possible pharmacological explanation for at least part of the synergistic interaction between platinum complexes and 5-FU, which could be based on DPD inhibition. Indeed, DPD inhibition at the target level may reduce the loss of 5-FU by a DPD-mediated catabolic route. Secondly, the data also suggest that patients with relatively low intrinsic DPD activity may be placed at risk of marked toxicity when receiving a platinum complex–5-FU combination. The mechanistic origin of the DPD inhibition remains to be elucidated.

N. Magné1,2, X. Pivot3, M. C. Etienne-Grimaldi2, E. François2, N. Renée2, A. Thyss2, M. Schneider2, F. Demard2 & G. Milano2*

1Department of Radiotherapy, Institut Jules Bordet, Brussels, Belgium; 2Oncopharmacology Unit, Centre Antoine Lacassagne, Nice; 3Department of Medical Oncology, Centre Hospitalier Universitaire Jean Minjoz, Besançon, France (*E-mail: gerard.milano@cal.nice.fnclcc.fr)

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DOI: 10.1093/annonc/mdg351

Wound healing is not impaired by the epidermal growth factor receptor-tyrosine kinase inhibitor gefitinib

Epidermal growth factor receptor (EGFR) is over expressed in many solid tumors [1]. Specific inhibition of EGFR-tyrosine kinase (TK) has become possible with the availability of drugs such as gefitinib (ZD 1839, Iressa) and OSI 774 (Tarceva). Since EGFR is thought to play a critical role in wound healing, there is a concern that EGFR inhibitors may be associated with impaired wound healing. We describe four instances in which patients underwent surgical procedures while receiving gefitinib 250 mg p.o. once a day for the management of advanced non-small-cell lung cancer (NSCLC).

Case 1
A 70-year-old woman with metastatic NSCLC underwent emergency laparotomy for acute abdominal pain on day 48 of therapy with gefitinib. She underwent adhesiolysis and a 15 cm skin wound was sutured using acrylic sutures. She resumed therapy with gefitinib on day 55 (7 days after the operation) and had normal wound healing.

Case 2
A 72-year-old man with a history of metastatic NSCLC required internal fixation for bony metastasis 2 months after initiation of therapy with gefitinib. A 4 cm skin incision on the left forearm was made for the procedure. He continued to take gefitinib until the day before surgery and resumed gefitinib 24 h after the surgery. His skin wound healing was unremarkable.

Case 3
A 69-year-old woman required incision and drainage of a labial abscess 4 months after starting gefitinib for recurrent NSCLC. A 3 cm incision was made on the left labia for drainage of the infection. She was on gefitinib without any interruption. After drainage of the abscess and treatment with antibiotics, the labial wound healed without any complications.

Case 4
The patient described in case 3 subsequently underwent emergency laparotomy, after receiving gefitinib for 5.5 months, in view of sudden enlargement of a lesion in the spleen and a concern for splenic hematoma. The splenectomy was done by laparotomy and a 12 cm incision was made in the skin. She received gefitinib until the day before surgery and resumed gefitinib on the third postoperative day. She had normal wound healing.

Figure 1. Impact of the administration of platinum derivatives (cisplatin, oxaliplatin) on dihydropyrimidine dehydrogenase (DPD) activity in peripheral blood mononuclear cells (22 patients). There was a 24-h interval between the two DPD measurements.
Discussion

Wound healing is a complex and coordinated process beginning with tissue injury [2–4]. After tissue injury, a coagulation cascade is activated to stop bleeding. Inflammatory mediators are then activated, resulting in an outpouring of cytokines and growth factors that initiate collagen repair and granulation tissue formation. The final process, which completes the healing process, involves extracellular tissue remodeling, angiogenesis and reproduction of the original tissue.

Keratinocytes play a key role in skin healing in response to injury. Keratinocytes not only proliferate to complete tissue healing, but they also serve as a source of several cytokines. EGFR ligands are among the most prominent cytokines secreted by the keratinocytes [2]. EGFR ligands include epidermal growth factor (EGF), transforming growth factor-α, amphiregulin, heparin binding EGF-like growth factor (HB-EGF), betacellulin and epiregulin [5]. These secreted cytokines stimulate adjacent keratinocytes. There appears to be a biphasic production of EGFR ligands during the wound healing process. The first phase of production of EGFR ligands is secondary to local induction in response to injury; the second wave of production is secondary to autocrine activation of the keratinocytes. Some evidence suggests that HB-EGF is the most important of the ligands. The activation of EGFR and vascular endothelial growth factor receptor promotes wound healing. Consequently, agents that inhibit EGFR could potentially interfere with wound healing. Topical application of OSU 8-1, an inhibitor of EGFR ligand shedding, has been shown to decrease keratinocyte migration and delay cutaneous wound healing [3]. In addition, systemic administration of gefitinib has been shown to decrease epithelial proliferation and stratification in response to corneal injury [5].

Gefitinib is absorbed orally and inhibits skin EGFR phosphorylation. Gefitinib accumulates in the skin, which means theoretically that patients treated with this agent could have problems with wound healing. Preclinical studies have shown that gefitinib can delay and inhibit corneal wound healing [5]. Gefitinib has not been shown to impair skin wound healing in our small series reported here. This data suggests that the role of EGFR in wound healing needs to be re-evaluated.

Disclosure

R. G. has received honoraria from Astra Zeneca for speaking engagements.

R. Govindan1,2*, D. Behnken1,2, W. Read1,2 & H. McLeod1,2

1Washington University School of Medicine, St Louis, MO; 2Alvin J Siteman Cancer Center, St Louis, MO, USA (*E-mail: rgovinda@im.wustl.edu)

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DOI: 10.1093/annonc/mdg352

Radiotherapy following breast-conserving surgery

I read Chung and Cady’s letter urging caution with repeat sentinel node biopsy [1] with some alarm. Surely the other pertinent point that this case illustrates is the imperative to irradiate the breast following breast-conserving surgery, a procedure now accepted as standard, to reduce local recurrence in the remaining breast tissue [2]. The patient reported in this case did not receive radiotherapy to the breast following wide local excision, despite this being a standard procedure, and 20 months after diagnosis she presented with local recurrence. As the authors themselves state, local recurrence is an indication that the patient is at risk of systemic disease [3, 4], and indeed 10 months later, this 48-year-old patient with a T1a tumour presented with lung and liver metastases. This is clearly a very poor outcome for all concerned. Whilst the role of radiotherapy following mastectomy for histologically high-grade but node-negative breast cancer remains controversial, its use following breast-conserving surgery, even in seemingly low-risk women such as the patient described, is clear, and this unfortunate case clearly illustrates this point.

A. L. Appleton

Unité de Sénologie, Clinique de Genolier, near Geneva, Switzerland, CH-1272 (E-mail: appleton@cdg.ch)

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DOI: 10.1093/annonc/mdg355