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SHORT COMMUNICATION

Tumor resensitization to erlotinib following brief substitution of cetuximab

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Abstract Targeted inhibition of epidermal growth factor receptors (EGFR) is becoming a standard anticancer treatment in defined clinical scenarios. EGFR inhibition may be achieved either by small-molecule orally bioavailable tyrosine kinase inhibitors, such as gefitinib or erlotinib, or else by large-molecule receptor antibodies, such as cetuximab or panitumumab. Here, we describe a case of pancreatic cancer in which the small-molecule EGFR antagonist erlotinib was used before and after the EGFR antibody cetuximab, with unexpected potentiation of both toxic and therapeutic sequelae.

Keywords Epidermal growth factor receptor · Tyrosine kinase inhibitors · Receptor antibodies · Targeted anticancer drugs · Sequential drug scheduling

A 45-year-old female smoker presented with primary pancreatic adenocarcinoma metastatic to the L1 vertebra, acetabulum, lungs and supraclavicular nodes. The Ca-19.9 level was 18,900 IU/ml, while the CEA level was 150 ng/ml. The tumor overexpressed epidermal growth factor receptor (EGFR), but no EGFR mutation was detectable. Treatment with gemcitabine and erlotinib was commenced, and resulted in minimal toxicity; skin toxicity was limited to mild facial acne and one paronychial lesin. A near-complete clinical and CT-PET remission was induced and maintained for 9 months on this regimen, at which time the disease recurred in the left supraclavicular and midjugular nodal regions. Re-biopsy of the latter lesions confirmed similar histology to the original, persistent EGFR overexpression, and persistent lack of EGFR mutation. Weekly cetuximab was substituted for erlotinib, with continuation of gemcitabine, but was discontinued after one further month due to rapid acceleration of clinical disease progression associated with a sharply increased rate of tumor marker rise. Recommencement of erlotinib (150 mg/day) immediately triggered a severe desquamative rash involving the entire skin surface, requiring drug discontinuation for 1 week. Subsequent reintroduction at a lower dose (100 mg/day) was associated with manageable toxicity associated with a further progressive decline in serum tumor marker levels to near-normal levels (see Fig. 1).

Although in vitro studies have documented the synergistic superiority of combined EGFR antibody and kinase domain antagonists over single-agent treatments [1, 2], there is as yet little clinical experience with the utility and hazards of combining target-specific drug therapies, whether simultaneously or sequentially. One key difference between large- and small-molecule EGFR antagonists is that the former tend to directly downregulate the receptor [3], whereas the latter—which primarily render the intracellular domain of the receptor kinase-inactive—lead to secondary EGFR upregulation [4]. Hence, in the present case, the dramatic induction of skin toxicity—a recognized predictor of anticancer efficacy [5]—following reintroduction of erlotinib after cetuximab substitution is consistent with the finding that erlotinib resistance arises in vitro partly in response to EGFR upregulation [4]. This in turn raises the possibility that judicious coadministration of EGFR

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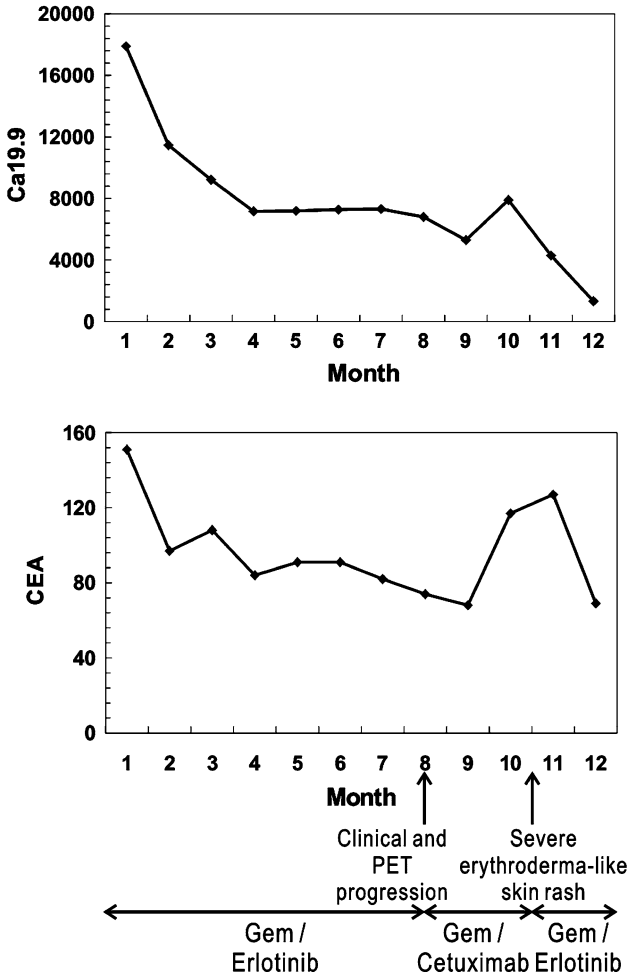

Fig. 1 Variation in tumor marker level (Ca-19.9, top; CEA, bottom) in response to combination therapy with gemcitabine (Gem) and EGFR antagonists: initially erlotinib, then cetuximab, then erlotinib again

antibody treatment to previously effective EGFR kinase inhibition may counteract receptor upregulation and thus delay the emergence of drug resistance and tumor progression. We conclude that interactions between biologically targeted drugs may be clinically advantageous, and recommend that controlled clinical studies be conducted to better define the nature and clinical value of combination treatments.

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