Precision medicine for patients with lymphoma; the Bloodwise Precision Medicine for Aggressive Lymphomas (PMAL) consortium

Authors: Bridgin Merron,[A] Shamim Kazmi-Stokes,[B] Thomas Cummin,[B] Sharon Barrans,[C] Shamzah Araf,[D] Koorosh Korfi,[D] Laura D Lopez Pascua,[E] Josh Caddy,[A] Kelly Cozens,[A] Francesco Cucco,[F] Rahman Uddin,[G] Chulin Sha,[G] Reuben Tooze,[G] Gareth Griffiths,[A] Ming Qing Du,[F] Cathy Burton,[C] David Westhead,[G] Jude Fitzgibbon,[D] Anna Schuh,[E] Andrew Davies[B] and Peter Johnson[B]

Aims

While conventional therapy is curative for most patients with high grade lymphomas, there is considerable heterogeneity in this diagnosis, with scope to refine treatment according to the precise molecular phenotype. This is increasingly used to guide specific therapy and to predict outcomes. The Precision Medicine for Aggressive Lymphomas (PMAL) consortium is a national multi-partner network, established to develop robust predictive molecular assays for patients with high grade lymphomas and to optimise their treatment through trials of novel targeted therapy based on the results.

Methods

Biopsy samples from patients with lymphoma are studied by genomic, transcriptomic, molecular and immunophenotypic analysis, to establish their precise sub-type and to suggest options for targeted therapy. In parallel, studies of circulating free DNA are used to track actionable somatic mutations and monitor the response to therapy, and sequential biopsies from patients with recurrent disease are analysed to examine clonal emergence and evolution. A network of four laboratories undertakes this work, linked to a portfolio of clinical trials for patients with newly diagnosed or recurrent disease, coordinated by the Southampton Clinical Trials Unit. Complex bioinformatics analysis is used to refine the classification of the diseases according to detailed biological understanding and its impact on pathological behaviour.

Authors: [A]Southampton Clinical Trials Unit; [B]Cancer Research UK Centre, University of Southampton, Southampton; [C]HMDS, Leeds Cancer Centre, Leeds; [D]Centre for Haemato-Oncology, Barts Cancer Institute, Queen Mary University of London, London; [E]Department of Oncology, Division of Molecular Histopathology, University of Oxford, Oxford; [F]University of Cambridge, Cancer Research UK Centre, Cambridge; [G]School of Molecular and Cellular Biology, University of Leeds, Leeds, UK

Results

Over 1,100 patients have had whole transcriptome analysis performed in the REMoDL-B study, and the results linked to somatic deoxyribonucleic acid changes. This confirmed the existence of at least three distinct subgroups (germinal centre (GCB), activated B-cell like (ABC) and unclassifiable) within the overall diagnosis of diffuse large B-cell lymphoma, showing differential responsiveness to therapy including a proteasome inhibitor, bortezomib. The mutational frequency of *MYD88, PRDM1, CD79B* was higher in ABC, while mutations in *CREBBP, EZH2, DDX3X, FAS* and *KMT2D* were more frequent in GCB. There was no difference in 30-month progression-free survival (PFS) in the combined GCB + ABC population between RB-CHOP and R-CHOP; 74.3% and 70.1% respectively. Bortezomib did not significantly affect PFS in either GCB or ABC, however some patients with ABC and low international prognostic index had a significantly better PFS with the addition of bortezomib. Retrospective application of a Burkitt-like molecular classifier identified a group of GCB patients (17%) with a particularly poor prognosis and higher proportion of *c-MYC* gene rearrangements than other GCBs. With the addition of bortezomib, there was a trend towards improved PFS in this sub-group.

This targeted approach is now being applied in a new Cancer Research UK funded trial of first-line therapy, ACCEPT. The addition of a Bruton's tyrosine kinase inhibitor, acalabrutinib, to standard chemo-immunotherapy, stratified according to their mRNA profile is being examined. Characterisation of the microenvironment by gene expression profile is being used to analyse the results of new immunotherapy studies for patients with recurrent disease. The immune checkpoint inhibitor atezolizumab, is being tested in combination with conventional salvage chemotherapy in the ARGO trial. Broad genomic panel testing is being piloted to determine the utility of prospective identification of somatic changes as a guide to therapy. In the MaPLe study over 2,000 routine biopsies have been analysed, and prospective screening is underway to identify cases bearing an activating mutation in the epigenetic modifying gene *EZH2*, in support of a trial of the *EZH2* inhibitor tazemetostat. The overall incidence of mutations

is 10–15%, with early evidence to suggest that these may predict responsiveness to the inhibitor.

Conclusion

The PMAL consortium continues to refine the diagnostic platforms of high grade lymphoma. Analysis of the expanding genotype/phenotype database is being used to inform patient treatment decisions and shape a portfolio of future clinical trials, in collaboration with a number of pharma company partners. ■

Conflict of interest statement