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Editorial Comment

Evaluation of epidermal growth factor receptor tyrosine kinase inhibitors combined with chemotherapy: Is there a need for a more rational design?

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Thirty years of cancer biology has resulted in the development of targeted therapies. Drugs or antibodies that specifically target HER-2, BCR-AbL, C-Kit, and CD20 are now approved for use in cancer patients. Recently, two types of new "biological" agents against the epidermal growth factor receptor (EGFR), monoclonal antibodies IMC-C225 (Cetuximab, Erbitux; ImClone Systems Incorporated, New York, NY, and Bristol-Myers Squibb Company, Princeton, NJ) and small molecular receptor tyrosine kinase (TK) inhibitors, ZD1839 (Gefitinib, Iressa; AstraZeneca, Alderley Park, Macclesfield, United Kingdom) and OSI-774 (Erlotinib, Tarceva; OSI Pharmaceuticals, Uniondale, New York, NY), have shown antitumour activity in a variety of tumour types [1–3]. Although these EGFR inhibitors have demonstrated encouraging activity, the observed response rates were modest. Therefore, the addition of an EGFR inhibitor to chemotherapy regimens is expected to confer significant benefits. Regardless of the mechanism of action of the cytotoxic agents, combination treatments of a receptor targeted inhibitor with cytotoxic agents have shown enhanced antitumour effects in a range of *in vitro* and *in vivo* models [4,5]. These results have provided the rationale to combine these agents with chemotherapy in cancer clinical trials. Clinical phase II and phase III trials of receptor inhibitors in combination with cytotoxic agents have been carried out or are ongoing for several tumour types [6–8].

Synergy is the best model for the observed enhancement of *in vitro* and *in vivo* antitumour activities of cytotoxic agents when they are combined with receptor TK inhibitors. Nevertheless, this mechanism is still not fully understood. Understanding the mechanism of action of an EGFR inhibitor will be important in designing combination schedules. Activation of EGFR enhances the chemosensitivity of cancer cells [9,10] and chemoresistance is associated with a decrease in growth factor signalling [11]. Therefore, preceding or simultaneous blockade of EGFR could reduce the sensitivity to chemotherapy. Furthermore, receptor inhibitor following chemotherapy may be more appropriate for tumours with elevated EGFR expression after multi-cycle chemotherapy [12]. Receptor inhibitors block cells in the G1 phase of the cell cycle. Since cells begin to repair DNA damage and mitose in the G2/M phase, receptor inhibition subsequent to chemotherapy does not allow cells an opportunity to repair the chemotherapy-induced DNA damage [13,14]. Previous studies [15] have also demonstrated that the increased efficacy of regimens containing chemotherapy and receptor inhibition may be as a result of increased apoptosis. In fact, some studies raised the possibility that this combination effect is schedule-dependent [16,17]. Recent studies reported that chemotherapy (oxaliplatin, SN-38 or 5-fluorouracil (5Fu))-induced apoptosis was prolonged by the sequential exposure of tumour cells to a cytotoxic agent followed by ZD1839 treatment compared with cells treated with chemotherapy alone [18]. Receptor inhibitors have also been shown to reduce vascularisation by reducing the tumour expression of numerous angiogenic factors (including transforming growth factor (TGFα), vascular endothelial growth factor (VEGF), interleukin-8

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and basic fibroblast growth factor (bFGF)) [2,19]. However, the neovessels of advanced tumours may be more difficult to inhibit through anti-angiogenetic mechanisms compared with microscopic disease, where there may be a more nascent vasculature. Thus, it may be more appropriate to use these agents in tumours that have been successfully treated by chemotherapy.

Since the possible mechanisms of action of EGFR inhibitors are critical for the development of an optimal sequence in combination with chemotherapy, several important factors regarding the most effective use of receptor inhibitors in the clinical combination schedule should be considered. The maximum tolerated dose (MTD) of the chemotherapy should be administered, since the prerequisite for receptor inhibitor exerting its potential synergy with chemotherapy is that chemotherapy is inducing or has induced maximal cell damage, so that the subsequent receptor blockade could interfere with repair of this cell damage [15]. Therefore, the timing of receptor inhibitor administration is important.

In the design of most current clinical trials of chemotherapy in combination with an EGFR inhibitor, the inhibitors were administered either concurrently [8,9,20,21] or following chemotherapy [22,23]. For example, in the phase III trials of ZD1839 with carboplatin/paclitaxel or gemcitabine/cisplatin in patients with non-small-cell lung cancer (NSCLC), ZD1839 was administered simultaneously for 6 cycles of chemotherapy. However, the two chemotherapeutic regimens led to overall response rates of 30%–40%, with a complete response in less than 5% of chemotherapy-naïve patients [24,25]. This means that ZD1839 can exert its potential synergy with chemotherapy in (at most) 30%–40% of patients. Furthermore, a large body of evidence has demonstrated that chemosensitivity is significantly related to the proliferative activity of tumour cells, and decreases in the proliferation rate are associated with chemoresistance [16]. In this regard, the clinical efficacy of chemotherapy could be influenced by the simultaneous administration of ZD1839, which leads to a decrease in growth factor signalling. As a consequence, the overall response rate could be less than a summation of first-line chemotherapy and first-line ZD1839 therapy. Clearly, the overall response duration obtained should not be expected to significantly improve when compared with chemotherapy alone. Recently, the final efficacy analysis of these initial large trials [26,27] demonstrates that there was no clinical benefit when ZD1839 was added to chemotherapy in NSCLC. Whether the negative results are simply a lack of efficacy of ZD1839 in combination with the two chemotherapeutic regimens in advanced NSCLC or a result of poor patient selection warrants further investigation.

In summary, sequential EGFR inhibition after chemotherapy administration could enhance/maintain cell damage. Novel strategies for future study designs need to be considered, such as the randomised discontinuation approach [28]. One design could be to administer an initial course of chemotherapy, with direct or surrogate (e.g., positron emission tomography (PET) scan, circulating markers, etc.) measurement of response. Time to progression and survival should be used as study endpoints for responding patients that receive the combination of chemotherapy and EGFR inhibitor. EGFR inhibitors offer great promise for the treatment of cancer, but greater attention to mechanistic data will be needed if we are to realise this potential.

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