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RESEARCH

Low-dose methadone added to another opioid for cancer pain: a multicentre prospective study

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Abstract

Context The use of methadone for cancer pain management is gaining wider acceptance. However, switching to methadone treatment can still pose challenges. Consequently, there is ongoing development of its use in low doses in combination with other opioids, despite a lack of clinical evidence regarding its efficacy and safety.

Objectives This study aimed to evaluate the efficacy and tolerability of low-dose methadone in combination with another opioid in patients with moderate-to-severe cancer-related pain in a clinical setting.

Patients and methods This was a prospective, open-label study conducted in 19 pain and/or palliative care centres treating patients with cancer-related pain. Pain intensity, patients' global impression of change, and adverse effects were assessed on day 7 and day 14. The main outcome measure was the proportion of responders.

Results The study included 92 patients. The daily dose of methadone was 3 [3–6] mg at baseline, 9 [4–10] mg on day 7 and 10 [6–15] mg on day 14. The NRS pain ratings significantly decreased from 7 [6–8] at baseline to 5 [3–6] on visit 2 ($p < .0001$) and 4 [3–6] on visit 3 ($p < .0001$). Similarly, the VRS pain ratings decreased from 3 [3–3] at baseline to 2 [2–3] on visit 2 ($p = 0.026$) and 2 [1–3] ($p < 0.001$) on visit 3. At Visits 1 and 2, half of the patients were considered Responders. Of those responders, 73.5% were High-Responders at Visit 1 and 58.7% were High-Responders at Visit 2. No adverse events related to the risk of QT prolongation, overdose, or drug interactions were reported.

Conclusion For patients experiencing moderate to severe cancer-related pain despite initial opioid treatment, our study found that low-dose methadone, when used in combination with another opioid, was both safe and effective. This supports the use of methadone as an adjunct to opioid-based treatment for cancer pain.

Keywords Cancer pain · Methadone co-analgesia · Titration · Efficacy · Tolerance

Introduction

Pain is a prevalent symptom among cancer patients. As cancer progresses, nearly two-thirds of patients experience an exacerbation of pain. Overall, more than 40% of individuals with cancer endure moderate to severe pain, which can significantly affect their quality of life [1, 2].

The management of cancer-related pain generally involves the combination of multiple drugs, with opioids as a key component of most therapeutic strategies. In some cases, pain relief is not achieved due to lack of efficacy or because of intolerable adverse reactions, defining refractory pain. Opioid rotation is frequently employed in such circumstances to improve pain relief while simultaneously managing opioid side effects [3, 4].

Methadone is frequently utilised in opioid rotation due to its distinctive properties, including a rapid onset of action, prolonged effects, high oral bioavailability, and incomplete cross-tolerance with other opioids. These characteristics render it an optimal choice for opioid rotation [5, 6].

However, methadone-based opioid rotation can pose challenges. The frequent need for high doses and the possibility of tissue accumulation carry the risk of overdose and QT lengthening-related cardiac complications [7, 8]. For these reasons, opioid rotation to methadone is usually

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conducted in specialised pain management units, where the objective of a stable pain control can be achieved with adequate safety [9, 10].

Using methadone as co-analgesic with other opioids can improve its risk profile through dose reduction while preserving the benefits derived from its pharmacological specificities. This approach is increasingly considered in clinical practice, facilitating access to methadone-optimized analgesic treatment, including in outpatient settings [11–14].

To date, few studies—mostly retrospective—have assessed the safety and efficacy of low-dose methadone co-analgesia in cancer patients with moderate to severe cancer pain [15–18]. We therefore designed a multicentre prospective observational study to evaluate the effectiveness and tolerability of low-dose methadone co-opiate analgesia in a real-world clinical setting.

Patients and methods

Ethics

This observational study was conducted from January 2021 to May 2022 across 19 palliative care and pain management centers in France. It was approved by the Comité de Protection des Personnes Ile de France III in accordance with French law (ID-RCB registration number: 2020-A01818-31). All participants received detailed information about the study and provided written consent.

Inclusion criteria

All cancer pain patients receiving care from the participating palliative care and pain teams were consecutively screened. Inclusion criteria were: age 18 or older; a diagnosis of cancer (any type); moderate to severe cancer-related pain (NRS: Numeric Rating Scale $\geq$ 5/10 or VRS: Verbal Rating Scale $\geq$ 3/5) despite first-line opioid use; no history of cardiac disease; no cognitive or consciousness impairments. Non-inclusion criteria mirrored the inclusion criteria.

