BMJ Case Reports

Novel treatment (new drug/intervention; established drug/procedure in new situation)

Cetuximab alleviates neuropathic pain despite tumour progression

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Summary

The authors present the case of a 68-year-old male patient with metastatic rectal cancer. A pelvic recurrence resulted in neuropathic pain, radiating down his left leg. The pain was resistant to standard treatments. However, after nearly 3 years of debilitating pain, the patient experienced dramatic relief just hours after an infusion of the antiepidermal growth factor receptor antibody cetuximab. The analgesic effect lasted for 10–12 days and was repeated roughly every 12 days for three and a half years. To test for placebo effect, the patient received (unknown to him) 20% of his usual cetuximab dose and experienced no pain relief. The dramatic analgesic effect was documented in clinical notes, medication lists and in numeric rating scales even while his cancer was in radiological progression. Mitogen-activated protein kinase (MAPK)-signalling is believed to be an important driver of neuropathic pain and therefore, the authors hypothesise a direct inhibition of MAPK-signalling by cetuximab in neuronal or glial cells.

BACKGROUND

Neuropathic pain (NP) is defined as 'pain caused by a primary lesion or disease of the somatosensory system'.[1] It is commonly characterised by patients as burning, tingling or electric shock-like and is often associated with other neurological symptoms or deficits.[2] Due to its severity, chronicity and the poor side effect to benefit ratio of current pharmacotherapy,[3 4] NP often causes psychological distress, sleep deprivation, functional impairment and overall poor quality of life.[5] With an annual incidence of up to 1% in the general population[6] and a rising prevalence,[3] NP is a common and formidable health problem worldwide.

NP has numerous aetiologies, including mechanical nerve injury, toxic and ischaemic effects, infections and immune-mediated damage. The mechanism of perpetuation of NP, regardless of origin, involves the interaction of neuronal, glial and immune cells.[7] However, a better pathophysiological characterisation of NP is needed in order to promote the development of more individualised, targeted therapies.[8]

Communication between the involved cells is complex and depends partly on signalling via the family of mitogen-activated protein kinase (MAPK) proteins which have been proposed as targets for therapies directed against NP, as well as other chronic neurological diseases.[9–12] Several small molecules designed to inhibit the intracellular MAPK-signalling pathway are currently undergoing clinical phase I and II studies.[13] To date, we are not aware of any reports of extracellular epidermal growth factor receptor (EGFR) inhibition to target MAPK-signalling upstream of RAS, extracellular-signal-regulated kinase, p38 and c-Jun N-terminal kinases. However, several other ligands with the potential to signal via MAPK have been proposed as possible pharmaceutical targets.[14]

We describe a patient's remarkable analgesic response to treatment with the EGFR-inhibitor cetuximab. The drug was initially given to treat metastatic rectal cancer, but serendipitously served as an effective analgesic. The treatment was well tolerated and allowed the patient to maintain a quality of life that otherwise would seem impossible.

If this observation can be repeated and its mechanism understood, it could potentially have important therapeutic consequences for a large group of patients with chronic NP.

CASE PRESENTATION

A previously healthy 62-year-old male underwent curative resection of a rectal tumour in April, 2001. The tumour proved to be a Dukes B, moderately differentiated adenocarcinoma with wild-type K-ras status. At a routine follow-up 29 months later, he was found to have an anastomotic recurrence, without distant metastases. He then received preoperative chemoradiotherapy (50 Gy) and the subsequent surgical re-excision was regarded as R0. Over the course of several months following the second operation, the patient developed pelvic pain radiating down his left lower extremity. Nine months postoperatively (corresponds to figure 1a) he was diagnosed with asymptomatic pulmonary metastases, and systemic palliative treatment was initiated with the Nordic FLIRI (irinotecan and 5-fl ourouracil) chemotherapy regimen.

