European Review for Medical and Pharmacological Sciences 2021; 25: 5310-5317

NEPA (netupitant/palonosetron) for the antiemetic prophylaxis of nausea and vomiting induced by chemotherapy (CINV) with Folfirinox and Folfoxiri even during the COVID-19 pandemic: a real-life study

R. DE LUCA[1], C. VOLPE[1], O. MISTRETTA[1], R. PACI[1], G. FERRERA[2], V. CAPUTO[3], G. ROSATI[4], G. CICERO[1]

[1]Department of Surgical, Oncological and Oral Sciences, Section of Medical Oncology, University of Palermo, Palermo, Italy
[2]ARNAS Civico Hospital, Radiation Oncology Unit, Palermo, Italy
[3]Department of Health Promotion, Mother and Child Care, Internal Medicine and Medical Specialties, Section of Dermatology, University of Palermo, Palermo, Italy
[4]Ospedale San Carlo, Medical Oncology Unit, Potenza, Italy

Abstract. – OBJECTIVE: The outbreak of coronavirus disease 2019 (COVID-19) has affected the treatment of cancer patients, with particular regard to the management of both chemotherapy and side effects. Chemotherapy-induced nausea and vomiting (CINV) are amongst the most troublesome side effects that impair patients' adherence to treatments and their quality of life (QoL). NEPA (Akynzeo®), is an oral fixed-dose combination of netupitant [a neurokinin-1 receptor antagonist (NK1RA), 300 mg] and palonosetron [(5-hydroxytryptamine (serotonin or 5HT) type3 receptor antagonist (5HT3RA), 0.5 mg] which has been shown to be effective in preventing CINV.

PATIENTS AND METHODS: This prospective study started before the outbreak of COVID-19 and was carried out during the pandemic period. The aim was to evaluate the efficacy and safety of a single oral dose NEPA plus 12 mg of dexamethasone (DEX) in patients treated with Folfoxiri plus Bevacizumab and Folfirinox. The patients were diagnosed with advanced colorectal cancer (CRC) or advanced pancreatic ductal adenocarcinoma (PDAC). They were divided into two groups: naïve patients and patients previously treated with serotonin receptor antagonists (5HT3-RA) and neurokin-1 receptor antagonists (NK1-RA).

RESULTS: During the overall phase, the complete response (CR) rate was 96.8% in naïve patients treated with Folfoxiri plus Bevacizumab, and 94.6% in patients treated with Folfirinox. During the acute and delayed phases, the CR rate was 92.8% and 94.2%, with Folfoxiri and Bevacizumab, as well as 96.2% and 94.6%, with Folfirinox. There was no adequate control of CINV events in patients on antiemetic prophylaxis with 5HT3-RA or NK1-RA associated with cortisone. During the overall phase, the CR rate was 74.6% with Folfoxiri plus Bevacizumab and 75.8% with Folfirinox. During the acute and delayed phases, the CR rate was 72.5% and 74.8% with Folfoxiri plus Bevacizumab, as well as 75.2% and 74.6% with Folfirinox.

CONCLUSIONS: This study has shown the therapeutic benefits of NEPA in the management and prophylaxis of CINV events, both in naive patients and patients previously treated with 5HT3-RA and NK1-RA. In addition, NEPA has been shown to be safe, both before and during the COVID-19 pandemic.

Key Words:
CINV, Netupitant, Palonosetron, Emetogenic chemotherapy, COVID-19, Colorectal cancer, Advanced pancreatic cancer.

Introduction

The highly infectious nature of the new coronavirus pandemic (COVID-19), and its widespread prevalence, have created new obstacles in managing cancer patients[1,2]. As a result, new priorities – such as the execution of rapid swabs and the restriction of access into the wards – have been set in order to reduce the risk of contagion amongst patients with cancer. This strategy is also

Corresponding Author: Giuseppe Cicero, MD, Ph.D; e-mail: giuseppe.cicero@unipa.it

