

REVIEWS

Supportive care of palliative chemotherapy for advanced stage lung cancer patients: Summary for the daily practice

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Abstract

Supportive care during palliative chemotherapy of advanced stage lung cancer is essential to enable successful control of the disease. Active oncologic treatment most often used in lung cancer has many side effects which may impair patients' quality of life and compromise the effectiveness of therapy. Most side effects of chemotherapy are preventable or treatable with optimal supportive care which enhances success in patient care. The aim of this review is to summarize the most important conditions that may be associated with palliative chemotherapy of advanced stag lung cancer, their prevention or treatment from the daily clinical point of view, with additional special focus on the important role of oncology nurses.

Key words

Advanced stage lung cancer, Chemotherapy, Supportive therapy

Introduction

Lung cancer is the leading cause of cancer death worldwide including Hungary^[1]. Active treatment after surgery can only be omitted in cases of resected stage IA non-small cell lung cancer (= localized non-small-cell lung cancer with no spread to lymph node or other organs). Otherwise, in patients with lung cancer palliative (IIIB-IV), adjuvant (IIA-IIIA, optional in IB), or neoadjuvant (IIIA stadium) chemotherapy is recommended if allowed by the patient's general condition^[2].

Palliative chemotherapy traditionally includes the combinations of cytostatic drugs which have several known side effects that may impair the quality of life as well as the success of oncotherapy. In most cases these symptoms can be prevented or can be treated. The physician's challenge is to anticipate and prevent side effects that pose risks to the patient's health, or if they have already been developed, to manage them. Appropriate supportive care allows even long-term chemotherapy to be well tolerated without the necessity of reducing the doses, thereby improving the likelihood of treatment success. Oncology nurses are always involved not only into the management of chemotherapies, but also supportive care. It is crucial that patients are well informed about the effects and side effects of the therapy and get additional life management counselling including smoking cessation.

The following short review will summarize the most important conditions during palliative chemotherapy in lung cancer and the management strategies used in everyday practice. The article aims to provide a clinically useful, focussed, short advice, hence does not cover all the details. Supportive care guidelines of symptoms are available on the websites of EORTC (European Organisation for Research and Treatment of Cancer) and NCCN (National Comprehensive Cancer Network), American Society of Clinical Oncology (ASCO) and European Society of Medical Oncology (ESMO). However these guidelines are very detailed and do not specifically address palliative chemotherapy of lung cancer care.

Prevalence of different side effects was collected using European Medicines Agency summaries of product characteristics for each drug. European public assessment reports classification was used to show frequency of symptoms or side effects:

- very common: affects more than 1 user in 10
- common: affects 1 to 10 users in 100
- uncommon: affects 1 to 10 users in 1,000
- rare: affects 1 to 10 users in 10,000
- very rare: affects less than 1 user in 10,000
- not known: frequency cannot be estimated from the available data.

Most common side effects and severity are summarized in Table 1. Table 2 resumes the very commonly observed side effects specific to the drugs analyzed that were not included into Table 1.

Table 1. Prevalence of side effects of the most commonly used first line chemotherapeutic agents and targeted therapies for advanced stage lung cancer according to European Medicines Agency summaries of product characteristics for each drug

| | CINV | FN | CIA | Thrombocytopenia | VTE | Nephrotoxicity | Cardiotoxicity | Neurotoxicity |
|-------------|------|----|-----|------------------|-----|----------------|----------------|---------------|
| Cisplatin | 1 | 1 | 1 | 1 | NK | 1 | 2 | 5 |
| Carboplatin | 1 | NK | 1 | 1 | NK | 1 | 2 | 2 |
| Paclitaxel | 1 | 2 | 1 | 1 | 3 | NK | 2 | 1 |
| Docetaxel | 1 | 1 | 1 | 2 | NK | 1 | 2 | 1 |
| Vinorelbine | 1 | 2 | 1 | 2 | NK | 1 | 5 | 1 |
| Pemetrexed | 1 | NK | 1 | 1 | NK | 1 | NK | 1 |
| Etoposid | 1 | 1 | 1 | 1 | NK | NK | 2 | 4 |
| Gemcitabine | 1 | 2 | 1 | 1 | NK | 1 | 4 | 2 |
| Erlotinib | 1 | NK | NK | NK | NK | NK | NK | 1 |
| Gefitinib | 1 | NK | NK | NK | NK | 2 | NK | NK |
| Bevacizumab | 1 | 1 | 2 | 1 | 2 | 2 | 2 | 1 |

