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Clinical trial design issues: Session 1

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ABSTRACT: Anticancer therapeutic intervention in patients with solid tumours still relies on the necessity of empirically treating many patients to obtain benefit for a limited few. The activity of a given drug in patients with advanced cancer is the result of a pharmacodynamic interaction with a pathway. Such putative pathways must be both prevalent in the cancer cells and relevant to the process of uncontrolled cell proliferation. Several examples have clearly demonstrated the value of measuring the molecular target and using it as inclusion criteria for clinical trials. Adaptive trial designs and the definition of clinical surrogate end-points can be helpful tools to further improve clinical drug development. In general go/no go decisions must be established prospectively.

Keywords: Target expression; Molecular signatures; Adaptive trial design; Surrogate end-points

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ROLE OF TARGET EXPRESSION AS INCLUSION CRITERIA

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Anticancer therapeutic intervention in patients with solid tumours still relies on the necessity of empirically treating many patients to obtain benefit for a limited few. The activity of a given drug in patients with advanced cancer is the result of a pharmacodynamic interaction with a pathway. Such putative pathways must be both prevalent in the cancer cells and relevant to the process of uncontrolled cell proliferation.

Many molecularly targeted anticancer agents have demonstrated limited effectiveness thus far. An example is the marginal impact on overall survival of erlotinib (Tarceva®), an epidermal growth factor receptor inhibitor, after first- or second-line treatment, compared to placebo. The respective study involved 731 patients with advanced non-small-cell lung cancer (NSCLC).[1] After adjusting for stratification factors and epidermal growth factor receptor (EGFR) status, the survival curves for the two treatments started to diverge after 2 or 3 months. At 1 year, 31% of patients treated with erlotinib were still alive, compared with 22% of those on placebo.

Similarly, new therapeutic schemes for treating hormone-refractory prostate cancer have shown only limited effects on overall survival. In one study involving 674 men, the median overall survival was 17.5 months in the group given docetaxel and estramustine, and 15.6 months in those given mitoxantrone and prednisone. The corresponding hazard ratio for death was 0.80.[2]

DESIGNING TRIALS: One way to streamline clinical trials of new anticancer agents is to use biomarkers rather than clinical end-points. Several examples of novel markers for assessing effectiveness and predicting response to therapy were discussed.

Methylation-dependent transcriptional silencing of 14-3-3σ, a major G2-M checkpoint control gene, could be a new, independent prognostic factor for survival in NSCLC patients receiving platinum-based chemotherapy.[3] 14-3-3σ methylation was observed in all histologic types of 39 patients (34%). And median survival was significantly longer in the methylation-positive group (15.1 versus 9.8 months). Median time to progression was 8 months in the methylation-positive group and 6.3 months in the methylation-negative group. Furthermore, 14-3-3σ methylation might be a prognostic marker. The estimated survival rate at 18 months was 64% amongst methylation-positive responders and 21% amongst methylation-negative responders. Methylation-negative responders had a fourfold greater risk of death during follow-up than those who were methylation-positive. Additionally, translational research studies in advanced NSCLC are limited by a lack of tumour biopsy tissue, but methylation of 14-3-3σ can be reliably and conveniently detected in the serum, thus obviating the need for tumour tissue analysis in translational studies.

As another example trabectedin (Yondelis) induced long lasting responses and tumour control in a clinically relevant proportion of sarcoma patients resistant or relapsed to conventional chemotherapy.[4] After the EMEA/CHPM positive opinion and

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