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Methadone as anticancer treatment: hype, hope, or hazard?

A series of case reports and a short review of the current literature and recommendations of the societies

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Summary Recently, the use of methadone in cancer patients has increased due to in vitro studies indicating that methadone is capable of inducing cell death. However, thus far there are no relevant clinical studies indicating that the use of methadone can prolong survival in cancer patients. Based on low-quality evidence, methadone is a drug that has similar analgesic benefits to morphine and has a role in the management of cancer pain in adults. Other opioids such as morphine, hydromorphone, and fentanyl are easier to manage but may be more expensive than methadone in many economies. Methadone is an opioid that is only approved for replacement therapy in Austria. Methadone can be used as a second- or third-line agent for severe cancer-related pain, but its use should be restricted to experts. Here we report a series of cases of patients who developed problems when using methadone as an antitumor treatment, with a brief review on the role of methadone as a pain medication and the current lack of value as an anti-tumor therapy. Methadone is not approved or recommended as an anticancer treatment in Austria or Germany. The Austrian Association for Hemato-oncology (OeGHO), the Austrian Association for the Management of Pain (ÖSG), and the Austrian Association for Palliative Care (OPG) do not recommend the use of methadone as an anticancer treatment. Thus, from a medical and ethical point of view, the use of methadone as an antitumor therapy is to be rejected, based on the views of various Austrian (OeGHO, ÖSG, OPG) and German specialists. Unqualified use of methadone by nonexperienced pain therapists is dangerous and must also be rejected.

Keywords Methadone · Anticancer treatment · Tumor therapy · Palliative

Methadon als Antitumortherapie: Schwindel, Hoffnung oder Risiko?
Eine Serie von Kasuistiken und kurzer Überblick über aktuelle Literatur sowie Empfehlungen der Fachgesellschaften

Zusammenfassung In letzter Zeit hat die Verwendung von Methadon bei Krebspatienten zugenommen, weil Daten zeigten, dass Methadon in vitro in der Lage ist, den Zelltod zu induzieren. Bisher gibt es jedoch keine relevanten klinischen Studien, die darauf hinweisen, dass die Verwendung von Methadon das Überleben bei Krebspatienten verlängern kann oder das Tumorwachstum zurückdrängt. Gemäß Nachweisen von geringer Qualität ist Methadon eine Substanz, die einen ähnlichen analgetischen Nutzen wie Morphin hat und zur Linderung von Tumorschmerzen bei Erwachsenen eingesetzt wird. Andere Opioide wie Morphin, Hydromorphon und Fentanyl sind leichter zu handhaben, aber möglicherweise in vielen Wirtschaftssystemen teurer als Methadon. Methadon ist ein Opioid, welches in Österreich lediglich zur Substitutionstherapie

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zugelassen ist. Von sehr erfahrenen Schmerztherapeuten kann es als Schmerzmittel eingesetzt werden, wenn die Wirkung anderer Opioide nicht ausreicht. Anbei ergänzen die Autoren eine Reihe von Fallberichten von Patienten, die unter erheblichen Nebenwirkungen von Methadon, welches bei ihnen als Antitumormittel eingesetzt wurde, mit einem kurzen Review über den Stellenwert von Methadon als Schmerzmittel und den derzeit nicht vorhandenen Stellenwert als Antitumortherapie. Methadon ist in Österreich oder Deutschland nicht als Antitumortherapie zugelassen oder empfohlen. Die Österreichische Gesellschaft für Hämatoonkologie, die Österreichische Gesellschaft für Schmerzbehandlung und die Österreichische Gesellschaft für Palliative Care sprechen sich gegen die Anwendung von Methadon als Antitumortherapie aus. Aus medizinischer und ethischer Sicht ist daher die Anwendung von Methadon als Antitumortherapie nach Ansicht verschiedener österreichischer (OeGHO, ÖSG, OPG) und deutscher Spezialisten abzulehnen. Die unqualifizierte Verwendung von Methadon durch unerfahrene Ärzte ist gefährlich und muss ebenfalls abgelehnt werden.