Notes. 1: very common: affects more than 1 user in 10; 2: common: affects 1 to 10 users in 100; 3: uncommon: affects 1 to 10 users in 1,000; 4: rare: affects 1 to 10 users in 10,000; 5: very rare: affects less than 1 user in 10,000; Not known (NK): frequency cannot be estimated from the available data. CINV=chemotherapy induces nausea and vomiting, FN = febrile neutropenia, CIA= chemotherapy induced anaemia, VTE = venous thromboembolism.

Chemotherapy induced nausea and vomiting (CINV) [3, 4]

In patients receiving highly emetogenic chemotherapy, nausea and vomiting are most likely to occur within 2-5 days after administration of the therapy. In case of moderately emetogenic chemotherapy this period may be 2-3 days. Serotonin released from gastrointestinal mucosa and platelets act on the central nervous system playing a key role in the pathomechanism of acute CINV occurring within 24 hours after chemotherapy. The pathway of delayed CINV (>24 hours post-treatment) is different. Neurokinin (NK)-1 receptors located in the nucleus tractus solitarius and area postrema are key elements of the vomiting centre in the central nervous system. Substance P (SP) is one of the most important signalling molecule in the development of chemotherapy induced delayed nausea and vomiting. Its emetogenic effect is mediated through NK-1 receptor pathways. Symptoms observed after the first 24 hours may cause serious problems with fluid and food intake, physical capability and thus the patients' quality of life.

Table 2. Very common side effects ($\geq 1/10$) not stated in Table 1 specific for the most commonly used first line chemotherapeutic agents and targeted therapies for advanced stage lung cancer

| | |
|--------------------|---|
| Cisplatin | Hyponatraemia Hyperuricaemia |
| Carboplatin | Elevation of liver transaminases Hyperuricaemia |
| Paclitaxel | Loss of hair, rash Reduction in the number of lymphocytes in the blood Reduction in the number of platelets in the blood Effect on peripheral nerves (pain and numbness) Pain in a joint or joints Pain in the muscles Weakness and tiredness, fever |
| Docetaxel | Infections including sepsis and pneumonia Hypersensitivity Dyspnea Anorexia Stomatitis Diarrhea Alopecia Skin reaction Nail disorders Myalgia |
| Vinorelbin | Stomatitis Obstipation Alopecia Elevation of liver enzymes Local phlebitis |
| Pemetrexed | Diarrhea Pain, redness, swelling or sores in your mouth Loss of appetite Fatigue (tiredness) Skin rash Hair loss Constipation Loss of sensation |
| Etoposid | Anorexia Alopecia |
| Gemcitabin | Dyspnea –usually mild and passes rapidly without treatment Elevation of liver transaminases (AST and ALT) and alkaline phosphatase Allergic skin rash frequently associated with pruritus Alopecia Influenza-like symptoms - the most common symptoms are fever, headache, chills, myalgia, asthenia and anorexia. Cough Rhinitis Malaise Perspiration and sleeping difficulties Oedema/peripheral oedema including facial oedema. |
| Erlotinib | Diarrhea Rash which may occur or worsen in sun exposed areas Infection Loss of appetite, decreased weight Depression Headache, altered skin sensation or numbness in the extremities Difficulty in breathing Cough Nausea Mouth irritation Stomach pain, indigestion and flatulence Abnormal blood tests for the liver function Itching, dry skin and loss of hair |
| Gefitinib | Diarrhea Skin reactions such as an acne-like rash, which is sometimes itchy with dry and/or cracked skin Loss of appetite Weakness Dry, red or sore mouth Increase of a liver enzymes |
| Bevacizumab | High blood pressure Problems with wound healing after surgery Feeling of numbness or tingling in hands or feet Lack of energy or tiredness Diarrhea |

Among drugs used for palliative treatment of lung cancer cisplatin poses a high (>90%) carboplatin a moderate (30%-90%) risk for the development of CINV, therefore complex supportive therapy should be administered accordingly. In protocols including the administration of cisplatin during the first hours serotonin-antagonists (5HT3), combined with NK-1 antagonist aprepitant and steroids should be used. When using combinations of moderately emetogenic carboplatin or other drugs 5HT3-antagonists combined with steroids should always be administered. In addition to steroids, H2-blocker or proton pump inhibitor (PPI) may be applied for ulcer prophylaxis. Currently available and recommended combinations are summarized in Figure 1.

