Supportive Care in Hemato-Oncology: A Review in Light of the Latest Guidelines

Hemato-Onkolojide Destek Tedaviler: Son Kılavuzlar Işığında Gözden Geçirme

Eren Gündüz¹, Zafer Gülbaş²

¹Eskişehir Osmangazi University, School of Medicine, Department of Hematology, Eskişehir, Turkey
²Anadolu Health Center, Bone Marrow Transplantation Center, Kocaeli, Turkey

This study received no financial support.
The authors have no commercial, proprietary, or financial interest in any drug, device, or equipment mentioned herein.

Abstract

Recent developments in cancer therapy have resulted in increases in treatment success rates and survival. One of the basic goals of such therapy is improving patient quality of life. Chemotherapy protocols for solid or hematological malignancies-most of which include multiple agents-negatively impact patient quality of life. Additionally, there have been developments in supportive care, which seeks to ameliorate or minimize the negative effects of chemotherapy. Herein we present a review and brief summarization of some of the agents used for supportive care in cancer patients in light of the latest guidelines.

Key Words: Hematology, Supportive care, Nausea/vomiting, Anemia, Neutropenia

Özet

Son yıllarda kanser tedavisi alanında sağlanan gelişmeler hastaların tedavi şanslarının artması ve yaşam sürelerinde uzama ile sonuçlanmıştır. Bu sıkıntılı tedavi sürecinde yaşam kalitesinin artırılması temel hedeflerden biri olarak görülmektedir. Solid ya da hematolojik maligniteler için verilen çoklu çoklu ajanlar içeren kemoterapi protokolleri hastaların yaşam kalitesini olumsuz etkiler. Bu olumsuz etkilerden hastayı kurtarmak ya da en az hasar görmesi sağlamak amacıyla yapılan destek tedavilerde de gelişmeler vardır. Bu derlemeye, destek tedavi olarak verilen bu ajanlardan bazılarını en son kılavuzlarda işğında hızla özetledik.

Anahtar Sözcükler: Hematoloji, Destek tedavi, Bulanti-kusma, Anemi, Nötropeni

Introduction

Supportive care aims to ameliorate the adverse effects of chemotherapy, and to prevent reductions in the chemotherapy dose and delays in its schedule. These adverse effects include nausea/vomiting, diarrhea, constipation, pain, infections, cytopenia, allergic reactions, mucositis, osteoporosis, and neuropathy. Cancer patient quality of life increases with supportive care. The success of treatment increases along with the level of treatment compliance. Supportive care is critical in intolerant and elderly patients with multiple comorbidities. Chemotherapy and/or radiotherapy target the disease, whereas patient quality
of life is the target of supportive care. Physicians sometimes overlook developments in supportive care, as they primarily concentrate on disease-targeted therapy. Herein we present a review of supportive care in light of the latest guidelines, focusing only on nausea/vomiting, anemia, and myeloid growth factors, as each side effect of cancer treatment warrants individual attention.

Chemotherapy-Induced Nausea/Vomiting

Chemotherapy-induced nausea/vomiting (CINV) is a common adverse event associated with cancer treatment that occurs in 70%-80% of patients undergoing chemotherapy. CINV results in significant morbidity and negatively affects quality of life [1,2]. The risk of CINV is associated with the type of chemotherapy, and increases with age <50 years, female gender, a history of CnIv during chemotherapy, pregnancy-induced nausea/vomiting, a history of motion sickness, and anxiety [3,4]. Chemotherapeutic agents cause vomiting via activation of neurotransmitter receptors located in the chemoreceptor trigger zone, gastrointestinal tract, and vomiting center. Serotonin, substance P, and dopamine receptors are the primary neurotransmitter receptors involved in the emetic response [5].

CINV is classified into 5 categories: acute, delayed, anticipatory, breakthrough, and refractory. Acute-onset CINV refers to nausea and/or vomiting that occurs within 24 h of chemotherapy administration [3]. Nausea and/or vomiting that develop >24 h after chemotherapy administration is known as delayed emesis [2]. Anticipatory nausea and/or vomiting occur prior to the administration of next chemotherapy; because it is a conditioned response, it can occur only after a negative past experience with chemotherapy [6]. Vomiting that occurs within 5 d of prophylactic antiemetic use or requires rescue antiemetic treatment is known as breakthrough emesis. Vomiting in response to subsequent chemotherapy cycles that follow failed prophylactic and/or rescue antiemetic treatment during previous cycles is known as refractory emesis [7].

Antiemetic Agents

1. Dopamine Receptor Antagonists

Dopamine receptors are located in the chemoreceptor trigger zone and dopamine receptor antagonists primarily affect this area; however, high doses of dopamine receptor blockades result in extrapyramidal reactions, disorientation, and sedation, which limit the clinical use of such agents, including phenothiazines and butyrophenones (droperidol and haloperidol) [8].

2. Serotonin (5-HT3) Receptor Antagonists

Serotonin receptors—specifically 5-HT3 receptors—are present in the central nervous system and gastrointestinal tract. First-generation 5-HT3 receptor antagonists (azasetron, dolasetron, granisetron, ondansetron, ramosetron, and tropisetron) are equally effective and toxic when used at the recommended doses, and differ only in terms of cost. The primary symptoms of their toxicity are mild headache, constipation, and occasional diarrhea. The second-generation 5-HT3 receptor antagonist palonosetron might more effectively control delayed CINV than the first-generation 5-HT3 receptor antagonists [8].

