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# Visceral osteopathic manipulative treatment reduces patient reported digestive toxicities induced by adjuvant chemotherapy in breast cancer: A randomized controlled clinical study

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ABSTRACT

*Objective:* Breast cancer patients often benefit from adjuvant chemotherapy, a protocol whose effectiveness is accompanied by disabling adverse effects. The aim of this controlled clinical study was to determine the impact of visceral osteopathy on the incidence of nausea/vomiting, constipation and overall quality of life (QoL) in women operated for breast cancer and undergoing adjuvant chemotherapy in Centre Georges François Leclerc, CGFL.

*Study Design:* Ninety-four women operated for a breast cancer stage 1–3, in complete resection and to whom a 3 FEC 100 chemotherapy was prescribed, were randomly allocated to experimental or placebo group. Experimental group underwent a visceral osteopathic technique and placebo group was subjected to a superficial manipulation after each chemotherapy cycle. Rate of grade ≥1 nausea/vomiting or constipation, on the first 3 cycles of FEC 100, were reported. QoL was evaluated using the EORTC QLQ-C30 questionnaire.

*Results:* Rate of nausea/vomiting episodes of grade ≥1 was high in both experimental and placebo group. Constipation episodes of grade ≥1 were also frequent. No significant differences were found between the two groups concerning the rate of nausea/vomiting ($p = 0.569$) or constipation ($p = 0.204$) according to clinician reported side-effects but patient reported impact of constipation and diarrhoea on quality of life was significantly lower in experimental group ($p = 0.036$ and $p = 0.038$, respectively).

*Conclusion:* Osteopathy does not reduce the incidence of nausea/vomiting in women operated for breast cancer and undergoing adjuvant chemotherapy. In contrast, patient reported digestive quality of life was significantly ameliorated by osteopathy. Clinicaltrials.gov Identifier: NCT02840890.



## Introduction

Breast cancer is the most common cancer in women in the world. In France, over 56 000 new cases were estimated in 2018 [1]. Despite the increasing number of tumours discovered at a localized stage, the majority of patients benefit from adjuvant chemotherapy whose current standard is 3 cycles of FEC 100 (fluoracil, epirubicin, cyclophosphamide) and 3 cycles of docetaxel [2–4]. The effectiveness of this protocol is accompanied by disabling adverse effects, namely nausea and vomiting [5]. Current guidelines on treatments to prevent these gastrointestinal toxicities include an association of neurokinin (NK)1 receptor antagonists (e.g Aprepitant) from day 1 to day 3, to serotonin (5-HT)3 receptor antagonists (Setron) on day 1 and corticosteroid therapy from day 1 to day 3 [6,7].

Pilot studies suggested that massage reduces nausea in women with breast cancer undergoing chemotherapy [8,9]. A RCT with a cross-over design assessed the impact of an osteopathic treatment on the QoL of in 40 cancer patients undergoing chemotherapy. Breast cancer patients represented 33% of the study population. A significant reduction of nausea and vomiting, pain and insomnia were found. Improvement of constipation was noted [10]. Although these results are encouraging, different patients were submitted to different osteopathic techniques depending on patient's motility dysfunctions. Moreover, patient's chemotherapy and anti-emetic regimen were not standardized.

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The aim of this randomized controlled clinical study was to determine the impact of visceral osteopathy manipulation (VOM) on the incidence of nausea and vomiting occurring during the first 3 cycles of chemotherapy 3 FEC100/Docetaxel in women operated for breast cancer and undergoing adjuvant chemotherapy in Centre Georges-François Leclerc, CGFL. The impact of visceral osteopathy on the incidence of constipation and overall QoL was also studied.

## Methods

### *Study design*

Single-centre, randomized, double–blind, parallel, controlled clinical study with allocation of participants into the experimental group, undergoing visceral osteopathic technique or placebo group, subjected to a superficial manipulation. Study protocol was approved by an ethics committee and registered in Clinical tial. gov (NCT02840890) PREDIGOSTEO.