Due to progressive pain despite antineoplastic treatment, neurological consultation was obtained. Examination revealed decreased sensibility over the dorsum of his left foot and decreased strength of dorsiflexion. Electromyography and electroneuronography revealed findings consistent with lumbosacral plexopathy. Repeated neurological testing showed worsening neurological pathology after 1 month. MRI (corresponding MRI 1 in figure 1a) confirmed a presacral re-recurrence of rectal cancer, involving the patient's sacral plexus and left sciatic nerve. His pain was regarded as neuropathic, caused by the cancer recurrence.

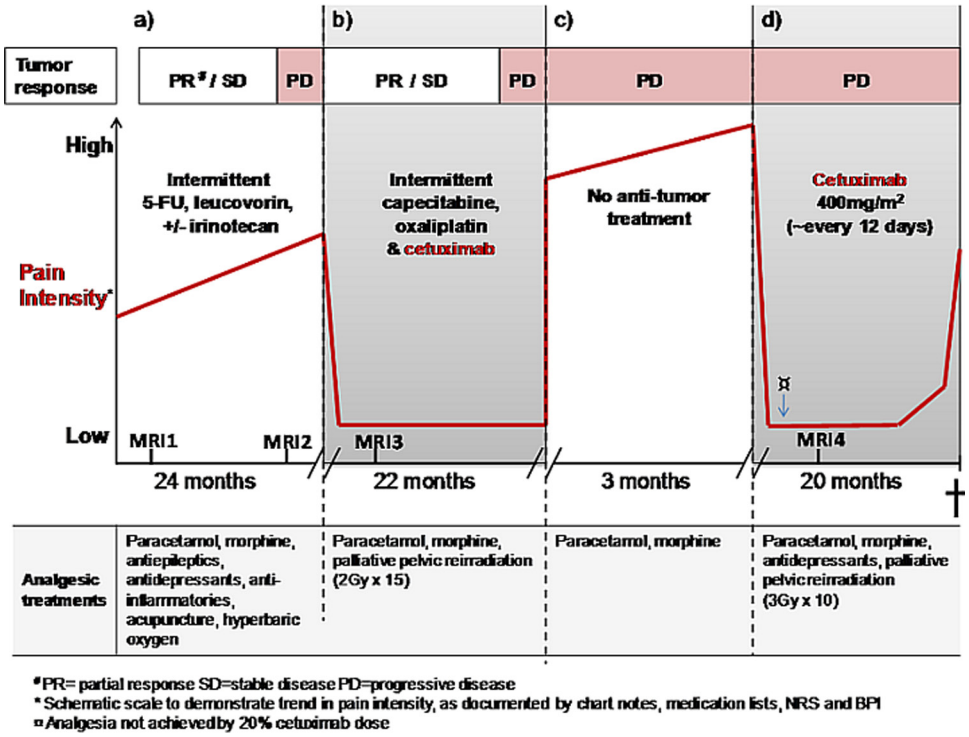

Figure 1 (a–d) Cetuximab alleviates neuropathic pain despite tumour progression.

The patient's pain gradually increased to a level that he characterised as 'unbearable'. Several treatments, including the triplet chemotherapy, paracetamol, morphine (90 mg/24t), antiepileptics, antidepressants, antinflammatories, acupuncture and hyperbaric oxygen, were attempted without satisfactory analgesia (table 1).

After nearly 2 years of intermittent first line palliative chemotherapy, MRI (corresponding to MRI2 in figures 1a and 2a) revealed progression of the tumour affecting the sciatic nerve, and CT scan showed progression of lung metastases.

Due to failure of first line chemotherapy, second line treatment with XELOX (capecitabine and oxaliplatin) chemotherapy and the anti EGFR antibody cetuximab was initiated (figure 1b). At the outset of this treatment the patient required 200 mg morphine/24 h. After nearly 3 years of worsening pain, the patient experienced dramatic relief just hours after an infusion of oxaliplatin and cetuximab. Three weeks after his first course, he reported that the pain had diminished from eight to two on a ten-point numeric rating scale and he no longer required opiates.

