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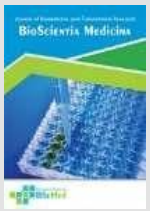

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Pain Management in Blast Crisis Phase of Chronic Myeloid Leukemia: A Case Report

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A B S T R A C T

Background: Chronic myeloid leukemia (CML) is a slow-growing type of cancer that begins in the bone marrow's blood-forming cells and is caused by a chromosomal mutation that is assumed to develop spontaneously. As CML advances into the rapid or blast phase, it can cause significant pain. This study aimed to describe pain management in the blast crisis (BC) phase of CML. **Case presentation:** A 48-year-old female diagnosed with CML in the BC phase complained of severe pain in the head, shoulders, back, and tailbone area with a numeric rating scale (NRS) of 9/10. The patient received multimodal analgesic therapy with continuous IV fentanyl at a rate of 0.25 mcg/kg/hour and ketamine at 1.3 mcg/kg/minute for 24 hours. The dosage was gradually increased through titration with a target NRS of 4/10. On the fifth day, we replaced fentanyl with morphine at 0.04 mg/kg/hour and ketamine at 1.3 mcg/kg/minute, and we reduced the titration dose according to the patient's NRS, and her pain was controlled with NRS 3-4/10 after 7 days of treatment. On the 9th day, she was discharged with oral therapy. **Conclusion:** Multimodal analgesia has been shown to effectively reduce the intensity of the pain in blast crisis phase.

1. Introduction

Chronic myeloid leukemia (CML) is a slow-growing type of cancer that begins in the bone marrow's blood-forming cells and is caused by a chromosomal mutation that is assumed to develop spontaneously.[1] Generally, CML consists of three phases: the chronic phase, the accelerated phase, and the blast crisis (BC) phase.[2] The majority of CML patients are diagnosed in the chronic phase, which progresses to the accelerated phase and, if untreated, results in BC.[1] Each phase is defined by the number of immature cells (blasts) found in the bone marrow.[2] As CML advances into the rapid or blast phase, it can cause significant pain.[3] The pain experienced by patients with CML can be due to both cancer-related mechanisms and the use of definitive medications.[3,4] The management provided to these patients is complex and challenging due to the rapid progression to the BC phase and the high pain scale despite using opioid therapy when first consulted. This study aimed to describe pain management in the blast crisis (BC) phase of CML.

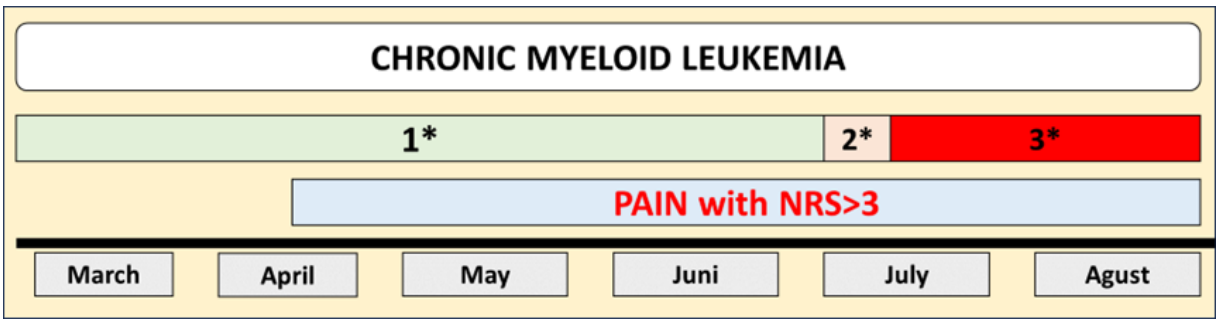
2. Case Presentation

A 48-year-old female patient diagnosed with CML in the BC phase complained of severe pain in the head, shoulders, back, and tailbone area. She had been treated at our institution for 30 days and received imatinib for four months, which was then switched to nilotinib. She was consulted by our department for pain management. The patient had been experiencing pain for approximately four months. Initially, it was felt only in the shoulders and back, but it gradually

worsened and extended to the head and tailbone. The pain was constant but improved with morphine sulfate slow-release tablet (MST) 10 mg every 12 hours and Paracetamol 500 mg tablet every 8 hours. Due to the increasing pain intensity, the dosages were then increased to MST 20 mg every 12 hours (q12h) and Paracetamol 750 mg q8h. A month later, the dosages were further increased to MST 20 mg q8h, Paracetamol 750 mg q8h, and Amitriptyline 12.5 mg q12h was added. Three days before consultation, the patient was given an additional fentanyl patch of 25 mcg/hour, but the pain persisted.

