Short Communication

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Safety and efficacy of netupitant/palonosetron and dexamethasone in classical Hodgkin's lymphoma patients with inadequate chemotherapy-induced nausea and vomiting prophylaxis with palonosetron and dexamethasone: a single-center real-life experience

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We analyzed safety of NEPA (netupitant/palonosetron) and dexamethasone (NEPA+DEX) for the management of chemotherapy-induced nausea and vomiting (CINV) in classical Hodgkin's lymphoma patients that experienced CINV with a prophylaxis with palonosetron (PALO + DEX). In a retrospective, monocentric, noncomparative study, we analyzed adverse events and CINV grading in patients who switched from PALO + DEX to NEPA + DEX. Among 32 patients treated with ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine) during the study period, 47% did not properly control CINV with PALO + DEX and were shifted to NEPA + DEX. Among these, 53.3% properly controlled CINV is for all the remaining chemotherapy cycles. We did not observe an increase of adverse events after switching to NEPA. In our study, NEPA did not show drug–drug interaction with ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine) chemotherapy agents and NEPA administration was well tolerated with mild and transient adverse events.

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Chemotherapy-induced nausea and vomiting (CINV) is one of the most feared chemotherapy-related adverse events and can considerably impact the quality of life of cancer patients and their compliance to the therapeutic plan [1–4]. CINV particularly affects young patients and tends to increase along treatment periods, especially if not properly managed [5]. The standard of care for the first-line treatment of classical Hodgkin lymphoma is the ABVD chemotherapy regimen (doxorubicin, bleomycin, vinblastine, dacarbazine). This regimen is associated with a high emetic risk and therefore international guidelines strongly recommend a highly effective CINV prophylaxis [6–8]. However, safety and drug–drug interaction studies are not always available for specific antiemetic combinations associated with specific chemotherapy regimens, especially in hematological settings.

In clinical practice, a combination of palonosetron (PALO), a second-generation serotonergic receptor antagonist and dexamethasone is largely used for the prophylaxis of CINV in several treatment settings, including treatment with ABVD [9]. However, after many chemotherapy cycles, patients frequently need to add other antiemetic drugs to obtain a good control of their symptoms. Neurokinin 1 receptor antagonists, which include aprepitant and

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netupitant, are used in combination with serotonergic receptor antagonists to improve CINV control [6–8]. In particular, netupitant has been demonstrated to work synergistically with PALO and the two drugs are available as a fixed oral combination, named NEPA (300 mg/0.5 mg) [10,11]. NEPA provides an optimal option for ABVD-treated patients, by acting on the two main molecular pathways involved in emesis in a single dose, simplifying the prophylactic therapy and improving patient compliance [12]. Among ABVD drugs, doxorubicin and vinblastine are metabolized by the enzyme CYP3A4. Both netupitant and aprepitant are also metabolized by CYP3A4 and therefore could interact with this chemotherapy regimen. In particular, netupitant is a moderate CYP3A4 inhibitor, while aprepitant is both a moderate inhibitor and inducer of CYP3A4 [13]. Since no safety data are currently available for netupitant in this setting, at our center we started to use NEPA in ABVD-treated patients for whom adequate CINV control could not be achieved with PALO plus dexamethasone and assessed their safety profile. In this way, we could directly compare efficacy and tolerability of NEPA in the same population that first received PALO.

Methods

This is a retrospective, monocentric, noncomparative study conducted from September 2016 to December 2018, and it was approved by the ASST Grande Ospedale Metropolitano Niguarda local ethics committee.

