



ORIGINAL ARTICLE

Evaluation of numerical rating scale and neuropathic pain symptom inventory pain scores in advanced ovarian carcinoma patients undergoing surgery and first-line chemotherapy

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ARTICLE INFO

Article history:

Received: August 18, 2021

Revised: November 27, 2021

Accepted: January 14, 2022

Published online: January 25, 2022

Keywords:

ovarian cancer

pain

chemo-induced neuropathy

carboplatin

paclitaxel

movement-associated pain

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ABSTRACT

Background and Aim: Advanced epithelial ovarian cancer (OC) has a high disease manifestation with difficult-to-manage symptoms that limit the patients' functionality. Abdominal pain, persistent back pain, and neuropathic pain are among the common discomforts associated with OC and its treatment. Our study aims to determine pain scores in advanced OC patients undergoing surgery and chemotherapeutic treatment with carboplatin and paclitaxel.

Methods: One hundred and ten patients with advanced epithelial OC were enrolled and treated with surgery and an adjuvant/neoadjuvant chemotherapy regimen of carboplatin-paclitaxel for six cycles (triweekly). Pain intensity was analyzed using the validated numerical rating scale for resting, movement, sleep interference-associated pain, and neuropathic pain scores were evaluated using the neuropathic pain symptom inventory scale. Pain was correlated with QoL according to Fact-O questionnaires. Chemo-response was evaluated using the CA125 blood biomarker and CT scan of the abdomen and thorax. Data were recorded at baseline, 2, 4, and 6 months of the six chemotherapy cycles.

Results: Of the 110 patients, no statistically significant differences were found in pain at baseline and after treatment ($P > 0.05$) and between the responder and non-responder categories ($P > 0.05$). However, movement-associated pain had a significant correlation with chemo-response and a strong positive correlation with the patients' physical and functional wellbeing. There were more chemo-induced neuropathy occurrences ($P = 0.001$) in the neoadjuvant chemotherapy group.

Conclusion: Patients in the neoadjuvant chemotherapy arm experienced more chemo-induced neuropathy that was persistent and did not improve with the treatment.

Relevance for Patients: Peripheral neuropathy is a common adverse effect of platinum and taxane chemotherapeutic drugs that persists throughout cancer treatment and in survivorship. This research provides evidence that chemotherapy-associated neuropathy affects QoL of patients and it will be helpful to improve pain and palliative care management policies.

1. Introduction

Carcinoma of the ovaries ranks fifth in cancer deaths among women, with an estimated 295,414 new cases and 184,799 deaths worldwide and India records 36170 new cases and 24,015 deaths per year with a 5-year survival rate of 48% [1,2]. The most relevant clinical symptoms of OC include persistent abdominal swelling, pain, bloating, vaginal bleeding, altered bowel habits, indigestion, and loss of appetite [3,4]. Pelvic and abdominal

pain is expected in the advanced stages before diagnosis due to adnexal mass and accumulation of ascitic fluid leading to increased abdominal girth [5]. The standard chemotherapy comprising carboplatin and paclitaxel is the most important cause of neurotoxicity and neuropathic pain (painful paresthesia, diminished vibratory sense, and numbness among patients) [6]. Chemo-induced sensory neuropathy is reported as burning, pins and needles sensation, tingling, shooting, cramping, and deep aching [7,8]. About 60-85% of patients with ovarian cancer (OC) experience cancer or chemotherapy-related pain during their treatment or even afterward [9]. Persistent pain in cancer patients is associated with decreased quality of life (QoL), mostly lower levels of physical well-being, and an increase in dependency on healthcare services [10,11]. Advances in cancer diagnosis and treatment have dramatically increased the survival probability of patients with several cancers. For most cases pain is the first sign of cancer and the majority will experience low, and moderate to severe pain and/or neuropathy during their disease, chemotherapy, and survivorship [12].

To the best of our knowledge, there are limited reports of pain assessment among OC patients during their first-line treatment, and thus, we aim to evaluate the pain experienced and its impact on the physical and functional well-being of the OC patients at different time points.

