HAEMATOLOGICAL CANCER

ctDNA predicts outcomes in DLBCL

Despite general improvements in the outcomes of patients with diffuse large B cell lymphoma (DLBCL), a subset of patients have high-risk disease and require more intensive therapy. Now, an analysis of circulating tumour DNA (ctDNA) demonstrates the potential of ctDNA levels as predictors of outcome and of high-risk disease requiring more aggressive treatment.

Samples from 217 patients diagnosed with DLBCL or primary mediastinal large B cell lymphoma at six treatment centres were obtained, and 98% were found to have detectable ctDNA before treatment. Patients were then assigned to either the discovery ($n=130$) or validation ($n=73$) sets for ctDNA monitoring during treatment, with changes in somatic alterations being used to quantify changes in ctDNA.

Initial investigations indicated that ctDNA levels were dramatically reduced in responders within 1 week of commencing treatment, such that responders and nonresponders could be perfectly discriminated by the end of the first treatment cycle. These promising findings were then confirmed in the discovery cohort, in which patients with an early molecular response (EMR; defined as >100-fold (2-log) decrease in ctDNA levels after one cycle of treatment) and those with a major molecular response (MMR; defined as a >2.5-log decrease after two cycles) had significantly improved 24-month event-free survival (EFS) of 83% versus 50% ($P=0.0015$) and 82% versus 46% ($P<0.001$), respectively. Patients with an EMR who ultimately required salvage therapy also had superior 24-month EFS of 100% versus 13% ($P=0.011$). Both EMR and MMR were predictive of outcomes independent of the findings of PET–CT imaging.

These data provide evidence that dynamic alterations in ctDNA levels can provide early indications of clinical outcome. Such measures could be incorporated into novel trial designs and enable improved patient stratification in this setting.

Peter Sidaway

ORIGINAL ARTICLE Kurtz, D. M. et al. Circulating tumor DNA measurements as early outcome predictors in diffuse large B-cell lymphoma. *J. Clin. Oncol.* https://doi.org/10.1200/JCO.2018.78.5246 (2018)

LUNG CANCER

Mesothelioma risk genes revealed

The existence of families with multiple members having malignant mesothelioma has been known for some time and suggests the existence of germline variants that confer an increased risk, even in the absence of exposure to asbestos. However, the prevalence of variant forms of known cancer susceptibility genes in patients with mesothelioma is largely unknown. Now, data from a next-generation sequencing analysis provide evidence for the genetic basis of familial mesothelioma risk.

DNA samples from a cohort of 198 unrelated patients with mesothelioma of the pleura (75%), peritoneum (22%), pleura and peritoneum (2%), and tunica vaginalis (2%) were analysed for germline mutations in 85 established cancer susceptibility genes. At least one germline mutation was detected in 12% of patients, of which a quarter had mutations in ubiquitin carboxyl-terminal hydrolase BAP1 (*BAP1*), an enzyme involved in BRCA1 signalling. The majority of other variants were also in genes involved in DNA repair and/or regulation of the cell cycle.

Germline mutations were significantly less likely to be detected in patients with tumours in a pleural location and in those with previous asbestos exposure, but were more likely to be detected in those with a second diagnosis of cancer.

Mutations in *BAP1* have been previously identified in patients with an increased familial risk of mesothelioma, although this was not a consistent observation. These findings demonstrate that mutations in genes that encode other DNA repair and/or cell cycle proteins, or even those that encode proteins with other functions, might also be associated with mesothelioma, thus explaining this apparent dichotomy.

Investigators note that the prevalence of germline alterations observed in this study is similar to that of patients with other solid tumours. Investigations designed to target vulnerabilities created by these alterations, including selective use of poly(ADP-ribose) polymerase (PARP) inhibitors, are currently underway.

Peter Sidaway

ORIGINAL ARTICLE Panou, V. et al. Frequency of germline mutations in cancer susceptibility genes in malignant mesothelioma. *J. Clin. Oncol.* https://doi.org/10.1200/JCO.2018.78.5204 (2018)

BREAST CANCER

EMBRACing a new PARP inhibitor?

Talazoparib is a potent inhibitor of the catalytic activity of poly(ADP-ribose) polymerase (PARP) that is also able to trap PARP–DNA complexes with a 100-fold greater affinity than that of other PARP inhibitors. Talazoparib has now been associated with promising survival and patient-reported outcomes (PROs) compared with standard chemotherapy in patients with breast cancer.

In the phase III EMBRACA trial, 431 patients with advanced-stage breast cancer harbouring germline mutations in *BRCA1* and/or *BRCA2* who had previously received ≤3 lines of cytotoxic chemotherapy were randomly allocated in a 2:1 ratio to receive either talazoparib ($n=287$) or standard single-agent chemotherapy of physician's choice ($n=144$). Median progression-free survival was longer in the talazoparib group compared with chemotherapy (8.6 months versus 5.6 months; HR 0.54; $P<0.001$). Median overall survival was also longer with talazoparib, but the difference was not statistically significant (22.3 months and 19.5 months for talazoparib and chemotherapy, respectively; $P=0.11$). The overall response rate was 62.6% with talazoparib and 27.2% with chemotherapy.

Grade 3–4 haematological adverse events (AEs) were more frequent with talazoparib (55% versus 38%), whereas the frequencies of grade 3 non-haematological AEs were 32% and 38% with talazoparib and chemotherapy, respectively. "PROs were also very impressive, with improvements in function and decreased time to clinical deterioration," highlights Jennifer Litton, principal investigator of EMBRACA. Indeed, patients receiving talazoparib reported improvements in global health status and quality of life according to the EORTC QLQ-C30 scale, which contrasted with the deterioration reported by patients receiving chemotherapy (3.0 versus −5.4; $P<0.001$).

"Further studies in the neoadjuvant setting are ongoing — we recently observed a pathological complete response rate of 53% with preoperative talazoparib. Combination studies involving PARP inhibitors and targeted therapies and/or immunotherapies are also underway," explains Litton.

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ORIGINAL ARTICLE Litton, J. K. et al. Talazoparib in patients with advanced breast cancer and a germline *BRCA* mutation. *N. Engl. J. Med.* **379**, 753–763 (2018)