3. Dopamine-serotonin Receptor Antagonists

Metoclopramide has antiemetic properties, both at low doses as a dopamine antagonist and at high doses as a serotonin antagonist. Use of a relatively high dose (20 mg t.i.d. p.o.) may result in sedation and extrapyramidal side effects [9,10].

4. Substance P (Neurokinin-1) Receptor Antagonists

Substance P is a mammalian tachykinin in the vagal afferent neurons that innervate the brainstem nucleus tractus solitarius, which sends impulses to the vomiting center. Substance P induces vomiting and binds to neurokinin 1 (NK-1) receptors in the abdominal vagus, the nucleus tractus solitarius, and the area postrema. Compounds that block NK-1 receptors, including vofopitant, CP-122,721, CJ-11,794, fosaprepitant (L758,298), aprepitant (MK-869), and casopitant, reduce emesis following cisplatin, ipecac, apomorphine, and radiation therapy [8,11].

5. Corticosteroids

Corticosteroids have been shown to be effective in the prevention of CINV, although their antiemetic mechanism of action remains unknown. The control of CINV is markedly enhanced when corticosteroids are used in combination with 5-HT3 and NK-1 receptor antagonists [12,13]. The most widely used corticosteroid antiemetic is dexamethasone [8].

6. Olanzapine

Olanzapine is an antipsychotic that blocks multiple neurotransmitters, including dopamine at the D1, D2, D3, and D4 brain receptors, serotonin at the 5-HT2A, 5-HT2C, 5-HT1A, and 5-HT1D receptors, catecholamines at alpha 1 adrenergic receptors, acetylcholine at muscarinic receptors, and histamine at H1 receptors [14,15]. Common side effects are sedation, weight gain, and an association with the onset of diabetes mellitus [16-18]. Olanzapine’s anti-
emetic property is due to its activity at multiple receptors involved in nausea and emesis [8].

7. Gabapentin

The anticonvulsant gabapentin has been reported to reduce delayed nausea in a small number of patients undergoing adjuvant chemotherapy for breast cancer; however, additional research is necessary to determine its efficacy more precisely [19].

8. Cannabinoids

Cannabinoid receptors of the CB1 type are present in the area postrema, nucleus tractus solitarius, and dorsal motor nucleus, which are key sites of emetogenic control in the brainstem. Cannabinoid CB2 receptors are present on brainstem neurons and may play a role in mediating the effects on emesis [20,21]. Dronabinol and nabilone have been approved by the US FDA for use in CINV refractory to conventional antiemetic therapy, but the role of cannabinoids in the prevention of CINV remains to be established [22].

Clinical Management of CINV

All of the following recommendations are those of the National Comprehensive Cancer Network (NCCN) Practice Guidelines in Oncology v.2.2010 [23].

1. Emesis Prevention For High Emetic Risk Intravenous Chemotherapy

   Data for post-cisplatin (≥50 mg m$^{-2}$) emesis prevention category 1; others are category 2A.

   Serotonin (5-HT3) antagonist

   Dolasetron 100 mg p.o. or 1.8 mg kg$^{-1}$ IV on d 1
   or
   Granisetron 2 mg p.o., 1 mg b.i.d. p.o., or 0.01 mg kg$^{-1}$ (maximum: 1 mg) IV on d 1
   or
   Ondansetron 16-24 mg p.o. or 8-12 mg (maximum: 32 mg d$^{-1}$) IV on d 1
   or
   Palonosetron 0.25 mg IV on d 1

   Steroid

   Dexamethasone 12 mg p.o. or IV on d 1 and 8 mg d$^{-1}$ p.o. on d 2-4

   Neurokinin 1 antagonist

   Aprepitant 125 mg p.o. on d 1 and 80 mg d$^{-1}$ p.o. on d 2-3
   or
   Fosaprepitant 115 mg IV on d 1 only, and then aprepitant 80 mg d$^{-1}$ p.o. on d 2-3
   ± Lorazepam 0.5-2 mg p.o. or IV
   ± H2 blocker or proton pump inhibitor

2. Emesis Prevention for Moderate Emetic Risk Intravenous Chemotherapy

   Day 1

   Serotonin (5-HT3) antagonist

   Dolasetron 100 mg p.o., 1.8 mg kg$^{-1}$ IV, or 100 mg IV (category 1)
   or
   Granisetron 1-2 mg p.o., 1 mg b.i.d. p.o. (category 1), or 0.01 mg kg$^{-1}$ (maximum: 1 mg) IV,
   or
   Ondansetron 16-24 mg p.o. or 8-12 mg (maximum: 32 mg d$^{-1}$) IV (category 1)
   or
   Palonosetron 0.25 mg IV on d 1 only

   Steroid

   Dexamethasone 12 mg p.o. or IV

   with/without

   Neurokinin 1 antagonist

   Aprepitant 125 mg p.o.
   Fosaprepitant 115 mg IV on d 1 only
   ± Lorazepam 0.5-2 mg p.o. or IV
   ± H2 blocker or proton pump inhibitor

