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Methadone dose escalation in patients with opioid use disorder and cancer as a strategy for controlling cancer-related pain: A case series

Marco Carli, M.D.[1], Elisabetta Fini, M.D.[2], Giulia De Luca, M.D.[2], Marco Scarselli, PH.D.[1], Francesco Lamanna, M.D.[3], Tiziana Vico, M.D.[3] and Guido Bocci, M.D., PH.D.[2]

[1]Dipartimento di Ricerca Traslazionale e delle Nuove Tecnologie in Medicina e Chirurgia, Università di Pisa, Pisa, Italy; [2]Dipartimento di Medicina Clinica e Sperimentale, Università di Pisa, Pisa, Italy and [3]Pisa Ser.D., Azienda USL Toscana Nord Ovest, Pisa, Italy

Case Report

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Corresponding author: Guido Bocci;
Email: guido.bocci@unipi.it

Abstract

Objectives. Opioid use disorder (OUD) and cancer gained attention as co-occurring diseases in the last 2 decades due to the possible relationship between opioid prescriptions for cancer pain and the risk of developing substance use disorder in cancer patients. However, little is known about patients previously diagnosed with OUD who develop cancer and how to manage both OUD symptoms and control pain.

Methods. The present case series deals with this subpopulation and proposes a dose escalation of methadone to control both the cancer-related pain and drug addiction symptoms.

Results. This approach is peculiar because methadone is not used as a first-line treatment in cancer pain management and is not often used as a second-line treatment as well. Our 4 patients experienced good clinical control of symptoms and no major adverse reactions.

Significance of results. The subgroup of patients with OUD who develop cancer could be the perfect population to reconsider the use of methadone as a first-line treatment for cancer pain. Prospective studies are needed to evaluate the efficacy and safety of increasing doses of methadone in these patients to validate our clinical approach.

Introduction

Substance use disorder (SUD) and cancer gained attention as co-occurring diseases in the last 2 decades for the possible relationship between opioid prescriptions for cancer pain and the risk of developing addiction in cancer patients (Whitcomb et al. 2002). However, the issue of SUD patients who subsequently develop cancer at a second time remains understudied, particularly for those patients with opioid use disorder (OUD).

Data are limited on pain management in patients who are in methadone maintenance therapy for their OUD. A recent systematic review addressing the issue comprised only 7 studies, with a total of 142 participants and an overall poor quality of evidence, most of the studies being case series or case reports (Taveros and Chuang 2017).

Methadone use in cancer pain as a first-line choice is limited due to its difficult titration and its severe adverse drug reactions (ADRs), such as cardiac arrhythmias (Nicholson et al. 2017). However, some studies suggest that methadone could be as effective and safe as other opioids in cancer analgesia, used at doses up to 25 mg/day (Mercadante and Bruera 2018). At the moment, its use is limited compared to other opioid drugs (Wiffen et al. 2017), but it could be of particular interest in patients already taking it for their OUD and administered by experienced practitioners, although the current literature is not strong enough to give solid basis to this statement (Taveros and Chuang 2017).

We describe the clinical management of methadone-treated patients with OUD developing cancer and highlight a possible role of methadone dose escalation in controlling both their cancer-related pain and OUD. We also speculate on the role of methadone in cancer progression and possibly on overall survival (OS).

Cases description

Patient 1 is a 63-year-old Caucasian woman with a history of heroin and cocaine use disorder and tetrahydrocannabinol (THC) use. In 2020, at the age of 61, she was diagnosed with gastric cancer. At that time, she was on buprenorphine therapy with very low dosage

(2 mg/day per os) to treat the addiction. In 2021, she had a relapse with the appearance of peritoneal carcinomatosis and she was treated by palliative care with tapentadol (75 + 50 mg/day) and buprenorphine transdermal 8 mg/day. When she came back to our attention, she was switched to methadone 60 mg/day (baseline) to control the metastatic pain with a progressive reduction of tapentadol and buprenorphine. Methadone was titrated up to 220 mg/day fractionated into 2 doses per day in the following 7 months (366.7% increase in her methadone intake). In addition, fentanyl was prescribed as a rescue for breakthrough pain. Interestingly, when she was 49, she had already been diagnosed with breast cancer, and she was on methadone 80 mg/day at the time.

The patient is alive at the moment of data collection. Her SUD is under control and cancer pain under satisfying control.