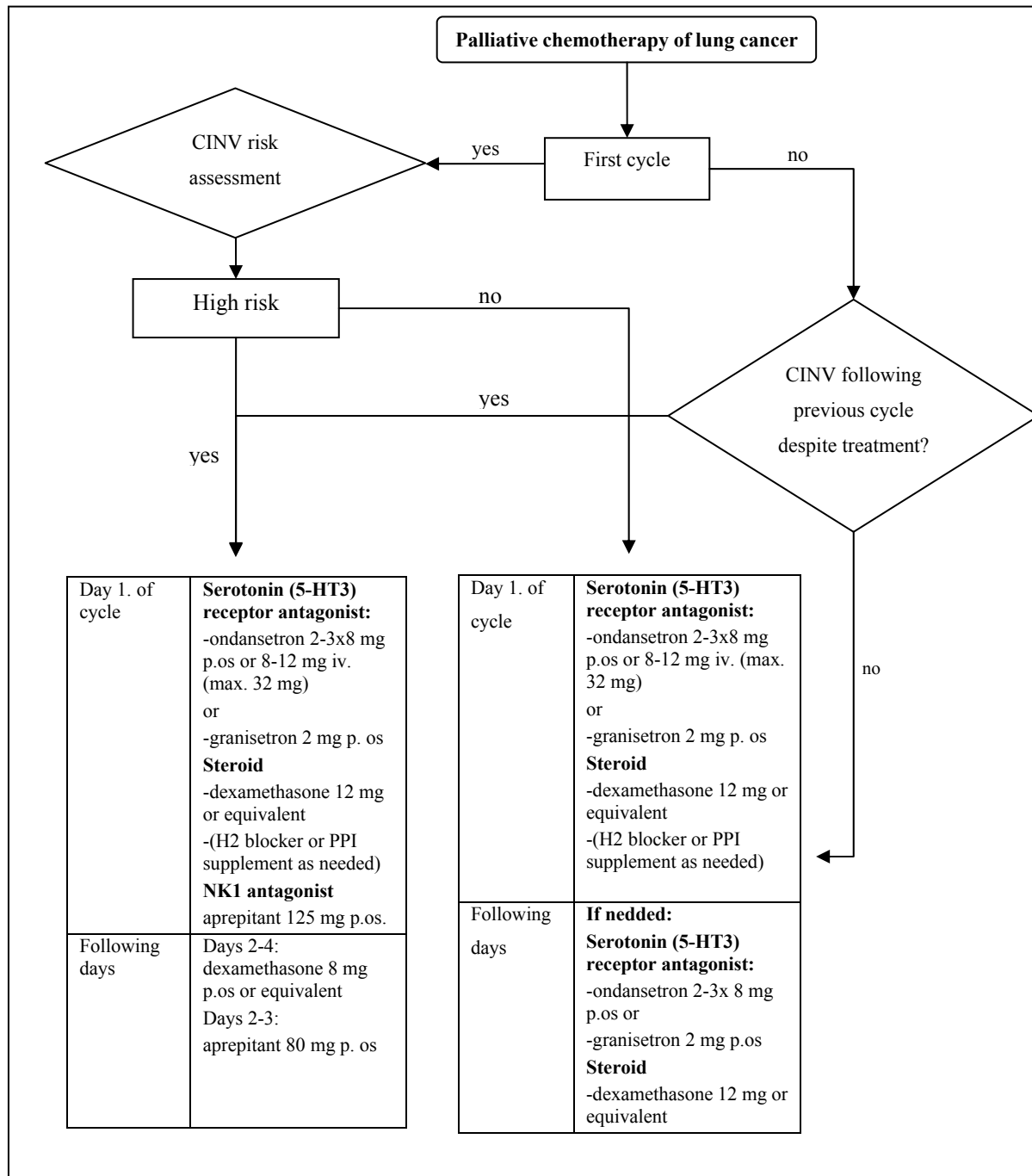