Schlüsselwörter Methadon · Anti-Krebs-Behandlung · Tumortherapie · Palliativ

Introduction

More than 80% of all cancer patients need an opioid as an analgesic during the course of their disease [1]. According to the guidelines for tumor pain therapy of the European Association for Palliative Care (EAPC), oral morphine is the gold standard for moderate to severe pain [2, 3]; however, inadequate analgesia is present in 10–30% of all cancer patients treated with morphine. Patients who receive high doses of oral morphine can develop side effects due to morphine metabolites, such as morphine-3-glucoronide or morphine-6-glucuronide. These metabolites can lead to hyperalgesia and neurotoxicity, resulting in myoclonus and increased pain [4]. In addition, morphine is only marginally effective for neuropathic pain.

Hence, rotation to another opioid is indicated in the following situations:

1. A lack of pain control with morphine, where a further escalation of morphine has already led to side effects.
2. A lack of pain control with morphine, even without side effects.

The European Association for Palliative Care recommends methadone as a second-line therapy for patients who do not benefit from morphine or who suffer from side effects of morphine metabolites. Methadone is a strong World Health Organization (WHO) step 3 opioid and may be efficient against neuropathic pain [5]. The lack of neurotoxic metabolites as well as the possibility of using lower opioid doses have proven to be beneficial in the rotation to methadone [6].

The WHO categorizes methadone in the list of essential drugs (2007) under “Medicines used in substance dependence programs” and refers to the guidelines of the expert committee of 1990 regarding the use of the drug in palliative medicine [7]. Experienced pain therapists should only prescribe methadone as pain therapy.

Methadone is a fully synthetically produced opioid, which is structurally classified in the class of diphenylpropylamines [8]. It was first synthesized in 1937. It is a μ-opioid receptor agonist [9] and is presumably also a δ-opioid receptor agonist [10]. In addition, methadone is also an *N*-methyl-D-aspartate (NMDA) receptor antagonist, which may explain its effect on neuropathic pain. Its function as a serotonin and norepinephrine reuptake inhibitor probably contributes to analgesia [11].

Racemic methadone is a basic synthetic opioid with excellent oral and rectal bioavailability [12] of up to 80% as well as pronounced lipophilia [13]. The substance also has a high distribution volume in the body, up to 5.3 L/kg in chronic pain patients. Only about 1% of the substance is found in peripheral blood, where it is mainly bound to α-1 acid glycoprotein. The metabolism of methadone is hepatic, via the enzymes of the cytochrome P450 group. Interindividual differences in enzyme activity due to genetic factors (polymorphisms, etc.) as well as interactions with other drugs metabolized by the P450 group impair the predictability of the methadone effect at the pharmacokinetic level [14]. Methadone and its metabolites are excreted half renally and the other half via the intestine. The pH of the urine has an influence on the extent of the renally eliminated parts, as acid urine (pH < 6) leads to increased renal excretion. In case of renal failure, the substrates do not accumulate, which allows the use of methadone even in renal insufficiency. However, caution is advised with severe compromised liver function [15, 16].

Polymorphisms or mutations in genes of proteins involved in pharmacokinetic processes may possibly affect the effect of racemic methadone [17]. The same applies to mutations or polymorphisms in the genes of receptors involved in pharmacodynamic processes [18]. In healthy volunteers who had mutations, the miosis was less pronounced. This suggests that mutations or polymorphisms may be related to the response to levomethadone. All these factors, but especially interindividual differences between plasma time and duration, can lead to accumulation and to subsequent undesirable toxicities (including respiratory depression).

A recent Cochrane analysis from 2017 by Nicholson et al. revised the versions of 2004 and 2007 and analyzed six studies with 388 patients [19]. The authors concluded, based on low evidence, that methadone

is a drug with similar analgesic effects to morphine and other opioids, but that it is more difficult to handle than other opioids (i.e., morphine and fentanyl), because of its side profile. In countries where fentanyl-based drugs are too expensive, methadone is used more frequently, because it is more cost effective.