During chemotherapy holidays, a common practice in palliative oncologic treatment, the patient's pain recurred and he required increasing doses of opiates. On two such occasions (figure 1b,d), trials of palliative pelvic radiotherapy, intended to relieve pain, were not effective.

However, re-introduction of the combination of chemotherapy and cetuximab repeatedly led to analgesic response within hours. Although the remarkable analgesic effect continued, there was an approximately 20% increase in size of the sciatic nerve lesion on pelvic MRI (corresponding to MRI3 in figures 1b and 2b) after 4 months of treatment. Due to continued good clinical response and stable disease by response evaluation criteria in solid tumours,[15] chemotherapy in combination with cetuximab was continued. After 22 months of this treatment, CT scan revealed progressive lung metastases and as a result, both chemotherapy and antibody were discontinued.

Table 1 Treatments given in an attempt to relieve the patient's pain

Type of intervention	Specific treatment
Analgesic medication	Paracetamol
	Morphine
Antiepileptic medication	Gabapeintin
	Carbamazepine
	Pregabalin
Antidepressant medication	Amitriptyline
Anti-inflammatory medication	Prednisolone
	Non-steroidal anti-inflammatories
Chemotherapy	5-Fluorouracil/leucovorin
	Capecitabine
	Irinotecan
	Oxaliplatin
Other	Hyperbaric oxygen
	Acupuncture
	Palliative radiation

Over the next 3 months, the patient's pain increased profoundly (figure 1c). Standard treatments for NP were inadequate or their side-effects prohibitive. His morphine requirement rose to 320 mg/24 h, without satisfactory effect.

Based on its previously observed rapid analgesic effect, cetuximab monotherapy was attempted (figure 1d). Within 3–4 h after the first infusion, the patient experienced significant pain relief, analogous to that seen after earlier infusions of the XELOX and cetuximab combination (figure 1b). Once again, the patient was able to reduce his dose of depot opiates (from 290 mg/day to 150 mg/day) and he no longer required immediate release morphine. He

