Neutropenic sepsis rates in patients receiving BEP chemotherapy using olanzapine and reduced doses of dexamethasone compared to a standard antiemetic regimen

Dr Ernese Gjafa[1#], Dr Kenrick Ng[2#], Dr Tami Grunewald[2], Dr Myria Galazi[1], Dr Erik Skyllberg[1], Peter Wilson[1], Dr Constantine Alifrangis[1,2], Dr Jonathan Shamash[1]

[1]Department of Medical Oncology, St Bartholomew's Hospital, Bart's Health NHS Trust,

[2]Department of Medical Oncology, University College London Hospital NHS Foundation Trust

Keywords: BEP chemotherapy, Olanzapine, Febrile neutropenia, Steroids, Antiemetics

Corresponding Author: Ernese Gjafa

Email: ernese.gjafa1@nhs.net

# These authors contributed equally to this manuscript

Abstract

Background

Bleomycin, Etoposide and Cisplatin (BEP) chemotherapy is the conventional treatment regimen for patients with germ cell tumours. The regimen is highly emetogenic and immunosuppressive. High dose steroids are often prescribed with this regimen as antiemetic prophylaxis but may have adverse effects in the context of immunosuppression.

Objective

To investigate whether the use of a steroid-sparing antiemetic protocol (substituting dexamethasone with olanzapine) affects the incidence of neutropenia and associated hospital admissions in patients receiving BEP chemotherapy.

Design, setting, participants and statistical analysis

Records from 108 patients who received BEP in St Bartholomew's Hospital, London were divided into two groups by antiemetic regimen. Group 1 (treated 2008-2013) were treated with a steroid-containing antiemetic protocol and Group 2 (treated 2014-2017) were given a steroid-sparing protocol, i.e. using olanzapine.

Outcomes include incidence of neutropenia at nadir blood count, severity of neutropenia, hospital admissions due to febrile neutropenia (FN) and baseline risk factors associated with FN. Statistical analyses were performed using two-sided Chi-squared tests.

Results and limitations

Baseline characteristics were balanced in age, gender, histology, and proportion of IGCCCG poor-risk patients. The incidence of neutropenia of any grade (Group 1, 96.2%, Group 2, 98.1%) was comparable although Group 2 had more patients with severe neutropenia (77.7%, G1 vs 88.8%, G2). There was a significant difference in FN Incidence (22%, G1 vs 7.5%, in G2, p=0.030). Most cases of FN occurred in Cycle 1. Two baseline characteristics were over-represented in patients who developed FN – females and patients ≥ 50 years old.

Conclusion

By comparing two cohorts who received prophylactic antibiotics, our audit suggests that rates of febrile neutropenia related admissions have decreased in the cohort of patients that we employed a steroid-sparing antiemetic protocol.

Introduction:

Germ cell tumours are rare, only accounting for 1% of new cancer diagnoses in males in the United Kingdom, however they are the most common solid tumour affecting young men in their second or third decade of life (1). The use of cisplatin based combination chemotherapy regimens has revolutionised the treatment of metastatic germ cell tumours, with cure rates in the majority of patients with metastatic disease exceeding 90% (2). However, the conventional treatment combination, BEP (Bleomycin, Etoposide and Cisplatin), is highly emetogenic and immunosuppressive (3, 4). Given that germ cell tumours are curable neoplasms, the focus of clinical research in recent years in this subgroup of patients is on long term survivorship, as well as in efforts to minimise acute chemotherapy-related toxicities for patients.

Reported rates of febrile neutropenia (FN) in patients receiving BEP chemotherapy are approximately 10-20% (5). Febrile neutropenia can result in life-threatening infections and is associated with lengthy hospitalisations, early mortality and high medical costs (6). Risk factors for FN in patients with germ cell tumours include older age, poorer performance status, seminomatous histology, poor International Germ Cell Cancer Collaborative Group (IGCCCG) risk class and prior radiotherapy (7).