Patient 2 is a 65-year-old Caucasian woman with alcohol and heroin use disorder and cocaine use. At 63, she was diagnosed with colon cancer. At that time, she was not under treatment in our center because she had previously discontinued methadone 150 mg/day. She came back in 2022 after the last ostomy surgery, and she was taking methadone 80 mg/day as prescribed by surgeons for post-surgical pain. To ensure the best antalgic coverage, methadone was increased to a dose of 145 mg/day within 7 days (161% increase). She never needed rescue doses. The patient is currently alive and in control with OUD.

Patient 3 was a 62-year-old Caucasian man with cannabinoid abuse who developed an OUD secondary to tramadol prescription for low back pain. In 2010, he started his treatment with methadone. In December 2017, he received a diagnosis of oropharyngeal squamous cell carcinoma with lymph node metastasis (stage II). At that time, he was under treatment with buprenorphine/naloxone 24 mg/day but soon gave up the follow-up at our center. He returned in October 2021, following a relapse of cancer with pulmonary metastasis, with the aim of receiving analgesic therapy for metastatic pain. The prescribed analgesic therapy was based on methadone, initially at a dosage of 20 mg/day. Methadone regimen was progressively augmented to reach 240 mg/day 3 doses per day in June 2022 (1200% increase from baseline). The constant increase permitted to control both cancer pain and OUD, and rescue doses were necessary during the escalation period for the worsening of pain. No sedation was observed at dose escalation, while the social compromission was linked to the cancer progression and not to the drug administered. The patient died in September 2022.

Patient 4 was a 51-year-old Caucasian woman who referred to our clinical unit since the age of 46. Her first diagnosis was heroin use disorder and THC, cocaine, and alcohol abuse. Thus, physicians prescribed methadone as opioid agonist therapy. In May 2021, the patient was diagnosed with right upper lobe lung cancer. At diagnosis, the tumor was already in stage IV with involvement of mediastinal lymph nodes and extensive metastases at bone level (skull and pelvis). The major concern was the pain related to skull metastasis. At that time, the patient was taking 45 mg/day methadone. The dosage of methadone was gradually increased up to 110 mg/day 3 doses *per* day in December 2021. This dose escalation, which reached a percentage increase of 244% compared to the baseline, was necessary to achieve a control of both pain symptoms and OUD. The patient died in August 2022.

In the 4 reported cases, we have not found ADRs to methadone. We tried to keep methadone as a monotherapy by avoiding the use of other drugs, with the exception of patient 1 who was also occasionally treated with fentanyl for breakthrough pain.

Discussion

The present case series deals with patients with OUD who develop cancer and the possible control of both OUD symptoms and cancer pain with a dose escalation of methadone. Patients with OUD are a subgroup with special needs when they develop cancer, and the problem has been only recently addressed, particularly after the opioid epidemics. Cancer-related pain is often treated with opioids and the major use of opioids determines an increase in the risk of developing OUD (Dowell et al. 2016). Patients with OUD should be identified as soon as possible to ameliorate their quality of care. Healthcare professionals facing a patient with OUD and cancer should obtain a series of information such as the history, the frequency, and the methods of drug use (McNally and Sica 2021). In fact, the control of OUD symptomatology is crucial for compliance and adherence to cancer treatments and to decrease the risk of serious complications (McNally et al. 2019; 2022; McNally and Sica 2021).

Moreover, a recent clinical study showed that patients with cancer pain and a history of OUD were 90% less likely to receive a dose escalation of opioids when admitted to the hospital compared to patients with no history of OUD, regardless of OUD remission status (Singh et al. 2021).

In our clinical experience, patients with OUD developing cancer undertake a methadone dose escalation once they are referred to the addiction unit. With the increase of methadone administration, a good control of both cancer pain and OUD is achieved, with no relevant ADRs. Different approaches are possible in this subpopulation of patients taking methadone who experience intercurrent pain. A recent case report describes a minimal increase in the dose of methadone administered and a better modulation of administration intervals (Mercadante et al. 2023). Other cases are described with a titration of methadone, together with or rotating with other opioids to control pain (Manfredi et al. 2001).