   Day 2-3

   Serotonin (5-HT3) antagonist monotherapy

   Dolasetron 100 mg d$^{-1}$ p.o., 1.8 mg kg$^{-1}$ IV, or 100 mg IV,
   or
   Granisetron 1-2 mg d$^{-1}$ p.o., 1 mg b.i.d. p.o., or 0.01 mg kg$^{-1}$ (maximum: 1 mg) IV
   or
Ondansetron 8 mg b.i.d. p.o. 16 mg d⁻¹ p.o., or 8 mg (maximum: 32 mg d⁻¹) IV

or

**Steroid monotherapy**
Dexamethasone 8 mg d⁻¹ p.o. or IV

or

**Neurokinin 1 antagonist ± steroid**
Aprepitant 80 mg p.o. ± dexamethasone 8 mg d⁻¹ p.o. or IV
± Lorazepam 0.5-2 mg p.o. or IV
± H2 blocker or proton pump inhibitor

3. Emesis Prevention for Low and Minimal Emetic Risk Intravenous Chemotherapy

No routine prophylaxis is recommended for minimal emetic risk intravenous chemotherapy.
Dexamethasone 12 mg d⁻¹ p.o. or IV
or
Metoclopramide 10-40 mg or IV, and then every 4 or 6 h
or
Prochlorperazine 10 mg p.o. or IV, and then every 4 or 6 h
± Lorazepam 0.5-2 mg p.o. or IV every 4 or 6 h
± H2 blocker or proton pump inhibitor

4. Breakthrough Treatment for CINV

The general principle is to add 1 agent of a different class to the current regimen.

**Antipsychotic**
Haloperidol 1-2 mg p.o. every 4-6 h
Olanzapine 2.5-5 mg b.i.d. p.o. (category 2B)

**Benzodiazepine**
Lorazepam 0.5-2 mg p.o. every 4 or 6 h

**Cannabinoid**
Dronabinol 5-10 mg every 3 or 6 h
Nabilone 1-2 mg b.i.d. p.o.

**Dopamine receptor antagonist**
Metoclopramide 10-40 mg p.o. or IV every 4 or 6 h

**Phenothiazine**
Promethazine 12.5-25 mg p.o. or IV every 4 h

**Serotonin (5-HT3) antagonist**
Dolasetron 100 mg d⁻¹ p.o., 1.8 mg kg⁻¹ IV, or 100 mg IV
Granisetron 1-2 mg d⁻¹ p.o., 1 mg b.i.d. p.o., or 0.01 mg kg⁻¹ (maximum: 1 mg) IV
Ondansetron 16 mg d⁻¹ p.o. or 8 mg d⁻¹ IV

**Steroid**
Dexamethasone 12 mg d⁻¹ p.o. or IV

5. Anticipatory Emesis Prevention/Treatment

Alprazolam 0.5-2 mg t.i.d. p.o. beginning the night before treatment
or
Lorazepam 0.5-2 mg p.o. on the night before and morning of treatment

**Cancer and Chemotherapy-Induced Anemia**

Anemia is a frequent complication of cancer and occurs in 30%-90% of patients [24]. At the time of diagnosis, 30%-40% of patients with non-Hodgkin’s lymphoma or Hodgkin’s lymphoma, and ≤70% of patients with multiple myeloma are anemic; rates are higher among patients with myelodysplastic syndromes. Among patients with solid cancers or lymphomas, ≤50% develop anemia following chemotherapy [25]. Anemia is a frequent cause of morbidity and might increase mortality [26].

Tumor cells activate the immune system of the host and a number of cytokines are produced. This inflammatory response affects erythropoietin production, suppresses burst-forming unit-erythroid, and colony-forming unit-erythroid, and impairs iron utilization. Tumor cells may also decrease erythrocyte survival either via tumor necrosis factor or by causing erythrophagocytosis [27]. Nutritional deficiency, hemolysis, bleeding, hereditary diseases, renal insufficiency, and anemia of chronic disease can also contribute to anemia in cancer patients [28,29]. The myelosuppressive effects of chemotherapy and radiation therapy are also significant factors associated with anemia [30,31]. Anemia can be corrected by treating the underlying etiology, transfusion with packed red blood cells, or erythropoiesis stimulating agents, with or without iron supplementation.

The NCCN concurs that a hemoglobin level ≤11 g dL⁻¹ in cancer patients should be investigated. In patients with a high baseline level, a drop of ≥ 2g dL⁻¹ should also be assessed. There are 3 general anemia categories described by the NCCN:
1. Asymptomatic anemia without significant comorbidity, for which observation and periodic reevaluation are appropriate;

2. Asymptomatic anemia with comorbidity or high risk, for which transfusion should be a consideration;

3. Symptomatic anemia, for which transfusion should be performed.

If the hemoglobin level decreases following chemotherapy, transfusion may be appropriate even in the absence of symptoms or significant comorbidity [23]. Packed red blood cell (PRBC) transfusion is the only treatment option in patients that require immediate correction of anemia. Risks associated with PRBC transfusion include transfusion-related reactions, congestive heart failure, bacterial contamination, viral infections, iron overload, and an increase in thrombotic events [32].