### *Population*

Ninety-four women older than 18 years operated for a breast cancer stage 1–3, in complete resection and to whom a 3 FEC 100 chemotherapy (5-fluorouracil 500 mg/m2, epirubicin 100 mg/m2, cyclophosphamide 500 mg/m2, given intravenously) has been prescribed. Study main exclusion criteria were metastatic breast cancer, operated breast cancer with incomplete resection, known digestive disorders/diseases and inability to receive any of the elements of the antiemetic treatment. Detailed description of all inclusion and exclusion criteria is provided in Supplementary Table 1.

### *Antiemetic regimen*

All patients were treated with an antiemetic prophylactic regimen that consisted of aprepitant 125, 80, 80 at D1, D2, D3, intravenous ondasetron 8 mg at D1, intravenous methylprednisolone 80 mg at D1, 3 pills per day of metoclopramide 10 mg from D1 to D3 and 1 morning and 1 evening pill of alprazolam 0.25 mg from D1 to D3.

### *Osteopathic manipulative treatment*

After each of the 3 initial cycles of FEC 100-Taxotere chemotherapy, each patient was seen by the osteopath for a 15 min session. All osteopathic sessions were held in a dedicated room. All patients were managed by a single board-certified osteopath.

In treatment group, patients received a visceral manipulation consisting of chest wall and diaphragm muscle relaxation through manual thoracic compression [11]. In control group, patients received a superficial/soft tissue manipulation without action on deeper chest wall and abdominal structures. Of note, compression intensity was reduced in this group to avoid any manipulation of diaphragm and intercostal muscles.

### *QoL*

Health related QoL was assessed using the European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30 [12]. Assessment was performed after each of the 3 cycles of FEC 100-Taxotere chemotherapy, after each active or placebo manipulation.

### *Sample size calculation*

The expected rate of patients suffering from at least one episode of nausea and/or vomiting during the first 3 cycles of FEC 100-Taxotere chemotherapy was 65% in placebo and 35% in experimental group. Accordingly, 86 patients would be sufficient to demonstrate a difference between groups, with a type I error $\alpha$ of 5% and a power of 80%. By taking into account a 10% rate of patients lost to follow-up, a sample of 94 patients would be sufficient to demonstrate a difference between groups, therefore 47 patients should be included per arm.

### *Study description*

A 1: 1 ratio simple randomization technique (Tenalea software) was used.

The main objective was to evaluate the impact of VOM on the incidence of nausea and vomiting occurring during the first 3 cycles of FEC 100 during chemotherapy with 3 FEC100/Docetaxel in women with operated breast cancer and adjuvant treatment. The primary endpoint was rate of patients reporting at least one episode of nausea and/or one or more vomiting episodes of grade 1 or higher on any of the first 3 cycles.

The secondary objectives of the study were to evaluate the impact of VOM on the incidence of constipation during the first 3 cycles of FEC 100 during chemotherapy and to evaluate the impact of VOM on overall QoL for the first 3 cycles. The secondary endpoints were the rate of patients reporting at least one episode of constipation of grade greater than or equal to 1 on one of the first 3 cycles and the QLQ-C30 questionnaire. Nausea and/or vomiting and constipation rates were calculated based on the clinician reported side-effects using the Common Terminology Criteria for Adverse Events V4.03 (CTCAE) [13].

Individual patient participation lasted 9 weeks, the duration of the first 3 cycles of FEC 100 cycles of chemotherapy. Patients were included from November 2015 to April 2018 in CGFL.

### *Statistical analysis*

Primary objective and the secondary objectives analysis were carried out in intention to treat population and were repeated on the per-protocol population.

Continuous variables were described using means with standard deviations (SD) and medians with ranges. Comparisons between the two arms were done using the Wilcoxon test. Categorical variables were described by their frequency (percentage) and compared by a Chi2 test or Fisher exact test.

Quality of life scores were described at each visit in both arms by means with standard deviations and medians with ranges. Mean scores at inclusion were compared using a Wilcoxon test. To study the temporal evolution of quality of life scores, non-parametric mixed models for repeated measures were performed for each of QoL score.