Procedure

At the outset of the study, the following variables were documented: patient demographics, cancer diagnosis, pain intensity, neuropathic pain component, oral morphine equivalent daily dose (OMEDD) for prior pain treatment, and care setting. Pain intensity, the patients' global impression of change (PGIC), the oral morphine equivalent daily dose (OMEDD), and adverse effects were assessed on days 7 and 14. Pain intensity was evaluated using either the Numeric Rating Scale (NRS), an 11-point numerical scale ranging from 0 (no pain) to 10 (the worst possible pain), or the Verbal Rating Scale (VRS), a five-category verbal rating scale comprising the following categories: no pain (=0), mild (=1), moderate (=2), severe (=3), and the worst possible pain (=4).

The Patient Global Impression of Change (PGIC) is a commonly used tool to assess the clinical significance of improvements in pain ratings [19]. It is a single-item rating, completed by participants during a clinical trial, that uses a 7-point scale with the options 'very much improved', 'much improved', 'minimally improved', 'no change', 'minimally worse', 'much worse', and 'very much worse'. The study evaluated adverse events associated with opioids, utilizing the Common Terminology Criteria for Adverse Events (CTCAE v5.0) [20]. Medical professionals meticulously documented the presence, severity, and absence of adverse events, including somnolence, confusion, hallucinations, myoclonus, hypoxia, nausea, vomiting, constipation, pruritus/itching, and dry mouth. The test results were thoroughly evaluated, interpreted, and described by highly qualified medical professionals.

The study comprised a baseline assessment visit (visit 1), followed by on-site consultations for analgesic titration on day 7 (visit 2) and day 14 (visit 3). At visit 1, the attending physician made the decision to introduce a low dose of methadone (ranging from 3 to 10 mg/day, taken 1–3 times per day) in combination with the previously prescribed opioid. The dosage of methadone was subsequently (visit 2 and visit 3) adapted on an individual basis under the supervision of the attending physician, with the aim of ensuring adequate pain relief and minimizing adverse reactions. Adjustments relied on pain evaluation using a Numerical Rating Scale (NRS) and a Verbal Rating Scale (VRS), the patients' global impression of change (PGIC), and a systematic recording of adverse reactions.

Outcomes

The study aimed to determine the percentage of patients who met the 'Responder' criteria on the seventh and fourteenth day. The study's secondary endpoints included evaluating various factors, such as the percentage of patients who met the 'Responder' and 'High Responder' criteria on days 7 and 14, safety evaluations through adverse events, and a reduction in opioid consumption.

A 'responder' was defined as a patient who experienced a 30% or greater reduction in pain intensity compared to baseline or had a significant improvement in their condition compared to baseline (PGIC < 3). The term 'High Responder' refers to a patient who has experienced at least a 50% improvement in pain intensity from their baseline or a significant improvement in their condition compared to their baseline (PGIC < 2).

Statistical analyses

The analysis was conducted on an intention-to-treat basis, including all the patients who had received at least one dose of methadone. Missing data were imputed using the last-observation-carried-forward technique. Categorical variables are presented as numbers and percentages with 95% confidence intervals (CI). Continuous variables are summarized as medians and interquartile ranges (IQR). Repeated measures over time were compared with Friedman's non-parametric analysis of variance with Dunn's post-hoc test.

To assess the statistical significance of the VRS scores between the baseline (visit 1) and subsequent visits (visit 2 and visit 3), the range of VRS was modified from 0 (indicating no pain) to 4 (indicating extreme pain). Additionally, to confirm the statistical significance of the PGIC at each subsequent visit, the range of PGIC was modified from {1,7} to {-3,3} by assigning -3 to 'very much worse', 0 to 'no change', and 3 to 'very much improved'.

The statistical analyses were confidently deemed significant when the two-sided p-value was less than 0.05. The analyses were conducted using GraphPad Prism version 9.3.0 (345).