valid for patients with side effects, such as nausea and vomiting, caused by emetizing chemotherapy[3]. Chemotherapy-induced nausea and vomiting (CINV) events occur in approximately 60-70% of patients and are amongst the most feared side effects, along with alopecia[4,5]. The CINV onset depends on the emetogenic potential of chemotherapy, which varies in relation to drugs, doses and possible combinations[6]. Persistent nausea and vomiting cause dehydration with loss of nutrients and minerals, as well as anorexia with decreased intake of food and liquids. These conditions worsen the patients' health and compromise their adherence to treatment and quality of life (QoL)[7,8]. Two neurotransmitters play a crucial role in mediating the emetic response: serotonin acting on the 5HT3 receptor and the substance P targeting the NK1 receptor. Several drugs[9,10] are currently available for prophylaxis of nausea and vomiting caused by antineoplastic treatments. However, most effective ones belong to the class of 5HT3 receptor antagonists (5HT3-RAs) or to the NK1 receptor antagonists (NK1-RAs). New treatments for advanced colorectal cancer (CRC) and advanced pancreatic ductal adenocarcinoma (PDAC) include three drug regimens, Folfoxiri plus Bevacizumab and Folfirinox. Such drugs induce nausea and vomiting that standard antiemetics cannot adequately control. It has been recently shown that an oral combination of a 5HT3 receptor antagonist (5HT3-RA) and an NK1 receptor antagonist (NK1-RA), together with dexamethasone, is highly effective[11,12]. Netupitant 300 mg and Palonosetron 0.5 mg (NEPA) has been developed for CINV prophylaxis[13,14]. This simultaneous action mechanism, of two anti-emetic pathways, combines into a single administration of NEPA. As a result, the protection against CINV events is effective, safe and longer-lasting[15]. NEPA (netupitant/palonosetron) is the only fixed-dose combination of antiemetics currently available. It is composed of the long-lasting second-generation palonosetron (5HT3-RA) and the highly selective netupitant (NK1-RA)[16,17]. The present study aimed to evaluate the efficacy and safety of a single dose NEPA plus 12 mg DEX in CINV prophylaxis, during the treatment with Folfoxiri plus Bevacizumab and Folfirinox, for CRC and PDAC, both in naïve patients and in patients previously treated with 5HT3-RA. This prospective study, conducted before and during the COVID-19 pandemic, evaluated the complete response rate (CR), any vomiting events. It also considered the use of rescue medication during the overall phase (0-120 h), after the first cycle of chemotherapy and subsequent ones. The secondary endpoints were CR rates during the acute (0-24 h) and delayed (25-120 h) phases. During the acute, delayed, overall phase and QoL, no nausea was assessed. In response to COVID-19, preventive measures have been taken. These included swabs for patients and the building of a multidisciplinary team of general practitioners, psychologists, and healthcare professionals. The main aims were to optimize the results in this challenging time and restrict patients' access to the wards where the risk of contagion is high[18,19].

Patients and Methods

Study Design

This prospective study was conducted before and during the COVID-19 pandemic in full compliance with the provisions of the Declaration of Helsinki. These were communicated to the Palermo 1 Ethics Committee, and all patients provided written informed consent to the treatment. Between March 2017 and December 2020, one hundred consecutive patients were inserted at Oncology Department of University Palermo. Eligibility criteria included: histological or cytological diagnosis of CRC or PDAC; locally advanced or metastatic disease that can be measured and evaluated in accordance with Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1; performance status score between 0 and 1 according to the Eastern Cooperative Oncology Group (ECOG); adequate hematologic, renal, and liver function. Ineligibility criteria included hypersensitivity to NEPA or its constituents and other drugs used. The patients were divided into two groups according to their oncological pathology. In the first group, 50 patients with advanced CRC were treated with Folfoxiri plus Bevacizumab, every 15 days, for eight cycles. In the second group, 50 patients with advanced PDAC were treated with Folfirinox every 15 days for eight cycles.

Method of Administration

A capsule of NEPA (300 mg/0.5 mg) along with dexamethasone (12 mg) was administered approximately an hour before chemotherapy, on day one of each cycle (every 15 days)[20]. Any episode of nausea and vomiting was assessed in compliance with the Common Terminology Criteria for Adverse Events (CTCAE) v5.0. Clinical evaluations, as well as physical tests and labora-

tory studies, were carried out to monitor tolerability. In order to avoid coronavirus (COVID-19) infection, patients were asked to comply with mandatory rules, such as: a) avoid crowded places; b) wear PPE when going to the hospital for examinations or treatments; c) wash hands properly, in compliance with the instructions provided by the World Health Organization (WHO); d) avoid any contact with friends and relatives who have COVID-19 symptoms or live in endemic areas; e) ensure social distancing with other people: "protect yourself to protect others". In addition, it was built a multidisciplinary team of general practitioners, psychologists, and health professionals. The main aims were to optimize results in this difficult time and restrict patients' access to the departments, where the risk of contagion is high.

Outcomes

Following the outbreak of the global pandemic of COVID-19, managing patients enrolled in this study has required new measures to reduce the risk of exposure to the virus. In order to restrict access to the wards, patients interacted with hospital staff by telephone.

