Review

DOI: 10.5505/tjh.2012.10327

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

Hemato-Onkolojide Destek Tedaviler: Son Kılavuzlar Işığında Gözden Geçirme

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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 arttırılması temel hedeflerden biri olmalıdır. Solid ya da hematolojik maligniteler için verilen çoğu 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 derlemede, destek tedavi olarak verilen bu ajanlardan bazılarını en son kılavuzlar ışığında kısaca özetledik.

Anahtar Sözcükler: Hematoloji, Destek tedavi, Bulantı-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

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Received/*Geliş tarihi* : February 6, 2011
Accepted/*Kabul tarihi* : May 17, 2011

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 neuroreceptors 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-HT_3) Receptor Antagonists

Serotonin receptors—specifically 5-HT_3 receptors—are present in the central nervous system and gastrointestinal tract. First-generation 5-HT_3 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-HT_3 receptor antagonist palonosetron might more effectively control delayed CINV than the first-generation 5-HT_3 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-HT_3 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-HT_{2a}, 5-HT_{2c}, 5-HT_3, and 5-HT_6 receptors, catecholamines at alpha 1 adrenergic receptors, acetylcholine at muscarinic receptors, and histamine at H_1 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

and

Steroid

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

and

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

and

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

Prochlorperazine 10 mg p.o. or IV every 4 or 6 h

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 occured 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} [25]. 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 epoietin 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 $\mu g \cdot kg^{-1} \cdot d^{-1}$ 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 intitution 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.

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