Results

Study population

A total of ninety-two patients were recruited from 13 of the 19 centers participating in the investigation. Figure 1 provides a flow chart illustrating the progression of these patients through three visits, detailing the number of patients who remained in the study and those who withdrew, along with specific reasons for withdrawal at each stage. Table 1 summarizes the demographic and clinical characteristics of the study population.

Baseline opioid treatment

Thirty-nine percent of the patients received morphine and 39% received oxycodone, orally in 46% of cases and intravenously in 35%. Two patients received intrathecal analgesia. The median Oral Morphine Equivalent Daily Dose (OMEDD) at V1 was 286.5 mg [144.5–607.5].

Methadone administration

The most frequently prescribed regimen was three times daily (53.3%), followed by twice daily (39.1%). The initial daily dose of methadone was 3 mg (with a range of 3–6 mg), with the dose at visit 2 being 9 mg (with a range of 4–10 mg) and 10 mg (with a range of 6–15 mg) at visit 3.

Effects of methadone on opioid prescription

The OMEDD decreased from 286.5 [144.5–607.5] mg at the initial visit to 240 [120–460] mg at visit 2 and 216 [90–454.5] mg at visit 3. However, the observed difference did not reach statistical significance.

Pain response

The NRS pain ratings significantly decreased from 7 [6–8] during visit 1 to 5 [3–6] during visit 2 ($p < 0.0001$) and 4 [3–6] during visit 3 ($p < 0.0001$). Similarly, the VRS pain ratings decreased from level 3 [3] at baseline to 2 [2, 3] on visit 2 ($p = 0.0026$) and 2 [1–3] ($p < 0.001$) at visit 3. (Fig. 2).

Global impression of change

The PGIC score was 1[0–2] at visit 2 ($p < 0.0001$) and 1[0.5–2] at visit 3 ($p < 0.0001$) (Fig. 3).

Responders vs. Non-Responders

Out of the 92 patients enrolled, 49 (53.2%) and 46 (50%) patients were considered responders at visit 1 and visit 2, respectively. Responders and Non-Responders did not differ regarding demographic characteristics, baseline clinical conditions or the dose of methadone administered. Thirty-six (73.5%) and 27 (58.7%) of the Responders reported a pain reduction of 50% or more at visit 1 and visit 2, respectively (Fig. 4). In the responder group, the OMEDD decreased from 240 mg (125–517 mg) initially to 166 mg (100–422.5 mg) at visit 2 and 182.5 mg (60–323 mg) at visit 3. This resulted in a significant opioid-sparing effect, as evidenced by a p-value of 0.038 for the comparison between baseline and visit 2 and a p-value of 0.0023 for the comparison between baseline and visit 3 (Fig. 5).

Methadone safety

During the second visit, ten patients reported adverse events attributable to methadone, all of which were typical opioid side effects, including somnolence, constipation, myoclonus, disorientation, confusion, hallucinations, pruritus, and nausea. The majority of these events (in seven of the ten patients) were classified as "mild" (grade 1 CTCAE) or "moderate" (grade 2 CTCAE), with one patient experiencing grade 2 somnolence. However, two patients encountered "severe" (grade 3 CTCAE) side effects, necessitating their withdrawal from the study—one due to grade 3 constipation and the other due to grade 3 nausea. By the third visit, methadone-related adverse effects were observed in five patients, including somnolence in two patients (one mild and the other moderate) and