Statistical analyses were performed using SAS version 9.4. All tests were two-sided, and P values $< 0.05$ were considered statistically significant.

## Results

### *Study flow and population characteristics*

94 patients were included and randomized. 54 patients were allocated to the VOM (experimental group) and 40 patients to the superficial manipulation (placebo group). 5 patients in the experimental and 3 patients in the placebo group discontinued the study. 13 patients in the experimental and 12 in the placebo group did not meet at least one of the inclusion/non-inclusion criteria. These patients were excluded from the *per protocol* analysis (experimental group N = 41; placebo group N = 28) but not from the ITT analysis (experimental group N = 54; placebo group N = 40) (Fig. 1).

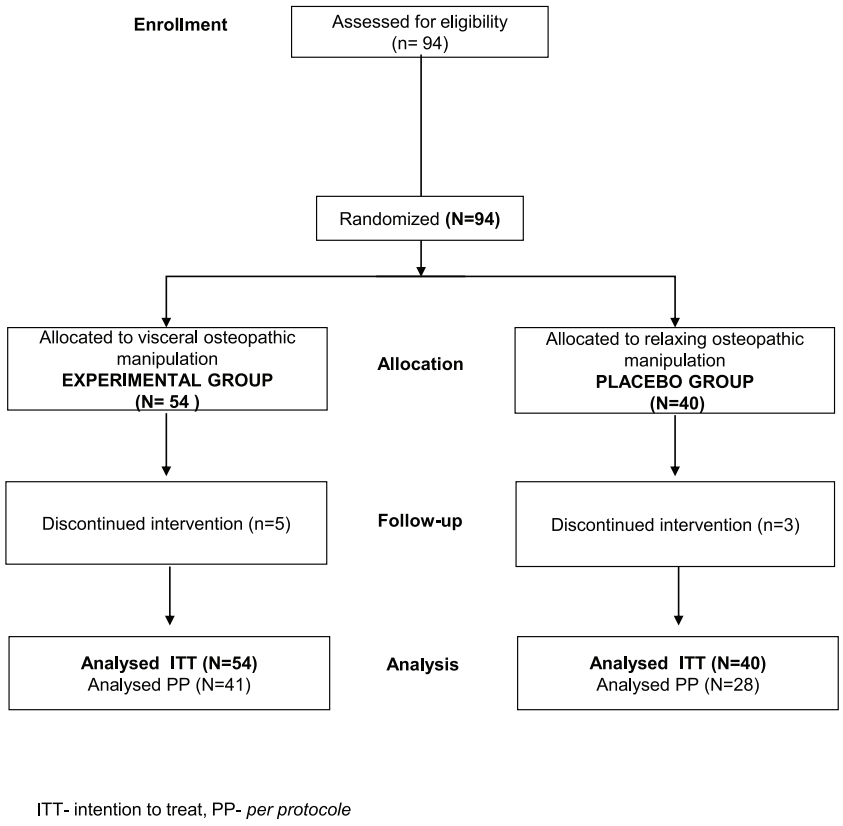


**Fig. 1.** Study Flow.

Median age at inclusion was 57.5 [min = 32.1–max = 71.8] in the experimental and 53.1 [min = 27.7–max = 76.9] in the placebo group. Median age at diagnosis was 57.3 [min = 31.9–max = 71.6] in the experimental and 52.9 [min = 27.6–max = 76.5] in the placebo group. No significant differences were found between group's age at inclusion or diagnosis. No patient died during the study (Table 1).

*Effect of visceral osteopathic manipulation on nausea and vomiting and constipation*

Report rate of at least one episode of nausea and/or vomiting of grade 1 or higher, on any of the first 3 cycles of FEC 100, was 80.4% in the experimental versus 87.2% in the placebo group (Table 2). Report rate of at least one episode of constipation of grade 1 or higher, on any of the first 3 cycles, was 47.1% in the experimental versus 61.5% in the placebo group. No significant differences between the rate of nausea and/or vomiting and constipation were found between groups according to the clinician reported side-effects using the CTCAE (Fisher's test- p-value 0.569 for nausea and/or vomiting and 0.204 for constipation) (Table 2). *Per protocol* analysis led to similar results.