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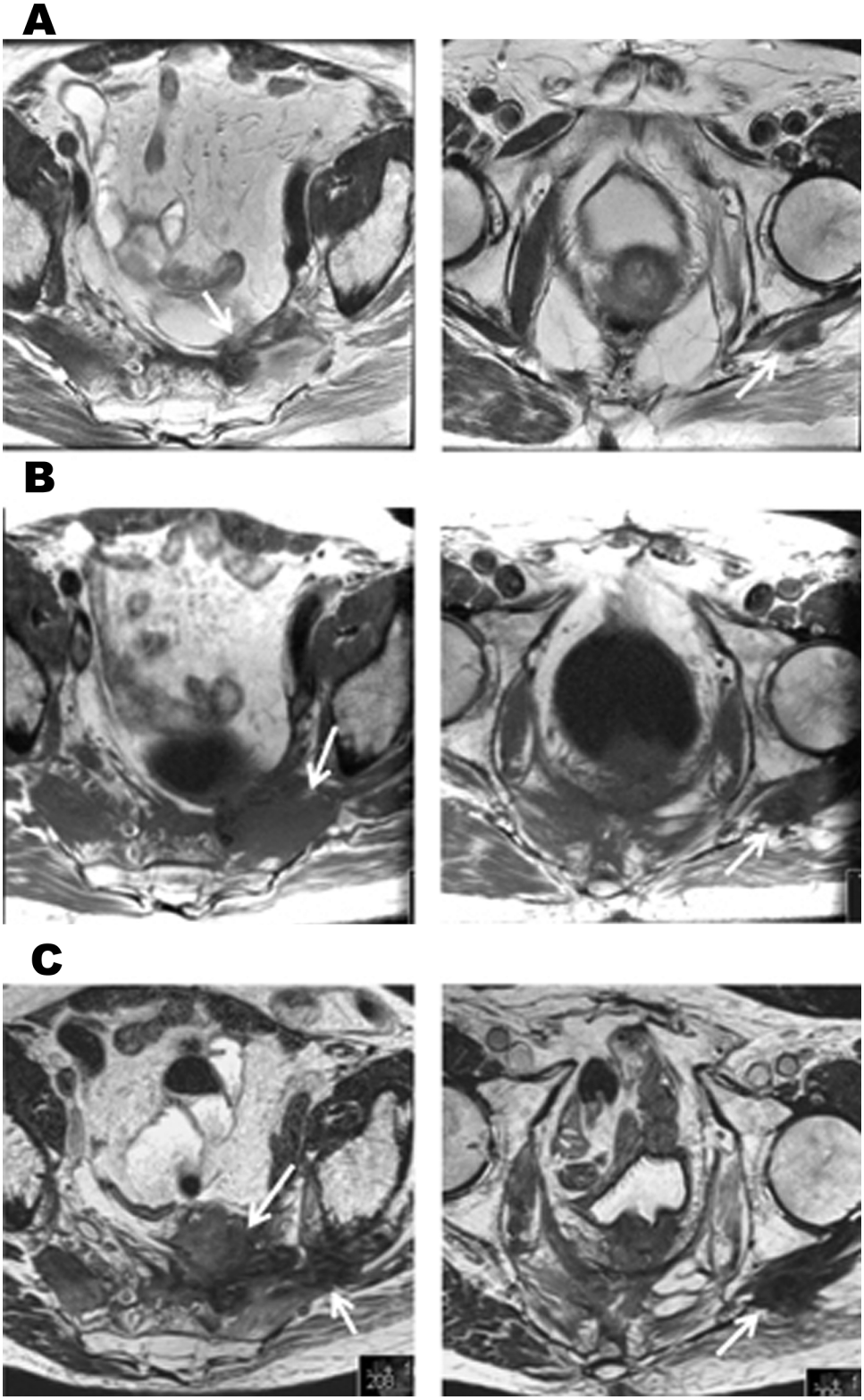

Figure 2 Recurrent and progressive rectal cancer. Arrows indicate tumour changes affecting the left sacral plexus and left sciatic nerve. (a) MRI taken three months prior to starting capecitabine, oxaliplatin and cetuximab (corresponds to MRI 2 in figure 1a). There is a presacral recurrence that extends along the left sciatic nerve. (b)MRI taken 4 months after starting capecitabine, oxaliplatin and cetuximab (corresponds to MRI 3 in figure 1b). Both the presacral recurrence and its extension along the sciatic nerve have increased in size. (c) MRI taken eight months after starting cetuximab monotherapy for analgesia (corresponds to MRI 4 in figure 1d). There is further progression of the recurrence in the presacral area and along the left sciatic nerve.

Table 2 The effect of cetuximab monotherapy during progression of rectal cancer recurrence causing neuropathic pain and a detailed description of the patient's clinical course during the first months of treatment (as depicted in Figure 1d)

Time	0*	4 weeks	6 weeks	2-4 months	5-8 months†
Performance Status	ECOG 2	ECOG 0			ECOG 1
Clinical picture	Increasing pain despite increasing morphine dose.	"A new man" Significantly less pain. Pain recurrence during last few days of each 14-day treatment cycle, necessitating increasing depot morphine.			Continued positive effect within hours, especially on peak pain. Continues to experience end-of-cycle failure.
Cetuximab intervention	Dose: 450 mg	Dose: 350 mg	**Dose: 150 mg**	Dose: 450 mg	Dose: 550 mg
	First infusion of cetuximab monotherapy given as a trial of analgesic effect.	Third infusion	Lower dose of cetuximab in order to assess dose-response and placebo effect.	Continuation of 12-day cycles with cetuximab monotherapy.	Trial of increased cetuximab dose in order to assess end-of-treatment failure.
Result of treatment	**Less pain within 4 hours** of cetuximab infusion, lasting 2 weeks.		**No resultant analgesic effect.**	Less pain within 4 hours of cetuximab infusion, lasting 10-14 days.	Increased dose did not prolong the analgesic response. Interval shortened to 10-12 days.
24-hour morphine requirement	Depot: 290 mg	Depot: 150 mg	Increased morphine requirement	Depot: 90 mg just after infusion, 180 mg just before next dose	Depot: 290 mg just after infusion and up to 480 mg just before next dose
	Immediate release: 120 – 180 mg	Immediate release: none		Immediate release: none except the last few days of the cycle	