To date, there is no validated conversion factor of morphine or even of other opioids for racemic methadone in tumor pain therapy. However, due to existing data, no conversion factor should be expected in the near future [20]. For methadone/levomethadone, there are some titration schemes based on clinical experience that facilitate the adjustment to methadone/levomethadone [21]. However, due to the side effects occurring at any time, close clinical monitoring of patients is recommended. Titration and/or opioid rotation should therefore only be carried out by experienced pain therapists and palliative care physicians, and is usually associated with an inpatient stay [2].

Methadone as "new antitumor treatment?" NO!

In German and Austrian media reports (Bayrischer Rundfunk, Tagesschau24, Stern TV, Horner Bezirksblatt), it was reported that methadone or levomethadone should increase the effect of oncological chemotherapy. An improvement in the response to oncological therapy was said to be found in the case of pretreated tumor patients [22]. Discussions, forums, and reports on these messages can also be found online. These reports often convey the false impression that methadone has a positive influence on survival in glioma and leukemia patients. Because of this one-sided reporting, an increasing number of patients ask for methadone as an oncological therapy but not as pain therapy.

The reasons for these media reports are, above all, investigations of the working group around Dr. Friesen from the Institute for Legal Medicine of the University Hospital Ulm [23, 24]. Her investigations detected direct apoptosis induction in tumor cells under in vitro conditions and in animal experiments with methadone. Opioid receptors induce a reduction of cyclic AMP (cAMP) via inhibitory G proteins, which leads to the cell death of leukemia cells via caspase activation. On the other hand, in the cell cultures, a methadone-induced sensitization of tumor cells to the cytostatic doxorubicin was observed via the cAMP mechanism. The investigations were performed on established leukemia and glioma cell lines, and on nude and severe combined immunodeficient (SCID) mice. These were merely experimental treatment approaches.

A possible inhibition of tumor cell proliferation has also been studied in the past regarding other opioids, NMDA receptor antagonists, local anesthetics, or other substances; however, a transfer of the in vitro results to the clinic failed [25–30]. Nor are there valid clinical data for patients. It is currently unclear whether these effects are relevant in the treatment of patients and, if so, which of them are relevant.

Friesen et al. retrospectively described the tolerability and toxicity of adding methadone to any other treatment given to a heterogeneous group of 27 patients with various gliomas at various stages of disease (grades II–IV) [31]. The control group to which the outcomes are compared is not mentioned at all. In this extremely heterogenous group with a life expectancy varying from a few months to more than 10 years, exclusively PFS-6 rates after start of methadone treatment are presented. Only readers not familiar with neuro-oncology are able to see any benefit in whatever results are presented by such a "study!"

The starting dose of methadone was 2.5 mg daily, and the maximum was a total daily dose of 20–35 mg. The study cited in Friesen's work, regarding the safe administration of D, L-methadone in tumor patients as a pain medication, used significantly lower doses, with daily doses of ≤15 mg [32]. Although Friesen et al.'s study was a purely retrospective analysis of tolerability, this work is often referred to in various media relating to a better survival for brain tumor patients with methadone therapy. However, this claim is not justified, for several reasons. Firstly, this was not a randomized prospective study with the primary endpoint being overall survival. The progression-free survival was compared with historical controls, and there was no difference in survival. Secondly, even the authors themselves mention that due to the low number of cases in this study, no overall survival by methadone can be concluded. From a scientific point of view, it is not understandable why this study is still cited in terms of better survival.

Currently, no clinical trials are investigating the use of methadone as an antineoplastic agent. However, a growing number of media reports and articles promote the use of methadone as successful oncologic therapy, thus leading to an increasing number of patients demanding the drug. It is particularly problematic that tabloids and various internet forums, which advertise methadone as anticancer drug, conceal its severe side effects.