Methadone is an opioid drug with high affinity for μ and δ opioid receptors and acts as an NMDA receptor antagonist. NMDA receptors are involved in allodynia, hyperalgesia, opioid tolerance, and neuropathic pain, and methadone could exert some adjunctive extra-opioid analgesic action blocking NMDA receptors (Fürst 2022). Moreover, methadone induces a long-lasting analgesia, has high potency, has high oral bioavailability, and is relatively safe in patients with renal impairment (Ding et al. 2022; Paice et al. 2023). However, it is not broadly used as a first-line opioid analgesic in cancer pain for its long half-life and titration difficulties as well as its potential cardiac ADRs (Nicholson et al. 2017). It has been proposed as an alternative for opioid refractory cancer pain after switching from a previously administered opioid (Ding et al. 2022; Tan et al. 2020), and it should only be prescribed by experienced clinicians (Paice et al. 2023). A growing body of literature indicates its possible use as a first-line opioid analgesic (Mammana et al. 2021; Mercadante et al. 2022; Mercadante and Bruera 2018), starting with low doses and with a slow titration. In a recent study, opioid naïve patients were treated with an initial dose of 6 mg/day, while patients who already had opioids before with 9 mg/day. The 2 months dose increase in the 2 groups was limited (35% and 15%, respectively) (Mercadante et al. 2022). Moreover, low dose methadone was proposed as an add-on therapy in patients already taking an opioid (other than methadone) but with insufficient pain control (Fürst 2022). In fact, the adjunct of methadone with another drug may enhance analgesia and limit ADRs (Hanna and Senderovich 2021). In these cases, the dose of methadone is

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usually very low at the beginning (1–5 mg/day) and after titration not higher than 20 mg/day (Fürst 2022).

The use we propose in our case series is slightly different to the mentioned approaches and consist of a high initial dose, such as the ones used in patients with OUD in the chronic setting, and a rapid titration once the intercurrent pain is not controlled. Three out of 4 of our patients start with high methadone doses (45–80 mg/day), while only one with a standard dose (20 mg/day). Following most of the literature, opioid-tolerant patients should start methadone at doses not exceeding 30–40 mg/day (Hanna and Senderovich 2021). However, in our clinical experience, this is not surprising because methadone is used at high doses in patients with OUD (Donny et al. 2002; Fareed et al. 2009) and can be further titrated to obtain analgesia in patients with concomitant pain (Manfredi et al. 2001). Moreover, case reports of exceptionally high doses of methadone are reported, although with a higher risk of developing severe arrhythmias when doses are above 600 mg/day (Walker et al. 2003). Patient 1 was switched from buprenorphine to methadone and the 60 mg/day dosage was calculated based on the equivalence with buprenorphine. Patient 2 was prescribed a high dose following surgery. Patient 4 was already under treatment at diagnosis with 45 mg/day. The titration was rapid in the case of patient 2, going from 80 mg/day to 145 mg/day in 7 days, while more gradual for other patients. All patients were aware of treatment management and ADRs already for their medical history and were closely monitored by experienced clinicians for pain control, OUD symptoms, and ADRs. The use of methadone in this subgroup is particularly advantageous for its demonstrated efficacy on both analgesia and addiction and should be considered as a first choice.

The possibility that patients exposed to opioids have a higher risk of cancer and a worse outcome has been described in some studies, reporting both an increased incidence and a lower survival rate (Carli et al. 2020; Oh and Song 2020; Sheikh et al. 2020; Song et al. 2022). However, the confounding factors are numerous, and a direct effect of opioids on cancer causation and progression is far from trivial. For methadone, in particular, a "theralgesic" action was proposed a few years ago (Michalska et al. 2017). Based on some preclinical evidence, methadone was defined as a chemosensitizer agent, augmenting the efficacy of chemotherapeutic agents via the downregulation of the threshold for apoptosis (Michalska et al. 2017). However, this hypothesis lacks strong preclinical evidence and most of all clinical correlates, nor even retrospective (Kreye et al. 2018). Our sample, although limited and anecdotical, shows a survival that is in line with published OS for the corresponding cancer types. Patient 1 was diagnosed with gastric cancer and subsequent peritoneal carcinomatosis, with a reported median OS ranging from 2 to 9 months (Rijken et al. 2021) and was alive after 8 months. Patient 2 has a localized colon cancer, whose survival is around 92% at 5 years follow up (van Eeghen et al. 2015), and she is alive after 2 years. Patient 3 was diagnosed with a stage II squamous oropharyngeal cancer and died after 57 months (the corresponding 5 years OS is 75%) (Kowalski et al. 2020). Patient 4 had a stage IV lung cancer and the reported median OS is 9–11 months (Jackman et al. 2017; Rasco et al. 2010). He died 15 months after diagnosis.

In conclusion, the use of methadone and its dose escalation in patients with OUD who develop cancer pain may be proposed as an effective treatment for both pain and OUD symptoms control. However, still after many years, this issue is not properly addressed by clinical studies, with most of the existing literature comprising case series and case reports. Methadone safety and management was not a major issue in our sample. Prospective trials evaluating the efficacy and safety of methadone dose escalation in such patients are needed to validate this clinical approach.

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