Laboratory results showed a low leukocyte count of 160 cells/µL, haemoglobin of 4.7 g/dL, and platelets at 2,000 cells/µL. Bone marrow pathology indicated decreased megakaryocyte system activity, hypercellularity, decreased erythroid system activity, and increased myeloid system activity with 80% myeloblasts. Bone marrow biopsy pathology showed a dominance of blast cells with an increase of more than 20%, indicating blast transformation. At bedside examination, she was conscious but markedly weak, so she could only lie down on the bed. Her blood pressure was 130/70 mmHg, heart rate 124 beats per minute, respiratory rate of 24 breaths per minute, peripheral oxygen saturation (SpO_2) of 99% at 3 liters per minute, oxygen supplementation per nasal cannula, and a numerical pain rating scale (NRS) score of 9 out of 10. At that moment, she was receiving MST 30 mg q12h, Paracetamol 1 g q8h, methylprednisolone 8 mg q8h, and Amitriptyline 12.5 mg q12h. We provide pain management with multimodal analgesics with a target NRS of 4/10. MST and fentanyl patch were temporarily halted, and we administered a rescue dose of fentanyl 25 mcg and ketamine 6 mg intravenously (IV). At the 15-minute evaluation, the pain scale decreased to 7/10, but she still reported discomfort with no significant change in pain. Another dose of rescue analgesic regimen was administered, resulting in a further NRS decrease to 4/10 at the following 15-minute evaluation.

Upon achieving the targeted NRS, we further prescribed continuous IV fentanyl at a rate of 0.25 mcg/kg/hour and ketamine at 1.3 mcg/kg/minute for 24 hours. The dosage was gradually increased through titration with a target NRS of 4/10. On the fifth day, we replaced fentanyl with morphine at 0.04 mg/kg/hour and ketamine at 1.3 mcg/kg/minute, and we reduced the titration dose according to the patient's NRS. On the seventh day, the patient's pain was controlled with NRS 3-4/10, and we changed therapy with MST 30 mg q12h and paracetamol 1 g q8h. The patient was able to sit in the afternoon and do light activities on her own, such as eating and changing clothes. The patient was discharged the next day. The patient's disease progression and the analgesic therapy provided can be seen in detail in Figures 1 and 2.



Notes: 1* = chronic phase, 2* = acceleration phase, 3* = blast crisis phase.

Figure 1. The course of CML in our case.