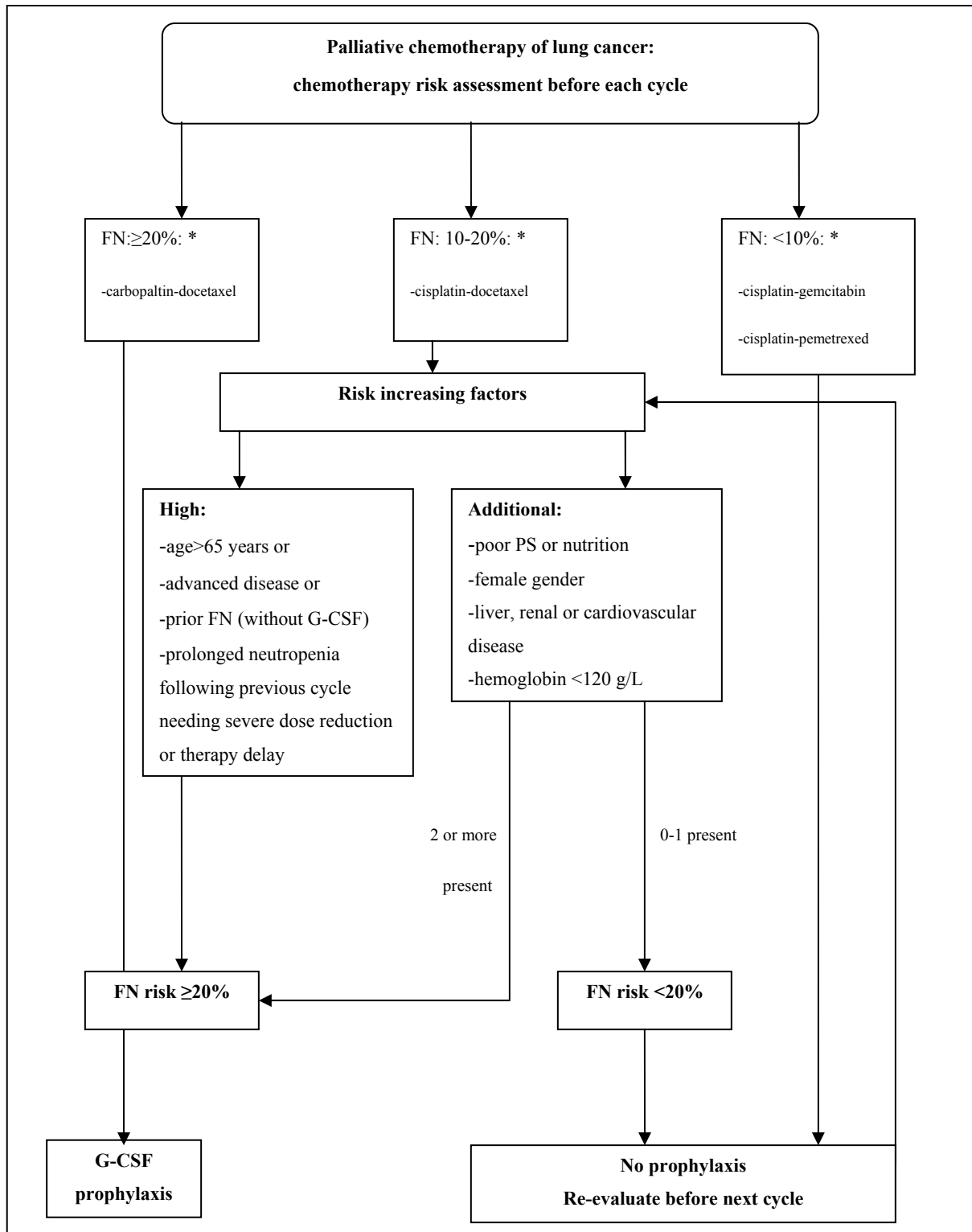