ECOG; Eastern Cooperative Oncology Group.
*Corresponds to line 1d in figure 1.
†Corresponds to MRI 4 in figure 1 (MRI 2c in figure 2).

received cetuximab monotherapy infusions every 10–14 days for 20 months (figure 1d). During this period, he consistently responded with effective analgesia within hours, lasting nearly 2 weeks each time.

Increasing opiate requirements that were observed during the last days before treatment suggest an end of dose effect. Observed side effects of cetuximab consisted of mild and transient acne. The most prominent burden of treatment was the need for repeated intravenous infusions.

In order to test for placebo effect, the patient received (unknown to him) 20% of his usual cetuximab dose on one occasion and experienced no resultant pain relief (table 2). A trial of dose escalation from 450 mg to 550 mg did not prolong the analgesic effect. Thus, the treatment interval was shortened to 10–12 days.

Eight months after starting cetuximab monotherapy, MRI again demonstrated growth of the offending lesion (figure 1d, MRI4 and figure 2c). Despite this growth, cetuximab consistently produced a remarkable analgesic response for a total of 12 additional months.

INVESTIGATIONS

See figure 2.

TREATMENT

See tables 1 and 2.

OUTCOME AND FOLLOW-UP

Toward the end of his life, the patient required increasing doses of depot morphine and tended to experience shorter time intervals without 'unbearable' peak pain. On the day before his very last cetuximab infusion, which was administered after 20 months of monotherapy, the patient was admitted to hospital with intense pain. Just hours after the cetuximab infusion, the patient reported that pain at rest had been reduced from five to two and pain on movement had been reduced from nine to two on a ten-point numeric rating scale (figure 3), without increase in analgesic medications or any other interventions. The patient died 1 month later.

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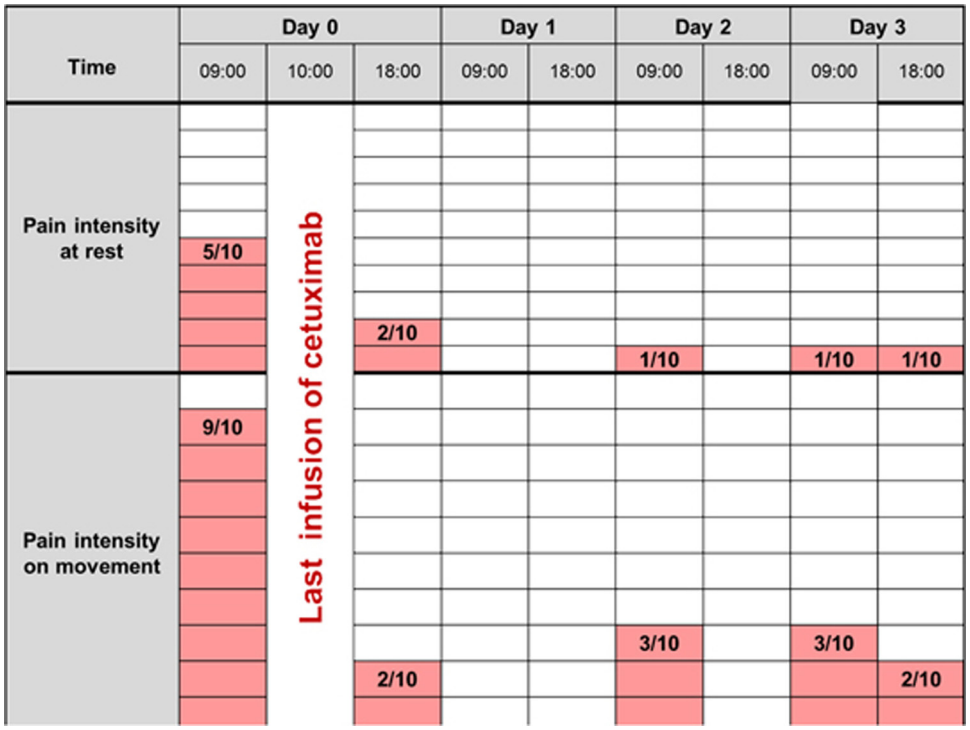