Chemotherapy induced nausea and vomiting (CINV) can be debilitating and has a huge impact on a patient's quality of life (8). The BEP chemotherapy regimen is highly emetogenic, and effective prevention and prophylaxis is therefore recommended (9). The pathophysiology of CINV is complex, with multiple different pathways and neurotransmitters involved. These

include serotonin, dopamine, histamine and substance P (8, 10). Current chemotherapy protocols recommend the use of prophylactic anti-emetic combination therapies that include phenothiazines, dopamine receptor antagonists, serotonin 5-HT_3 receptor antagonists, NK_1 receptor antagonists and corticosteroids.

Steroids, particularly dexamethasone, have been used within chemotherapy regimens for years as part of preventive therapy of CINV in highly emetogenic regimens. Despite its effective antiemetic properties, prolonged use of dexamethasone can be toxic. Potential side effects include insomnia, indigestion, mood changes, agitation, increased risk of infection, diabetes, osteoporosis, and long-term risk of avascular necrosis. In addition, the use of steroids is associated with immunosuppression and may increase risk of febrile neutropenia (11, 12) , but it is unclear whether its use with cytotoxic chemotherapy impacts severity or day of onset of neutropenia.

Olanzapine is an atypical antipsychotic drug that works by blocking multiple neuroreceptors including dopaminergic, serotonergic, adrenergic, muscarinic and histamine receptors, making it an effective antiemetic (13). Olanzapine has recently been added to European Society of Medical Oncology (ESMO) and American Society of Clinical Oncology (ASCO) guidelines as an option in highly emetogenic regimens, in addition to conventional 5HT3 antagonists, NK1 receptor antagonists and dexamethasone (14, 15). The efficacy and tolerability of olanzapine as an antiemetic has been evaluated in a few randomised studies which demonstrated its superior properties as an effective anti-emetic in the control of delayed CINV (16).

Aim and Methods

The aim of this audit was to determine whether the introduction of olanzapine as an antiemetic to the BEP chemotherapy regimen, in lieu of high doses of dexamethasone, reduced the rates of febrile neutropenia related admissions to hospital, thereby improving quality of life and reducing costs to the National Health Service (NHS).

St Bartholomew's Hospital, London, is a tertiary referral centre for germ cell tumours. Prior to 2014, standard doses of dexamethasone were used in combination with ondansetron and domperidone/metoclopramide as anti-emetic prophylaxis. The detailed anti-emesis regimens are detailed in Figures 1A (3-day regimen) and 1B (5-day regimen). Following randomised data showing that olanzapine may possess favourable anti-emetic properties the germ cell team in our institution introduced this routinely for patients treated with BEP chemotherapy.

A protocol change was instated in 2014, introducing olanzapine as an antiemetic largely substituting dexamethasone in the protocol, with the exception of Day 1 where dexamethasone is administered as a single dose intravenously.

All patients received 5HT3 antagonists and either metoclopramide or domperidone. An additional antiemetic, usually aprepitant, was added to this antiemetic regimen in patients who experienced prolonged nausea and vomiting in spite of the initial anti-emetic prophylaxis.

We retrospectively collected data from patients treated with BEP chemotherapy over 10 years (2008-2017). We specifically looked at rates of neutropenia, number of admissions to hospital, number of patients on olanzapine and reduced dexamethasone (post 2014) *versus* dexamethasone without olanzapine (pre 2014), patients' requirement for GCSF (prophylactic or treatment) and prophylactic use of antibiotics. Patients on clinical trials were excluded.

Between 2008-2013, we selected fifty four (n=54) consecutive patients treated with BEP. Patients in this group received conventional antiemetics, namely Ondansetron 8mg intravenously, domperidone or metoclopramide 10mg three times a day for 5 days, together with dexamethasone IV and PO as described in Fig 1.

We selected an equivalent number of patients treated consecutively after the protocol change in January 2014 ie, fifty four (n=54) patients treated between 2014-2017 with BEP to facilitate comparison. In Group 2, patients received a loading dose of olanzapine (10mg) orally, dexamethasone and ondansetron intravenously followed by olanzapine 5mg orally twice daily for five days (days 2-6) and domperidone 10mg three times daily for 5 days.

A schematic of the 3-day and 5-day BEP treatment regimen, alongside differences in dexamethasone dosages in Groups 1 and 2, are shown in Figure 1A and 1B.