Eligible patients were 18 years old or older; they were diagnosed with classical Hodgkin lymphoma, treated with ABVD chemotherapy and were undergoing an initial CINV prophylaxis with PALO + dexamethasone (DEX). Patients who experienced either nausea or vomiting (grade $\geq$1) during the overall phase (0–120 h from chemotherapy administration) were switched to NEPA + DEX at the start of the next chemotherapy cycle. The entire series consisted of 32 patients. We collected data regarding demographics, diagnosis, planned and performed chemotherapeutic treatment, acute (0–24 h) and delayed (25–120 h) nausea and vomiting (during both PALO- and NEPA-based prophylaxis), laboratory findings – including transaminase, creatinine and electrolytes – and adverse reactions (during both PALO- and NEPA-based prophylaxis). Adverse events, as well as CINV grading, were collected by interviewing the patient during a face-to-face visit and recorded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. In regard to grading, vomiting grade 1 was classed as one to two episodes in 24 h; vomiting grade 2 was three to five episodes in 24 h; vomiting grade 3 was greater than or equal to six episodes in 24 h; nausea grade 1 meant loss of appetite without alteration in eating habits; nausea grade 2 was oral intake decreased without significant weight loss, dehydration or malnutrition; nausea grade 3 was inadequate oral caloric or fluid intake.

As a first-line CINV prophylaxis, PALO 0.25 mg and dexamethasone 8 mg were given from day one of the first cycle, while NEPA and dexamethasone 8 mg were introduced on day one of subsequent cycles for patients who inadequately controlled CINV. As part of the chemotherapy regimen, methylprednisolone 20 mg, which is equivalent to approximately 3.75 mg of dexamethasone, was also administered together with ABVD drugs to all patients.

The primary end point of the study was safety of NEPA in ABVD-treated patients, while NEPA efficacy on CINV control (no nausea or vomiting) was the secondary end point. NEPA-related safety data have been compared with the same data collected at the moment of the last previous PALO-containing regimen.

Results

Among the 32 patients treated with ABVD during the study period, 15 (47%) experienced vomiting and/or nausea with a PALO + DEX prophylaxis and therefore were shifted to NEPA + DEX. Of these 15 patients, five were male and ten female and the median age was 36 years (range 18–61). According to the disease characteristics at diagnosis, the scheduled regimens were six ABVD cycles (corresponding to 12 administrations) in 11 patients, four cycles (eight administrations) in three patients and two cycles (four administrations) in one patient. Twelve patients completed the planned chemotherapy, one patient skipped the last administration for personal reason and two patients were still on treatment at the time of analysis. NEPA was started after a median of five ABVD administrations (range 2–11), for a total of 59 NEPA administrations (median number of three NEPA administrations for each patient, range 1–11).

Toxicity analysis

In the 15 patients who failed a first-line CINV prophylaxis, we did not observe significant organ toxicity, such as reduced pulmonary capacity or cardiac damage, during the PALO + DEX-containing regimens, although one

Table 1. The observed adverse events collected in all 32 patients involved in the study: 17 patients with adequate chemotherapy-induced nausea and vomiting prophylaxis with palonosetron + dexamethasone and fifteen patients that were switched to netupitant/palonosetron–dexamethasone.

Clinically relevant adverse events	Patients with adequate PALO + DEX prophylaxis	Patients who switched to NEPA + DEX prophylaxis	
	During PALO (n = 17)	During PALO (n = 15)	During NEPA (all cycles, n = 15)
Pulmonary toxicity (reduced vital capacity)	2 pts (grade 2)†	–	–
Cardiac damage	–	–	–
Electrolyte abnormalities	–	–	–
Headache	–	1 pt (grade 1)	1 pt (grade 1)
Abdominal pain	6 pts (grade 1)	–	1 pt (grade 1)
Constipation	–	–	1 pt (grade 1)
Renal dysfunction	–	–	–
Transaminase elevation	3 pts (grade 1) 3 pts (grade 2)† 3 pts (grade 3)†	1 pt (grade 1) – –	1 pt (grade 3)‡ – –
Dizziness, nasopharyngitis, somnolence	1 pt (grade 1)	–	–
Dose reduction due to CINV	–	–	–
Neutropenia	6 pts (grade 1)§ 1 pt (grade 2)§ 3 pts (grade 3)§ 2 pts (grade 4)§	1 pt (grade 1)§ 3 pts (grade 2)§ 5 pts (grade 3)§ –	2 pts (grade 1) 1 pt (grade 2) – –
Anemia	2 pts (grade 1) –	2 pts (grade 1) 1 pt (grade 2)	3 pts (grade 1) –