Patients were asked to complete a self-assessment diary of nausea, recording any vomiting episodes that occurred from day one to day seven after chemotherapy. Each episode was classified according to the Likert scale (none, mild/moderate or severe). The European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30 questionnaire[21] was provided to assess QoL at baseline and after eighth cycles. The questionnaire consists of 30 items on a 4-point Likert scale (1 = "No"; 4 = "a lot"). A high score indicates a high level of response, whereas a high score on a physical symptoms scale indicates a higher number of health issues. The association between the overall CR and CINV events was analyzed using the Bravais-Pearson (r) linear correlation index. All analyses were conducted using SAS version 9.4 (SAS Institute, Cary, NC, USA).

Results

Patients Characteristic

During the COVID-19 pandemic, the collaboration between teams of local specialists has refrained many patients from accessing the hospitals, reducing the risk of contagion. All staff accessing the oncology wards have been screened, and the use of face masks is mandatory. All of one hundred patients have completed the eight cycles arranged. In the first group, amongst the 50 patients enrolled, 22 were females and 28 males, with a median age of 58 years. In the second group, 24 patients out of 50 were females and 26 males, with a median age of 62 years.

In the first group: 25 patients (11 females and 14 males) received NEPA plus 12 mg of DEX for each of the eight cycles agreed. The other 25 patients (13 females and 12 males) randomly received either 5HT3-RA or NK1-RA for the first four cycles and NEPA plus 12 mg of DEX for the last four cycles.

In the second group: 25 patients (12 females and 13 males) received NEPA plus 12 mg of DEX for each of the eight cycles agreed. The other 25 patients (12 females and 13 males) were randomly given either 5HT3-RA or NK1-RA for the first four cycles and NEPA plus 12 mg of DEX for the remaining four cycles. The patients' clinical and pathological characteristics are shown in Table I.

Response Rate

During overall phase the CR in naïve patients who received Folfoxiri plus Bevacizumab, was 96.8% and 94.6% in patients who received Folfirinox. During the acute and delayed phases, the CR rate was 92.8% and 94.2% in patients who were administered Folfoxiri and Bevacizumab. In patients who received Folfirinox, the CR rate was 96.2% and 94.6% (Figure 1 and Figure 2). These responses were maintained throughout the subsequent cycles. Control of nausea raised as well, with NSN rates > 90% (Figure 3 and Figure 4) and no home rescue medication (metoclopramide/cortisone) was required. Appetite and nutrition remained substantially unchanged.

The patients treated for the first four cycles with standard antiemetic therapy (5HT3-RA and NK1-RA) did not have adequate control of CINV. During the overall phase the CR was 74.6% with Folfoxiri plus Bevacizumab and 75.8% with Folfirinox (Figure 1 and Figure 2). These responses remained the same even during subsequent cycles. During the acute and delayed phase, the CR was 72.5% and 74.8% with Folfoxiri and Bevacizumab. It was 75.2% and 74.6% with Folfirinox (Figure 1 and Figure 2). Control of nausea decreased significantly, with an NSN rate of 50%. Nausea was more frequently detected in females, whereas amongst all patients, the grade was predominantly G-2 (Figure 3 and Figure 4). Appetite and nutrition decreased due to nausea with weight loss, fatigue and adynamia. Metoclopramide 10 mg was the most frequent rescue drug taken. Finally,

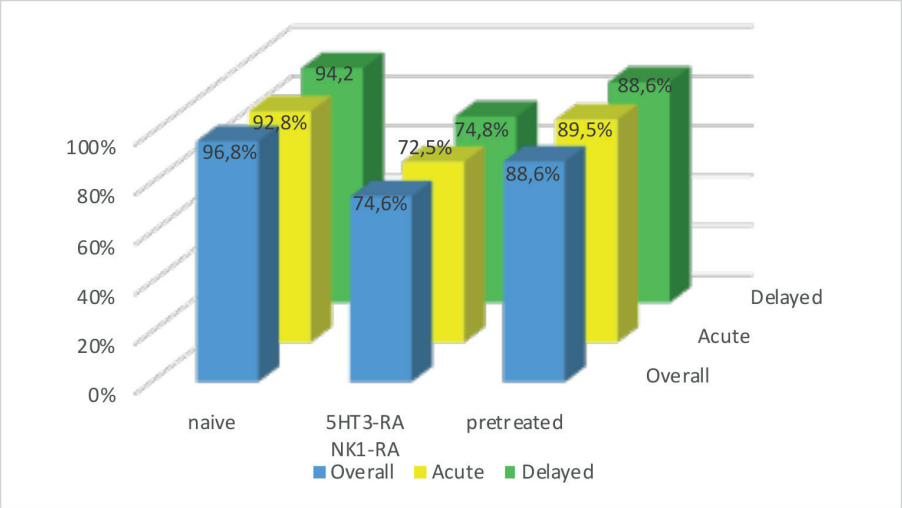

Figure 1. CR during acute (0-24 h), delayed (25-120 h) and overall (0-120 h) phase in CRC patients with Folfoxiri plus Bevacizumab treatment (n. 50). Note: CR = Complete response (no vomiting and no rescue medication); CRC = Colorectal cancer.

