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Editorial comment

A new treatment principle for neuropathic pain? Approved oncologic drugs: Epidermal growth factor receptor (EGFR) inhibitors dramatically relieve severe neuropathic pain in a case series

Harald Breivik[a,b,*], Audun Stubhaug[a,b]

[a] University of Oslo, Oslo, Norway
[b] Department of Pain Management and Research, Oslo University Hospital, Rikshospitalet, PB 4950 Nydalen, 0424 Oslo, Norway

In this issue of the *Scandinavian Journal of Pain*, Christian Kersten, Marte Grønlie Cameron and Svein Mjåland report dramatic pain relief from approved oncologic drugs in four of five patients with severe neuropathic pain. The patients received monoclonal antibodies to epidermal growth factor receptor (EGFR) and inhibitors of intracellular EGFR-associated mitogen-activated protein kinase (MAPK) [1]. Kersten and Cameron reported in the *British Medical Journal*–Case Report in 2012 on their first observation of this effect from the monoclonal antibody cetuximab when this drug was administered as palliative treatment of a patient with a metastasizing rectal cancer [2]. The patient had a pelvic recurrence of his cancer, resulting in severe radiating pain down his left leg. A few hours after the infusion of the EGFR-antibody cetuximab the patient reported dramatic relief of his pain.

1. Vigilance, clinical acumen, and serendipity behind this discovery

For a less vigilant observer, this could easily have been understood as a result of the anti-tumour effect of cetuximab. However, this patient had already a 3-years history of severe pain that had not responded to potent opioids, antidepressants, or antiepileptic drugs. The marked and rapid pain relief of cetuximab made Kersten and Cameron wonder if there could be a specific, hitherto unknown pain relieving mechanism. This suspicion was strengthened by the fact that the pain gradually came back at the end of the known duration of effect of cetuximab, i.e. 10–12 days. They then repeated the cetuximab every 12 days, for 3.5 years while the tumour was in progression, every time with the same dramatic effect on the radiating lower extremity pain. This happened, in spite of progression of the tumour. They even tried to reveal any strong "context-sensitive-therapeutic-effect" (also called placebo-effect!) by administering, unknown to the patient, a tiny dose of cetuximab in the same volume of infusion. This had no effect on the patient's pain [2].

Cetuximab (Erbitux®) and panitumumab (Vectibix®) are recombinant monoclonal IG-antibodies that bind to EGFR with higher affinity than endogenous ligands, thereby blocking the receptor. Endogenous stimulation of the EGF receptor causes intracellular processes that lead to cell proliferation and angiogenesis. These antibodies to the EGFR stop cellular proliferation and cause apoptosis. They are approved oncologic drugs with side effects that are mostly transient and manageable, according to experienced oncologists [1,2].

The intracellular processes caused by endogenous EGFR activations, are in part due to mitogen-activated protein kinases (MAPK). Blocking MAPK with the proteinkinase inhibitors gefitinib (Iressa®) or erlotinib (Tarceva®), that can be administered orally, had similar dramatic effects as the EGFR-antibodies [1].

The four patients (of the five in the present report [1]) who responded had relatively well-defined pain conditions with, at least, components of neuropathic pain mechanisms, two had cancer-related pain and two had chronic non-cancer pain: one had a typical complex regional pain syndrome (CRPS) of the right hand. One had failed back surgery syndrome (FBSS) with scar tissue formation at the L4/L5 segmental level. One had a recurrent bladder cancer, locally infiltrating sacral nerves, and one had a pancreatic cancer with liver metastases; however, her major pain problem was a long lasting phantom-limb pain after a below-the-knee amputation due to non-healing ulcers from peripheral vascular disease. The one patient who did not respond had a long-lasting (6 years) progressive, painful polyneuropathy of unclear aetiology, possibly related to a Borrelia infection [1].

