American Society of Hematology
Atlanta, USA, 8–11 December

Rare mutations are a major influence in the pathogenesis of myelodysplastic syndromes

Comprehensive mapping of the genomic lesions implicated in the pathogenesis of myelodysplastic syndromes reveals a diverse molecular landscape of mostly rare mutations.

The absence of known oncogenic mutations in 22% of patients with myelodysplastic syndromes indicates that further yet uncharacterized genomic events are likely to be operating.

'Most importantly,' reported Dr Elli Papaemmanuil, Postdoctoral Research Fellow, Cancer Genome Project, Wellcome Trust Sanger Institute, Cambridge, UK, 'our data highlight the potential of well-defined gene mutations as reproducible diagnostic and predictive biomarkers to support myelodysplastic syndromes patient management and clinical decision-making in the future.'

To evaluate the genomic architecture of myelodysplastic syndromes in more detail, targeted sequencing analysis was performed for 111 genes implicated in myeloid malignancy across 738 myelodysplastic syndrome patients.

Oncogenic lesions were identified in 78% of myelodysplastic syndrome patients with 43% displaying two or three oncogenic events and approximately 10% harbouring four or more oncogenic mutations.

Among the less characterized genes, inactivating mutations in CUX1 and IRF1 were confirmed in 2% and 0.5% of patients respectively.

Genome Research Limited

Dr Elli Papaemmanuil, Postdoctoral Research Fellow, Cancer Genome Project, Wellcome Trust Sanger Institute, Cambridge, UK

'This provides strong evidence that these two genes are bona-fide rare tumour suppressors in myelodysplastic syndromes,' said Dr Papaemmanuil.

For the new myelodysplastic syndrome genes described, loss of function truncating mutations in CUX1 were associated with a poor prognosis (P=0.02).

Patients with fewer oncogenic events displayed lower rates of leukaemic transformation and better overall survival, whereas patients with higher number of mutations had significantly worse outcomes (P<0.0001).

Dr Papaemmanuil added: 'Strikingly we find that the prognostic information contained within the gene sequencing data and peripheral blood counts at diagnosis appears to be equivalent to that derived from existing outcome indicators, suggestive of a potential redundancy between the molecular markers and the morphological variables used to classify patients.

She concluded: '...the number of oncogenic point mutations is an independent biomarker and may therefore be used to refine the prognosis based on existing IPSS categories.'

Stephen Pinn

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Is prophylactic platelet transfusion necessary in patients with haematological malignancies?

New data from the multicentre TOPPS (Non-inferiority Trial of Prophylactic Platelet Transfusions) trial indicates that despite a role for prophylactic platelet transfusions in patients with haematological malignancies and severe thrombocytopenia, rates of bleeding in patients remain high.

TOPPS investigators failed to demonstrate that a no-prophylaxis policy is non-inferior to prophylaxis. They reported that patients randomized to no prophylaxis had more days with a ≥WHO (World Health Organization) grade 2 bleed, and a shorter time to first bleed.

Presenting the data, Dr Simon Stanworth, John Radcliffe Hospital, NHS Blood and Transplant, Oxford University Hospital NHS Trust, Oxford, UK, said that TOPPS was designed to give a greater understanding of the haemostatic benefit of a non-prophylactic strategy in patients with haematological malignancies.

'The effectiveness of prophylactic platelets to prevent bleeding in patients with blood-related cancers remains unclear,' he commented. 'The aim of TOPPS was to test the hypothesis that a policy of non-prophylactic platelet transfusions is as effective and safe as a policy of prophylactic platelet transfusion.'

In TOPPS, 600 patients recruited from 14 UK and Australian centres were randomized equally to one treatment strategy or the other.

Dr Stanworth reported that a WHO grade 2–4 bleed occurred in 50% of patients in the non-prophylaxis arm compared to 43% in the prophylactic group (P=0.06). The time to first grade 2–4 bleed was significantly shorter in the non-prophylaxis group (mean 1.7 days *vs* 1.2 days; odds ratio 1.52).

There was no significant difference between treatment groups in period of thrombocytopenia, number of days in hospital or number of serious adverse events experienced.

Dr Stanworth concluded: 'The high burden of bleeding requires new therapeutic strategies in patients with haematologic malignancies. In particular, the role of prophylactic platelet transfusions in different patient groups needs to be studied further.'

Stephen Pinn

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