2. Methods

2.1. Study design

This is a non-randomized and prospective study on advanced epithelial OC (FIGO stages III-IV) patients recruited after obtaining written informed consents, who underwent surgery from the Dept. of Gynecological Oncology and received their respective chemotherapy at Medical Oncology. The study was conducted between July 2018 and January 2021 and included patients older than 18 years, with histopathologically confirmed epithelial OC, adequate bone marrow, hepatic, neurologic, and cardiologic functions, adequate coagulation parameters, and ECOG performance status ≤ 3 . Patients under the age of 18 years; with recurrent disease who have received prior radiotherapy, chemotherapy and; pregnant or nursing women; patients with other malignancies; acute hepatitis; active infection, uncontrolled diabetes, serious non-healing wound, bleeding disorder, coagulopathy, bone fracture; significant proteinuria; clinically significant cardiovascular complications and significant autoimmune disease uncontrolled with treatment, were ineligible and excluded from the study.

According to operability, patients underwent either primary debulking surgery with adjuvant chemotherapy or interval debulking surgery and neoadjuvant chemotherapy. The chemotherapy regimen consisted of intravenous doses of 175 mg/m² paclitaxel on Day 1 (3 h) + carboplatin AUC 5-6mg. min/mL (over 1 h) on Day 2 [13]. The regimen was repeated every 3 weeks for six cycles. The clinical pain intensity scores were recorded at hospital visits and the Palliative Care Unit for the admitted patients. Patient follow-up and data analysis were

Table 1. Demographic characteristics of ovarian cancer patients

Characteristics (n=110)	Frequency (%)
Age (years)	
20-40	24 (21.8)
41-60	76 (69.09)
61-80	10 (9.09)
Education	
Illiterate	39 (34.5)
School education	61 (54.0)
Graduates and above	10 (8.8)
Religion	
Hindu	90 (79.6)
Muslim	20 (10.7)
Marital status	
Unmarried	7 (6.2)
Married	86 (76.1)
Widowed/Divorced	17 (15.0)
Occupation	
Unemployed/Housewife	83 (73.5)
Self employed/business	8 (7.1)
Professional/Desk job	7 (6.2)
Laborer	7 (6.2)
Farmer	5 (4.4)
Setup	
Urban	37 (32.7)
Rural	73 (64.6)
Monthly income	
<Rs 2000/-	26 (23.6)
Rs 2001 to Rs 5000/-	75 (68.2)
Rs 5001 and above	9 (8.2)

n=numbers of the patients; percentage (%) and all values represent in frequency

performed at Pathology and Cancer Screening, Chittaranjan National Cancer Institute (CNCI). The core dataset was compiled with demographic profile, clinical features, and post-chemo clinical response analyzed by blood biomarker CA125 and CT- scan of abdomen and thorax to categorize the responders, partial responders, and non-responders (NRs) [14-16].

This study was approved by Institutional Ethical Committee, CNCI (A-4.311/VN/27/06/2018-10).

2.2. Pain intensity and QoL measurement

The evaluation of pain intensity scores of patients was conducted using the numerical rating scale (0-10) for spontaneous resting, movement, sleep interference-associated pain, and neuropathic pain (neuropathic pain symptom inventory scale) [17-19]. Patients reported pain score 0, as no pain; and pain score of 10, as the worst pain imaginable [20,21]. QoL was assessed using FACT-O (Version 4) questionnaire (FACT-O) [22] and common adverse effects were also recorded and graded as per CTCAE [23]. The analysis was done at baseline, 2-, 4- and 6-months during hospital visits. Most of the patients were prescribed paracetamol, diclofenac (topical), tramadol, and rarely morphine for rescue