<Please Insert Figure 1 Here – Figure Legend After References>

All patients had their full blood count (FBC) checked weekly on days 1, 8 and 15 and received prophylactic antibiotics with Ciprofloxacin 500 mg twice daily for ten days (days 8-18). No Granulocyte Colonising Stimulating Factor (GCSF) was administered as primary prophylaxis. Use of GCSF as secondary prophylaxis was documented and included in our results. Secondary GCSF was routinely administered on Day 1 of the subsequent cycle of treatment, if the patient had a documented episode of FN in the prior cycle. Due to the curative nature of this treatment regimen, no dose reductions were instated as a result of FN.

All patients receiving active chemotherapy are advised to contact the Chemotherapy Hotline for any treatment-related concerns, and particularly if their measured body temperature exceeds >38 °C. Whenever possible, the patient is subsequently directed to a local Accident and Emergency Department within Barts Health NHS Trust network – which encompass four large hospitals in East London. Any occurrence of FN and associated admissions were rigorously reviewed prior to commencement of each cycle of chemotherapy and clearly documented in the hospital electronic records.

STATISTICAL METHODS

Data in the form of categorical variables was analysed using a Chi-square test to assess the relationship between the use of antiemetic regimen and the occurrence of neutropenia or neutropenic sepsis admissions.

RESULTS

The baseline characteristics of our two patient groups are shown in Table 1. The two groups were comparable in age, gender, histology, and proportion of IGCCCG poor-risk patients.

There was a numerically higher proportion of patients receiving 4 cycles of BEP and 5-day BEP in Cohort 1. However, these differences were not statistically significant (p=0.41 for 3 vs 4 cycles of BEP, p=0.27 for 3- vs 5-day BEP). Notably, the proportion of patients with pure seminoma was lower than the general population (approximately 16% of total). This was because of competing studies recruiting patients with good-risk metastatic seminoma into clinical trials of alternative regimens which accounts for the under-representation of patients with pure seminoma in our cohort.

	Group 1 (2008-2013), n=54	Group 2 (2014-2018), n=54
Age (years)		
Median (IQR)	**30 (26.25-42.25)**	**35 (27-41)**
≥50	**8 (14.8%)**	**8 (14.8%)**
30-49	**24 (44.4%)**	**30 (55.6%)**
≤30	**22 (40.7%)**	**16 (29.6%)**
Gender		
Male	**49 (90.7%)**	**52 (96.3%)**
Female	**5 (9.3%)**	**2 (3.7%)**
Histology (n, %)		
Pure Seminoma	**10 (18.5%)**	**8 (14.8%)**
Non-Seminomatous/Mixed GCT	**44 (81.5%)**	**46 (85.2%)**
IGCCCG *		
Good	**33 (67%)**	**43 (83%)**
Intermediate	**13 (27%)**	**8 (15%)**
Poor	**3 (6%)**	**1 (2%)**
Number of cycles (n, %)		
1-cycle	**0**	**3 (5.6%)**
2-cycle	**0**	**0**
3-cycles	**39 (72.2%)**	**41 (75.9%)**
4- cycles	**15 (27.8%)**	**10 (18.5%)**
Duration of BEP (n, %)		
3-day BEP	**30 (55.6%)**	**36 (66.7%)**
5-day BEP	**24 (44.4%)**	**18 (33.3%)**
Neutropenic patients (n, %)		
3-day BEP	**29 (96.6%)**	**35 (97.2%)**

5-day BEP	**23 (95.8%)**	**18 (100%)**
Neutropenia		
Severe (≤0.5x10^9/L)	**42(77.7%)**	**48(88.8%)**
0.5-1.0 x10^9/L	**10(18.5%)**	**5(9.25%)**
No neutropenia	**2(3.7%)**	**1(1.85%)**
Primary GCSF	**0**	**0**
Secondary GCSF	**11**	**6**
Additional Antiemetics		
Aprepitant	**5**	**1**
Cyclizine	**1**	**2**
Levopromazine	**1**	**0**
Total	**7(12.9%)**	**3(6.5%)**

Table 1: Baseline demographics of patients in Group 1 and Group 2.