Methadone is a very potent opioid with side effects such as constipation, nausea/vomiting, or central side effects. Prolonged QT intervals also are reported to occur, with the risk of arrhythmias [33, 34]. The very long and quite different half-life of methadone entails the risk of accumulation, with possible overdoses and the potential danger of respiratory depression. Similar to other opioids, the respiratory depressive potential of methadone is higher when it is not used for pain therapy, especially in opioid-naïve humans and patients with sleep apnea syndrome [35].

There is also a habituation potential with the risk of misuse, which makes uncritical use problematic.

The conversion from other opioids to methadone is also sometimes difficult and potentially risky, since the equivalent doses of this substance to those of morphine and other opioids are very variable, which may lead to overdoses or withdrawal symptoms. It is particularly difficult to convert methadone to another opioid as a pain killer in patients who already receive methadone.

Currently, the ready-to-use formulations of methadone are only approved for oral maintenance therapy (substitution treatment) for adults who have demonstrated opioid dependency, in the context of appropriate medical surveillance and comprehensive psychosocial care. The prescription must be made by physicians who are specialized and experienced in the treatment of drug addiction. To provide cost coverage for patients, the approval of medical insurance is required.

"Off-label" prescription is possible, but in addition to an adequate indication, it requires special documentation and patient information [36].

It is therefore possible for every licensed physician to prescribe a drug preparation, according to which a solution from the raw substance is mixed by the pharmacist. Methadone is not approved for oncological tumor therapy. Therefore, the application in this indication is "off-label," without guaranteeing a liability risk and justification for a cost reimbursement.

The unconsidered use of methadone for tumor therapy outside of tumor pain therapy, in the sense of an individual healing test, cannot be justified by the available data or by the lack of alternatives.

The patients mentioned in the contributions of the media or Internet who are treated with methadone for tumor control received this treatment outside of clinical trials. The extent to which the described therapy results can be attributed to the accompanying chemotherapy or to other reasons cannot be clarified. Nor have any well-documented individual case reports been published so far.

In March 2015, a common statement of the "Neuroonkologische Arbeitsgemeinschaft in der Deutschen Krebsgesellschaft (NOA)" and the "Deutsche Gesellschaft für Neurologie (DGN)" was released, indicating that the use of methadone as curative treatment in patients with gliomas was rejected by both societies [37].

In June 2017, the Austrian Society for Hematology and Medical Oncology (OeGHO) warned against the use of methadone in cancer patients, based on the opinion of the German equivalent association, the Deutsche Gesellschaft für Hämatologie und medizinische Onkologie (DGHO) [38]. Based on the current data, the Austrian Pain Society (ÖSG) also confirms that while methadone has a fixed value in the pain therapy of tumor patients, an off-label application of methadone for tumor therapy is not justifiable; the ÖSG thus follows the opinions of the working group on cancer pain, the German Pain Society, and the Austrian Society for Hematology and Medical Oncology [39]. The Austrian Palliative Society refers to the opinion of the OeGHO.

Reflecting available data, the use of methadone for tumor therapy outside the indication for tumor pain therapy cannot be justified in the sense of individual healing. The use of methadone as an antitumor therapy is therefore more than questionable and is not recommended.

The case reports listed below are intended to illustrate the problems to which the uncritical use of methadone in cancer patients can lead.

Case report 1: Severe withdrawal symptoms after rotation to hydromorphone

A 59-year-old woman was diagnosed with adenocarcinoma of the stomach in 2009. A transhiatal gastrectomy with jejunojejunostomy was performed. The initial tumor stage was stage III (pT2b G3 pL1 pN1 (3/15) pV1). In May 2014, splenic metastases were detected, with no further signs of metastatic disease. A complete splenectomy was done in June 2016. Histology revealed adenocarcinoma cells in the spleen, Her-2-neu negative. The patient received pseudoadjuvant chemotherapy with docetaxel, cisplatin, and 5-fluorouracil. After the first cycle, the patient suffered from pain in the whole body and from severe fatigue. According to the patient's wish, the therapy was switched to capecitabine monotherapy. From July 2014 to December 2014, the patient received five cycles of capecitabine. Restaging showed no sign of relapse.

