Molecular diagnosis and site-specific therapy in cancer of unknown primary: an important milestone

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Cancer of unknown primary (CUP)—ie, metastatic cancer for which the anatomical primary site is not clinically detectable despite an adequate workup—has posed a difficult challenge for patients and physicians for decades.[1,2] Treatment for metastatic cancers has traditionally been based on the primary site. Patients with CUP presenting with a constellation of clinicopathological features suggestive of a primary tumour have favourable outcomes when treated accordingly.[1] Patients with unfavourable CUP, who account for about 80% of cases, without recognised presumptive primaries, have been treated with empirical chemotherapy for the last four decades with very poor outcomes.[3] Gene-expression profiling (GEP) done on biopsies can frequently diagnose presumptive primaries.[1,3] Site-specific therapy based on GEP has shown promising outcomes in prospective single-arm and retrospective studies, particularly for molecularly diagnosed responsive cancer types.[2,4-6] However, subsequent randomised trials of unfavourable CUP did not show superiority of GEP-directed site-specific therapy compared with standard empirical chemotherapy.[7,8] These trials were done before the advent of substantially improved therapies for many different metastatic cancers, particularly molecularly guided therapy (MGT) and immunotherapy. Furthermore, these studies had an over-representation of molecularly predicted primaries with an expected poor prognosis, for which site-specific therapy was similar to empirical chemotherapy for many patients.

In *The Lancet Oncology*, Xin Liu and colleagues[9] report a randomised trial in 182 patients with unfavourable CUP documenting a significant improvement in progression-free survival from GEP-guided site-specific therapy versus empirical chemotherapy for all 182 patients in the intention-to-treat population. After a median follow-up of 33·3 months (IQR 30·4–51·0) for the site-specific therapy group and 30·9 months (27·6–35·5) for the empirical chemotherapy group, site-specific therapy showed a significant and clinically meaningful improvement in progression-free survival (9·6 months [95% CI 8·4–11·9] *vs* 6·6 months [5·5–7·9]; hazard ratio [HR] 0·68 [95% CI 0·49–0·93]; p=0·017) and a longer, albeit not statistically significant, overall survival (28·2 months [95% CI 23·3–46·5] *vs* 19·0 months [17·1–26·4]; HR 0·74 [95% CI 0·52–1·06]; p=0·098) even though 23 (25%) patients in the control group received second-line immunotherapy or MGT. There was no difference in grade 3 or 4 toxicities. Patients in the two study groups were well matched, but the overall survival of the control group was longer than in many other trials; this could be due to patients in the control group having cancers that were sensitive to empirical chemotherapy (eg, cancers of the ovary, breast, and gastro-oesophagus, based on the predicted primary tissue types in the site-specific therapy group) and due to about half the patients having lymph node-only metastasis, which is associated with a better prognosis. There was a mix of several common GEP-predicted cancers, many expected to respond favourably to site-specific therapies, in contrast to the two older randomised studies that did not show superiority of GEP-directed site-specific therapy over standard empirical chemotherapy.[7,8] The site-specific therapies in this trial, with few exceptions, included chemotherapy, MGT, immunotherapy, and anti-angiogenic therapy, but MGT and immunotherapy are generally considered to be the most efficacious. Notably, only a minority of patients (eight of 31) with predicted cancer types that would be expected to respond favourably to immunotherapy actually received standard immunotherapy (three of ten with predicted lung cancer, excluding two others who received MGT; two of 14 with predicted gastro-oesophageal cancer; and three of seven with predicted head and neck cancer), since immunotherapy was not yet standard or available when the trial was done. In patients with other predicted carcinomas, including a total of eight with urothelial, renal, and cholangiocarcinoma, none received immunotherapy as it was not standard at the time, although it is now indicated. The results of this trial would likely be even more impactful had more of these patients received immunotherapy, which is included as standard therapy today.

This pivotal trial emphasises the importance of GEP in helping to improve the management of patients,

notably when coupled with adequate delivery of MGT or immunotherapy-based regimens according to tissue of origin. The use of site-specific therapy guided by GEP should be recommended and has relevance for patients with molecularly diagnosed cancers now requiring precision site-specific therapy rather than empirical chemotherapy. GEP-guided therapy should emerge as a new standard of care in view of Liu and colleague's study along with the recent report of the findings of the large randomised CUPSICO trial.[10]

The CUPISCO trial required comprehensive genomic profiling on tissue or blood before induction empirical chemotherapy for unfavourable CUP. A significant improvement in progression-free survival from MGT or immunotherapy was reported after disease control following three courses of empirical chemotherapy compared with continued chemotherapy alone. This study, along with Liu and colleagues' study,[9] documents the clinical importance of both GEP diagnoses and comprehensive genomic profiling in patients with CUP and should stimulate further studies to reconcile both approaches. The two strategies are not mutually exclusive since site-specific therapy does not preclude appropriate guidance from comprehensive genomic profiling. Consequently, both options are practice changing, each involving molecular profiling: (1) GEP diagnosis followed by site-specific therapy, and (2) induction empirical chemotherapy followed by MGT based on comprehensive genomic profiling. It will be essential to study the concomitant use of GEP predictions and comprehensive genomic profiling in guiding precision therapy in patients with unfavourable CUP. The applicability of these findings is important but might be clinically limited as molecular profiling is not currently widely available, cumbersome in low-resource settings, and a potential financial burden for patients; these disparities should be addressed.

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