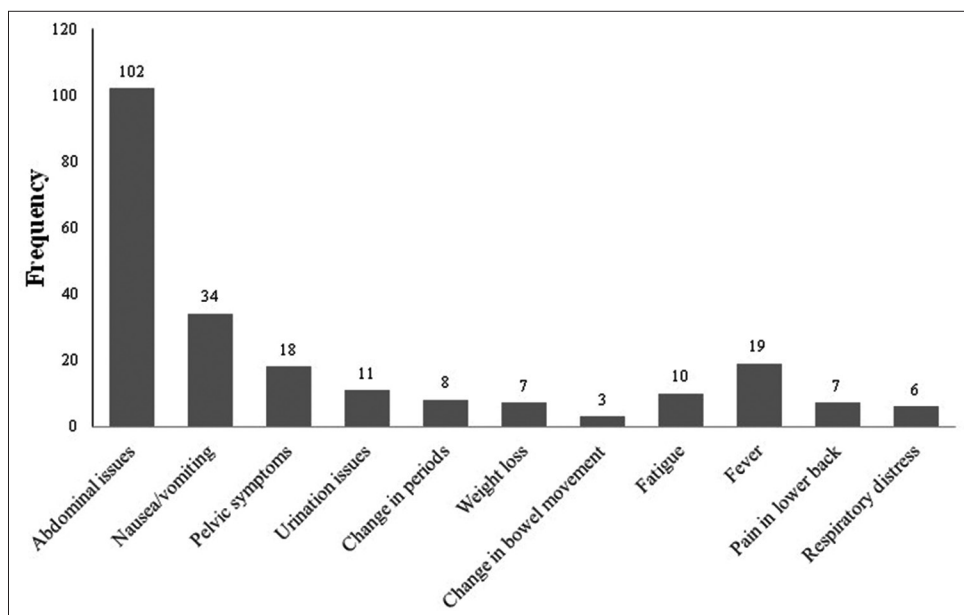


Figure 1. Distributions of symptom in patients with advanced ovarian cancer. Abdominal issues include pain, swelling, and bloating.

Table 2. Clinical characteristics of ovarian cancer patients

Characteristics (n=110)	Group	Frequency (%)
ECOG performance status	0	20 (18.9)
	1	68 (62.2)
	2	15 (13.5)
	3	7 (5.4)
FIGO Stage	III	91 (82.02)
	IV	19 (17.98)
Tumor histology	Serous/papillary	80.41 (81.0)
	Other	29.59 (26.9)
Gross type	Solid Cystic	65 (58.8)
	Cystic	32 (29.4)
	Solid	13 (11.8)
Size of tumor mass (pre-treatment)	>5 cm	80 (73.2)
	<5 cm	30 (26.8)
Clinical response	Responders	41 (37.3)
	Partial responders	44 (40)
	Non responders	25 (22.7)

n=numbers of the patients; percentage (%) and all values represent in frequency. Non Responders include Stable disease, Progressive, Time to treatment, palliative care and Not evaluable

analgesia. Gabapentin and Vitamin B12 were advised to them as a supportive treatment of chemo-induced neuropathy.

2.3. Statistical analysis

Descriptive statistics were used to analyze the frequencies of symptoms, clinical characteristics, and commonly observed toxicities among patients. Cross-tabulation was applied to find out significance (Chi-square, χ^2) of pain occurrence in groups (adjuvant and neoadjuvant chemotherapy). Two-way repeated

measure analysis of variance was used for tests of within-subject effect for numerical rating scale (NRS) pain versus groups (responders, partial responders, and NRs). Greenhouse-Geisser and Wilk's Lambda significance values ($P < 0.05$) were taken into consideration. The correlation coefficient (R2) was analyzed between pain experienced by the patients with their functional and physical wellbeing.

3. Results

The demographic profile of the patients shows a majority in the age range of 41-60 years (69.09%), school-educated (54%), Hindu (79.6%), married (76.1%), unemployed/housewives (73.5%) belonging to rural setup (64.6%) (Table 1) and their symptoms are represented in Figure 1. As per FIGO 2018 staging, most cases were of Stage III (82.02%), serious histology subtype (81%). After clinical evaluation 41, 44, and 25 patients were responders, partial responders, and NRs, respectively (Table 2). The NRS score of resting, movement, and sleep interference were non-significant within-subjects and in multivariate analysis (Wilk's Lambda $P > 0.05$). Movement-associated pain was significant ($P = 0.032$) in within-subject effect using Greenhouse-Geisser indicating a difference of pain in various chemotherapy response categories (Table 3). Frequencies of various types of neuropathic pain were recorded throughout 6 months of treatment for burning, pressure, cold sensation, pins and needles, and tingling (Table 4). There were no significant changes observed in the physical and functional well-being of the patients at the end of the study (Table 5). However, movement-associated pain had a strong positive correlation ($R^2 = 1$) with the physical and functional wellbeing of the patients (data not shown), indicating that higher pain scores diminish the normal physical activity and functionality. Anemia ($n = 65$), vomiting ($n = 26$), depression ($n =$

Table 3. Mean NRS scores in responders, partial responders and non-responders at various time intervals