*IQR= Interquartile range. BEP = Bleomycin, Etoposide, Cisplatin, GCT = Germ Cell Tumour IGCCCG = International Germ Cell Cancer Collaborative Group. *Female patients were excluded from risk classification as there is no formally defined classification for ovarian germ cell tumours.*

The incidence of neutropenia in both groups are shown in Figure 2A, alongside the incidence of total cases of neutropenia (Absolute Neutrophil Count, ANC<1.0x10^9/L), proportion of severe neutropenia (ANC<0.5 x10^9/L), and incidence of febrile neutropenia, FN (pyrexia > 38°C in the presence of any degree of neutropenia). All patients with febrile neutropenia required hospital admission.

<Please Insert Figure 2 Here – Figure Legend After References>

Most patients in Group 1, G1 (n=52, 96.2%) and Group 2, G2 (n=53, 98.1%) developed neutropenia at some point during treatment. There was no difference in number of neutropenic patients based on treatment regimen, 3 vs 5 days BEP chemotherapy. The proportion of severe neutropenia was marginally higher in Group 2 (n=42, 77.7% in G1 vs n=48, 88.8% in G2) – measured as a reflection of the nadir blood count through full blood count measurements on Day 8 and Day 15 of treatment. However, there was a significant difference in the incidence of febrile neutropenia in both groups of patients, with twelve (12, 22%) patients in Group 1 requiring admission for FN vs four (4, 7.5%) in Group 2 (p=0.030).

Having established the significant disparity between the two groups in incidence of FN, we further investigated the characteristics of this subpopulation to try to investigate similarities and differences in baseline characteristics and subsequent management. Figure 2B reveals that most cases of FN occurred with cycle 1 of treatment (8/12, 66.6% in G1 and 3/4, 75% in G2) with only 1 patient in cycle four of treatment.

The good-risk prognostic group represented 70% of FN admissions in G1 vs 100% in G2. Older patients, i.e. those greater than 50 years old, were equally represented in both groups.

	Group 1 (2008-2013) n=12	Group 2 (2014-2017) n=4
Histology (n %)		
Seminoma	**3 (25%)**	**0**
NSGCT	**9 (75%)**	**4 (100%)**
IGCCCG*		
Good	**7 (70%)**	**3 (100%)**

Intermediate	**3 (30%)**	**0**
Poor	**0**	**0**
Age		
≥50	**3 (25%)**	**1 (25%)**
30-49	**3 (25%)**	**2 (50%)**
≤30	**6 (50%)**	**1 (25%)**
Gender		
Female	**2 (16.7%)**	**1 (25%)**
Male	**10 (83.3%)**	**3 (75%)**
Number of chemotherapy cycles received:		
1 x cycle	**0**	**1(25%)**
2 x cycles	**0**	**0**
3 x cycles	**8(66.7%)**	**3(75%)**
4 cycles	**4(33.3%)**	**0**
5 days BEP	**4 (33.3%)**	**1 (25%)**
3 days BEP	**8 (66.7%)**	**3 (75%)**
Neutropenia		
Severe (<0.5x10^9/L)	**11 (91.7%)**	**4 (100%)**
0.5-1.0x10^9/L	**1 (8.3%)**	**0**
Onset of neutropenia in relation to cycles		
1st	**8(66.6%)**	**3(75%)**
2nd	**0**	**1(25%)**
3rd	**3(25%)**	**0**
4th	**1(8.3%)**	**0**
FN admission admissions in relation regimen and cycle		
3 days BEP		
1st	**5 (62.5%)**	**2 (66.6%)**
2nd	**0**	**1 (33.3%)**
3rd	**3 (37.5%)**	**0**
4th	**0**	**0**
5 days BEP	-	-
1st	**3 (75%)**	**1 (100%)**
2nd	**0**	**0**
3rd	**0**	**0**
4th	**1 (25%)**	**0**
GCSF primary	**0**	**0**
GCSF secondary	**8 (67%)**	**4 (100%)**

Table 2: Baseline Characteristics of Patients with Febrile Neutropenia

BEP = Bleomycin, Etoposide, Cisplatin, GCT = Germ Cell Tumour, IGCCCG = International Germ Cell Cancer Collaborative Group, GCSF = Granulocyte Colony Stimulating Factor. *Female patients were excluded from risk classification as there is no formally defined classification for ovarian germ cell tumours.