2. How do EGFR-inhibitors relieve so effectively severe neuropathic pain?

Four different EGFR-inhibiting drugs were used, the two monoclonal antibodies cetuximab and panitumumab acting extracellularly by binding avidly to the EGF receptors, and the two intracellular protein kinase inhibitors (gefitinib and erlotinib). The latter two inhibit intracellular processes resulting from

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* Corresponding author at: Department of Pain Management and Research, Oslo University Hospital, Rikshospitalet, PB 4950 Nydalen, 0424 Oslo, Norway. Tel.: +47 23073691.
E-mail address: harald.breivik@medisin.uio.no (H. Breivik).

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endogenous ligands activating the EGF receptors. All four drugs had the same dramatic effect, typically reducing "worst-pain" from intolerable 9/10 to barely noticeable pain of 1/10 (Numeric Rating Scale – NRS 0–10), improving physical and psychosocial functioning, as well as quality of life. These improvements lasted as long as the pharmacokinetics of the EGFR-inhibitors predicted. Therefore, the authors suggest that this most likely is a class-effect of EGFR-inhibitors, and that a putative mechanism could be via hindering MAPK-signalling and interactions between neuronal, immune, and glia cells, the "neuropathic pain triad" of Scholz and Woolf [3,4].

The EGFR-inhibitors clearly are not curative for neuropathic pain, since successfully treated patients had pain recurring when the drugs were discontinued [1,2]. But two patients had satisfactory pain relief from a low dose pregabalin after the EGFR-inhibitors were discontinued [1].

3. Caveat: some not-so-innocent adverse effects can occur

These four oncologic drugs are approved for treatment of certain types of cancer, as mono-therapies or in combination with cytotoxic drugs or radiation therapy. The adverse effects are considered by oncologists to be "transient and manageable" [1,2]. However, even in this small number of patients there were adverse effects that are not often seen by non-oncologists. One had iridiocyclitis after cetuximab as well as after panitumumab (resolved after local treatment). One had aseptic meningitis after cetuximab (resolved after five days intensive care), and one had significant elevation of liver enzymes while on oral gefinitib treatment (resolved after discontinuation of gefinitib). One had a bacterial pneumonia, which left some dyspnoea after curative antibiotics; this may have been due to insipient interstitial lung disease from gefinitib. After discontinuation of gefinitib, his pain was controlled with a low dose pregabalin.

If the dramatic effects reported in this issue of the *Scandinavian Journal of Pain* are reproduced in clinical trials, several questions will need an answer before general use can be recommended. We need to know whether the treatment works for all neuropathic pain or if it works only for certain subgroups, e.g. only when peripheral parts of the somatosensory nervous system are involved. This is expensive, about NOK 1000 (€140) per day at present drug-prices in Norway, and potentially harmful treatment as demonstrated by the six cases published so far [1,2]. Therefore, we need to know if short-term treatment may induce long-term effects, making traditional drugs for neuropathic pain more effective, as happened with two of the patients reported by Kersten et al. [1]. More knowledge on the potential long-lasting adverse effects is needed before EGFR-inhibitors can be administered long-term to a non-cancer population with a long life expectancy.

4. Our recommendations

These case histories document dramatic effects on severe, physically and psychosocially debilitating, and resistant to traditional-treatment chronic pain conditions with lesion or disease of the somatosensory nervous system. It will be tempting now for physicians, who have in their care patients who suffer horrendously from pain that failed to respond to all available traditional pain management, to offer these patients a trial treatment with epidermal-growth-factor-receptor-inhibitors.

We publish these well documented patient-stories to make pain clinicians and pain researchers, as well as drug companies and government medicines agencies aware of these highly interesting observations.

The applications of these drugs in chronic non-cancer pain should now be in the context of clinical studies. Otherwise, we may risk seriously harming patients.

Our colleagues who are specialists in oncologic drugs must take an active interest in clinical trials. Specialists in palliative medicine may be able to do good clinical trials in their patient populations.

Trials are most urgently needed in patients with severe, chronic non-cancer pain, resistant to other available treatment options. Such trials should be planned and conducted by experienced pain clinicians with special interest in research and treatment of neuropathic pain.

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