Figure 1. Treatment algorithm of chemotherapy induced nausea and vomiting (CINV) during palliative chemotherapy of lung cancer.



*chemotherapeutic combinations with known FN risk

Figure 2. Suggested risk assessment of febrile neutropenia (FN) and G-CSF profilaxis in lung cancer patients receiving first line palliative chemotherapy.

If patients experience symptoms of CINV despite appropriate therapy, it is important to rule out other possible underlying causes. Most often increase in brain pressure (brain metastases), hyponatraemia (SIADH = paraneoplastic syndrome of inadequate antidiuretic hormone secretion), hyperglycaemia, hypercalcaemia, other medications (mostly opiates) and psychological factors may be in the background. In many cases anxiolytics can reduce symptoms, particularly in cases of anticipatory vomiting. If symptoms occur despite adequate prevention - after exclusion of other organic causes - treatment may be supplemented by one of the followings: metoclopramide 10-40 mg (every 4-6 hours), haloperidol 0.5-2 mg (every 4-6 hours) or promethazine 12.5-25 mg.

From the nurse's point of a view, optimal nutrition is important during chemotherapy cycles. When patients can eat, they may be encouraged to have appropriate calorie and protein intake. To avoid nausea smaller portions are suggested, and food intake in the morning is preferred. Smaller amount of fluids, cold, not carbonated drinks, or decarbonised cold coke is the best in our clinical practice to ensure fluid intake when nausea has developed. In case of vomiting, sucking at ice cubes is worth to try. Patients are recommended to drink more the day before and at the day of chemotherapy, and never get the treatment fasting. The timing of antiemetic drug intake is important, as well as obstipation management which is a common side effect of 5HT3-antagonists.

Prevention and treatment of febrile neutropenia (FN) ^[5, 6]

The most dangerous complication of bone marrow suppression associated with chemotherapy is the decrease of circulating neutrophil counts, called neutropenia. Neutropenia can be divided into four groups based on severity by the absolute number of neutrophils:

- Grade I: 1.5 - <2 G / L
- Grade II: 1.0 - <1.5 G / L
- Grade III: 0.5 - <1.0 G / L
- Grade IV: <0.5 G / L.

Only severe neutropenia of grade III and IV requires therapy. Neutropenia with body temperature of >38°C (sustained for >1 hour) or with a single measure of >38.5°C is defined as FN. If neutropenia with any body temperature persists for at least 6 weeks, it is called prolonged neutropenia. These conditions significantly increase the risk of infection-related mortality and therefore may require dose intensity reduction or delay of chemotherapy. Many types of chemotherapeutic drugs used for lung cancer treatment present high risk for the development of neutropenia.

FN risk of all patients receiving chemotherapy should be determined before each cycle of chemotherapy and granulocyte colony-stimulating factor (G-CSF) should be applied as prophylactic treatment accordingly. To estimate the risk, chemotherapy-related risk factors should be weighted by patient-related factors (see Table 1 and Figure 2) thus defining the cumulative risk of FN. Prophylactic G-CSF administration is needed if the cumulative risk taking into account all factors of FN is $\geq 20\%$. A single dose of long-acting pegfilgrastim may be given after 24 hours of chemotherapy in protocols that recommend a 2-week intermission between two cycles of the treatment. In other cases, a daily dose of filgrastim or lenograstim starting 24 hours after the administration of chemotherapy, once a day for 5-10 days in total may be used. If the cumulative risk of FN is <20%, prophylactic treatment should not be given, however, before each repeated cycle, the risk should be estimated again (see Figure 2). If the risk rises above the critical level in subsequent cycles of treatment, a secondary G-CSF prophylaxis is needed.

If FN develops, it has a significant mortality up to 7% ^[7]. Management of FN includes identification of the pathogen(s), adequate antibiotic therapy, filgrastim treatment and frequent blood tests for follow-up. Risk analysis of adult FN patients

is based on the index of Multinational Association for Supportive Care in Cancer (MASCC) including the followings: No burden of illness or mild symptoms 5 points, moderate burden of illness 3 points, severe burden of illness or severe symptoms 0 points, systolic blood pressure >90 mmHg 5 points, no chronic obstructive pulmonary disease 4 points, no previous fungal infection 4 points, no dehydration 3 points, outpatient status (at onset of fever) 3 points, age <60 years 2 points. A score of ≥ 21 (out of maximal 26 points) is classified as low risk and a score of < 21 as high risk^[8]. In low-risk patients outpatient antibiotic therapy may be safe and effective, patients at high-risk or those who have difficulties with taking oral antibiotics need to be hospitalized.

