THE USE OF KETAMINE FOR REFRACTORY CANCER RELATED HEADACHE — CASE REPORTS

Elwira Góraj, Małgorzata Lipiec, Beata Stypuła–Ciuba

Pain and Palliative Medicine Clinic, Clinic of Diagnostic Oncology and Cardio-Oncology,
M. Skłodowska–Curie Memorial Cancer Centre and Institute of Oncology in Warsaw, Poland.

INTRODUCTION

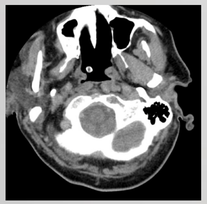
Ketami ne inhibits the activation of an of N-methyl-D-aspartate receptor (NMDA-R) in secondary afferent neurons, which are important in progress of sensitivity (wind up) caused by repeated nociceptive stimulation. Also has opioid's sparing effect. NMDA antagonists has been utilized in the treatment of opioid-resistant pain and combat opioid tolerance and hyperalgesia, allodynia with positive response to ketamine ≥67% .

The treatment algorithms of severe cancer pain usually incl ude, dose escalation, opioid rotation, drug holidays and combination of drugs with different mechanisms of action (additive or synergistic mechanism). The benefits and risks of the addition of ketamine to an opioid regimen in this setting have not been well established.

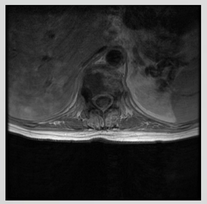
Key Words: Palliative care, brain metasthasis, neuropathic pain, NMDA – receptor, psychotomimetic side effects.

CASE No 1

41 year old female with advanced breast cancer and metastases to the bones, liver and meninges. Cerebrospinal fluid (CSF) cytology revealed cellulae carcinomatosae – metastasis of breast tumor. Contrast-enhanced magnetic resonance imaging (MRI) of the brain showed narrowing of the frontal lobe fissures as well as infiltration of the meninges by tumor cells. Skull base and right branch of mandibular metastasis.



Infiltration of the meninges by tumor cells



Selective nerve root infiltration on the level Th11-L1

Diagnosis: leptomeningeal (LM) metastasis.

Computed tomography (CT) of the spine and vertebrae in the neck and upper back found metastasis on cervical level and selective nerve root infiltration on the level Th11-L1 where tumor mass entered the epidural space. CNS metastasis as a symptoms of breast cancer recurrence, reduce overall survival, particularly when LM is diagnosed. More often susceptible are individuals with ER/PR negative HER-2 positive tumors. This patient was ER 100% pos/PR 20%pos and HER-2 positive.
She was referred to Palliative Medicine specialist due to excruciating headache and pain of the right eyeball which even increase after chemiotherapy. Pain was a diagnosed as mixed neuropathic and nociceptive.

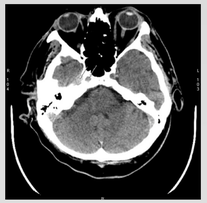
Current treatment: oxycodone sustained-release 160mg/d, Methadone 90mg/d, Dexaven 8-16mg/d, Lorazepam 2,5mg qd.
As a noncurative anticancer treatment, to reduce symptoms, she received intrathecal chemotherapy – liposomal cytarabine.

Headache is the most common symptoms of LM due to infiltration of the meninges or/and elevation in intracranial pressure (ICP). Any new headache in a patient with cancer, and especially headaches that are worse upon awakening or in recumbent positions should heighten suspicion for LM also other neurological dysfunctions affecting CNS.

Protocol of Ketamine use:
Initial Ketamine dose was 0,08 – 2 mg/kg/h up to 4mg/kg/h, titrating up to a target.
Clonazepam 0.5mg iv/sc (q4h) every 4 h was used to prevent psychotomimetic side effects.
Monitoring: respiratory frequency, heart rate, blood pressure, sedation depth, NRS

CASE No 2

57 year old male patient with advanced colorectal cancer, metastasis to bones, liver and vertebral column with Th8 fracture. In CT image meningioma, Neurologic status – conscious with restlessness (periodically screaming), difficult to examine due to strong pain in occipital area. Left side paresis with predominance of left upper extremity, exophthalmos of the right eyeball and peripheral palsy of right n.VII. Negates symptoms such as neck stiffness nausea and vomiting. Pain describes as stabbing and bursting NRS 10.
CT scan with contrast agent revealed small mass 19x14mm in the area of sella turcica, meninges infiltrations of temporal zone. CT of cervical spina – abnormal structure (meta) to atlas and arc of odontoid.



Meninges infiltrations of temporal zone

Treatment:
Morphine 100 mg bid, Dexaven 8 mg IV b.i.d., Ketoprofen 100 mg IV b.i.d.,
Paracetamol 1 g IV q.i.d.,
Furosemide 20 mg IV, Morphine 10 mg SC. q.s.
Mannitol 200 mg IV, Metamizol 2,5 g q.s., Midazolam 1 mg/h IV, Amitryptylinum 25 mg q.d.
Pain reduced to NRS 3 but returned.
Ketamine was started according to protocol (as above).
Because of irreversible changes in CNC, active systemic disease and concurrent metastasis patient was disqualified from surgery and anticancer therapy. Despite acceptable pain controlled presented high level of psychological suffering. After consultations was suggested palliative sedation to relive distress what the patient has consented. We started fentanyl with midazolam with lower doses of Ketamine. Ketamine was titrated 10-30mg TDS SC till his death.
Monitoring: respiratory frequency, heart rate, blood pressure, sedation depth, NRS

RESULTATES:
Pain score

Patient No 1
Pain was recorded by NRS 0–10 scale every 1 hour during first 8 hours and twice a day after.
NRSo 9, after 2h of Ketamine injection, pain score improved from 9 to 5
and the patient was satisfied with analgesia. Other treatment was continued.

Patient No 2
Pain was recorded by NRS 0-10 scale every 1 hour during first 8 hours
and twice a day after.
NRSo 8, after 2h of Ketamine injection NRS1 was 6,
after following 2 h Nrs2 was ≤3.

CONCLUSIONS:

1. No untoward side-effects were noted except drowsiness which responded to a reduction in the opioids dose.
2. Small-doses of Ketamine given with opioids to neuropatic nonresponsive terminal cancer pain where more effective then opioids itself.

Bibliography

1. *Scott B., Kesari S. Leptomeningeal metastases in breast cancer. Am J Cancer Res. 2013; 3(2): 117–126.*
2. *Mercadante S, Arcuri E, Tirelli W, et al. Analgesic effect of intravenous ketamine in cancer patients on morphine therapy: a randomized, controlled, double-blind, crossover, double-dose study. J Pain Symptom Manage 2000;20:246-52.*
3. *Cohen P.S, Wang S et all. An Intravenous Ketamine Test as a Predictive Response Tool in Opioid-Exposed Patients with Persistent Pain. Journal of Pain and Symptom Management Vol. 37 No. 4 April 2009.*
4. *Chaudhary W, A, Kennett J et all. CASE SERIES – Ketamine as an adjuvant to opioids for cancer pain management. Anaesthesia, Pain & Intensive are. ISSN 1607-8322, ISSN (Online) 2220-5799*

CANCER CENTRE – INSTITUTE
MARIA SKLODOWSKA–CURIE MEMORIAL
IN WARSAW POLAND

Corresponding author:
egoraj@coi.waw.pl, mlipiec@coi.waw.pl, bciuba@coi.waw.pl

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