Table I. Clinical characteristics of patients' 1st group with CRC (n. 50) in treatment Bevacizumab with Folfoxiri and 2nd group with PC (n. 50) in treatment with Folfirinox.s.

Characteristics	Patients 1st group		Patients 2nd group
Mean age [range] years	58 [45-66]		62 [48-75]
Gender			
Male	56 % (28)		48% (24)
Female	44% (22)		52% (26)
ECOG performance status			
0	64% (32).		88% (44)
1	36% (18).		2% (6)
Primary tumor location			
Colon		*Pancreas*	
Single left-site	32% (16)	Head	50% (25)
Single right-site	68% (34)	Body	36% (18)
		Tail	14% (7)
K-RAS status			
Mutated	78% (34)		
Wilde type	22% (11)		
Location of metastasis			
Liver	12% (6)	8% (4)	
Lung	2% (1)	0% (-)	
Peritoneum	12% (6)	6% (3)	
Locally advanced not operable ab initio	74% (39	86% (43)	

Note: ECOG = Eastern Cooperative Oncology Group; CRC = Colorectal cancer; PC = Pancreatic cancer.

patients initially treated with 5HT3-RA and NK1-RA and switching to NEPA plus 12 mg of DEX after the first four cycles immediately showed an improvement in CINV events control. During the overall phase, the CR rate was 88.6% with Folfoxiri plus Bevacizumab and 89.2% with Folfirinox. During the acute and the delayed phases, the CR rate was 89.5% and 88.6% with Folfoxiri plus Bevacizumab and 88.6% and 89.4% with Folfirinox (Figures 1 and Figure 2). These CR rates remained

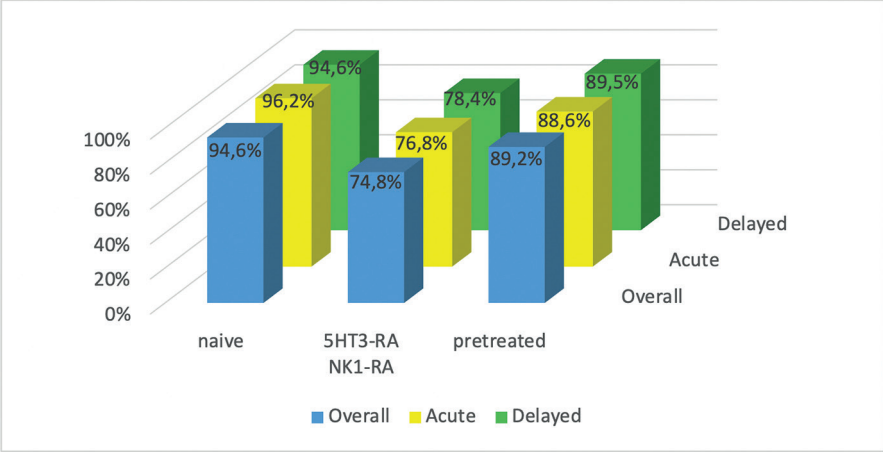

Figure 2. CR during acute (0-24 h), delayed (25-120 h) and overall (0-120 h) phase in CP patients with Folfirinox treatment (No. 50). Note: CR = Complete response (no vomiting and no use of rescue medication); PC = Pancreas cancer.

high in the subsequent cycles. Control of nausea significantly increased with an NSN rate >80%. (Figures 3 and Figure 4). Very few patients (3-4%) resorted to rescue drugs (metoclopramide / cortisone). Appetite and weight gain have increased.

Safety

The antiemetic treatment with NEPA was well tolerated and with no evidence of increased adverse events (AEs) in both naïve and in pretreat-

Table II. Average scores EORTC QLQ C-30 before and after treatment with Paired Samples Test (No. 100).

	Mean	SD	*t*	*p*
Global Health QLQ (pre-treatment)	30.1	6.59		
Global Health QLQ (post-treatment)	58.7	7.31	11.90	0.005

Note: EORTC QLQ C-30 = European Organization for Research and Treatment of Cancer.