- Choice of antibiotic therapy for FN^[9]:
- Low risk, p.o. medication can be taken: p.o. ciprofloxacin and amoxicillin-clavulanate combination
- High risk or p.o. medication can not be taken: piperacillin / tazobactam or imipenem / cilastatin or cefepime or meropenem
- Added vancomycin or teicoplanin is required: known methicillin resistant *Staphylococcus aureus* (MRSA), skin and soft tissue infections, septic shock, pneumonia, Gram positive bacteria isolated from blood cultures prior to identification.

GCS-F treatment added to antibiotic therapy may reduce the infection-related mortality by half. If FN has occurred, only filgrastim is applicable as treatment, duration of the therapy takes 5-10 day, dosing from 30,000 to 48,000 IU / day (depending on the patient's weight).

Nurses are involved into haematological blood sampling, and are often discussing signs of neutropenia and infections. Big proportion of lung cancer patients has chronic obstructive lung disease (COPD) simultaneously with former experiences of acute exacerbations and increase of sputum production. It is important that patients are aware of possible signs of infection, changes in sputum volume and/or colour. It is recommended not to visit family members with known infections, not to attend public places during times of respiratory infection epidemics. Increased attention should be paid on personal hygiene, hand disinfection and handling of rough grocery. Nurses are of a great help in patient education regarding the recognition and non-pharmaceutical treatment of haematological side effects.

Management of chemotherapy-induced anaemia (CIA)^[10-13]

Anaemia is another common complication of bone marrow suppression associated with chemotherapy. Nephrotoxic side effect of platinum the fundamental antineoplastic drug for lung cancer (especially cisplatin) may lead to reduced renal erythropoietin production thereby increasing the risk of anaemia. To choose the correct therapeutic option it is important to differentiate CIA from anaemia accompanying cancer (anaemia develops mainly due to direct tumour infiltration of the bone marrow) or infection. As stated in international guidelines haemoglobin level below 110 g/L or a decrease in haemoglobin level of more than 20 g/L is used to define anaemia. It is important to determine the mean volume of red blood cells (MCV) and reticulocyte counts during the laboratory analysis to identify the aetiology of anaemia. All treatable conditions should be excluded, including bleeding, haemolysis, iron-, folic acid-, vitamin B12-deficiency, renal failure (glomerular filtration rate (GFR) <60 ml/min) and irradiation-induced myelosuppression. If treatable disease can be confirmed, therapy should be chosen accordingly. Anaemia severity is classified according haemoglobin level and graded according to the National Cancer Institute-Common Toxicity Criteria of Adverse Events:

- I: normal lower limit to 100 g/L
- II: 80 - 100 g/L

- III: 65 - 80 g/L
- IV, life threatening: <65 g/L.

Red blood cell transfusion may be a possible treatment in CIA as also used in other forms of severe anaemia. Additionally different synthetic erythropoietin formulations (ESA= erythropoiesis stimulating agents) may also be considered to be an alternative to blood transfusions.

According to current guidelines ESA therapy may be given to lung cancer patients with significantly decreased haemoglobin level (usually of less than 100 g / L), especially if anaemia causes symptoms and persists despite adequate iron supplementation. It is also worth noting that ESA therapy can be safely applied until reaching the target haemoglobin level of 120 g / l. If the patient does not respond to treatment adequately, the dose may be increased according to the Summary of Product Characteristics. According to our clinical observations only 50% of lung cancer patients qualifying for ESA treatment did receive therapy. In patients with CIA not receiving ESA support delay of chemotherapy or dose reduction was observed, so dose intensity could not be maintained [14].

Nurses can discuss possible early signs of anaemia and give nutritive advice including increased iron and folic acid uptake by diet. The prescribed therapies are discussed, with training of the ESA injection devices and avoidance of possible complications.