Administration of erythropoiesis-stimulating agents (ESAs) decrease the need for PRBC transfusion in cancer patients undergoing chemotherapy [33-35]; however, there are risks associated with ESA therapy, including an increase in mortality, and an increase in tumor progression of breast cancer [36], head and neck cancer [37], cervical cancer [38], non-small cell lung cancer [39], non-myeloid cancer [40], and lymphoid malignancy [41]. Elevated thromboembolic risk has also been associated with ESA treatment [42-44]. Hypertension/seizures and pure red cell aplasia 90% of occurred with epoetin alfa have also been reported in chronic renal failure [23]. In addition to safety concerns, ESAs also have considerable impact on healthcare financial resources [45].

Historically, ESA treatment strategies were designed to achieve and maintain hemoglobin levels >12 g dL\(^{-1}\), decrease the need for transfusion, and improve patient quality of life [46]. In 2008 the US FDA prohibited use of ESAs in cancer patients seeking cure. Reimbursement is limited to patients with hemoglobin levels <10 g dL\(^{-1}\) [23]. The University of Texas MD Anderson Cancer Center mandates that following initial administration of ESAs, subsequent doses be given only to those with a hemoglobin level <11 g dL\(^{-1}\), leading to intermittent treatment versus the once standard continuous treatment pattern [47]. Myelodysplastic syndrome patients with low intermediate-1 IPSS risk, hemoglobin <10 g dL\(^{-1}\), and serum erythropoietin <500 mIU mL\(^{-1}\) should be considered for ESA treatment [48].

According to the package insert dosing schedule, the initial dose of epoetin alfa is 150 U kg\(^{-1}\) t.i.w.; the dose can be increased to 300 U kg\(^{-1}\) t.i.w. if there is no response after 4 weeks. The initial dose of epoetin beta is 30,000 IU week\(^{-1}\) and the dose can be increased to 60,000 IU week\(^{-1}\) in there is no response after 4 weeks. The initial dose of darbepoetin alfa is 2.25 µg kg\(^{-1}\) QWK; the dose can be increased to 4.5 µg kg\(^{-1}\) QWK if there is no response. The dose should be adjusted individually for each patient, so as to maintain the lowest hemoglobin level sufficient to avoid red blood cell transfusion. If the hemoglobin level is such that transfusion is unnecessary or increases >1 g dL\(^{-1}\) in any 2 week period the epoetin alfa or epoetin beta dose should be reduced by 25%, and the darbepoetin alfa dose should be reduced by 40%.

If ferritin is ≤800 ng mL\(^{-1}\) and transferrin saturation is <20%, IV iron supplementation should be considered along with erythropoietin therapy; however, patients with active infection should not receive IV iron therapy. IV Iron dextran 100 mg is administered over the course of 5 min QWK for 10 doses or as a 1-g infusion administered during the course of several hours. Ferric gluconate is administered as 125 mg IV over the course of 60 min QWK for 8 doses or as 200 mg IV over the course of 3-4 h repeated every 3 weeks for 5 doses. Iron sucrose is given as 200 mg IV over the course of 60 min every 2-3 weeks or as 200 mg IV over the course of 2-5 min every 1-4 weeks [23].

**Myeloid Growth Factors**

Myelosuppression is the major dose-limiting toxicity associated with many chemotherapy regimens and can also result in chemotherapy schedule delay, compromising the effectiveness of chemotherapy [49-52]. Infections associated with neutropenia may be accompanied by sepsis and occasionally death. Severe myelosuppression is accompanied by impaired quality of life, even in the absence of fever [53]. Myeloid growth factors stimulate proliferation of neutrophil progenitors and enhance neutrophil function. The use of myeloid growth factors is designed to reduce the duration of myelosuppression and the depth of neutropenia, and decrease the likelihood of infection [54].

A meta-analysis of myeloid growth factors trials reported that there were significant reductions in severe neutropenia, neutropenic fever, and infections in patients treated for non-Hodgkin’s lymphoma and Hodgkin’s lymphoma [55]. Trials of myeloid growth factors in patients treated for acute leukemia indicate they can reduce the duration of both neutropenia and hospitalization during induction therapy; however, their benefit is modest, and remission and survival rates associated with their use are inconsistent. The concern that using myeloid growth fac-
tors may interfere with the evaluation of remission may be dealt with delaying the start of growth factors until after the day 14 bone marrow and stopping at neutrophil recovery several days prior to performing the bone marrow biopsy to assess remission. Stimulation of leukemic cell proliferation has not been observed in clinical trials. Recruitment leukemia into cycling, making the leukemia cells more sensitive to chemotherapy, has also not demonstrated convincing evidence of clinical benefit. Thus, use of granulocyte colony-stimulating factor (G-CSF) in patients with acute leukemia should be based only on preventing neutropenic complications. During post-remission consolidation therapy the benefits may be more substantial [54,56].

The most common toxicity associated with G-CSF therapy is mild-to-moderate bone pain, which is usually effectively controlled with non-narcotic analgesics. There have also been reports of splenic rupture in patients treated with G-CSF [54]. A retrospective review reported that a high rate of bleomycin toxicity has been linked to G-CSF use in Hodgkin’s lymphoma patients receiving bleomycin-containing therapy [57]. Some patients develop allergic skin, respiratory system, and cardiovascular system reactions [58].