*QoL*

*Score description*

The rate of EORTC QLQ-C30 questionnaire filling at inclusion and during the first 3 cycles of chemotherapy ranged from 92.6% to 100% (Table 3). A total of 376 observations were done, representing 4 observations for each of the 94 patients at inclusion and during the first 3 cycles of chemotherapy. 85% of QLQ-C30 questionnaires were totally completed, 10% were partially completed and 5% were completely missing.

Experimental and the placebo groups had similar baseline QLQ-C30 scores in all domains (Table 4). Global Health status, nausea

**Table 1**
Patient demographic characteristics.

| | **Experimental group** (visceral osteopathic manipulation) **N = 54** | **Placebo group** (superficial/soft tissue manipulation) **N = 40** | **p-value** |
|---|---|---|---|
| **Age at inclusion** | | | |
| Mean (SD) | 57.2 (10,2) | 54.4 (12.1) | |
| Median [min - max] | 57.5 [32.1–71.8] | 53.1 [27.7–76.9] | 0.259[a] |
| **Age at diagnosis** | | | |
| Mean (SD) | 56.8 (10,1) | 54.3 (12) | |
| Median [min - max] | 57.3 [31.9–71,6] | 52.9 [27.6–76.5] | 0.297[a] |
| **Death** | | | |
| No | 54 (100%) | 40 (100 %) | |

[a]Wilcoxon.

**Table 2**
Rate of patients reporting at least one episode of nausea and/or vomiting or constipation of grade equal or superior to 1 in one of the first 3 cycles of FEC 100.

| | **Experimental group** (visceral osteopathic manipulation) **N = 54**[§] | **Placebo group** (superficial/soft tissue manipulation) **N = 40**[#] | **p-value** |
|---|---|---|---|
| **Nausea and / or vomiting** | | | |
| No | 10 (19.6 %) | 5 (12.8 %) | |
| Yes | 41 (80.4 %) | 34 (87.2%) | 0.569[b] |
| 95% CI | [0.669–0.902] | [0.726–0.957] | |
| **Constipation** | | | |
| No | 27 (55.9 %) | 15 (38.5 %) | |
| Yes | 24 (47.1%) | 24 (61.5 %) | 0.204[b] |
| 95% CI | [0.329–0.615] | [0.446–0.766] | |

[b] Fisher.
[§] m.d = 3.
[#] m.d = 1, m.d missing data.

**Table 3**
EORTC QLQ-C30 questionnaire filling rate at inclusion and during the first 3 cycles of chemotherapy.

| Experimental group (visceral osteopathic manipulation) | Placebo group (superficial/soft tissue manipulation) |
|---|---|
| Inclusion | |
| N = 54 | N = 40 |
| 54 (100 %) | 40 (100 %) |
| Cycle 1 | |
| N = 54 | N = 39 |
| 50 (92.6 %) | 39 (100 %) |
| Cycle 2 | |
| N = 51 | N = 39 |
| 50 (98 %) | 39 (100 %) |
| Cycle 3 | |
| N = 49 | N = 37 |
| 48 (98 %) | 36 (97.3 %) |

and vomiting, constipation and diarrhoea QLQ-C30 scores evolution during the first 3 cycles is represented in Fig. 2 (B to E). Median delay between inclusion and cycle 1 was 16 days [min = 0– max = 49], while median delay between cycle 1 and 2 and cycle 2 and 3 was 21 days ([min = 20– max = 31]; [min = 11– max = 42] respectively) (Fig. 2 A). Approximately, cycle 1 took place 2 weeks after inclusion, cycle 2 five weeks upon inclusion and cycle 3 eight weeks post-inclusion (Fig. 2 A).