Groups	Baseline	2 nd month	4 th month	6 th month	P-value [†] (within groups)
Resting stage					
Rs (n=41)	3.00±3.30	3.07±3.27	3.34±3.36	3.15±3.36	0.385
PRs (n=44)	2.93±3.40	2.57±3.2	2.48±3.34	2.86±3.38	
NRs (n=25)	3.84±3.78	3.72±3.72	2.96±3.47	3.40±3.62	
P-value* (between groups)			0.343		
Movement stage					
Rs (n=41)	2.37±3.11	2.46±3.09	2.63±3.23	2.76±3.12	0.032
PRs (n=44)	2.16±3.02	2.30±3.08	2.36±3.12	3.09±3.48	
NRs (n=25)	3.92±4.06	3.88±4.10	2.96±3.55	3.36±3.70	
P-value* (between groups)			0.081		
Sleep interference					
Rs (n=41)	2.32±3.36	2.17±3.19	2.51±3.23	2.54±3.37	0.499
PRs (n=44)	2.63±3.61	2.84±3.72	2.37±3.55	2.35±3.30	
NRs (n=25)	3.20±4.03	3.08±4.03	2.80±3.73	2.72±3.69	
P-value* (between groups)			0.603		

Responders (Rs); Partial Responders (PRs); Non Responders (NRs). All values are expressed as mean±SD. The NRS scores of resting, and sleep were non-significant within-subject effect and multivariate analysis. Only the movement stage pain was significantly ($P=0.032$) associated with chemotherapy response.

* Multivariate analysis (Wilk's Lambda)

[†] Greenhouse-Geisser

Mauchly's sphericity was significant ($P<0.05$).

Table 4. Patient distribution having different types of neuropathic pain at various time intervals

Neuropathic pain type	Baseline	2 months	4 months	6 months
Burning	18	18	15	20
Squeezing	21	16	17	14
Pressure	17	13	10	17
Electric Shock	16	11	10	15
Stabbing	13	11	10	15
Light touch	16	15	11	13
Pressing	18	14	14	20
Cold	18	14	12	24
Pins/Needles	14	19	19	23
Tingling	13	13	16	20

37), neuropathy ($n = 43$), weight loss ($n = 30$), constipation ($n = 40$), indigestion ($n = 47$), and renal toxicities ($n = 25$) were the most commonly noticed adverse effects in the patient population during the time of treatment (Table 6). 55 patients received adjuvant and 55 received neoadjuvant chemotherapy and significantly more occurrences of neuropathic pain were reported in the neoadjuvant chemotherapy arm ($P = 0.001$) (Table 7).

4. Discussion

Pain is one of the most distressing and constant symptoms reported in 60% of women with cancer and its treatment [24-27]. In this study, maximum patients (92.7%) reported abdominal pain similar to Ferrell et al. [27]. The persistent abdominal issues, including pain and distension, are one of the most prevalent and discomforting symptoms that lead patients to seek medical attention followed by the diagnosis with ovarian carcinoma.

No Grade 4 abdominal pain was observed in our study similar to Coleman et al. [28] and Cristea et al. [29] but contradictorily, Dizon et al. [30] reported dose-limiting toxicity and Grade 4 abdominal pain with intraperitoneal cisplatin therapy.

The patients were assessed for different kinds of pain from baseline to 6 months of their treatment. 57 (51.8%), 49 (44.5%), and 44 (40%) of patients reported resting, movement, and sleep interference-associated pain, respectively, at the time of study recruitment. Upon follow-up, after 6 cycles of chemotherapy, the frequencies of resting and sleep interference-associated pain remained the same but movement-associated pain increased by 6.4%. Movement-associated pain includes physical activity related to household work, certain individualized exercises, and specific functional tasks that patients do during the day [31]. Similar results were observed in the study by Portenoy et al. that reported 60% of advanced-stage OC patients experiencing pain at disease onset [24].

There are strong reports of sleep disturbances linked to depression/anxiety in OC patients [32,33]. Pain, however, is also not an isolated symptom and is mostly linked with fatigue, worrying, and disturbed sleep. In the present study, we could not assess pain associated with depression/anxiety, but the population represented significant percentages of sleep interference-associated pain (40%) and depression/anxiety (33.6%) that needed interventions to manage.

The movement-associated pain was significantly different in the responders and NRs throughout the study duration with higher intensities in the NRs group. It was also found to be associated with their physical and functional well-being.