The baseline characteristics and treatment of patients with FN are shown in Table 2. It was difficult to establish differences between the two groups due to the low incidence of FN. However, two baseline factors were over-represented in the FN cohort: Although we had low number of females in our audit, two (2/5, 40%) in Group 1 and one (1/2, 50%) in Group 2 were admitted with FN.

Older patients were also marginally over-represented in the cohort that developed FN. Despite comprising less than 15% of the population of both groups, 25% of patients who developed FN were above the age of 50.

In the cohort which developed FN, there was no significant difference between the incidence of FN in the 3- or 5-day regimens.

Discussion

Our study compared two cohorts of patients with GCTs who received BEP chemotherapy with different supportive regimens for anti-emesis. The results show that patients in Group 2, who received olanzapine in the context of a steroid-sparing regimen, had significantly lower rates of admissions due to febrile neutropenia (p=0.030). This occurred despite the higher overall rates of severe neutropenia in Group 2.

We postulate that the significant reduction in total steroid dose is the reason behind this disparity. The use of steroids has traditionally been associated with lymphopenia (17, 18), and arguably a direct effect on lymphocyte function, leading to an escalated degree of immunosuppression in any neutropenic patient. Dexamethasone may also interact with the chemotherapy agents or with the lymphocytes and modulate immune response (19). Glucocorticoids also downregulate antigen presentation and expression of human-leukocyte class II antigen molecules by macrophages (20), and directly inhibit monocytic function (21). In support of our observation, Kang et al has shown that a low-dose dexamethasone premedication protocol has comparable efficacy to the conventional dexamethasone protocol in the prevention of docetaxel hypersensitivity with significantly fewer infection complications (22).

Several studies have confirmed that olanzapine is a safe and effective antiemetic for CINV. Evidence from a Phase III trial that compared the effectiveness of olanzapine for the prevention of CINV in patients receiving highly emetogenic chemotherapy, showed that this is effective for both acute and delayed CINV. Specifically, Navari et al compared olanzapine to aprepitant in combination with palonosetron and dexamethasone in patients receiving highly

emetogenic chemotherapy (23). More recent studies have shown effective emesis control at a lower dose of olanzapine 5mg, balancing efficacy with risks of sedation (24).

A novelty of the anti-emetic protocol in St Bartholomew's Hospital is the use of olanzapine along with a dopamine antagonist and 5HT3 receptor antagonist in a steroid-sparing fashion. Prior studies have instead adopted the more conservative approach of adding olanzapine to a steroid-containing protocol. One could caution that the omission of steroids may result in poorer control of emesis. The absence of patient-related outcomes about emetic control constitutes a limitation to our retrospective audit. However, anecdotal evidence (through our experience) suggests that there was no indication of increased rates of CINV. Furthermore, our records indicate that Group 1 required more additional antiemetics than Group 2 (12.9% vs 6.5%), indicating effective anti-emesis with olanzapine in lieu of steroids.

A further limitation is the imbalance in baseline characteristics of both cohorts. There was a numerically higher proportion of patients receiving 4 cycles of BEP and 5-day BEP, although this was not statistically significant. Most patients who developed FN experienced them after the 1st cycle of treatment, and thus this imbalance is unlikely to have contributed to our main observation. Furthermore, a large randomised study by de Wit et al in 2001 demonstrated equivalence in the rates of neutropenic fevers between the regimens, regardless of number of days of treatment delivery (3- or 5- days) and number of cycles of BEP administered (5). Another area of imbalance was in the IGCCCG prognostic risk groups, with significantly more patients in the good-risk group in Group 2 compared to Group 1. However, the proportion of

poor-risk group patients were equivalent in both cohorts, and Terbuch et al demonstrated that only poor-risk IGCCCG group patients are predicted to be at higher risk of FN (7).

Conclusion

Although olanzapine use as an antiemetic is endorsed by major guidelines for highly emetogenic chemotherapy regimens, the role of it as a steroid sparing agent has been much less studied. This audit compared two similar cohorts of patients receiving BEP chemotherapy, one of which was treated with the routine dexamethasone regimen and the second which received olanzapine, with a significantly reduced dose of steroids.