For these patients, clinically relevant adverse events were collected during their PALO- and NEPA-containing regimens. Adverse events were recorded according to Common Terminology Criteria for Adverse Events, version 4.0.
† Adjustment of chemotherapy due to adverse events.
‡ Grade 3 was transient occurring after eight ABVD + NEPA administrations with transaminase level below threshold or at grade 1, and subsequently resolved without NEPA interruption.
§ Maximum grade of neutropenia before treatment with G-CSF for secondary prophylaxis.
ABVD: Doxorubicin, bleomycin, vinblastine, dacarbazine; CINV: Chemotherapy-induced nausea and vomiting; DEX: Dexamethasone; NEPA: Netupitant/palonosetron; PALO: Palonosetron; pts: Patients.

patient presented mild dacarbazine-related transaminase elevation (Table 1). One of the 15 patients presented with a headache (positive anamnesis for headache previously to any lymphoma-related treatments). No patient required a dose reduction or therapy delay due to CINV. All patients underwent a secondary G-CSF prophylaxis to reduce incidence of neutropenia; the maximum grade of neutropenia before G-CSF administration is also reported on Table 1. Similarly, during NEPA + DEX administration we did not observe significant organ toxicity, renal disfunction or electrolytes imbalance. No patient experienced nasopharyngitis, somnolence or dizziness and again, no patient required dose reduction or therapy delay because of CINV. One patient presented headache (same patient described above), one patient experienced grade 1 abdominal pain and one patient had grade 1 constipation. A grade-3 transaminase elevation was observed in one patient, who already experienced a mild transaminase elevation during the PALO + DEX-containing regimens. In this case we do not consider this abnormality as related to NEPA, as the elevation was transient and asymptomatic, and occurred after eight administrations of chemotherapy with NEPA in which transaminase levels were below threshold or at grade 1. Moreover, transaminase levels decreased without NEPA interruption in the subsequent cycles, in which only dacarbazine, a drug not metabolized by CYP3A4, was reduced.

CINV control

Among the 32 patients, 15 experienced CINV during PALO + DEX regimens and therefore were shifted to NEPA + DEX. Specifically, four had emetic events (all grade 2), while the other eleven only experienced nausea (four grade 1 and seven grade 2) during the overall phase with PALO + DEX administration (Figure 1A).

After switching to NEPA + DEX, nine patients (60%) properly controlled CINV at the first cycle and eight (53.3%) managed to control for all the remaining chemotherapy cycle (Figure 1A). In particular, one patient experienced emetic events (grade 2) and six had nausea (four grade 1 and two grade 2) during the overall phase.

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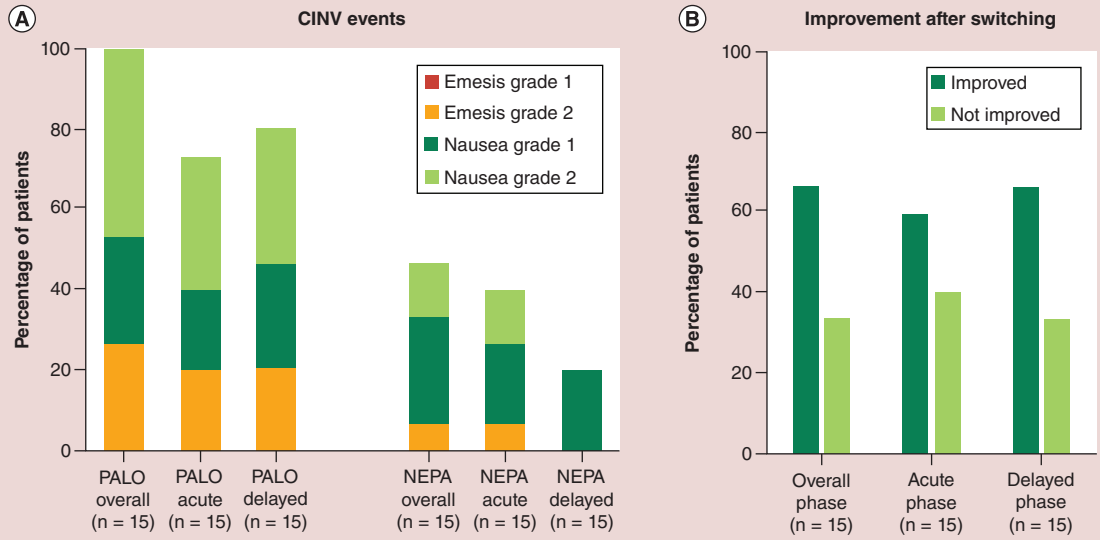