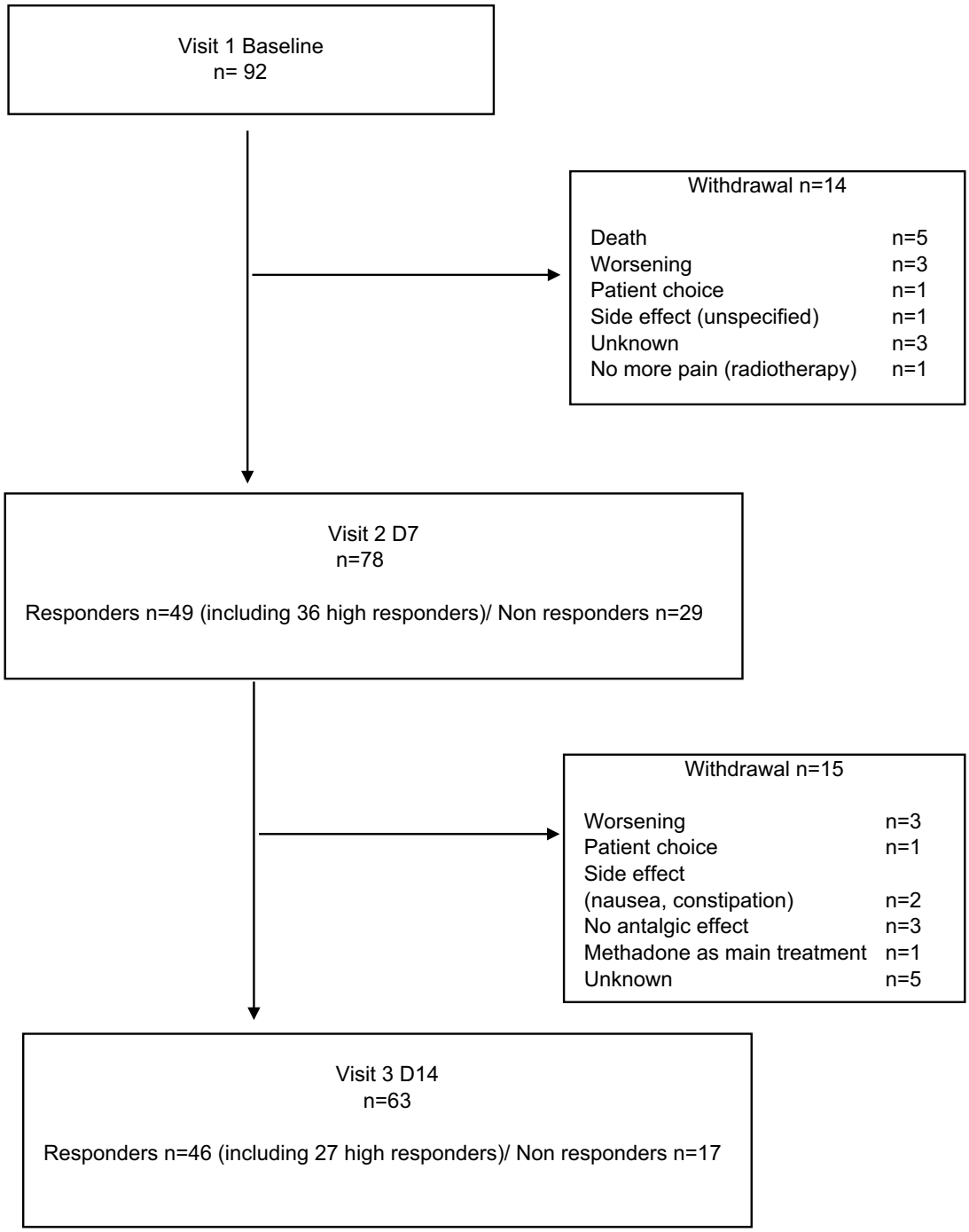

Fig. 1 Flow chart

hallucinations (one mild, and the severity of the other not documented). Additionally, one patient reported diarrhea, although the intensity was not recorded. The analysis of these adverse effects underscores the vital necessity of meticulous management of the transition from prior opioids, with specific attention to the potential risks of somnolence or diarrhea if the process is either excessively gradual or precipitous.

Discussion

Summary of results

This prospective observational study indicates that low-dose methadone can be safely and effectively used

Table 1 Baseline demographic and clinical characteristics of the cancer patients (IQR, interquartile range; NRS, Numeric Rating Scale; VRS, Verbal Rating Scale; OMEDD, Oral Morphine Equivalent Daily Dose)

Characteristics		*N*	%
Age, years	Median + IQR	60 [50–68.5]	
	(Min–Max)	(31–94)	
Sex	Male	53	57.6%
	Female	34	37%
	NA	5	5.4%
Care Setting	Outpatient	28	30.4%
	Inpatient	55	59.8%
	Unknown	9	9.8%
NRS at baseline	Number	79	85.9%
	Median + IQR	7 [6–8]	
VRS at baseline	Number	45	48.9%
	Median + IQR	3 [2, 3]	
Neuropathic pain at baseline	Yes	41	44.6%
	None	43	46.7%
	Unknown	8	8.7%
OMEDD at baseline (mg)	Number	69	75%
	Mean ± SD	424 ± 419.5	
	Median + IQR	270 [155–627]	
Cancer	Lung cancer	23	25%
	Gastrointestinal cancer	22	23.9%
	Gynecological cancer	12	13%
	Head and neck cancer	10	10.9%