Figure 3 The patient reported pain immediately prior and subsequent to his last infusion of cetuximab (10-point rating scale).

DISCUSSION

To our knowledge, there exist no reports describing an analgesic effect of cetuximab without tumour response. Until now, pain relief in response to cetuximab has been correlated with tumour shrinkage.[16]

Cetuximab was developed to inhibit EGFR1-activation and MAPK-signalling by EGF in cancers.[17] Side effects such as allergic reactions, skin changes and diarrhea are usually mild, manageable and transient.[18] By blocking EGFR1, cetuximab also has the potential to inhibit other EGFR1-binding ligands,[19] either directly or by inhibition of human epidermal growth factor receptor (HER) family heterodimerisation.[20 21] Our patient experienced dramatic analgesic effect just hours after treatment with cetuximab, although his tumour was in progression. The pain relief is well documented and importantly, did not respond to dose reduction. The timing of our patient's pain relief correlates with the pharmacokinetics of cetuximab.[22]

After nerve injury, neurons upregulate members of the HER-family of receptors,[7 23 24] thereby potentially increasing their activation of the MAPK signalling[10] cascade. This may lead to further interaction between cells in the NP triad. Additionally, it has been shown that EGF has the potential to act in a rapid, but short-lasting manner on nociceptive neurons, which is consistent with our clinical observation.[25] We therefore hypothesise a direct inhibition of MAPK-signalling by cetuximab in neuronal or glial cells.

Data from two published clinical trials may support the protective role of cetuximab on the development of oxaliplatin-induced neuropathy. Both the Nordic VII[26] and COIN[27] studies analysed the potential survival benefit of adding cetuximab to oxaliplatin-containing 5FU-based chemotherapy in patients with metastatic colorectal cancer. In both studies, no survival benefit was shown and patients treated with and without cetuximab received similar doses of the neuropathy-inducing chemotherapy, oxaliplatin. Interestingly, in both studies, the incidence of peripheral neuropathy was 30% less in the arms that also received cetuximab. This finding was statistically significant in the COIN study (p=0.0053).

At this time, we can only speculate about the analgesic mechanism in our patient, but the rapid onset indicates a direct effect on neuronal cells or on the communication among the NP triad.[7] If confirmed, these findings may have important implications for the treatment of NP. Further preclinical and clinical studies of EGFR-inhibition, including the use of oral agents are warranted.

Learning points

- Many treatments of NP are characterised by a narrow therapeutic index. Inhibition of MAPK-signalling is proposed to be a promising target.
- We present a case of repeated and dramatic relief of NP within hours after infusion of the EGFR-inhibitor cetuximab.
- The duration of analgesia is consistent with the pharmacokinetics of cetuximab and the patient recognised blinded dose reduction.
- EGFR-inhibition in NP warrants further study.

Competing interests We, the authors, have filed a US provisional patent application for the use of EGFR as a clinical target for treatment of neurological disorders. There are no other potential conflicts of interest.

Patient consent Obtained.

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