Primary prophylaxis is achieved via administration of myeloid growth factors during the initial chemotherapy cycle, in anticipation of the risk of neutropenic complications. The use of prophylactic myeloid growth factors is recommended for solid tumor/lymphoma patients that have ≥20% likelihood of developing fever; in patients with a 10%-20% risk of fever G-CSF should be considered if there are additional risk factors (advanced age, history of chemotherapy or radiotherapy, and pre-existing neutropenia, or tumor involvement in the bone marrow, poor performance status, and comorbidity, including renal and liver dysfunction). G-CSF should not be routinely used in patients with a <10% risk of fever. According to American Society of Clinical Oncology (ASCO) guidelines, secondary prophylaxis with G-CSF should be considered if maintaining the dose intensity is considered to be important [59-62].

Compared to its prophylactic use, there is less evidence supporting the therapeutic use of G-CSF for febrile neutropenia as an adjunct to antibiotics [63-65]. Patients with febrile neutropenia given prophylactic filgrastim or sargramostim should continue with G-CSF therapy; however, as pegfilgrastim is long acting patients given prophylactic pegfilgrastim should not be treated with additional G-CSF [66]. Currently, there is a lack of evidence supporting the therapeutic use of pegfilgrastim; therefore, only filgrastim or sargramostim should be administered in the therapeutic setting. In patients that have not received prophylactic G-CSF the NCCN recommends evaluating the risk factors for infection-related complications or poor clinical outcome, including advanced age (>65 years), sepsis syndrome, severe (absolute neutrophil count <100 µL) or anticipated prolonged (>10 d) neutropenia, pneumonia, invasive fungal infection or other clinically documented infections, hospitalization, and a history of febrile neutropenia. If risk factors are present G-CSF should be considered.

Myeloid growth factors currently used for the prophylaxis of febrile neutropenia and maintenance of scheduled dose delivery include filgrastim, pegfilgrastim (category 1), and sargramostim (category 2B). Filgrastim treatment is initiated within 1-3 d after the completion of chemotherapy at a dose of 5 µg·kg⁻¹·d⁻¹ until post nadir absolute neutrophil count (ANC) recovery is normal or near normal, according to laboratory standards. The dose may be rounded to the nearest vial site by institution defined weight limits. Moreover, evidence exists that supports the initiation of pegfilgrastim 24 h after completion of chemotherapy, administered every 3 weeks at a dose of 6 mg for each chemotherapy cycle. Same-day administration of filgrastim or pegfilgrastim (within 24 h of the completion of chemotherapy) is not recommended [67,68]

**Conclusion**

By means of all summarized supportive care interventions we are able to better treat our patients, prolong their survival and decrease complications of cancer chemotherapy. New therapies may add new complications but supportive care is also improving. If we know the complications of our therapy we can be able to choose the suitable supportive care intervention to increase the quality of life. Supportive care must be a more essential part of main therapy in the future.

**Conflict of Interest Statement**

The authors of this paper have no conflicts of interest, including specific financial interests, relationships, and/or affiliations relevant to the subject matter or materials included.

**References**

1. 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
2. Bloechl-Daum B, Deuson RR, Mavros P, Hansen M, Herrstedt J: Delayed nausea and vomiting continue to reduce patients' quality of life after highly and moderately emetogenic chemotherapy despite antiemetic treatment. J Clin Oncol 2006; 24: 4472-4478

3. Schwartzberg L: Chemotherapy-induced nausea and vomiting: state of the art 2006. J Support Oncol 2006; 4: 3-8

4. Grunberg SM, Osoba D, Hesketh PJ, Gralla RJ, Borjeson S, Rapoport BL, du Bois A, Tonato M: Evaluation of new antiemetic agents and definition of antineoplastic agent emetogenicity-an update. Support Care Cancer 2005; 13: 80-84

5. Baker PD, Morzorati SL, Ellet ML: The pathophysiology of chemotherapy-induced nausea and vomiting. Gastroenterol Nurs 2005; 28: 469-480

6. Kris MG, Hesketh PJ, Somerfield MR, Feyer P, Clark-Snow R, Koeller JM, Morrow GR, Chinery LW, Chesney MJ, Gralla RJ, Grunberg SM: American Society of Clinical Oncology guideline for antiemetics in oncology: Update 2006. J Clin Oncol 2006; 24: 2932-2947

7. NCCN Clinical practice guidelines in oncology; v.2.2006: Antiemesis. National Comprehensive Cancer Network (NCCN), 2006

8. Navari RM: Antiemetic control: Toward a new standard of care for emetogenic chemotherapy. Expert Opin Pharmacother 2009; 10: 629-644

9. Navari RM: Pathogenesis-based treatment of chemotherapy-induced nausea and vomiting: Two new agents. J Support Oncol 2003; 1: 89-103

10. Hesketh PJ: New treatment options for chemotherapy-induced nausea and vomiting. Support Care Cancer 2004; 12: 550-554

11. Diemunsch P, Grelot L: Potential of substance P antagonists as antiemetics. Drugs 2000; 60: 533-546

12. The Italian group for Antiemetic research: Dexamethasone, 430: 341-349

13. Navari RM: Apprepitant: A neurokinin-1 receptor antagonist for the treatment of chemotherapy-induced nausea and vomiting. Expert Rev Anticancer Ther 2004; 4: 715-724

