Long-term Use of Methadone for Refractory Cancer Pain: A Cohort Follow-up Study

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Background:

Up to 15% of cancer patients experience intractable cancer-related pain.
D-methadone is a mu-opioid receptor agonist (antinociceptive activity) as well as an anti-N-Methyl-D-Aspartate receptor (anti-NMDA).
The anti-NMDA activity offers the theoretical possibility to mitigate neuropathic pain.

Aim:
☞ To explore the effectiveness and security in time of methadone in mitigating cancer-related refractory pain as a third-line painkiller.

Methods:

- Mono-centric French prospective cohort study from Sept. 2014 to Dec. 2017.
- Inclusion criteria: cancer patients experiencing refractory cancer-related pain.
- Exclusion criteria : long QT interval condition.
- Substitution process: Opioid daily doses were converted into equivalent oral-morphine (EOM), used ratios were:

< 100mg → 1/5 – 1/3
100-300 mg → 1/5 – 1/10
300-600 mg → 1/10-1/15
600- 1000 mg → 1/15
> 1000 mg → 1/20

Daily doses were administered three times a day for 48h then twice a day .
Additional doses were 1/6 of daily doses.

Study schema:

Collected data:

- Pain components (VAS, Neuropathic pain score inventory)
- Methadone’s doses
- Cancer-related symptoms (Edmonton Symptom Assessment Scale: ESAS)
- Anxiety and depression (hospital anxiety and depression scale: HADS)
- Quality of life (EORTC QLQ-C30)
- Side-effects (Likert-scales)

Statistics were performed using the R-stat software version 3.3.3.
The significance level was defined as $\alpha=0.05$.

Characteristics	N (%)		
Gender ratio female/male (F/M)	0.4 (11/27)	Previous oncologic treatments	34 (89)
Mean age in years	61 [48-74]	Chemotherapy	25 (66)
Localisation of cancer		Radiotherapy	19 (50)
Head and neck	9 (24)	Surgery	
Lung	6 (16)	ECOG PS	
Pancreas	5 (13)	1	2 (5)
Breast	3 (8)	2	24 (65)
Gynaecologic	1 (3)	3	6 (16)
Gastrointestinal	6 (16)	4	5 (14)
Urologic	3 (8)	DN4 > 4 at day 0	13 (34)
Blood	3 (8)	Mean daily EOM (mg)	422 [104-740]
Other	2 (5)	Co-analgesic	
Stage of the disease		Acetaminophen	27 (71)
Metastatic	28 (74)	Antineuropathic drug	13 (34)
Recurrent	2 (5)	Mean daily dose of methadone at day 0 (mg)	32.5 [19.5-45.5]
Locally advanced	6 (16)		
Local	2 (5)		

Table 1 : Characteristics of the population (N=38).

Results :

Characteristics of included patients are summarised in table 1. Overall, they were mostly males (71%), aged 61 years old (48-74) and suffering head and neck (24%), and lung cancers (16%). Most patients suffered from advanced cancer (90%). The average daily EOM before rotation was 422 mg (104-1200). After rotation, the average daily dose of methadone was 32.5mg .

Primary outcomes:

- **Pain intensity tended to decreased, from day 14** (Table 2).
- **Intensity of components of neuropathic pain tends to decrease** (at least 2 points) for: 53% for compression, 29% for burning, 24% for allodynia, 24% for paroxysmal pain and 12% for paraesthesia (Figure 1).
- **Daily doses of methadone remained stable** during the follow up with an average dose of 39 mg at day 28 (p=0.54).

	VAS ≤ 40	40 < VAS ≤ 70	VAS > 70	p- value
D0	26.3% (10)	55.3% (21)	18.4% (7)	
D7	48.4 % (15)	32.3 % (10)	19.4 % (6)	0.12
D14	50 % (12)	46 % (11)	4 % (1)	0.08
D21	55 % (11)	35 % (7)	10 % (2)	0.09
D28	50 % (8)	44 % (7)	6 % (1)	0.19

Table 2: Visual analogic scale for pain by intensity of pain during follow-up.

Figure 1 : NPSI subscales ratings during follow-up.

Side effects:

- Confusion was significantly higher at day 7 (p= 0.04).
- Severe drowsiness tended to be higher at day 28 (p = 0.08).
- Sweating was significantly higher at week 1 (p=0.004).
- Myoclonus, dizziness, fatigue, lack of appetite, breathlessness, constipation and emesis remained stable.
- Overdose signs remained stable during the follow-up (p=0.7).

Anxiety and depression:

- A drop of 22% of patients reporting mild to severe anxiety has been found on the ESAS subscale at day 28 (p=0.006).
- No improvement in depression (HADS and ESAS subscales) nor in anxiety (HADS subscale) has been found.

Quality of life: No improvement has been shown, nor with the ESAS subscale “wellbeing” (p=0.24), nor with the EORTC QLQ-C30 (p=0.9).

Conclusions:

☞ **Our results supports a delayed effectiveness of methadone in alleviating the neuropathic component of cancer-related refractory pain.**