In October 2015, a CAT scan of the abdomen revealed a relapse close to the left kidney as well as two pre-aortic lymph node metastases. The patient received palliative chemoradiotherapy with 5-fluorouracil and local radiotherapy from November to December 2015. A complete remission of the lesions could be observed. But in February 2016, new lymph node metastases were detected close to the lumbar spine. Another palliative chemotherapy treatment with 5-fluorouracil and irinotecan was offered to the patient. After six cycles of 5-fluorouracil and irinotecan, the lesions were progressive, showing multiple lymph node metastases located retroperitoneally and mesenterially in October 2016.

The patient insisted on receiving another chemotherapy treatment, which was not offered to her in her primary oncology center. According to international guidelines, in such a situation, a third-line therapy is not recommended. However, she asked for a second opinion, and a third-line therapy, including ramucirumab and Paclitaxel, was offered to her in another hospital. From October 2016 to June 2017, the patient received six cycles of ramucirumab and Taxol. CAT scans in July 2017 showed progressive disease with lymph node metastases, lung metastases, and

peritoneal carcinosis. Para-aortal and aorto-intercaval lymph nodes measured up to 10 cm in diameter.

As the patient insisted on another antitumor therapy, an "antitumor treatment" with methadone was offered to her. She received 30 drops of methadone twice daily. According to a mixture of a local pharmacy, the patient's methadone drops were prepared as follows: 1 g methadone added to 100 ml purified water. One milliliter contained 10 mg of methadone, and one drop contained 0.4 mg methadone. Hence, the patient received a total of 24 mg methadone per day.

On July 17, the patient came to our palliative care outpatient clinic because she suffered from severe abdominal pain, which seemed to be related to the sites of disease progression. Methadone did not seem to control her tumor-related pain. Hence, the patient was rotated to hydromorphone instead of methadone. As there are no conversion factors to determine an adequate dose of hydromorphone when rotating from methadone, we wanted to admit the patient to our palliative care unit to be able to titrate another opioid to find the accurate opioid dose. Unfortunately, the patient signed a consent not to be admitted to the hospital.

In the outpatient center, she received a single 1.3 mg dose of hydromorphone and reported immediate relief of pain. In addition, she received 2 mg hydromorphone retard twice daily and was able to take 1.3 mg of hydromorphone every 3 h if needed. Permanent medication of 500 mg metamizole was added four times daily at fixed hours. Again, admission to the palliative care unit was highly recommended to the patient. The physician explained to her that the rotation from methadone to hydromorphone could be difficult and that withdrawal effects or other problems could occur during the rotation. Nevertheless, the patient left the clinic at 11:00 a.m., July 17. At 3:00 p.m. on July 18, the patient was admitted to the emergency room of the hospital. She suffered from severe pain attacks and cramps all over her body. Severe myoclonus was observed for several hours, and the patient was very agitated. She immediately received 5 mg of diazepam intravenously in the emergency department, without effect. Then she was admitted to the palliative care unit. The patient was crying due to severe pain and suffered from cramps in the intestine and reported total body pain. She was shivering, and myoclonus continued. Altogether, her symptoms were like those of a patient experiencing withdrawal symptoms. Her symptoms improved slightly with 10 mg of intravenous morphine in combination with lorazepam, but she still suffered from severe pain. Metamizol and paracetamol intravenously provided no further control of symptoms. An intravenous syringe driver with 2 mg per hour of morphine was started, with the possibility of 5 mg morphine for breakthrough pain every hour as needed. Whereas pain scores dropped down on the numeric rating scale from 10 to 7, the patient still suffered from myoclonus, jerks, and shivering. Hence, a syringe driver with 0.03 mg clonidine per hour was started to improve the withdrawal symptoms. Thirty minutes after starting the clonidine, the patient's myoclonus dissolved, and her reported numeric rating scale score was two.

The syringe driver with clonidine was continued for 24 h and then stopped. The patient was free from pain and without cramps, myoclonus, or shivering. The syringe driver with 2 mg/hour morphine was continued and changed to a patient-controlled analgesia (PCA) pump. Seven days later, the patient left the hospital with the PCA pump.