14. Bymaster FP, Calligaro DO, Falcone JF, Marsh RD, Moore NA, Tye NC, Seeman P, Wong DT: Radioreceptor binding profile of the atypical antipsychotic olanzapine. Neuropsychoendocrinology 1996; 14: 87-96

15. Bymaster FP, Falcone JF, Bauzon D, Kennedy JS, Schenck K, DeLapp NW, Cohen ML: Potent antagonism of 5-HT3 and 5-HT6 receptors by olanzapine. Eur J Pharmacol 2001; 430: 341-349

16. Allison DB, Casey DE: Antipsychotic-associated weight gain: A review of literature. J Clin Psychiatry 2001; 62: 22-31

17. Hale AS: Olanzapine. Br J Hosp Med 1997; 58: 442-445

18. Goldstein LE, Sporn J, Brown S, Kim H, Finkelstein J, Gaffey GK, Sachs G, Stern TA: New-onset diabetes mellitus and diabetic ketoacidosis associated with olanzapine treatment. Psychosomatics 1999; 40: 438-443

19. Guttuso T Jr, Roscoe J, Griggs J: Effect of gabapentin on nausea induced by chemotherapy in patients with breast cancer. Lancet 2003, 361: 1703-1705

20. Martin BR, Wiley JL: Mechanism of action of cannabinoids; How it may lead to treatment of cachexia, emesis and pain. J Support Oncol 2004; 2: 305-316

21. Slatim MD: Canabinoids in the treatment of chemotherapy-induced nausea and vomiting: Beyond prevention of acute emesis. J Support Oncol 2007; 5: 1-9

22. Van Sickle MD, Duncan M, Kingsley PJ, Moulihate A, Urbani P, Mackie K, Stella N, Makriyannis A, Piomelli D, Davison JS, Marnetti LJ, Di Marzo V, Pittman QJ, Patel KD, Sharkey KA: Identification and functional characterization of brainstem cannabinoid CB2 receptors. Science 2005; 310: 329-332

23. NCCN Clinical practice guidelines in oncology; v.2.2011: Antiemesis. National Comprehensive Cancer Network (NCCN), 2010

24. Knight K, Wade S, Balducci L: Prevalence and outcomes of anemia in cancer: A systematic review of the literature. Am J Med 2004; 116: 11-26

25. Bennett CL, McKoy JM, Henke M, Silver SM, MacDougall IC, Birgegard G, Luminari S, Casadevall N, Schellekens H, Sartor O, Lai SY, Armitage JO: Reassessments of ESAs for cancer treatment in the US and Europe. Oncology (Williston Park) 2010; 24: 260-268

26. Caro JJ, Salas M, Ward A, Goss G: Anemia as an independent prognostic factor for survival in patients with cancer: A systematic, quantitative review. Cancer 2001; 91: 2214-2221

27. Buck I, Morceau F, Grigorakaki C, Dicato M, Diederich M, Broeks A, Steenbergen R, Steenbergen W, Parmentier M, Diederich M: Identification and functional characterization of brainstem cannabinoid CB2 receptors. Science 2005; 310: 329-332

28. Schwartz RN: Anemia in patients with cancer: Incidence, causes, impact, management and use of treatment guidelines and protocols. Am J Health Syst Pharm 2007; 64: 5-13

29. Steensma DP: Is anemia of cancer different from chemotherapy induced anemia? J Clin Oncol 2008; 26: 1022-1024

30. Groopman JE, Itti LM: Chemotherapy induced anemia in adults: Incidence and treatment. J Natl Cancer Inst 1999; 91: 1616-1634