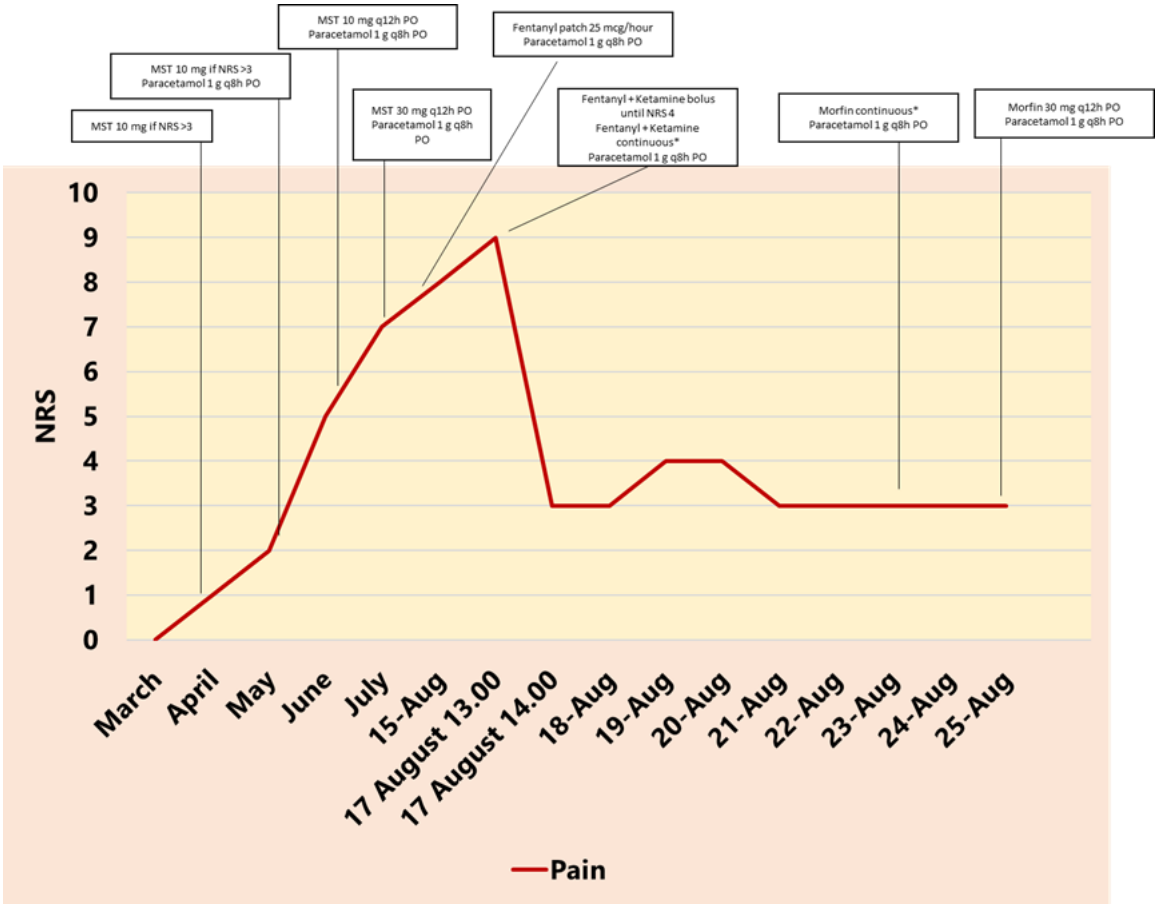


Figure 2. Pain progression and course of therapy.

3. Discussion

BC is the final stage of CML.[1] Symptoms can include bleeding diathesis, headaches, fever, joint pain, bone pain, night sweats, weight loss, and fatigue.[5] The World Health Organization (WHO) defines BC as 20% blasts in the bone marrow or peripheral blood.[3,5] In our case, two weeks after the patient was diagnosed with CML in the accelerated phase, the patient transitioned to the BC phase.

One of the most prominent symptoms reported by patients with blood-related diseases is bone pain, which is caused by two pathological processes: osteolytic lesions and malignant cell infiltration of bone marrow (BM).[6] The stimulation of sensory and sympathetic nerve fibers that extensively innervate the periosteum, mineralized bone, and BM causes pain in this disease.[7] Pain may be caused by consequences other than skeletal involvement, such as physical deconditioning syndrome, which is characterized by muscle atrophy and physical debility, resulting in bedsores, constipation, and rectal and bladder spasms with a negative impact on the quality of life.[8]

As with the treatment of solid tumour pain, the pharmacological management of pain in patients with blood-related cancer may include analgesic (opioid and non-opioid) and adjuvant agents, the selection of which should be based on the diagnosis of the type of pain (nociceptive, neuropathic and breakthrough) and its severity.[8] Several patient-related variables, such as the patient's clinical condition, comorbidities (e.g., renal failure, liver disease, peptic ulcer disease, mental health problems, cardiovascular disease, diabetes mellitus, and other chronic conditions), and concomitant medications (e.g., polypharmacy and the

risk of drug interactions) should be carefully considered because of their potential impact on analgesic efficacy and tolerability.[8-11]

