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GENETICS

CUP: discovering genetic opportunities

Around 5% of all cancer diagnoses present as metastatic cancer of unknown primary (CUP), and patients with this cancer have a poor prognosis. The diagnostic workup often fails to locate the primary tumour site, and although no drugs are approved for the treatment of CUP, cytotoxic chemotherapy is the main treatment.

Evidence indicates that selection of therapies based on genomic alterations can improve outcomes. Thus, there is great interest in the use of genetic profiling at the time of diagnosis to identify targeted treatment options that could improve response to therapy, despite not knowing the primary tumour site. Jeffrey Ross and coauthors used comprehensive genomic profiling (next-generation sequencing) to evaluate 200 CUP specimens to determine if this could guide personalized treatment.

At least one targetable genomic alterations was identified in 85% of the 200 samples analysed (125 adenocarcinomas of unknown primary [ACUP] and 75 carcinomas of primary lacking adenocarcinoma features [non-ACUP]). A total of 26 alterations identified were associated with targeted therapies approved for use in patients with a known primary tumour.

The analysis showed that comprehensive profiling of clinical specimens yielded an unexpectedly high frequency of actionable genetic alterations in CUP samples compared with tumours for which the site of the primary origin was known. Mutations and amplifications in *HER2*, *EGFR,* and *BRAF* were more common in the ACUP than the non-ACUP tumours. In addition, alterations in genes involved in the RAS pathway were also more common in ACUPs than non-ACUPs. These differences could be exploited therapeutically and highlight that next-generation sequencing is a key tool for the management of patients with CUP.

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Original article Ross, J. S. *et al.* Comprehensive genomic profiling of carcinoma of unknown primary. *JAMA Oncol.* doi:10.1001/jamaoncol.2014.216