Short communication

Evaluation of biological agents targeted at early-stage disease

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In breast cancer there are many novel molecule-targeted therapies in preclinical and clinical development. For the majority, if not all, of these therapies there is no clear biomarker profile in tumours to inform the inclusion or exclusion of patients into phase II efficacy trials of these drugs or combinations that include them. Some data suggest that short-term, tissue-based pharmacodynamic trials in newly diagnosed early-stage operable cancers provide information that can be later used in patient selection. For example, administration of anti-oestrogens for a period of 1 to 3 weeks has been shown to induce a significant antiproliferative effect in oestrogen receptor (ER)-positive breast cancers [1-3]. These studies have evaluated proliferation in the tumour by measuring the percentage of cells that stain with an antibody against the nuclear antigen Ki67 [4]. Interestingly, in all of these trials there was no effect in the ER-negative cancers.

In other neoadjuvant trials, short-term end-points have correlated with clinical outcome. For example, treatment-induced tumour cell apoptosis, as measured by cleaved caspase-3 immunohistochemistry 1 week after administration of the anti-human epidermal growth factor receptor (HER)-2 monoclonal trastuzumab, correlates with clinical response of HER-2 over-expressing breast cancers [5]. The neoadjuvant Immediate Preoperative Anastrozole Tamoxifen or Combined with Tamoxifen (IMPACT) trial compared anastrozole versus tamoxifen versus the two drugs combined. Drug-induced inhibition of tumour cell proliferation at 2 weeks, as measured using Ki67, was better in patients treated with anastrozole than in patients included in the other two arms [6]. This finding parallels the results of the large Anastrozole, Tamoxifen, Alone or in Combination (ATAC) adjuvant trial, in which relapse-free survival was greater in patients treated with adjuvant anastrozole than in those receiving tamoxifen or the combination [7].

Recent pharmacodynamic studies of epidermal growth factor receptor (EGFR) inhibitors have provided some clues that might be of clinical use, as this approach can be potentially applied to other novel compounds and/or combinations. Guix and coworkers [8] administered erlotinib for 6 to 14 days to women with operable untreated breast cancer in order to identify a biomarker associated with evidence of drug-mediated cellular activity in the surgical specimen. Erlotinib inhibited cell proliferation (Ki67) and phosphorylated EGFR, mitogen-activated protein kinase (MAPK), Akt and S6 only in ER-positive tumours, and not in HER-2-positive or triple negative tumours. These data are consistent with at least three reports showing that clinical activity of gefitinib appears to be limited to ER-positive breast cancers [9-11]. Interestingly, erlotinib inhibited phosphorylation of ER-α in Ser118. Similar results were reported by Polychronis and coworkers [11] in ER-positive/EGFR-positive newly diagnosed breast cancers treated for 6 weeks with neoadjuvant gefitinib. Because phosphorylation of this site is regulated mainly by MAPK [12], these findings provide evidence of operative crosstalk between ER and ErbB receptor signalling early in the natural history of hormone-dependent breast cancer. In addition, they imply that the use of EGFR antagonists in combination with anti-oestrogens should be explored in further clinical trials.

Indeed, preliminary communication of results from clinical trials already suggests this strategy to be effective. Cristofanilli and coworkers [13] recently reported the results of a randomized phase II study of anastrozole plus gefitinib versus anastrozole plus placebo in postmenopausal women with hormone receptor positive metastatic breast cancer. Fifty patients received anastrozole plus placebo and 43 the aromatase and EGFR inhibitors combined. Patients treated with this combination exhibited a median progression-free

EGFR = epidermal growth factor receptor; ER = oestrogen receptor; HER = human epidermal growth factor receptor; MAPK = mitogen-activated protein kinase; PFS = progression-free survival.

survival (PFS) of 14.5 months, as compared with 8.1 months in the anastrozole plus placebo control arm of the trial. Follow-up was too short to estimate overall survival. A similar randomized phase II trial was reported by Osborne and coworkers [14]. Patients with new ER-positive metastatic disease or who had recurred after adjuvant tamoxifen or had recurred during or after adjuvant therapy with an aromatase inhibitor were randomly assigned to tamoxifen with/without gefitinib. The PFS was 10.9 months versus 8.8 months in the combination versus the tamoxifen arm, with a PFS hazard ratio of 0.84 [14].

The results of these two studies in patients with ER-positive metastatic disease should be contrasted with those of a 16-week neoadjuvant trial of anastrozole with/without gefitinib in patients with stage I to IIIB ER-positive breast cancer [15]. In this study, objective response exhibited a nonsignificant trend against the combination versus the anastrozole arm (48% versus 61%). This difference was statistically significant in the progesterone receptor positive group. Lack of patient selection, prior adjuvant therapy, different stage of disease (localized versus metastatic) and study end-points (response versus PFS) may potentially account for the discrepancy in results.

The presurgical studies discussed above support the feasibility of testing novel therapies during the pre-approval process to investigate a tumour profile of potential use in subsequent clinical studies that address drug efficacy. This approach requires additional examples and experience. We speculate, though, that this trial design may expedite the drug development process by potentially informing the exclusion of nonresponsive patients who will dilute the net signal of clinical activity of a drug or a combination. In the case of erlotinib, these patients would be those with HER-2-positive and triple-negative, basal-like cancers. Interestingly, because of its relative over-expression in breast cancers with a basal-like gene expression signature [16], the EGFR has been proposed as a therapeutic target in tumours that lack ER and HER-2. However, in two recent trials in patients with triple-negative, basal-type metastatic breast cancer, the addition of the EGFR antibody cetuximab did not add to the effect of chemotherapy [17,18].

In summary, we believe that the evaluation of biological agents in early-stage breast cancer, where tumour tissue is available, provides outstanding opportunities for accelerated drug development, biomarker discovery and, eventually, patient selection. It can potentially validate inhibition of the molecular target of the drug; identify subgroups of patients who may not be candidates for the drug in question (triple negative tumours for EGFR inhibitors, to follow the example above); and provide knowledge to assist in a 'go versus no-go' decision regarding progression to phase II or III drug development.

Competing interests

The authors declare that they have no competing interests.

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