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Sequential tumour biopsies in phase I trials

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Keywords

Biological agents, phase I trials, sequential tumour biopsies

Context

The development of new target-based anticancer drugs has led to the concept of "target modulation" and "optimal biological dose". It is critical to establish that the observed preclinical activity of a drug is in fact determined by the modulation of the intended target, and this should be achieved in early phase clinical trials. Another evolving notion relies on the observation that the maximum tolerated dose may not necessarily correspond to the optimal biological dose. However, a major obstacle to these new agents is the difficulty of obtaining relevant tumour tissue for laboratory analysis.

Significant findings

A total of 192 biopsies were performed in 107 patients (including 77 colorectal and 7 breast cancers), of which 99 had sequential pretreatment and post-treatment biopsies. The majority of patients (78) had liver and lymph node (12) biopsies, but there were also breast (three patients), pelvic and intra-abdominal lesions, head and neck, and lung biopsies. In 99 (93%) patients pretreatment and post-treatment paired biopsies were obtained, and of these, 87 (88%) were successful. The most common reason for failure was obtaining necrotic, fibrous or normal tissue in one of the two biopsies. Complications were rare and manageable. The authors conclude that with adequate precautions (including careful patient selection and close postbiopsy monitoring) and experience, sequential tumour biopsies are feasible and safe.

Comments

The use of surrogate tissues, such as peripheral blood monoclonal cells or skin biopsies, can be used as additional methods for guiding dose escalation in phase I trials. However, with biological agents, the alterations seen in surrogate tissues may not accurately reflect what is occurring in the tumour.

Moreover, species specificity of molecular inhibitors makes evaluation in xenograft models difficult to interpret. Therefore, tumour tissue is the optimal target to prove the biological effect. The authors have shown that with a careful patient selection, excluding patients with coagulation abnormalities and/or highly vascularised lesions, close postbiopsy monitoring, and multidisciplinary commitment, sequential tumour biopsies are feasible. Most patients seem to be willing to accept the procedure. Nevertheless, caution must be taken before routinely recommending this approach: the target to measure, the correspondent assay, and the optimal timing for obtaining the tumour sample must be based on carefully reviewed preclinical data.

Methods

Sequential tumour biopsies (by direct visualisation or computed tomography guided) in a seven trial program spanning 12 years, 14-gauge needles, frozen tumour samples, molecular and biochemical assays, tumour cell lines, human tumour xenografts

Additional information

References

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