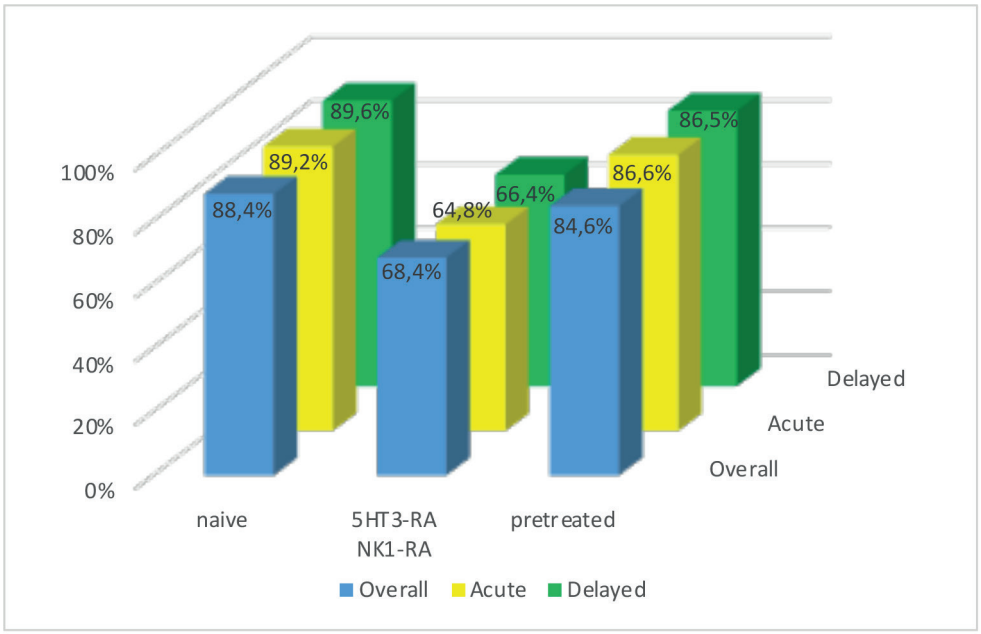

Figure 3. No nausea during the acute (0-24 h), delayed (25-120 h), and overall phase (0-120 h) in Folfoxiri plus Bevacizumab chemotherapy (No. 50).

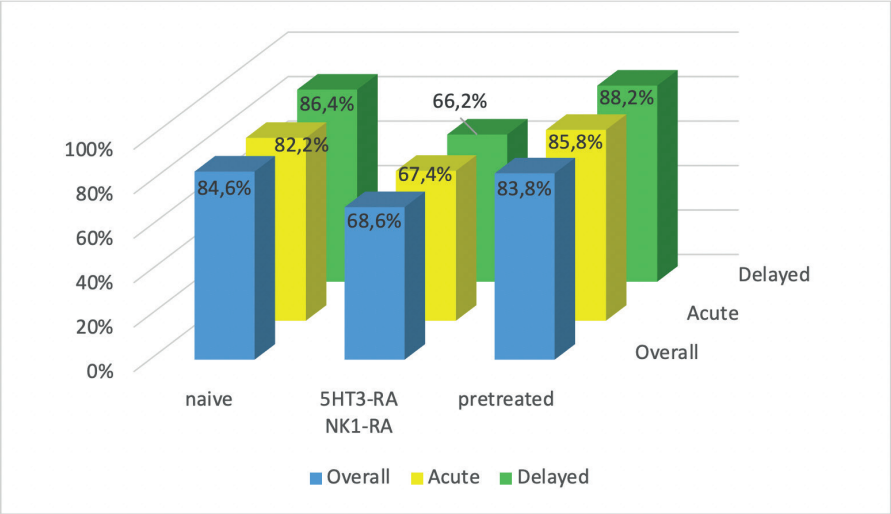

Figure 4. No nausea during the acute (0-24 h), delayed (25-120 h), and overall phase (0-120 h) in Folfirinox chemotherapy (No. 50).

ed patients. Adverse events reported by the three groups of patients were those expected for the 5HT3RA and NK1RA agents. No patient discontinued the treatment due to side effects, and there were no unexpected serious adverse events that could be attributed to the antiemetic regimen. The most frequent adverse events included headache, fatigue, and constipation. No patients showed symptoms or signs of either neurotoxicity or significant ECG changes. NEPA has not shown effects on QT to ECG. No G-4 toxicity led to the discontinuation of the treatment. Last follow-up has been done in March 2021.