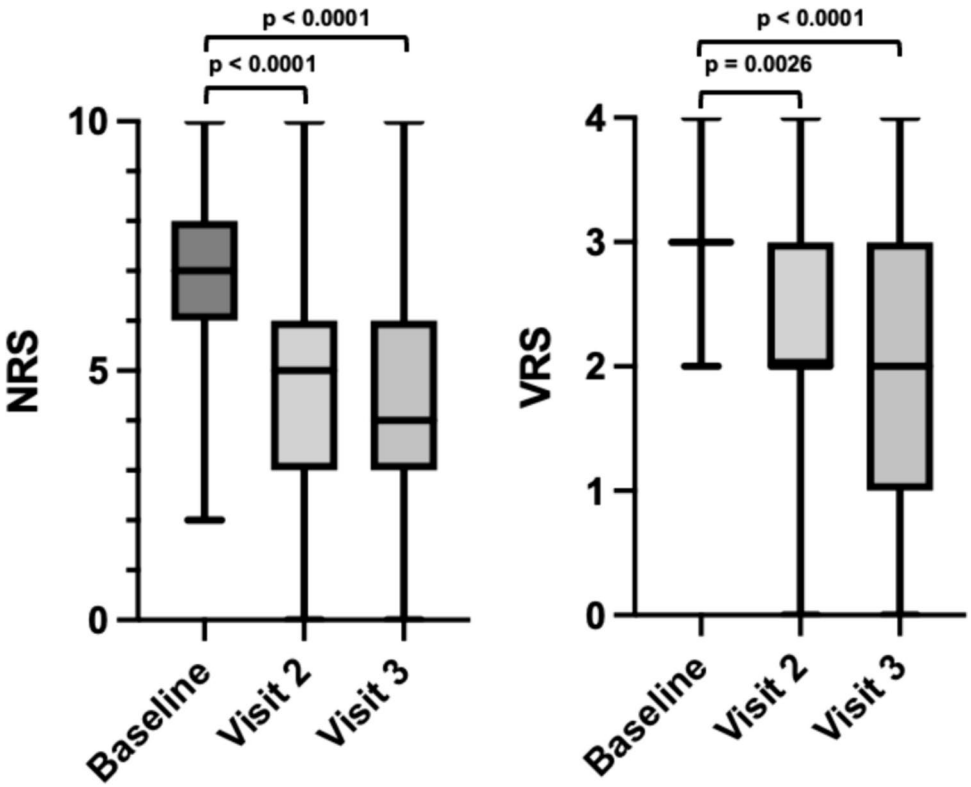

Fig. 2 Pain response. Changes in pain intensity were assessed using the Numeric Rating Scale (NRS) and the Verbal Rating Scale (VRS) over the study period. The box plot shows the interquartile range and median, with whiskers representing the full data range. NRS pain ratings significantly decreased from 7 [6–8] at Visit 1 to 5 [3–6] at Visit 2 ($p < 0.0001$) and 4 [3–6] at Visit 3 ($p < 0.0001$). VRS pain ratings also decreased from 3 [3] at baseline to 2 [2, 3] at Visit 2 ($p = 0.0026$) and 2 [1–3] at Visit 3 ($p < 0.001$)

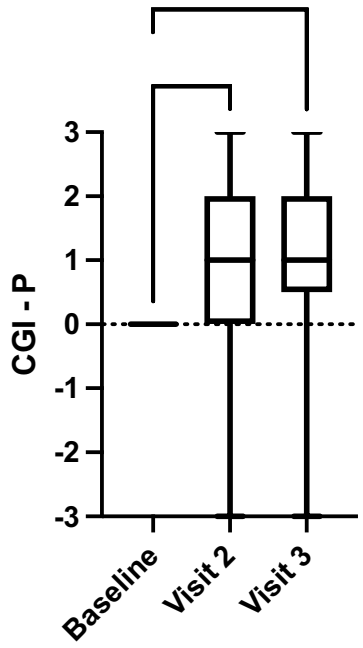

Fig. 3 Patients' Global Impression of Change during the study period. The box plot displays the interquartile range with the median value. The whiskers represent the maximum and minimum data values. ****$p < 0.0001$

