression-free survival benefit with MGT. The trial design categorised patients into two groups on the basis of their response to induction chemotherapy before random assignment into MGT versus standard chemotherapy. Only the patients who achieved complete response, partial response, and stable disease, accounting for 76% of the population, were included in this analysis which limits its straightforward extrapolation to clinical practice in which the implementation of MGT is limited by a worsening of the patients' performance status.[7] Notably, the benefit of the MGT was affected by the response to the induction chemotherapy, with patients achieving complete response having the largest benefit (23·2 months *vs* 6·5 months), whereas the

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differences in the other patients were less pronounced. This observation is limited by the small sample size but warrants further evaluation. More importantly, the forthcoming analysis of the group of patients with progressive disease, the hard-to-treat cancers, holds significant promise for the potential role of precision medicine in CUP. The CUPISCO trial had additional pragmatic implications in the management of CUP. It required central review for diagnostic confirmation to ensure the inclusion of a homogeneous population and encountered 39% ineligibility on screening. This finding, which has led to a revision of the European Society of Medical Oncology (ESMO) guidelines, advocates for comprehensive algorithm-based clinical assessments in routine clinical practice.[8] Lastly, the investigators opted for the use of liquid biopsy alongside tissue samples, which allows a more practical approach in clinical practice, as does the incorporation of novel therapies that are now widely available.

Over the past decade, targeted therapies have emerged as an intriguing approach to target driver mutations agnostically and immune checkpoint inhibitors have constituted a promising option of harnessing a potentially more effective anti-tumour immune response against the putative primary site.[8,9] The benefits of the two treatment strategies were not uniform across all patient subgroups. In the CUPISCO trial, patients with an actionable molecular profile treated with targeted therapies, accounting for 25% of the population, had a substantial benefit in progression-free survival (8·1 *vs* 4·7 months; HR 0·65, 0·42–0·99), compared with chemotherapy. This benefit was less pronounced in patients without actionable molecular profiles treated with atezolizumab immunotherapy plus chemotherapy compared with empirical chemotherapy (5·5 *vs* 4·4 months; HR 0·76, 0·54–1·06). These findings allude to, at least partly, the tissue of origin contributing to the agnostic classifications of cancers and response to therapy. For instance, atezolizumab for an occult lung adenocarcinoma would not have the same effect as for an occult cholangiocarcinoma. Furthermore, there are probably some tumours without a particular targetable alteration that would respond favourably to immunotherapy or site-specific therapy such as renal cell and gastro-oesophageal carcinomas, respectively.[10] In this regard, a randomised, phase 3 trial reported in 2023 showed that progression-free survival was significantly prolonged with site-specific therapies versus empirical chemotherapy (9·6 *vs* 6·6 months; HR 0·68, 0·49–0·93).[11]

The CUPISCO trial confirms the beneficial role of a biomarker-driven approach in selected patients with CUP following standard chemotherapy and marks a significant stride towards better outcomes. Therapies based on the molecular evaluation of tissue or blood biopsies represent a practice-changing step forward in the management of patients with CUP, although additional clinical research is necessary and agnostic approvals are warranted to move further forward.

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