special symposium: targeting signalling pathways in haematological malignancies: are we close to the end of histopathological classification and the chemotherapy era?

I. Ringshausen
3rd Department of Medicine, Technical University Munich, Munich, GERMANY

In spite of the enormous progress, first and foremost based on genome wide analyses of numerous B cell malignancies, the majority of these diseases remain incurable to date. Similar oncogenic mutations have been identified in indolent and aggressive BCL, however the frequency of most of these mutations is too low to provide sufficient evidence that they are the only drivers of B cell transformation. A unique characteristic of normal and malignant B cells is their dependence on functional B cell receptors (BCR), which engage a cascade of intracellular signalling proteins, ultimately causing activation of NF-κB. This continuous activation of the BCR-pathway is an essential prerequisite for transformation and lymphoma-maintenance and therefore constitutes an ideal target for therapeutic intervention. Over the past years numerous small molecule inhibitors have been developed which predominantly target protein kinases operating downstream of the BCR, such as Bruton tyrosine kinase (BTK), SYK, PI3K, PKC and mTOR. These kinase inhibitors have so far demonstrated impressive clinical responses in heavily pre-treated patients with BCL, however, which the exception of CLL, an objective response can generally be achieved in less than 60% of patients, who ultimately relapse within a year. It can be expected that the clinical benefit of these kinase inhibitors will be much better in treatment-naïve patients, but it still seems unlikely that using these drugs as mono-therapy can cure patients with BCL. Therefore, the challenge in the near future is to understand the molecular processes underlying drug resistance to kinase inhibitors. This knowledge will not only provide comprehensive insights into entity-specific pathway-dependence, but also to define the best sequence of drug applications in order to prolong and improve clinical remissions. Tied to this issue addressing the question of “What is the best combination of drugs?” will be of utmost importance. Therefore, the design of future clinical trials should not be based on commercial interests but rather be guided by scientific evidence based on preclinical experiments and translational analyses. This will likely be the key to revolutionize the treatment of BCLs and to truly launch a post-chemotherapy era.

Disclosure: The author has declared no conflicts of interest.