The effectiveness of pain management using the World Health Organization (WHO) analgesic ladder has been reported in these patients.[12,13] The WHO ladder is a stepwise approach in which the analgesic is chosen based on the intensity of the pain; as the severity of the pain increases, so does the strength of the prescribed analgesic. In individuals with quickly rising or uncontrolled pain, the intravenous route is the quickest means to deliver analgesia. In patients with oral mucositis, patient-controlled analgesia (PCA) using intravenous morphine is the preferred approach to pain treatment. Rapid-onset pain can also be controlled with highly lipophilic opioids like fentanyl, which is available in transmucosal, buccal, sublingual, and intranasal formulations for breakthrough pain.[8,14-16]

If pain occurs, the WHO Ladder recommends giving analgesic medication orally as soon as possible till the patient is pain-free. This guideline also suggests that medications should be administered “by the clock” (i.e., every 3-6 hours) rather than “on patient’s demand” to maintain “freedom from pain”.[16] Opioids remain the mainstay of pain management in cancer, but the risk of long-term consequences such as tolerance, dependency, hyperalgesia, and hypothalamic-pituitary axis suppression should be recognized and controlled, both in non-cancer and cancer pain.[16] Other medications and methods of administration, such as NSAIDs, antiepileptic pharmaceuticals, tricyclic antidepressants, NMDA receptor antagonists, sodium channel blockers, topical treatments, and neuraxial drug administration, are also important in the therapy of cancer pain.[16,17]

The WHO ladder recommends starting with non-opioids (paracetamol and NSAIDs), followed by weak opioids (codeine), and then, if necessary, strong opioids (morphine). It also suggests using adjuvant drugs to relieve fear and anxiety. This three-step process for delivering the correct drug at the right dose at the right time is cost-efficient and has been shown to be effective in 45-100% of cases worldwide.[16]

Opioids differ in terms of their affinity to bind to receptor sites, pharmacokinetics, and physicochemical features. This means that particular opioids may have an advantage over others due to differences in side effect profiles, administration routes, tolerance development, and immunomodulatory tendencies. Indeed, the present trend of "opioid rotation" may be influenced in part by the requirement to rotate between opioids that are not fully cross-tolerant in order to minimize inherent toxicities.[18-19]

“Adjuvants” have now been shown to act through nerve and synaptic ion channels and receptors that may be as important as opioid receptors. Voltage-gated calcium channels can be blocked by gabapentin or pregabalin. Sodium channels, which then activate calcium channels, can be blocked by local anesthetics and older-generation antiepileptics such as carbamazepine. Other drugs act by modulating the transmission and uptake of noradrenergic and serotonergic neurotransmitters, such as tricyclic antidepressants, serotonin-norepinephrine reuptake inhibitors, and tramadol. NSAIDs and COX inhibitors may exert antinociceptive effects by dampening peripheral nerve sensitivity and spinal synaptic transmission. In most forms of chronic pain, postsynaptic NMDA receptors are open, resulting in calcium influx, nitric oxide induction, nerve excitability, and gene expression leading to nerve plasticity, central sensitisation, allodynia, and hyperalgesia. NMDA channel blockers such as ketamine and the d-isomer of many opioids, particularly methadone, can reduce these adverse changes.[16,20-22]

The patient received multimodal analgesic therapy as per WHO’s step-ladder for the management of cancer pain. After 5 days of treatment, we changed the opioid from fentanyl to morphine. The pain was controlled after 7 days of treatment. On the 9th day, she was discharged with oral therapy.

4. Conclusion

CML is a malignancy of the bone marrow and blood, typically diagnosed in the chronic phase. Pain experienced by CML patients can result from both cancer-related mechanisms and the use of definitive medications. CML can lead to significant pain as the disease progresses. In this patient, we employed a multimodal analgesia therapy involving opioids, paracetamol, amitriptyline, and NMDA antagonists. This treatment approach yielded favourable results, with the patient's pain rating scale (NRS) decreasing from 9/10 to 3-4/10. Multimodal analgesia has been shown to effectively reduce the intensity of the patient's pain.

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