In August, the patient was admitted due to the progression of peritoneal and pleural carcinosis. A couple of pneumological interventions, including thoracoscopy, thoracentesis, and pleurodesis, were performed to ameliorate dyspnea in addition to morphine. Finally, the patient died on September 11, due to the progression of the disease. Regarding pain control, the treatment with morphine was switched to hydromorphone in the last days of life, because the pain as well as the dyspnea increased, and good symptom control could be reached with a combination of hydromorphone and midazolam.

Conclusion

A patient who was very focused on continuing anticancer therapy saw methadone as a last glimmer of hope and experienced serious side effects during the conversion to another opioid in her last stage of life. Implementation of withdrawal therapy was performed on the palliative ward instead of the intensive care unit, due to the very advanced underlying disease. It worked in this case, but it could also have resulted in the immediate death of the patient. Methadone treatment in the last phase of life can be quite dangerous if it may be necessary to use other opioids as more potent pain medications and to rotate methadone to another opioid.

Case report 2: Methadone treatment prior to tumor diagnosis and difficult rotation to hydromorphone

In July 2017, a 59-year-old female patient was admitted for bronchoscopy due to high suspicion of metastasized bronchial carcinoma. Although a histologic tumor diagnosis was not present, the patient had already received methadone as an antitumor therapy, prescribed by an external physician. The preparation of the patient's methadone drops was identical to that of case report 1. She received a total of 24 mg methadone per day.

At admission on July 27, a distinct right-sided pleural effusion was noticed, and therefore a chest tube was inserted. Three consecutive cytological exami-

nations of the exudative pleural fluid were negative for malignancy. Therefore, bronchoscopy in general anesthesia was performed on August 4 to obtain sufficient tissue samples for diagnostic purposes. Bronchoscopy showed that the mucosa of the right upper lobe was infiltrated by cancer tissue, and the final histologic sampling revealed a non-small cell adenocarcinoma of the lung with high PDL1 expression (80%). Examinations for EGFR, ALK, ROS1, and B-RAF were negative. The complete workup also showed metastases in the lungs, liver, and spleen, and several metastases in the thoracic spine necessitating stabilization by corsage. An MRI showed small metastases in the cerebrum without edema or neurologic symptoms. A palliative radiotherapy for the spine and brain was planned. To sum up, initial staging was cT4 cN3 M1c, stage IVB.

Although several liters of pleural fluid were evacuated (approximately 12.8 L within 22 days), pleural effusion did not cease and finally a permanent pleural drainage system was implemented on August 18. A first-line checkpoint inhibitor therapy with 200 mg pembrolizumab was started and denosumab was administered for osseous metastases.

The patient also suffered from pulmonary embolism, hypoxemia, and generalized pain. Despite her methadone intake, pain levels increased constantly during her stay, so she was rotated to hydromorphone. This led to myoclonus, shivering, and hyperventilation. When the patient received methadone again, the withdrawal symptoms ameliorated quickly, but the pain was aggravated. Methadone intake was then decreased gradually over 1 week, with a simultaneous increase of hydromorphone, which was tolerated with mild side effects. Finally, a discharge was possible on August 23.

Conclusion

In this patient, the rotation from methadone to hydromorphone was associated with severe withdrawal symptoms. It was remarkable that the patient had already been prescribed methadone by a licensed physician before the announcement of the definitive histology and diagnosis.

Case report 3: Rotation from methadone to fentanyl and self-rotation by the patient from fentanyl to methadone, despite inadequate pain control

In a 68-year-old patient, hepatic metastasized colorectal cancer was diagnosed during a gastrointestinal perforation in July 2016. Hartmann's procedure was performed. Subsequently, the patient received palliative chemotherapy with FOLFIRI/cetuximab until February 2016. After progression in the liver in June 2017, palliative chemotherapy with 5-flourouracil and bevacizumab was started.