31. Jefferies S, Rajan B, Ashley S, Traish D, Brada M: Haematological toxicity of cranio-spinal irradiation. Radiother Oncol 1998; 48: 23-27
32. Spivak JL, Gascon P, Ludwig H: Anemia management in oncology and hematology. Oncologist 2009; 14: 43-56
33. Littlewood TJ, Bajetta E, Nortier JW, Vercaemen E, Rapoport B: Epoetin Alfa Study Group: Effects of epoetin alfa on hematologic parameters and quality of life in cancer patients receiving nonplatinum chemotherapy: Results of randomized, double blind placebo controlled trial. J Clin Oncol 2001; 19: 2865-2874
34. Vansteenkiste J, Pirker R, Masutti B, Barata F, Font A, Fiegl M, Siena S, Gateley J, Tomita D, Colowick AB, Musil J; Aranesp 980297 Study Group: Double blind, placebo controlled, randomized phase III trial of darbepoetin alfa in lung cancer patients receiving chemotherapy. J Natl Cancer Inst 2002; 94: 1211-1220
35. Bohlius J, Wilson J, Seidenfeld J, Piper M, Schwarzer G, Sandercock J, Trelle S, Weingart O, Bayliss S, Djulbegovic B, Bennett CL, Langensiepen S, Hyde C, Engert A: Recombinant human erythropoietins and cancer patients: Updated meta analysis of 57 studies including 9353 patients. J Natl Cancer Inst 2006; 98: 708-714
36. Leyland-Jones B, Semiglazov V, Pawlicki M, Pienkowski 8, Gündüz E and Gülbaş Z: Supportive Care in Hemato-Oncology
37. Hanke M, Laszig R, Rube C, Schäfer U, Haase KD, Schilcher B, Henke M, Ali S, Hoebers FJ, Darcy KM, Rodgers WH, Patel 37. Henke M, Laszig R, Rube C, Schäfer U, Haase KD, Schilcher B, Hanke M, Ali S, Hoebers FJ, Darcy KM, Rodgers WH, Patel
38. Juneja V, Keegan P, Gootenberg JE, Rothmann MD, Shen YL, Lee KY, Weiss KD, Pazdur R: Continuing reassessment of the risks of erythropoiesis-stimulating agents in patients with cancer. Clin Cancer Res 2008; 14: 3242-3247
39. Santini V, Alessandrino PE, Angelucci E, Barosi G, Billio A, Di Maio M, Finelli C, Locatelli F, Marchetti M, Morra A, Ali S, Hoebers FJ, Darcy KM, Rodgers WH, Patel
40. Smith RE Jr., Aapro MS, Ludwig H, Pintér T, Smakal M, Ciuleanu TE, Chen L, Lillie T, Glasper JA: Darbepoetin alfa for the treatment of anemia in patients with active cancer not receiving chemotherapy or radiotherapy: results of a phase III, multicenter, randomized, double-blind, placebo-controlled study. J Clin Oncol 2008; 26: 1040-1050
41. Hedenus M, Adriasson M, San Miguel J, Kramer MH, Schipperus MR, Juvenen E, Taylor K, Belch A, Altés A, Martinelli G, Watson D, Matcham J, Rossi G, Littlewood TJ; Darbepoetin Alfa 20000161 Study Group: Efficacy and safety of darbepoetin alfa in anaemic patients with lymphoproliferative malignancies: Randomized, double-blind, placebo-controlled study. Br J Haematol 2003; 122: 394-403
42. Heit JA, Silverstein MD, Mohr DN, Petterson TM, O’Fallon WM, Melton LJ 3rd: Risk factors for deep vein thrombosis and pulmonary embolism: A population based case control study. Arch Intern Med 2000; 160: 809-815
43. Steinbrook R: Erythropoietin, the FDA and oncology. N Engl J Med 2007; 356: 2448-2451
44. Khorana AA, Francis CW, Kulakova E, Kuderer NM, Lyman GH: Thromboembolism is a leading cause of death in cancer patients receiving outpatient chemotherapy. J Thromb Haemost 2007; 5: 632-634
45. Juneja V, Keegan P, Gootenberg JE, Rothmann MD, Shen YL, Lee KY, Weiss KD, Pazdur R: Continuing reassessment of the risks of erythropoiesis-stimulating agents in patients with cancer. Clin Cancer Res 2008; 14: 3242-3247
46. Santini V, Alessandrino PE, Angelucci E, Barosi G, Billio A, Di Maio M, Finelli C, Locatelli F, Marchetti M, Morra A, Ali S, Hoebers FJ, Darcy KM, Rodgers WH, Patel
47. Steinbrook R: Erythropoietin, the FDA and oncology. N Engl J Med 2007; 356: 2448-2451
48. Khorana AA, Francis CW, Kulakova E, Kuderer NM, Lyman GH: Thromboembolism is a leading cause of death in cancer patients receiving outpatient chemotherapy. J Thromb Haemost 2007; 5: 632-634
49. Steinbrook R: Erythropoietin, the FDA and oncology. N Engl J Med 2007; 356: 2448-2451
50. Kwak LW, Halpern J, Olshen RA, Horning SJ: Prognostic significance of actual dose intensity in diffuse large cell lymphoma: Results of a tree-structured survival analysis. J Clin Oncol 1990; 8: 963-977
51. Kwak LW, Halpern J, Olshen RA, Horning SJ: Prognostic significance of actual dose intensity in diffuse large cell lymphoma: Results of a tree-structured survival analysis. J Clin Oncol 1990; 8: 963-977
52. Lepage E, Gisselbrecht C, Haioun C, Sebban C, Tilly H, Bosly A, Morel P, Herbriecht R, Reyes F, Coiffier B: Prognostic significance received relative dose intensity in non-Hodgkin’s lymphoma patients: application to LNH-87 protocol The GELA. Ann Oncol 1993; 8: 651-656
52. Chang J: Chemotherapy dose reduction and delay in clinical practice: Evaluating the risk to patient outcome in adjuvant chemotherapy for breast cancer. Eur J Cancer 2000; 36: 11-14