Quality of Life

An improvement in QoL was also observed in 58% of patients. On the symptom scale of the EORTC-QLQ-C30 questionnaire, nausea and vomiting have a median score of 48.7 (DS 22.6) in the pre-treatment period, whereas, after the treatment with NEPA, the median score was 31.2 (DS 18.8). The results showed that drug management highly reduces symptoms, improving patients' general health. In approximately 45-52% of patients, nausea does not impact daily life (Table II).

Discussion

CINV events are amongst the most feared side effects in cancer patients who receive chemotherapy. They compromise patients' adherence to treatments and have a negative impact on QoL[22,23]. Despite pharmacological prophylaxis, ~61% of patients experience CINV (34% acute, 58% delayed), while undergoing moderately or highly emetogenic chemotherapy (MEC and HEC)[24]. During the COVID-19 pandemic, it was essential to manage chemotherapy-induced adverse events at home, when possible. This study has shown the efficacy and tolerability of NEPA in patients with a high risk of CINV who received emetogenic chemotherapy with Folfoxiri plus Bevacizumab in advanced CRC, and Folfirinox in advanced PDAC[25,26]. Compared to standard antiemetic treatments (5HT3-RA and NK1-RA), NEPA achieved superior efficacy in all primary and secondary endpoints during the acute, delayed and general phases, including QoL. Furthermore, the efficacy of NEPA was maintained in those patients who had previously received a CINV prophylaxis with standard antiemetics (5HT3-RA or NK1-RA). The results have shown that NEPA is widely superior to standard antiemetics. Most importantly, when used after failing treatment with 5HT3-RA or NK1-RA, it does not lose its effectiveness, achieving the same CINV control rate as that achieved in naive patients[27,28]. These patients resumed eating and gained weight. Therefore, NEPA might be the best indication for patients in poor general health condition who undergo highly-emetic anticancer therapy. In addition, the data showed that the control of CINV events remained constant over the subsequent cycles[29]. NEPA has

been shown to be effective and safe in preventing chemotherapy-induced emesis. As a result, adherence to cancer treatments has increased with survival benefits and a higher level of QoL. The highly infectious nature and the widespread prevalence of COVID-19 have led to significant changes in managing cancer patients, which has become very complicated with the outbreak of the pandemic. Patients, or their caregiver, were reached by phone to monitor any side effects occurred, and when required, dose-reduction was performed to manage the DRT better. Precautionary measures have been taken, such as the delay of the post-treatment surveillance check-up and the increase of the treatment period between courses of systemic palliative therapy. This study has shown that during the COVID 19 pandemic, the use of NEPA as prophylaxis of CINV events has reduced the number of medical check-ups to clear up the complications of nausea and vomiting. The use of oral therapies, such as NEPA, to prevent the side effects induced by emetizing chemotherapy has allowed the hospital staff to restrict access to the wards, reducing the risk of contagion.

Conclusions

During the COVID-19 pandemic, while managing cancer patients has become complicated, NEPA has proven to be efficacious in the prophylaxis of nausea and vomiting and in preventing all complications. Therefore, the number of patients who needed supportive care at the hospital, where the risk of coronavirus infection was high, has been significantly reduced.

This study has shown that the use of NEPA plus 12 mg of DEX during chemotherapy with Folfoxiri and Folfirinox has improved the antiemetic control, compared to the results achieved with 5HT3-RA and NK1- RA[30]. These results have shown that NEPA could be a valid and effective antiemetic to treat patients who undergo highly emetogenic chemotherapy. NEPA has been proved to be highly effective and well-tolerated in preventing CINV events. Subsequentially, it has determined an increase in adherence to chemotherapy and a higher QoL, especially during the COVID-19 pandemic. This study was carried out during the pandemic, which implied several inconveniences, such as a limited number of patients to enrol. Nevertheless, the results obtained are consistent with other studies, and they may provide a valid premise for future studies.

Conflict of Interest

The Authors declare that they have no conflict of interests.