The patient suffered from abdominal pain. It was only over the course of several conversations that the patient told the nurse of the palliative care team that methadone had been prescribed to him by an external physician. He had not provided this information to his oncologists or to the palliative care physician. Only through targeted questioning was the methadone intake provided by the patient. The preparation of the patient's methadone drops was identical to that of case report 1. He received a total dose of 24 mg of methadone per day.

We converted this to a transdermal system with 12 µg/h of fentanyl, changed every 3 days, and 1.3 mg of short-acting hydromorphone on demand; we discontinued the methadone treatment. The opioid rotation was well tolerated by the patient, and the pain situation was ameliorated. However, he immediately turned back to methadone after his discharge from the hospital and removed the transdermal fentanyl on his own, because he wanted to take the methadone instead of fentanyl, despite its worse pain control. Subsequently, despite the pain, the patient renounced other opioids in favor of the antitumor drug methadone, which was effective in his eyes. The patient was confident that methadone would prolong his life, even though he was told that he had progressed. He finally died in September 2017.

Conclusion

This patient did not tell his treating physicians about the use of methadone and did not want to accept any opioids other than methadone to continue to use as an "antitumor agent." The secret intake of methadone is probably an underestimated phenomenon in tumor patients.

Case report 4: Inexplicable doses of morphine via patient-controlled anesthesia

In a 54-year-old female patient, a primary hepatic, pleural, and osseous metastasized non-small-cell lung carcinoma was diagnosed in March 2017. Palliative chemotherapy with cisplatin/etoposide was performed. A PCA pump with 10 mg morphine/ml, 1.5 mg ketamine/ml and 0.2 mg haloperidol/ml was established for sufficient analgesia.

Because of pain in the spine, a palliative percutaneous radiation from lumbar vertebrae I to sacral vertebrae, was performed in September 2017. An external palliative team adjusted the pain pump to 0.4 ml per hour with a bolus capability of 0.4 ml per hour.

From September 11–12, 2017, the patient tried to administer 55 boluses, but only 24 were administered. The flow rate was then increased. In general, increased bolus doses were observed in this patient, which indicated very much increased pain. We associated these with the presence of extensive metastasis and tried to adapt the pain medication accordingly.

The patient was then transferred back to her home hospital. After discharge, a mobile palliative care team reported that this patient had received methadone as an antitumor therapy, which our team unfortunately had not known.

Conclusion

This patient also held back information about the intake of methadone from her treating team at the hospital. The increased morphine bolus requirements by the patient could have been explained by the simultaneous use of methadone.

Case report 5: Patient with pain under methadone insisting on methadone treatment

This patient was diagnosed with carcinoma of the jaw in July 2014, and pT4b cN0 (0/1) cM0 IVB in July 2017. Hemimaxillectomy on the left via Weber–Ferguson access, submandibular access, and resection of the muscular and muscular process were performed and were followed by a curative adjuvant irradiation. In May 2015, maxillary reconstruction using a microvascular pelvic graft transplant and osteocutaneous radiosurgery were performed. Because of a recurrence, the patient received palliative chemotherapy with docetaxel cisplatin-cetuximab from July 2017, a total of three cycles, without substantial success.

Currently, the patient is to be presented for a new irradiation. She currently takes methadone as an "antitumor therapy."

She indicated that she took 50 drops of methadone distributed throughout the day. However, the exact dosage was not determinable, as the patient was reluctant to provide this information to the treating palliative care team. Since the size of the droplet or the drop count is important, it is therefore generally impossible to specify the exact quantities for methadone drops. Unfortunately, the patient and her relatives did not provide a precise description of the methadone formulation or the issuing pharmacy to the treating physician. Therefore, the precise dosage of methadone could not be evaluated.

The patient suffered from pain, but refused to take alternative opioids, because she was afraid of having to stop taking methadone.

It was explicitly pointed out by the palliative care physician that the patient should be hospitalized in case of a rotation to another opioid.

Conclusion

Here we present a patient suffering from a progressive disease and severe pain, who refused to take other opioids because she was afraid to stop methadone. Pain treatment may be impaired by methadone use.

