Introduction

Intractable neuropathic pain is a real challenge for any palliative care specialist, and problems add up when dealing with a young patient, still struggling with the acceptance of diagnosis and prognosis, raising the issue of total pain. Methadone and sub anesthetic dose of ketamine (1) in cancer patients with intractable neuropathic pain proved their efficacy (2-11).

Case Report

Phase I – August 2012

We report the case of a 50 year old woman who presented in our outpatient clinic with advanced cervical cancer diagnosed one year before. Patient, initially staged III B, progressed loco-regionally after chemo-radiotherapy and two lines of chemotherapy (Paclitaxel- Carboplatin and Gemcitabine).

The patient presented was admitted with locally advanced disease, metastases in pelvic lymph nodes, venous thrombosis of the left femoral vein and concomitant lymphedema of left foot. Her pain, with a strong neuropathic component, was previously well controlled with the following outpatient regimen: slow-release oral morphine in a dosage of 120mg bid (240 mg/24 hours), rapid-release oral morphine 40mg prn, Gabapentin 300mg tid, Metamizole 500mg tid. At the time of admittance, she reported severe pain of the pelvic region, rated 9/10 on VAS scale, associated with sciatalgia, hyperalgesia and allodynia, all being strong indicators of a important neuropathic component.

The only opioid with known activity on NMDA receptors, which actively contribute to central sensitization in certain types of neuropathic pain, is methadone. Therefore, in order to regain pain control, we considered opioid rotation from morphine to methadone and concomitant increasing of coanalgetic dose for neuropathic component (Gabapentin). Rotation on Methadone was done with slow, 14-days, up-titration to efficient dose of 30 mg bid (60 mg daily). We also increased the dose of Gabapentin to 600mg bid and added Mirtazapin 30mg daily for psychological distress/depression component of total pain. With this therapy, we were able to achieve complete pain control.

Phase II

The patient was pain-free for several months. With the increase of pain, methadone was escalated at home, with 5mg/dose till complete control of pain.
Phase III

In May 2013, the patient was pain-free at a Methadone dose of 80mg bid, but needed to be admitted when the external pharmacy ran out of available Methadone, and also Methadone was not available in the hospital’s pharmacy. No methadone could be provided in any pharmacy, so we decided rotating the patient to slow release oxycodone – 80mg bid, keeping the same regimen otherwise. The patient complained of severe pain (10/10 on VAS scale), high level of anxiety and depression, crying and becoming desperate as days passed and with the escalation of oxycodone we could not ameliorate her pain, then she became somnolent, complaining continuously of severe, neuropathic pain in her left foot. We decided adopting ketamine with oxycodone at a lower dose, considering its possible benefit in intractable neuropathic pain, especially in a short-duration (3 to 5 days) regimen in terminal ill patients, with a potential persistence of pain-free time after ketamine-stop. After a total of 5 days – the first 2 days (titration phase) with the increase of the qid dose from 10 mg to 25 mg, than to 50mg/dose, afterwards we kept the administration of 50 mg ketamine at 6h (qid) after achieving adequate pain control for additional 72h (maintenance phase).

The main adverse event for ketamine is its well-known psychomymetic effect. In order to prevent this side effect, we recommended concomitant prophylactic haloperidol and added small doses of midazolam (1mg/dose) for agitation and anxiety, acquiring complete control of the psychomymetic symptoms. The patient was discharged with slow release oxycodone 40mg tid which was reduced after two days (telephone contact) for sedation and high suspicion of overdosing, at a dose of 40mg bid. The patient died two weeks later completely pain free, with no usage of oxycodone in her last three days of life.

Discussion

In palliative care practice, ketamine has been administered as a coanalgesic, in addition to opioids and other coadjuvant drugs. Ketamine is now considered to be an essential adjuvant analgesic for refractory cancer pain, being on the WHO’s Essential Drug List for patients who no longer respond to high doses of opioids (12). The use of subanesthetic ketamine has no solid literature evidence to assess benefits and harms (13). The conclusion of the Cochrane Review 2003, with an 2009 update (14), and also a recent randomized double-blind phase 3 trial, designed to evaluate pain management in 185 cancer patients, was that there was no difference between ketamine and placebo (15). On the other hand, there are a multitude of guidelines (16-22) for the use of subanesthetic doses of ketamine in the management of intractable neuropathic pain in patients with terminal cancer illness. The mechanism of action of ketamine includes its features as a NMDA receptor antagonist, dopaminergic, cholinergic, noradrenergic, serotonergic, opiate and anti-inflammatory effect. The onset of action is 15-30 minutes after subcutaneous injection and 30 minutes after oral administration, respectively. Its plasma half-life is of 3h after oral administration, and has duration of action of 4-6h after oral administration (23). Psychomymetic side effects, as well as delirium, dizziness, diplopia, blurred vision, nystagmus, altered hearing, impaired attention, memory and judgement, hypertension, tachycardia, increased intracranial pressure, urinary tract symptoms are less with the oral administration (24). Prevention of sedation was considered by reducing the scheduled opiates with initially 25% of the previous dosage and prevention of psychomymetic side effects was made by using oral haloperidol in doses of 1.5 mg tid. The onset of undesired psychomymetic side effects was treated with low doses of midazolam (1mg/dose, repeated prn). No hypertension or tachycardia was observed. We preferred the oral route, through a fruit-juice vehicle, due to its unpleasant taste. We started with a 10mg dose p.o. qid, at 6h, and increased the second day to 25mg p.o. qid, and subsequently to 50mg p.o. qid in day 3, then continued at this dosage after good pain control. Onset of side effects were treated as noted. We chose the burst technique, and stopped 3 days after effective dose. Oral oxycodone was continued at a low, final 40mg bid dose.

We should also emphasize that, at the moment morphine was rotated on methadone, her oncologist formulated an estimated prognosis of under one month. She actually survived six more months with complete symptom control, at home with her children, where she desired to be and to live her life till the end. The last hospitalization was indeed not intended and it was determined only by the methadone’s unavailability.

Conclusion

This was the first case in our experience with a confirmed complete response to ketamine in an advanced cancer patient with terminal illness and intractable neuropathic pain, resistant to opioids and coanalgesics (antidepressant and anticonvulsivant), after burst-administration, with complete remission of pain for the rest of her life – i.e. two weeks. This case report should encourage other colleagues to use methadone and ketamine for intractable neuropathic pain.

References

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