Limiting the use of steroids in anti-cancer treatment regimens could have an important role in reducing the morbidity of chemotherapy and may also improve the efficacy of the newer chemo-immunotherapy regimens. Due to the limitations of its size and retrospective nature, we cannot definitively conclude that rates of FN related admissions have decreased as a consequence of employing a steroid-sparing antiemetic protocol. However, this audit is hypothesis generating and larger prospective study would be necessary to validate these findings. In addition, a future study should incorporate formal nausea and vomiting assessment, to ensure that anti emetic control has not been compromised.

Conflict of Interests

All authors have no conflicts of interest to declare.

References:

1. https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/testicular-cancer/incidence#heading-Zero [Internet]. Available from: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/testicular-cancer/incidence#heading-Zero.
2. Oldenburg J, Fossa SD, Nuver J, Heidenreich A, Schmoll HJ, Bokemeyer C, et al. Testicular seminoma and non-seminoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2013;24 Suppl 6:vi125-32.
3. Aoki S, Iihara H, Nishigaki M, Imanishi Y, Yamauchi K, Ishihara M, et al. Difference in the emetic control among highly emetogenic chemotherapy regimens: Implementation for appropriate use of aprepitant. Mol Clin Oncol. 2013;1(1):41-6.
4. Fossa SD, Kaye SB, Mead GM, Cullen M, de Wit R, Bodrogi I, et al. Filgrastim during combination chemotherapy of patients with poor-prognosis metastatic germ cell malignancy. European Organization for Research and Treatment of Cancer, Genito-Urinary Group, and the Medical Research Council Testicular Cancer Working Party, Cambridge, United Kingdom. J Clin Oncol. 1998;16(2):716-24.
5. de Wit R, Roberts JT, Wilkinson PM, de Mulder PH, Mead GM, Fossa SD, et al. Equivalence of three or four cycles of bleomycin, etoposide, and cisplatin chemotherapy and of a 3- or 5-day schedule in good-prognosis germ cell cancer: a randomized study of the European Organization for Research and Treatment of Cancer Genitourinary Tract Cancer Cooperative Group and the Medical Research Council. J Clin Oncol. 2001;19(6):1629-40.
6. Kuderer NM, Dale DC, Crawford J, Cosler LE, Lyman GH. Mortality, morbidity, and cost associated with febrile neutropenia in adult cancer patients. Cancer. 2006;106(10):2258-66.
7. Terbuch A, Posch F, Partl R, Zurl B, Bauernhofer T, Pichler M, et al. Risk stratification for febrile neutropenia in patients with testicular germ cell tumors. Cancer Med. 2018;7(2):508-14.
8. Ranganath P, Einhorn L, Albany C. Management of Chemotherapy Induced Nausea and Vomiting in Patients on Multiday Cisplatin Based Combination Chemotherapy. Biomed Res Int. 2015;2015:943618.
9. London Cancer Network: Antiemetic Guidelines for Adult Patients Receiving Chemotherapy and Radiotherapy. http://wwwlondoncancerorg/media/65597/antiemetic-guidelines-november-2010pdf. Last Reviewed November 2012.
10. Hesketh PJ. Chemotherapy-induced nausea and vomiting. N Engl J Med. 2008;358(23):2482-94.