Global health status QLQ-C30 scores were similar and remained constant over the time/chemotherapy cycles in both groups (Fig. 2 B). Nausea and vomiting QLQ-C30 scores significantly progressed ($p<0.0001$) over time/chemotherapy cycles in both groups (Fig. 2 C). Intestinal symptoms (constipation and diarrhoea) QLQ-C30 scores were statistically significantly higher in placebo (constipation $p = 0.036$; diarrhoea $p = 0.038$) than in experimental group (Fig. 2 D and E).

*Concomitant treatments*

No statistically significant differences concerning the use of concomitant medicines to treat constipation (bisacodyl, macrogol 4000, macrogol 3350, lactulose, glycerin suppository) and diarrhoea (loperamide hydrochloride, racecadotril, diosmectite) were observed between both groups. Nevertheless, there was a tendency to have a higher rate of anti-constipation medicines prescribed to the placebo group in cycle 2 and 3 (41.2% versus 53.8% cycle 2; 38.8% versus 47.2% cycle 3 for experimental and placebo groups respectively) (Table 5).

## Discussion

In this study, clinicians reported a high rate of nausea/vomiting episodes, of grade 1 or higher, in patients undergoing adjuvant chemotherapy despite a prophylactic anti-emetic regimen. VOM does not seem to reduce the nausea/vomiting episodes resistant to anti-emetic treatment. Impairment of patient reported QoL due to nausea/vomiting symptoms remains unchanged after VOM. Concerning constipation, physician reported rate of this adverse-event did not decrease upon VOM. In contrast, patient

**Table 4**
Patient quality of life at inclusion (EORTC QLQ-C30).

| | **Experimental group** (visceral osteopathic manipulation) | | | | | | **Placebo group** (superficial/soft tissue manipulation) | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | N = 54 | | | | | | N = 40 | | | | | | |
| EORTC QLQ-C30 scale | N | Mean | SD | Median | Min | Max | N | Mean | SD | Median | Min | Max | p-value Wilcoxon |
| Global health status | 54 | 71.1 | 20.1 | 75 | 16.7 | 100 | 57 | 70.2 | 21.8 | 75 | 25 | 100 | 0.938 |
| Physical functioning | 54 | 90.5 | 13.8 | 93.3 | 26.7 | 100 | 58 | 86.6 | 18.6 | 93.3 | 20 | 100 | 0.582 |
| Role functioning | 54 | 88.9 | 20.7 | 100 | 0 | 100 | 58 | 89.2 | 22.2 | 100 | 0 | 100 | 0.744 |
| Emotional functioning | 54 | 66.2 | 22.1 | 66.7 | 0 | 100 | 58 | 68.1 | 29.5 | 75 | 0 | 100 | 0.223 |
| Cognitive functioning | 54 | 89.2 | 16.9 | 100 | 33.3 | 100 | 58 | 86.7 | 18.2 | 100 | 33.3 | 100 | 0.642 |
| Social functioning | 54 | 86.1 | 19.1 | 100 | 0 | 100 | 57 | 88.3 | 21.1 | 100 | 16.7 | 100 | 0.310 |
| Fatigue | 54 | 27.6 | 22.9 | 22.2 | 0 | 88.9 | 58 | 24.2 | 24.4 | 22.2 | 0 | 88.9 | 0.449 |
| Nausea and vomiting | 54 | 3.4 | 8.2 | 0 | 0 | 33.3 | 58 | 7.5 | 14.6 | 0 | 0 | 50 | 0.175 |
| Pain | 54 | 20.1 | 23 | 16.7 | 0 | 83.3 | 58 | 25 | 28 | 16.7 | 0 | 100 | 0.508 |
| Dyspnoea | 54 | 11.7 | 19.6 | 0 | 0 | 66.7 | 58 | 10 | 21.6 | 0 | 0 | 100 | 0.472 |
| Insomnia | 54 | 38.9 | 30.9 | 33.3 | 0 | 100 | 58 | 39.2 | 33.7 | 33.3 | 0 | 100 | 0.932 |
| Appetite loss | 54 | 9.3 | 19.9 | 0 | 0 | 66.7 | 57 | 16.2 | 29.5 | 0 | 0 | 100 | 0.244 |
| Constipation | 54 | 11.7 | 23.5 | 0 | 0 | 100 | 58 | 13.3 | 22.4 | 0 | 0 | 100 | 0.479 |
| Diarrhoea | 53 | 6.8 | 15 | 0 | 0 | 66.7 | 58 | 12 | 20.9 | 0 | 0 | 100 | 0.177 |
| Financial difficulties | 53 | 15.4 | 27.3 | 0 | 0 | 100 | 58 | 15.8 | 30.2 | 0 | 0 | 100 | 0.794 |