References

1) Weiss SR, Navas-Martin S. Coronavirus pathogenesis and the emerging pathogen severe acute respiratory syndrome coronavirus. Microbiol Mol Biol Rev 2005; 69: 635-664.
2) Ueda M, Martins R, Hendrie PC, McDonnell T, Crews JR, Wong TL, McCreery B, Jagels B, Crane A, Byrd DR, Pergam SA, Davidson NE, Liu C, Stewart FM. Managing Cancer Care During the COVID-19 Pandemic: Agility and Collaboration Toward a Common Goal. J Natl Compr Canc Netw 2020; 18: 366-369.
3) Raymond E, Thieblemont C, Alran S, Faivre S. Impact of the COVID-19 outbreak on the management of patients with cancer. Targeted Oncol 2020; 15: 249-259.
4) Lindley CM, Bernard S, Fields SM. Incidence and duration of chemotherapy-induced nausea and vomiting in the outpatient oncology population. J Clin Oncol 1989; 7: 1142-1149.
5) Gilmore JW, Peacock NW, Gu A, Szabo S, Rammage M, Sharpe J, Haislip ST, Perry T, Boozan TL, Meador K, Cao X, Burke TA. Antiemetic guideline consistency and incidence of chemotherapy-induced nausea and vomiting in US community oncology practice: INSPIRE study. J Oncol Pract 2014; 10: 68-74.
6) Navari R, Aapro M. Antiemetic prophylaxis for chemotherapy-induced nausea and vomiting. N Engl J Med 2016; 374: 1356-1367.
7) Trigg ME, Higa GM. Chemotherapy-induced nausea and vomiting: antiemetic trials that impacted clinical practice. J Oncol Pharm Pract 2010; 16: 233-244.
8) Cohen L, de Moor CA, Eisenberg P, Ming EE, Hu H. Chemotherapy-induced nausea and vomiting: incidence and impact on patient quality of life at community oncology settings. Support Care Cancer 2007; 15: 497-503.
9) Hesketh PJ. Treatment of chemotherapy-induced emesis in the 1990s: impact of the 5-HT3 receptor antagonists. Support Care Cancer 1994; 2: 286-292.
10) Rojas C, Raje M, Tsukamoto T, Slusher BS. Molecular mechanisms of 5- HT3 and NK1 receptor antagonists in prevention of emesis. Eur J Pharmacol 2014; 722: 26-37.
11) Eisenberg P, Figueroa-Vadillo J, Zamora R, Charu V, Hajdenberg J, Cartmell A, Macciocchi A, Grunberg S; 99-04 Palonosetron Study Group. Improved prevention of moderately emetogenic chemotherapy-induced nausea and vomiting with palonosetron, a pharmacologically novel 5-HT3 receptor antagonist: results of a Phase III, single-dose trial versus dolasetron. Cancer 2003; 98: 2473-2482.

12) De Luca R, Alù M, Genova G, Grassadonia A, Cicero G. Use of Eribulin mesylate as second-line therapy in elderly patients with HER/2 negative metastatic breast cancer (MBC): efficacy, tolerability and Quality of Life. Eur Rev Med Pharmacol Sci 2020; 24: 12727-12734.

13) Grunberg SM, Rolski J, Strausz J, Aziz Z, Lane S, Russo MW, Wissel P, Guckert M, Wright O, Herrstedt J. Efficacy and safety of casopitant mesylate, a neurokinin 1 (NK1)-receptor antagonist, in prevention of chemotherapy-induced nausea and vomiting in patients receiving cisplatin-based highly emetogenic chemotherapy: a randomised, double-blind, placebo-controlled trial. Lancet Oncol 2009; 10: 549-558.

14) Bosnjak SM, Gralla RJ, Schwartzberg L. Prevention of chemotherapy-induced nausea: the role of neurokinin-1 (NK1) receptor antagonists. Support Care Cancer 2017; 25: 1661-1671.

15) Hesketh PJ, Rossi G, Rizzi G, Palmas M, Alyasova A, Bondarenko I, Lisyanskaya A, Gralla RJ. Efficacy and safety of NEPA, an oral combination of netupitant and palonosetron, for prevention of chemotherapy-induced nausea and vomiting following highly emetogenic chemotherapy: a randomized dose-ranging pivotal study. Ann Oncol 2014; 25: 1340-1346.

16) Aapro M, Karthaus M, Schwartzberg L, Bondarenko I, Sarosiek T, Oprean C, Cardona-Huerta S, Hansen V, Rossi G, Rizzi G, Borroni ME, Rugo H. NEPA, a fixed oral combination of netupitant and palonosetron, improves control of chemotherapy-induced nausea and vomiting (CINV) over multiple cycles of chemotherapy: results of a randomized, double-blind, phase 3 trial versus oral palonosetron. Support Care Cancer 2017; 25: 1127-1135.

17) Aapro M, Rugo H, Rossi G, Rizzi G, Borroni ME, Bondarenko I, Sarosiek T, Oprean C, Cardona-Huerta S, Lorusso V, Karthaus M, Schwartzberg L, Grunberg S. A randomized phase III study evaluating the efficacy and safety of NEPA, a fixed-dose combination of netupitant and palonosetron, for prevention of chemotherapy-induced nausea and vomiting following moderately emetogenic chemotherapy. Ann Oncol 2014; 25: 1328-1333.