11. Family L, Li Y, Chen LH, Page JH, Klippel ZK, Chao C. A Study of Novel Febrile Neutropenia Risk Factors Related to Bone Marrow or Immune Suppression, Barrier Function, and Bacterial Flora. J Natl Compr Canc Netw. 2018;16(10):1201-8.
12. Ng K PL, Barot H, Alifrangis C, McGovern U, Shamash J. A Multicentre Comparative Analysis of Use of Steroids and Prophylactic Antibiotics with First-line Docetaxel in Hormone Sensitive Metastatic Prostate Cancer. Clinical Oncology. 2020;32(5).
13. Brafford MV, Glode A. Olanzapine: an antiemetic option for chemotherapy-induced nausea and vomiting. Journal of the advanced practitioner in oncology. 2014;5(1):24-9.
14. F. Roila AM, J. Herrstedt, M. Aapro, R. J. Gralla, E. Bruera, R. A. Clark-Snow, L. L. Dupuis, L. H. Einhorn, P. Feyer, P. J. Hesketh, K. Jordan, I. Olver, B. L. Rapoport, J. Roscoe, C. H. Ruhlmann, D. Walsh, D. Warr and M. van der Wetering. MASCC and ESMO Consensus Guidelines for the Prevention of Chemotherapy and Radiotherapy-Induced Nausea and Vomiting: ESMO Clinical Practice Guidelines Ann Oncol; . 2016;27 (suppl 5): v119-v133.
15. Berger MJ, Ettinger DS, Aston J, Barbour S, Bergsbaken J, Bierman PJ, et al. NCCN Guidelines Insights: Antiemesis, Version 2.2017. J Natl Compr Canc Netw. 2017;15(7):883-93.
16. Tan L, Liu J, Liu X, Chen J, Yan Z, Yang H, et al. Clinical research of Olanzapine for prevention of chemotherapy-induced nausea and vomiting. J Exp Clin Cancer Res. 2009;28:131.
17. Fauci AS, Dale DC, Balow JE. Glucocorticosteroid therapy: mechanisms of action and clinical considerations. Ann Intern Med. 1976;84(3):304-15.
18. Craddock CG. Corticosteroid-induced lymphopenia, immunosuppression, and body defense. Ann Intern Med. 1978;88(4):564-6.
19. Nakagawa M, Terashima T, D'Yachkova Y, Bondy GP, Hogg JC, van Eeden SF. Glucocorticoid-induced granulocytosis: contribution of marrow release and demargination of intravascular granulocytes. Circulation. 1998;98(21):2307-13.
20. Gerrard TL, Cupps TR, Jurgensen CH, Fauci AS. Hydrocortisone-mediated inhibition of monocyte antigen presentation: dissociation of inhibitory effect and expression of DR antigens. Cell Immunol. 1984;85(2):330-9.
21. Rinehart JJ, Balcerzak SP, Sagone AL, LoBuglio AF. Effects of corticosteroids on human monocyte function. J Clin Invest. 1974;54(6):1337-43.
22. Kang RY, Yoo KS, Han HJ, Lee JY, Lee SH, Kim DW, et al. Evaluation of the effects and adverse drug reactions of low-dose dexamethasone premedication with weekly docetaxel. Support Care Cancer. 2017;25(2):429-37.
23. Navari RM, Gray SE, Kerr AC. Olanzapine versus aprepitant for the prevention of chemotherapy-induced nausea and vomiting: a randomized phase III trial. J Support Oncol. 2011;9(5):188-95.
24. Hashimoto H, Abe M, Tokuyama O, Mizutani H, Uchitomi Y, Yamaguchi T, et al. Olanzapine 5 mg plus standard antiemetic therapy for the prevention of chemotherapy-induced nausea and vomiting (J-FORCE): a multicentre, randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Oncol. 2020;21(2):242-9.

Figure Legends

Figure 1: Schematic diagram of Bleomycin, Etoposide, Cisplatin (BEP) intravenous treatment regimen with corresponding antiemetic supportive regimen between period of 2008-2017: **(A) Anti-emetic supportive regimen in 3-day BEP Treatment Regimen, (B) Anti-emetic supportive regimen in 5-day BEP Treatment Regimen.** Differences between Antiemetic Regimen in Group 1 and Group 2 highlighted in Bold. Legend – FBC: Full Blood Count, U&E: Urea and Electrolytes, LFT: Liver Function Tests, IU: International Units, BD: Twice Daily, TDS: Three Times daily, IV: Intravenously, PO: Orally, D1 etc: Day 1 etc

Figure 2: **Incidence of Neutropenia in Both Patient Cohorts** (A) Prevalence of Neutropenia in both groups. Neutropenia is defined as absolute neutrophil count (ANC) < 1.0 $x10^9$/L . Severe neutropenia is defined as ANC<0.5 $x10^9$/L while febrile neutropenia is defined as the presence of a pyrexia >38°C along with an ANC<1.0 $x10^9$/L. (B) Incidence of first episode of febrile neutropenia.