A

| DELAY (days) | Median | Min | Max |
|---|---|---|---|
| Inclusion and cycle 1 | **16** | 0 | 49 |
| Cycle 1 and cycle 2 | **21** | 20 | 31 |
| Cycle 2 and cycle 3 | **21** | 11 | 42 |

| TIME (median nr of weeks after inclusion) | |
|---|---|
| Inclusion | 0 |
| Cycle 1 | 2 |
| Cycle 2 | 5 |
| Cycle 3 | 8 |

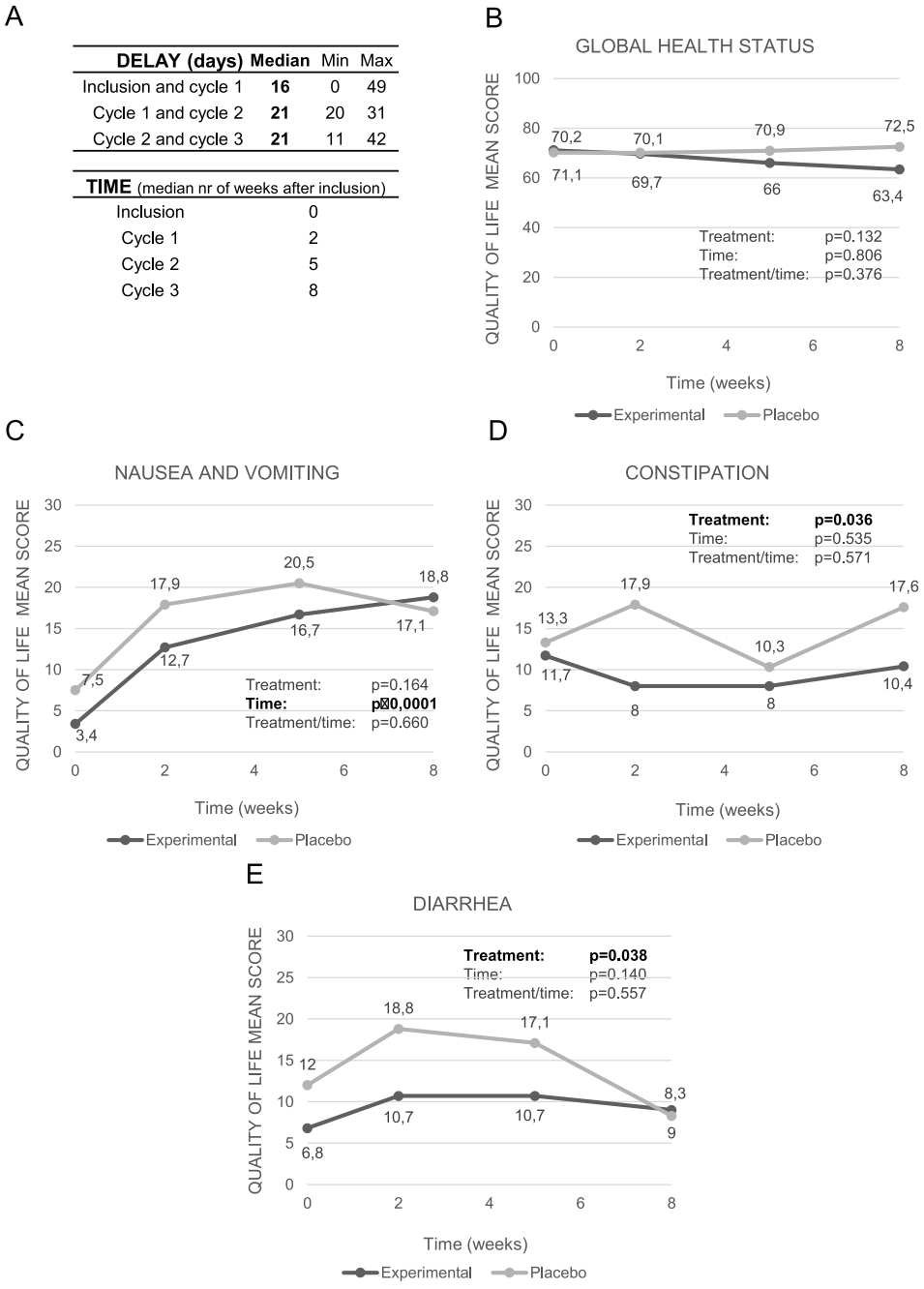


**Fig. 2.** QoL score description. General health status (B), nausea/vomiting (C), constipation (D) and diarrhoea (E) score evolution upon time. Mean time length delay between inclusion and treatment cycles (A).

reported QoL impairment due to constipation was significantly reduced by VOM, when compared to a superficial manipulation. In agreement with this observation, patients submitted to the placebo manipulation had a tendency to require more frequently anti-constipation medicines. Therefore VOM might reduce patient reported digestive toxicities induced by adjuvant chemotherapy and obviate medication usage.

Despite its randomized, double–blind, parallel and controlled nature, there are a number of limitations which need to be addressed in a future study. Patient number was not identical in the two groups. Indeed, due to the relatively small sample size, the simple randomization technique used resulted in an unequal number of participants among groups. Additionally, this was a monocentric study, involving only one osteopath practitioner in all the manipulations. Although, VOM is a an accepted and reproducible technique, a multicentre study involving several osteopathy practitioners and larger patient numbers will be required to confirm study results.