18) Loupakis F, Cremolini C, Masi G, Lonardi S, Zagonel V, Salvatore L, Cortesi E, Tomasello G, Ronzoni M, Spadi R, Zaniboni A, Tonini G, Buonadonna A, Amoroso D, Chiara S, Carlomagno C, Boni C, Allegrini G, Boni L, Falcone A. Initial therapy with FOLFOXIRI and bevacizumab for metastatic colorectal cancer. N Engl J Med 2014; 371:1609-1618.

19) Conroy T, Desseigne F, Ychou M, Bouché O, Guimbaud R, Bécouarn Y, Adenis A, Raoul JL, Gourgou-Bourgade S, de la Fouchardière C, Bennouna J, Bachet JB, Khemissa-Akouz F, Péré-Vergé D, Delbaldo C, Assenat E, Chauffert B, Michel P, Montoto-Grillot C, Ducreux M. Groupe Tumeurs Digestives of Unicancer; PRODIGE Intergroup. FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. N Engl J Med 2011; 364: 1817-1825.

20) Gralla RJ, Bosnjak SM, Hontsa A, Balser C, Rizzi G, Rossi G, Borroni ME, Jordan K. A phase III study evaluating the safety and efficacy of NEPA, a fixed-dose combination of netupitant and palonosetron, for prevention of chemotherapy-induced nausea and vomiting over repeated cycles of chemotherapy. Ann Oncol 2014; 25: 1333–1339.

21) Snyder CF, Blackford AL, Okuyama T, Akechi T, Yamashita H, Toyama T, Carducci MA, Wu AW. Using the EORTC QLQ-C30 in Clinical Practice for Patient Management: Identifying Scores Requiring a Clinician's Attention. Qual Life Res 2013; 22: 2685-2691.

22) Aapro M, Carides A, Rapoport B, Schmoll HJ, Zhang L, Warr D. Aprepitant and fosaprepitant: a 10-year review of efficacy and safety. Oncologist 2015; 20: 450-458.

23) Dranitsaris G, Molassiotis A, Clemons M, Roeland E, Schwartzberg L, Dielenseger P, Jordan K, Young A, Aapro M. The development of a prediction tool to identify cancer patients at high risk for chemotherapy- induced nausea and vomiting. Ann Oncol 2017; 28: 1260-1267.

24) Hesketh PJ, Kris MG, Basch E, Bohlke K, Barbour SY, Clark-Snow RA, Danso MA, Dennis K, Dupuis LL, Dusetzina SB, Eng C, Feyer PC, Jordan K, Noonan K, Sparacio D, Somerfield MR, Lyman GH. Antiemetics: American Society of Clinical Oncology clinical practice guideline update (ASCO). J Clin Oncol 2017; 35: 3240-3261.

25) Cicero G, De Luca R, Dieli F. Progression-free survival as a surrogate endpoint of overall survival in patients with metastatic colorectal cancer. Onco Targets Ther 2018; 11: 3059-3063.

26) The Lancet O. COVID-19: global consequences for oncology. Lancet Oncol 2020; 21: 467.

27) De Luca R, Blasi L, Alù M, Gristina V, Cicero G. Clinical efficacy of nab-paclitaxel in patients with metastatic pancreatic cancer. Drug Des Devel Ther 2018; 12: 1769-1775.

28) Roila F, Molassiotis A, Herrstedt J, Aapro M, Gralla RJ, Bruera E, Clark-Snow RA, Dupuis LL, Einhorn LH, Feyer P, Hesketh PJ, Jordan K, Olver I, Rapoport BL, Roscoe J, Ruhlmann CH, Walsh D, Warr D, van der Wetering M. participants of the MASCC/ESMO Consensus Conference Copenhagen. 2016 MASCC and ESMO guideline update for the prevention of chemotherapy- and ratiotherapy-induced nausea and vomiting in advanced cancer patients. Ann Oncol 2019; 27: v119-v133.

29) Lorusso D, Bria E, Costantini A, Di Maio M, Rosti G, Mancuso A. Patients' perception of chemotherapy side effects: expectations, doctor-patient communication and impact on quality of life – an Italian survey. Eur J Cancer Care 2017; 26: e12618.

30) Razvi Y, Chan S, McFarlane T, McKenzie E, Zaki P, DeAngelis C, Pidduck W, Bushehri A, Chow E, Jerzak KJ. ASCO, NCCN, MASCC/ESMO: a comparison of antiemetic guidelines for the treatment of chemotherapy-induced nausea and vomiting in adult patients. Support Care Cancer 2019; 27: 87-95.