In the present study, the neuropathic pain was primarily felt in the extremities (fingers, toes, and legs) similar to Ezendam et al. [34]. Burning, pressing, cold sensation, pins/needles, and

Table 5. Physical and functional QoL mean scores

QoL Domains	Groups	Baseline	2 nd month	4 th month	6 th month	P-value ¹
Physical	Rs (n=41)	8.15±7.18	8.37±6.97	9.54±7.24	9.90±6.94	0.425
	PRs (n=44)	8.43±8.01	8.32±8.00	8.95±7.58	9.52±7.86	
	NRs (n=25)	8.32±8.76	7.52±8.75	7.8±8.06	6.72±7.03	
P-value*			0.347			
Functional	Rs (n=41)	7.07±6.59	7.24±6.71	8.22±6.72	8.73±6.67	0.846
	PRs (n=44)	7.55±7.17	7.64±6.93	7.68±6.63	7.70±6.63	
	NRs (n=25)	6.72±6.73	5.92±6.72	6.32±6.75	6.68±7.25	
P-value*			0.609			

All values are expressed as mean±SD. The physical and functional well-being were non-significant for within-subject effect test and multivariate analysis. *Multivariate analysis (Wilk's Lambda). ¹Greenhouse-Geisser. Rs: Responders; PRs: Partial responders; NRs: Non responders

Table 6. Grades of common side effects experienced by the patients (n=110)

Toxicities	Frequency (%) of grades 1-2	Frequency (%) of grades 3-4
Anemia (n=65)	56 (50.9)	9 (8.1)
Leukopenia (n=16)	15 (13.6)	1 (0.9)
Thrombocytopenia (n=6)	6 (5.45)	0 (0)
Granulocytopenia (n=3)	3 (2.7)	0 (0)
Nausea (n=18)	16 (14.5)	2 (1.8)
Vomiting (n=26)	22 (20)	4 (3.6)
Anxiety/depression (n=37)	31 (28.1)	6 (5.4)
Neuropathy (n=43)	40 (36.36)	3 (2.7)
Weight loss (n=30)	30 (27.2)	0 (0)
Diarrhoea (n=35)	29 (26.3)	6 (5.4)
Constipation (n=40)	31 (28.1)	9 (8.1)
Indigestion (n=47)	40 (36.36)	7 (6.3)
Abdominal pain/swelling (n=33)	31 (28.1)	2 (1.8)
Renal toxicity (n=25)	24 (21.8)	1 (0.9)

Table 7. Distribution of different grades (CTCAE) of neuropathy in adjuvant and neoadjuvant chemotherapy arms

Adverse effect grades	0	1	2	3	Total	Pearson Chi-square
Adjuvant chemotherapy	42	7	3	3	55	P=0.001
Neoadjuvant chemotherapy	31	19	2	3	55	

tingling were the most reported chemo-induced peripheral neuropathy (CIPN) in the patient population. These symptoms were persistent throughout the study and did not significantly correlate with the treatment outcomes. The possible causes of persisting pain throughout the chemotherapy are tissue damage and nerve damage caused by carboplatin and paclitaxel [35,36] as common anti-neoplastic agents such as vinca alkaloids, platinum compound, and taxanes frequently induce a CIPN where both large and small primary afferent sensory neurons are injured.

Tumour-induced cancer pain tends to increase with advancing disease and can be driven by tumor-released products, acidosis, and direct injury to sensory nerve fibers present at the site of

the primary tumor or the site of tumor metastasis. Our study reported 39.09% of patients with neuropathy. The observation was similar to the study by Nho *et al.* that reports about pain and CIPN symptom clusters to negatively impact general QoL, and Bonhof *et al.* reported worse global QoL and functioning in patients with high motor peripheral neuropathy [37,38]. Between-group differences were not observed in neuropathic pain. Quality-of-life improvement was not observed in our study previously published [39] similar to the outcome reported by Magnowska *et al.* [40]. Unlike our study, they also reported gabapentin to benefit CIPN.

The limitations of the present study include its non-randomized design and small sample size that may have a chance of bias. The study also failed to follow up the patients till the recurrence of the disease and conclude about the role of pain. However, these reports will encourage further studies on better pain management on a personalized setup to improve QoL. With the incorporation of cancer pain research into conventional oncology research, it is possible that analgesic and oncologic therapies can be parallelly evaluated with regard to the effects on survival, overall health, and QoL of both cancer patients and survivors.

5. Conclusion

The summary of results demonstrates no improvement of pain at diagnosis and after completion of six cycles of chemotherapy. There were significantly more occurrences of neuropathic pain in the neoadjuvant chemotherapy arm than adjuvant chemotherapy and did not improve with the treatment. Movement-associated pain was worse in chemotherapy NRs that debilitates the physical and functional well-being of patients.

Acknowledgments

We would like to thank the patients for participating in the study. This work was supported by a grant from the Department of Health Research, Govt. of India (Ministry of Health and Family Welfare) (File No. R.12014/12/2018-HR) received to SS.

Conflict of Interests

The authors declare no conflict of interest.

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