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Identifying the molecular profile of a tumour where the primary site is unknown is crucial to the choice of treatment, the 2013 European Cancer Congress (ECC2013) [1], will hear on Monday. In up to five percent of all cancers, the site of the primary tumour is unknown and the disease is not diagnosed until it is at an advanced stage, when the cancer has metastasised (spread to other parts of the body). Until recently, the choice of treatment has been based on efforts to find biomarkers that could indicate the site of origin, but now a team of researchers has succeeded in identifying the particular molecular profiles of the metastatic tumours in a large group of patients. This is a major step on the road to being able to offer effective treatment to these patients, researchers say.

Dr Zoran Gatalica, MD, DSc, Executive Medical Director, Caris Life Sciences, Phoenix, Arizona, USA, and an Adjunct Professor of Pathology at Creighton University School of Medicine, will tell the congress that his team's research has shown that the biology of the tumour is more important than its primary site.

“Previous attempts to characterise cancer of unknown primary (CUP) have only managed to provide a statistical likelihood of a potential primary organ site, and for the most part have not addressed the question of whether a particular treatment is likely to be effective. We set out to do just that in a large group of over 1350 CUP patients. This is the largest group to date to have their molecular profiles characterised.”

Using a number of different molecular methods to assess the expression of biomarkers associated with the potential for drug response, including different gene sequencing techniques, in-situ hybridisation to assess gene copy numbers and translocations, and analysis of proteins expressed in cancerous cells, the researchers were able to find targets for which there are existing cancer drugs in 77% of the tumours profiled.

Not knowing the primary site of the cancer creates uncertainty in the selection of optimal treatment, the researchers say. Recent advances in translational medicine and cancer molecular profiling have shown that different cancers may share the same molecular pathways, which provides the biological basis for utilising the same, targeted therapy in many different cancer types, irrespective of primary site. This advance in the understanding of cancer biology

has allowed researchers to take the novel approach of looking for commonly altered cancer pathways in a group of patients with CUP.

In addition to finding druggable biomarkers such as targeted protein over-expression, protein loss, activating mutations, and gene copy number variations, the researchers were also able to use the results in some cases to reclassify disease from a metastatic state of unknown primary to a primary cancer. “Interesting though this was, it does not alter our conviction that the key to choosing effective treatment is the biology of the tumour and not the site of origin,” says Dr Gatalica.

CUP may occur because of biological reasons, such as the capacity of the cancer to acquire metastatic properties early on, or an unrecognised genetic predisposition of the patient, or because of patient education-related reasons, for example, ignoring or not recognising rectal bleeding, as well as through the limitations of available imaging technologies. For most cancers, treatment is usually determined by the site of the primary tumour, and also depends on careful staging (an estimate of the severity of the cancer depending on the size of the primary tumour and whether or not it has metastasised). Staging is not possible in CUP, and because the disease is only detected once the cancer has metastasised, there is no standard treatment, although broad-spectrum chemotherapy is most commonly used. Prognosis for such cancers is not good, with a usual overall survival time of between six and nine months.

Providing information on the potential benefit as well as the potential lack of benefit for a variety of oncology drugs in the context of the patient’s unique cancer molecular profile and overall clinical circumstances can provide the oncologist with critical information that will help them to select optimal treatment. Additionally, the molecular profiling of a tumour may allow the enrolment of CUP patients in trials designed around that molecular profile.

“As a reference laboratory performing molecular cancer profiling, we test samples referred to us by clinicians from all over the world and recognise the value of following the clinical outcomes for these patients. As a result we have developed the Caris Registry, an outcomes-based observational registry where treating physicians can input clinical outcome data over the course of a patient’s treatment. As yet, this registry is relatively small, with 1500 patients enrolled since 2010; but we believe that it will become increasingly useful as it gathers size and as clinicians become more aware of the benefits of molecular profiling in CUP and other cancer types. We know from published research that molecular profiling can significantly improve outcomes for these patients by allowing them to receive the most effective treatment for their cancer and prolong both overall and progression-free survival.

“We believe that our research signals a paradigm shift in the treatment of CUP, from treatment based on an attempt to define the location of the primary site to treatment based on the biology of the tumour, and that, as more targets and targeted therapies are discovered, the chances of finding those that will benefit individual patients will increase,” Dr Gatalica will conclude.

Professor Cornelis van de Velde, President of ECCO, said: “Any diagnosis of cancer is worrying for a patient, but cancer of unknown primary is particularly so. These encouraging results show that, even in cases where the primary site is not known, it is increasingly possible to select an effective targeted treatment and hence improve survival times.”

(ends)

[1] The 2013 European Cancer Congress is the 17th congress of the European Cancer Organisation (ECCO), the 38th congress of the European Society for Medical Oncology (ESMO) and the 32nd congress of European Society for Therapeutic Radiology and Oncology (ESTRO).

[2] The research was funded by Caris Life Sciences.

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