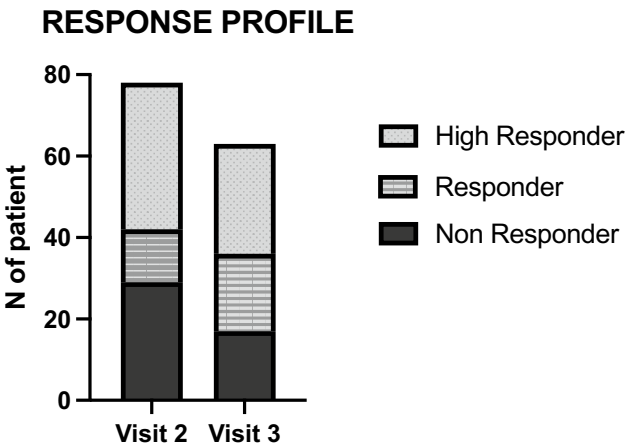

Fig. 4 Response profile: High Responder (≥50% reduction in pain intensity or 'very much improved' on the PGIC compared to baseline), Responder ((≥30% reduction in pain intensity or 'much improved' on the PGIC compared to baseline), Non-Responder (<30% reduction in pain intensity or 'minimally improved' or less on the PGIC compared to baseline)

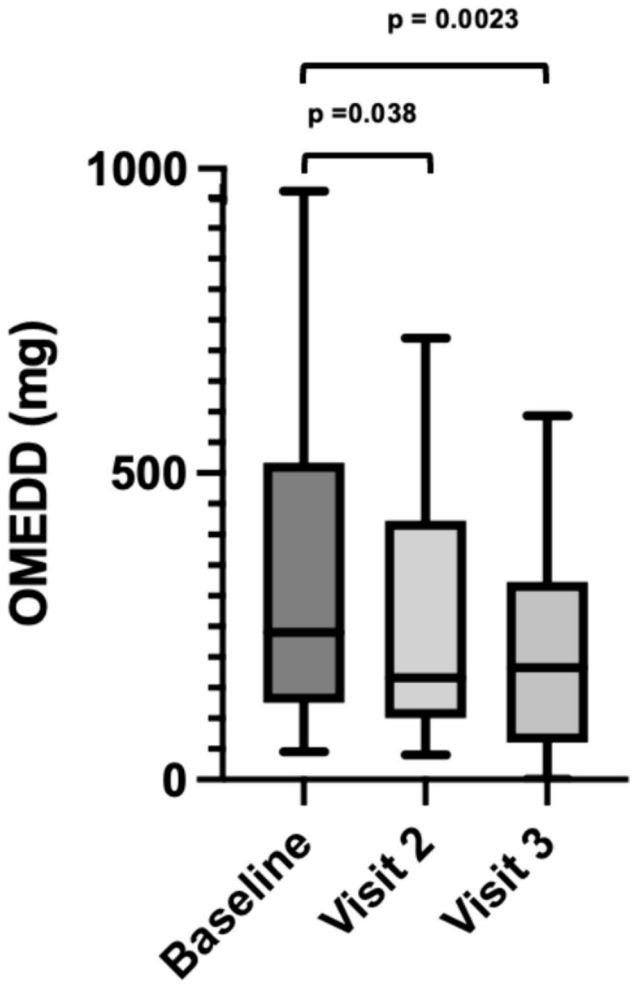

Fig. 5 Opioid-sparing effect among responders. The figure illustrates the opioid-sparing effect in responders, as indicated by the Oral Morphine Equivalent Daily Dose (OMEDD) over time. The box plot represents the interquartile range and median, with whiskers showing the full data range. Significant reductions in OMEDD were observed from baseline to Visit 2 ($p = 0.038$) and from baseline to Visit 3 ($p = 0.0023$)

alongside regular opioid treatment of cancer-related pain in a pragmatic clinical setting.

While the question of whether methadone is particularly relevant in neuropathic cancer pain was not specifically addressed in our study, we did investigate whether the proportions of responders were higher in the subgroup with neuropathic pain. We did not observe a statistically significant difference in the proportion of responders at days 7 and 14 in the subgroup with neuropathic pain compared to the subgroup without neuropathic pain. Consequently, it is not possible to conclude whether there is, or is not, a specific interest of methadone in this context.