Despite the effectiveness of antiemetic regimens, there are still patients who are not protected from nausea and vomiting. A recent report by Tamura et al. showed that 52% of patients subjected to chemotherapy presented nausea and vomiting, despite the prophylactic use of anti-emetics [14]. In this study, the severity of emesis and nausea was reported by the patient using a visual analogue scale (VAS). In our study, clinicians reported a high rate of nausea/vomiting episodes (≥80%). As assessment strategies are different, comparison between studies is not possible. It should be noted that in our study the majority of nausea and vomiting

**Table 5**
Concomitant treatments of constipation and diarrhoea in experimental and placebo groups during cycle 1, 2 and 3 of chemotherapy.

| Concomitant treatment | Experimental group (N = 54) | Placebo group (N = 40) | p-value |
|---|---|---|---|
| | Cycle1 | | |
| Constipation | 28 (53.8%) | 24 (61.5%) | 0.463[a] |
| m.d | 2 | 1 | |
| Diarrhoea | 2 (33.3%) | 1 (14.3%) | 0.559[b] |
| m.d | 48 | 33 | |
| | Cycle 2 | | |
| Constipation | 21 (41.2%) | 21 (53.8%) | 0.233[a] |
| m.d | 3 | 1 | |
| Diarrhoea | 3 (20%) | 1 (9.1%) | 0.614[b] |
| m.d | 39 | 29 | |
| | Cycle 3 | | |
| Constipation | 19 (38.8%) | 17 (47.2%) | 0.436[a] |
| m.d | 5 | 4 | |
| diarrhoea | 4 (26.7%) | 1 (10.0%) | 0.615[b] |
| m.d | 39 | 30 | |

m.d missing data.
[a] $Chi^2$.
[b] Fisher.

episodes were grade 1 and might be linked to food disgust (results not shown). Moreover, our population is exclusively composed of women and female gender seems to be a risk factor for chemotherapy induced emesis [15,16].