53. Fortner BV, Houts AC, Schwartzberg LS: A prospective investigation of chemotherapy-induced neutropenia and quality of life. J Support Oncol 2006; 4: 472-478
54. Wingard Jr, Elmongy M: Strategies for minimizing complications of neutropenia: prophylactic myeloid growth factors and antibiotics. Crit Rev Hematol Oncol 2009; 72: 144-154
55. Bohlius J, Reiser M, Scharze G, Engert A: Granulopoiesis stimulating factors to prevent adverse effects in the treatment of malignant lymphoma. Cochrane Database Syst Rev CD003189; 2004
56. Smith TJ, Khatcheressian J, Lyman GH, Ozer H, Armitage JO, Balducci L, Bennett CL, Cantor SB, Crawford J, Cross SJ, Demetri G, Desch CE, Pizzo PA, Schiffer CA, Schwartzberg L, Somerfield MR, Somlo G, Wade JC, Wade JL, Winn RJ, Wozniak AJ, Wolff AC: 2006 update of recommendations for the use of white blood cell growth factors: An evidence-based clinical practice guideline. J Clin Oncol 2006; 24: 3187-3205
57. Martin WG, Ristow KM, Habermann TM, Colgan JP, Witzig TE, Ansell SM: Bleomycin pulmonary toxicity has a negative impact on the outcome of patients with Hodgkin’s lymphoma. J Clin Oncol 2005; 23: 7614-7620
58. Tigue CC, McKoy JM, Events AM, Trifilio SM, Tallman MS, Bennett CL: Granulocyte-colony stimulating factor administration to healthy individuals and persons with chronic neutropenia or cancer: an overview of safety considerations from the Research on Adverse Drug Events and Reports Project. Bone Marrow Transplant 2007; 40: 185-192
59. Aapro MS, Cameron DA, Pettengell R, Bohlius J, Crawford J, Ellis M, Kearney N, Lyman GH, Tjan-Heijnen VC, Walewski J, Weber DC, Zielinski C; European Organisation for Research and Treatment of Cancer (EORTC) Granulocyte Colony-Stimulating Factor (G-CSF) Guidelines Working Party: EORTC guidelines for the use of granulocyte colony stimulating factor to reduce the incidence of chemotherapy induced febrile neutropenia in adult patients with lymphomas and solid tumours. Eur J Cancer 2006; 42: 2433-2453
60. Crawford J, Althaus B, Armitage J, Balducci L, Bennett C, Blayney DW, Cataland SR, Dale DC, Demetri GD, Erba HP, Foran J, Freifeld AG, Heaney ML, Htoy S, Kloth DD, Lyman GH, Messersmith WA, Michaud LB, Miyata SC, Robbins A, Tallman MS, Vadhan-Raj S, Westervelt P, Wong MK; National Comprehensive Cancer Network (NCCN): Myeloid growth factors, clinical practice guidelines in oncology. J Natl Compr Canc Netw 2007; 5: 188-202
61. Crawford J, Dale DC, Kuderer NM, Culakova E, Poniewierski MS, Wolff D, Lyman GH: Risk and timing of neutropenic events in adult cancer patients receiving chemotherapy: the results of a prospective nationwide study of oncology practice. J Natl Compr Canc Netw 2008; 2: 109-118
62. Pagliuca A, Carrington PA, Pettengell R, Tule S, Keidan J: Haematology-Oncology Task Force of the British Committee for Standards in Haematology: Guidelines on the use of colony stimulating factors in haematological malignancies. Br J Haematol 2003; 1: 22-23
63. Clark OA, Lyman GH, Castro AA, Clark LG, Djulbegovic B: Colony stimulating factors for chemotherapy induced febrile neutropenia: A meta analysis of randomized controlled trials. J Clin Oncol 2005; 23: 4198-4214
64. Berghmans T, Paesmans M, Lafitte J, Mascaux C, Meert AP, Jacqy C, Burniat A, Steels E, Vallot F, Sculier JP: Therapeutic use of granulocyte and granulocyte macrophage colony stimulating factors in the febrile neutropenic cancer patients. A systematic review of the literature with meta analysis. Support Care Cancer 2002; 10: 181-188
65. Garcia-Carbonero R, Mayordomo JJ, Tornamira MV, López-Brea M, Rueda A, Guillem V, Arcediano A, Yubero A, Ribera F, Gómez C, Trés A, Pérez-Gracia JL, Lumbereras C, Horredo J, Cortés-Funes H, Paz-Ares L: Granulocyte colony stimulating factor in the treatment of high risk febrile neutropenia: a multicenter randomized trial. J Natl Cancer Inst 2001; 93: 31-38
66. Johnston E, Crawford J, Blackwell S, Bjurstrom T, Lockbaum P, Roskos L, Yang BB, Gardner S, Miller-Messana MA, Shoemaker D, Garst J, Schwab G: Randomized dose escalation study of SD/01 compared with daily filgrastim in patients receiving chemotherapy. J Clin Oncol 2000; 18: 2522-2528
67. Vogel CL, Wojtukiewicz, MZ, Carroll RR, Tjulandin SA, Barajas-Figueroa LJ, Wiens BL, Neumann TA, Schwartzberg LS: First and subsequent cycle use of pegfilgrastim prevents febrile neutropenia in patients with breast cancer: a multicenter, double-blind, placebo controlled phase III study. J Clin Oncol 2005; 23: 1178-1184
68. Green MD, Koelbl H, Baselga J, Galid A, Guillem V, Gascon P, Siena S, Lalisang RI, Samonigg H, Clemens MR, Zani V, Liang BC, Renwick J, Piccart MJ; International Pegfilgrastim 749 Study Group: A randomized double-blind multicenter phase III study of fixed dose single administration pegfilgrastim versus dailyfilgrastim in patients receiving myelosuppressive chemotherapy. Ann Oncol 2003; 14: 29-35