Methadone's beneficial effects were more marked in patients deemed "Responders" to the treatment according to the definition retained in the study protocol. In these patients, a statistically significant opioid sparing effect was observed, which was not present in the overall population.

No case of overdose or torsade de pointe was reported. The most frequent side-effects were typical side effects associated with opioids, graded as "mild" in most cases. In three patients, moderate-to-severe somnolence,

constipation or nausea led to study withdrawal. The observation of side effects in both the responder and non-responder subgroups suggests that the tolerance profile differs from the response profile. Of note, the primary reason for reasons for discontinuation were clinical deterioration or death, highlighting the fragility of the study population.

Integration into available knowledge

Several studies have examined the effects of the co-administration of methadone and other opiates on cancer-related pain. Most of these studies are retrospective. Courtemanche et al. reported that 72 out of 146 patients responded with a NRS reduction of more than 30% of baseline to low doses of methadone (3 mg on average for 157 mg morphine equivalent) [15]. Wallace et al. found that 8 of 20 patients reported a 2-point decrease in pain NRS after 1 month with a mean dosage of 4.4 mg/d [17]. Fürst et al. observed that 80% of 80 patients improved with a methadone dosage of 10 mg/d [16]. Chary et al. described both a reduction in pain score and an opioid sparing effect with adjunctive methadone [12]. The interest of methadone as an adjunct to other opiates is also supported by the results of a prospective, randomized, partially blinded controlled study conducted at a single center in 40 patients by Duarte et al. [18]. In this study, patients with cancer-related pain started an opioid-based treatment with either morphine alone (5 mg/6 h plus rescue doses) or morphine and methadone (2.5 mg/12 h). Opioid consumption (primary objective) was similar in both groups. Pain intensity (secondary objective) was similar in both groups at inclusion, it was significantly lower in the morphine/methadone group after 2 weeks (50% difference in NRS) and was then similar in both groups over the next 3 months.

The patients studied by Duarte et al. were opioid-naïve at the time of their inclusion in the research protocol. In contrast, our patients were already established on opioid treatment, and in fact received quite high morphine equivalent dosage (270 mg [155–627]). The two studies, therefore, do not address the same clinical situation. We focus on refractory pain which is clinically relevant and not on opioid introduction with methadone. Our result suggest that methadone can bring benefits regarding pain control for refractory pain even in patients with advanced disease who have long been established on opioids.

Study limitations

We acknowledge that our study is not without weaknesses. These are inherent to its observational, non-controlled design. Additionally, the participating centres were not required to follow a specific methadone administration protocol, resulting in variability in dosing, frequency, and titration strategy between centres. Moreover, we did not formally record clinical events and treatment adjustments during the first days after treatment initiation. Consequently, it is possible that some patients considered non-responders may have responded to different protocols than the ones they followed. This heterogeneity also precludes the study from serving as a basis for practice recommendations. Furthermore, changes in practice occurred within the centres during the course of the study. Finally, the limited duration of observation (two weeks) represents a further limitation of our study. Nevertheless, the study also has some strengths, including its multicentre design and its pragmatic approach.

Conclusions

In conclusion, our study supports the validity of using methadone as an adjunct to opioid-based treatment for cancer pain. It adds to the current body of knowledge, especially for patients already on high doses of opioids without adequate pain control. This study justifies the design and conduct of prospective controlled studies aimed at providing clinical practice recommendations.

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Author contributions Study conception was performed by E.T. All authors (E.T, E.P–C, G.E, L.CH, SP, MF, JP, L. CA, F.T-F, MM, P-A.Q, R.C, A.E, M-A.S, A.L, I.H, A.B, O.R, P.B, O.G and L.S) contribute to data collection. E.T and L.S wrote the manuscript text and L.S prepared Figs. 1–5. E.P–C, G.E, L.CH, SP, MF, JP, L. CA, F.T-F, MM, P-A.Q, R.C, A.E, M-A.S, A.L, I.H, A.B, O.R, P.B and O.G reviewed the final manuscript.

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Data availability No datasets were generated or analysed during the current study.

Declarations

Competing interests The authors declare no competing interests.

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