Discussion

In Austria, methadone is approved as a substitute medication and can be used by experienced pain experts as a potential analgesic treatment. But methadone is by no means a "new antitumor medication." The uncritical representation of various data has aroused false hopes for patients and therapists, and currently, the proposed data cannot be considered scientifically proven.

The case reports listed above underline that propagating methadone as an antitumor drug may lead to the rejection of scientifically established therapies. Some patients also concealed their methadone intake from their treating hospital team, and further problems may occur when methadone is rotated to other opioids.

In most cases, the physician prescribing methadone as an "antitumor drug" is not the same physician, so the second physician may have to treat side effects or withdrawal symptoms. Since patients who use methadone as an "antitumor therapy" are mainly patients suffering from advanced cancer, having access to intensive medical monitoring in case of occurring problems in the form of adaptations or withdrawal symptoms is critical.

Also, physicians who prescribe methadone as an "antitumor treatment" generally lack experience with methadone and often do not have the expertise to prescribe this drug.

The need for intensive care monitoring and therapeutic measures in the use of methadone in critically ill cancer patients also reveals why it will likely be difficult to establish large randomized trials. Detailed patient information describing the effects and side effects of methadone or a necessary rotation to another opioid during better pain therapy entails the fact that the patient could also die from this treatment.

It is very difficult to rotate other opioids to methadone. In Germany, an algorithm to convert from any other opioid to oral levomethadone was developed [21] and approved [40] (German model of levomethadone conversion [GMLC]). According to this GMLC, the preexisting opioid is stopped, and then the titration of oral levomethadone is initiated with a starting dose of 5 mg orally every 4 h (plus, as needed, every 1 h). If necessary, the levomethadone dose is increased (pain) or decreased (side effects) by 30% every 4 h (plus, as needed, every 1 h). After 72 h, the achieved single dose is maintained, but the dosing interval increases twofold to every 8 h (plus, as needed, every 3 h). There is a lack of useful methods of conversion from other opioids to methadone [41]. And regarding conversion from methadone to other opioids, no universal method exists that allows methadone to be accurately and consistently converted to another opioid [42].

A recent study investigated the administration of low doses of oral methadone in addition to regular

opioid medication as an analgesic in end-of-life cancer patients, and it observed good analgesic effects but also an increased risk of sedation and delirium [43].

Methadone has not been proven so far as an anticancer treatment. Two studies did not show any difference in overall survival in patients receiving methadone [44, 45]. In contrast, regarding safety issues, a large study by a working group from Tennessee, who investigated the long-term course (1997–2009) of patients with non-tumor-related pain and who had received methadone or morphine, showed that already low methadone doses compared to low morphine doses led to an increased risk of death with a hazard ratio of 1.59 (CI 1.01–2.51, $p = 0.046$) [45].

In general, it must be noted that due to the uncritical data presentation discussed, false hopes can be aroused among patients and therapists. The use of methadone cannot be supported by the available scientific data. It can therefore be assumed that in patients suffering from advanced cancer, such misinformation may lead to a refusal of established and scientifically proven therapies in order to be treated with methadone instead.

Conclusion

From a medical and ethical point of view, the use of methadone as an antitumor therapy is to be rejected, based on the recommendations of various Austrian specialists (OeGHO, ÖSG, OPG). Unqualified use of methadone by nonexperienced pain therapists is dangerous and should be rejected.

The presented data on the efficacy of methadone in patients with gliomas are based on a single uncontrolled retrospective study. These data must be reviewed in controlled clinical trials, typically in a randomized trial or alternatively in a case–control study. Based on the existing data on the efficacy and the possible risk of increased mortality, an uncritical off-label application of methadone is not justified.

Conflict of interest G. Kreye, E.-K. Masel, K. Hackner, B. Stich, and F. Nauck declare that they have no competing interests.

Ethical standards This article does not contain any studies with human participants or animals performed by any of the authors. Additional informed consent was obtained from all individual participants for whom identifying information is included in this article.

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