Problems of the Design and Interpretation of Early Clinical Trials in Hemato-oncology

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The availability of new and active agents with novel mechanisms of action has led to major advances in the treatment of haematological malignancies; however, continued progress will require overcoming significant challenges in the design and interpretation of clinical trials. Preclinical models are often misleading or not available. In Phase I trials in solid tumours, identifying the dose-limiting toxicities (DLT) is the critical endpoint, and demonstration of major activity not a prerequisite for moving forward. In contrast, in haematological malignancies DLTs are often not encountered because of the nature of the agents tested, and evidence of substantial activity is important. A goal of phase II trials is not only how to limit the drugs inappropriately discarded, but also to reject those drugs presented as overly-promising based on response rates in small numbers of patients, waterfall plots, and survival curves with short follow-up which waste time and resources.

Once a potentially useful agent is identified, the next challenge is to integrate it into combinations using scientific rationale. However, an obstacle is the negative impact of success. Drugs with high response rates in both relapsed/refractory and upfront settings makes improvement on efficacy difficult to detect without accruing prohibitive numbers of patients. Also, given the durability of responses, detecting prolonged progression-free and overall survival differences would require excessive amounts of time. Thus, alternative endpoints need to be identified.

Standard response criteria have tended to assess response within a few weeks of completion of therapy. However, new biological agents may not achieve their greatest effect for a longer period following administration and differences among agents needs to be considered in future trials. Other agents have meaningful clinical activity which does not meet current standard response criteria. Most notable amongst the newer drugs are the PI3-kinase inhibitor CAL-101 and the Bruton kinase inhibitor PCI-32765. In CLL these two drugs induce a paradoxical, transient increase in the circulating lymphocyte count such that, despite a reduction in node and spleen size with normalization of other counts, patients cannot be considered responders. Revised response criteria must account for differences among new drugs to facilitate regulatory approval, bringing more effective agents to patients more quickly. In the end, it is critical to accrue to high quality clinical trials with novel agents to continue to improve the outcome of patients with haematological malignancies.