Figure 1. CINV observed before and after switching to NEPA. (A) Maximum grade of CINV observed in the population of patients that failed PALO + DEX CINV prophylaxis (n = 15). The plot shows the type of CINV event and its grade occurred during the overall (0–120 h), acute (0–24 h) and delayed (25–120 h) phase, associated with PALO administration and after switching to netupitant/palonosetron. Emesis grade 1: red; emesis grade 2: yellow; nausea grade 1: dark green; nausea grade 2: light green. **(B)** Percentage of patients that improved their CINV control after switching to netupitant/palonosetron + DEX (n = 15); improved: none or milder grade CINV experienced compared with PALO + DEX; not improved: same grade of CINV or worse compared with PALO + DEX.
CINV: Chemotherapy-induced nausea and vomiting; DEX: Dexamethasone; NEPA: Netupitant/palonosetron; PALO: Palonosetron.

Seven patients, after an initial improvement in CINV control, subsequently required to add additional antiemetics for controlling CINV.

Discussion

At the time the study was initiated, no safety data were available for either aprepitant or netupitant when co-administered with ABVD drugs. For this reason, we were first cautious in adding drugs that might interact with CYP3A4 and therefore affect the pharmacokinetic properties of doxorubicin and vinblastine. However, we were also interested in collecting and analyzing safety data in those patients who really required a neurokinin 1 receptor antagonist for controlling CINV. In our experience, NEPA toxicity profile was excellent with no major toxicities observed. NEPA did not show drug–drug interactions with ABVD chemotherapy agents, and NEPA administration was well tolerated with mild and transient adverse events.

Furthermore, NEPA represents a very effective drug for CINV control, especially if we consider that we have administered NEPA to a very difficult population to treat. Indeed, the study population consisted entirely in patients with no adequate CINV control with PALO + DEX administration. In addition, many patients were young and female, which are two risk factors for experiencing CINV [14]. In our study, we observed improved control of emesis and nausea with NEPA + DEX, which was demonstrated to be able to decrease, if not completely abolish, CINV intensity when compared with PALO + DEX prophylaxis. Indeed, less events with a milder grade were reported after switching to NEPA and the majority of the patients (66.7%) experienced an improvement in CINV management (Figure 1B).

These data are even more important for two reasons; first, even though some data are available for aprepitant in the ABVD setting [15], at our knowledge no data have been published regarding NEPA toxicities in the ABVD setting. Second, our data come from a real-life experience of consecutive patients treated homogeneously at a single center.

Conclusion

Within the limit of the small patient sample size of our study, NEPA has demonstrated for the first time to have a strong efficacy and an optimal safety profile in the ABVD setting. Further larger and randomized studies are needed to confirm these results.

Summary points

- At the time of study initiation, no safety data were available for NEPA (netupitant/palonosetron) in the ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine) treatment setting.
- We analyzed incidence of adverse events and chemotherapy-induced nausea and vomiting (CINV) grading in patients who switched to NEPA after failure of palonosetron-based antiemetic prophylaxis.
- We did not observe an increase of adverse events after switching to NEPA.
- Sixty-six percent of the patients improved their CINV management.
- The majority of the patients had controlled CINV for all the remaining chemotherapy cycles.
- We confirm that NEPA is well tolerated and effective when co-administered with ABVD drugs.

Financial & competing interests disclosure

VR Zilioli has acted as an advisor for Janssen and MSD, and received honoraria from Italfarmaco SpA and Roche. P Codega is an employee of Italfarmaco SpA. C Rusconi acted as an advisor for Roche, Takeda, Celgene and Italfarmaco SpA and received a research grant from Celgene. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

Ethical conduct of research

The authors state that they have obtained appropriate institutional review board approval or have followed the principles outlined in the Declaration of Helsinki for all human or animal experimental investigations. In addition, for investigations involving human subjects, informed consent has been obtained from the participants involved.

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