*Osteopathy/massage and relief of chemotherapy induced nausea/vomiting*

In our study, both clinician and patient reported data indicate that VOM is not able to reduce nausea/vomiting episodes resistant to anti-emetic treatment. A study by Billhult et al. reported that massage significantly reduced nausea, compared to control treatment, in 39 women with breast cancer undergoing chemotherapy. Massage consisted on soft strokes, lasting for 20 min, on foot/lower leg or hand/lower. Control patients were visited by a member of the hospital staff for an unstructured conversation about any subject [9]. Another study on 17 women reported that finger acupressure may decrease nausea among women undergoing chemotherapy for breast cancer [8]. A qualitative study described the experience of 16 cancer patients that received osteopathic treatment for the management of cancer-related symptoms in palliative care [17]. Patients described beneficial effects on pain but also on other symptoms such as constipation or fatigue. A recent randomized clinical trial (RCT) studied the impact of an osteopathic treatment on the QoL of in 40 cancer patients undergoing chemotherapy. A significant reduction of nausea was observed with osteopathy [10]. Osteopathic treatment in this study consisted on a muscular, articular or myo-fascial cephalic, thoracic or abdominal osteopathic treatment adapted to patient's motility dysfunctions. Treatment was then completed by the systematic application of the visceral therapeutic osteopathic manipulation. Moreover studied populations are different in both studies: while our study included exclusively patients with breast cancer, a heterogeneous population concerning tumour localization was evaluated in Favier et al. Consequently, although chemotherapy regimens characterization is lacking in Favier et al, these were probably heterogeneous. Additionally, no information on the antiemetic treatment is provided in this study. The differences mentioned, render the comparison between studies results difficult.

*Osteopathy and relieve of constipation*

Research on patient reported outcomes (PROs) in cancer treatment shows that constipation is one of the most common side effects of cancer therapy [18]. The use of a serotonin receptor antagonist, included as an anti-emetic, increases the severity of constipation [19]. Our results show that patient reported QoL impairment due to constipation was significantly reduced by VOM, when compared to a superficial manipulation. Studies evaluating nonpharmacological interventions for managing chemotherapy-related gastro intestinal symptoms tend to focus on nausea and vomiting and exclude other relevant gastro intestinal symptoms [20]. Two pilot studies reported beneficial effects of osteopathy in chronic constipation. Belvaux et al. reported that osteopathic manipulative treatment decreased abdominal pain, bloating and patient assessment of constipation quality score in women with chronic constipation [21]. In a different study, participants reported an improvement in the overall severity of constipation, symptoms and QoL upon osteopathic treatment [22].

*Discordance between clinicians and patient reported symptoms*

In our study, no discrepancy was observed between clinician and patient reported effect of osteopathy in nausea/vomiting induced by chemotherapy. However, concerning constipation, patients reported a beneficial effect of VOM, while results based on clinician symptom report show no significant differences. Clinicians register side-effects during cancer treatment using CTCAE [13]. Several studies have consistently shown that health care professionals (HCP) underestimate the incidence and severity of patients' symptoms, when compared with PROs [23–28]. Moreover the agreement between HCPs and patient reported symptoms incidence and severity seems to be dependent on the type of symptom being evaluated [25]. Indeed, agreement between HCP and patient reported symptom severity is very high for nausea and low for constipation [25].

Osteopathic manual therapy is clearly an essential component of osteopathic health care but it can be combined with other treatments or advice [29]. As we have specifically addressed the effect of a particular manual therapy, it can be expected that the impact of osteopathy in the management treatment related adverse events in real life might be stronger.

## Data availability statement

All relevant data are within the paper.

## Funding

This study was funded by Hoffmann-La Roche.

## Ethics statement

Study was approved by the local ethics committee, authorized by the French Health Agency (ANSM- Agence Nationale de la Sécurité du Médicaments et des produits de santé", n°: 2015-A00366-43) in May 2015, and by the French Ethical Research Committee - "Comité de Protection des Personnes (CPP Est N° 15.04.03) in June 2015. All subjects were informed about the procedures of the study and signed a consent form before any procedure.

## Declaration of Competing Interest

No conflicts of interest were disclosed by authors.

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## Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.ejogrb.2019.08.003.

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