Prevention of venous thromboembolism (VTE) [15-17]

VTE is inherently more likely to occur in cancer patients than in the population with other general medical conditions. In addition, a significant number of patients with lung cancer are active smokers, and consequently may suffer from COPD simultaneously. Lung cancer patients have a six- to sevenfold risk of developing VTE compared to the average population, as VTE affects 15%-20% of all patients [18]. The increased thrombotic tendency is primarily related to the release of tumour procoagulant factors (eg. large amounts of tissue factors), which enter the circulation as a consequence of chemotherapy related tissue necrosis. High, medium and low risk groups of VTE can be distinguished based on the tumour type. Lung cancer is placed into the high risk group. Start of prophylaxis is not an easy task. The decision making process can be supported by risk assessment (see Table 3) and can help to identify high risk patients who may benefit from prophylactic therapy [19]. In patients whose risk score reaches three points - lung cancer itself being 1 point - and there is no contraindication of anticoagulant therapy, regardless of being outpatient or hospitalized, VTE prophylaxis should be offered during chemotherapy. Low molecular weight heparin (LMWH) should be used as prophylactic treatment to avoid the detriments of oral anticoagulants (thrombosis despite of optimal prothrombin values, gastrointestinal symptoms, more frequent drug interactions etc.). While some studies suggested possible beneficial effects of heparin on cancer survival (inhibition of metastasis, heparin-induced apoptosis) these were not confirmed to date and there is no evidence to recommend the use of anticoagulation to influence prognosis of lung cancer [20].

Table 3. Chemotherapy associated VTE risk in lung cancer patients (modified from [17])

| | Risk score |
|--|------------|
| Cancer related risk factor | |
| Lung cancer = high risk | 1 |
| Haematologic risk factor | |
| Thrombocytosis (>350G/l) before chemotherapy | 1 |
| Anaemia (Hgb <100 g/l) or ESA use | 1 |
| Leukocytosis (>11 G/l) before chemotherapy | 1 |
| Patient related risk factor | |
| BMI>35 kg/m ² | 1 |

Note. low-risk = 0, intermediate-risk = 1-2, high-risk ≥3

Training of administration of subcutaneous injections is essential in thromboprophylaxis and oncology nurses may be of a great help in this. Our clinical practice shows that LMWH administered into the abdominal region is associated with less haematoma formation. If patients have multiple injection site lesions repeated training is advised. Additionally caution at nail management, selection of soft toothbrush can reduce unnecessary bleeding when under VTE or profilaxis treatment.

Eating disorders: anorexia, weight loss, constipation, diarrhoea [21]

The most important negative prognostic factor of cancer patients is weight loss [22]. Many factors can cause inadequate dietary uptake, some of these should be highlighted: medication side effects, endocrine disorders (thyroid dysfunction, hypercalcaemia, hypogonadism), quick feeling of fullness and other conditions reducing food intake, including depression, mucositis, nausea / vomiting, constipation, pain or fatigue. In addition to the treatable conditions metoclopramide may relieve the symptom of feeling quickly full, while megestrol acetate is effectively used as an appetite-stimulant in cachexia (> 10% body weight loss), 400-800 mg twice daily. Patients should be encouraged to eat according their desires. If food intake is not sufficient high energy and/or protein nutritional drink supplements are suggested. Activity on fresh air is increasing appetite and may be recommended.

Constipation, known as major side effect of antiemetic medications and major analgesics may also contribute to poor food intake. Laxative therapy complemented with stool softeners if needed, increased fluid intake, consuming fiber-rich foods and exercise may help to prevent constipation. If this treatment is not enough, the dose of laxatives may be increased or supplemented with glycerin suppositories or enema.

Using tyrosine kinase inhibitors diarrhoea is commonly observed. Dose reduction, short therapeutic holiday or loperidium can be used to reduce the symptoms. Adequate fluid intake is necessary.

Prevention of cisplatin nephrotoxicity [23]

Repeated combinations with high doses (75 mg/m^2) of cisplatin are a preferred palliative chemotherapy regimen in lung cancer patients. Nephrotoxicity of this agent has been known for a long time, it particularly often occurs in lung cancer patients with cardiovascular disease or diabetes as a side effect of the drug. Before the administration of high-dose cisplatin renal function should not be judged by the serum creatinine concentration alone, the value of creatinine clearance must always be calculated based at least on the Cockcroft-Gault equation to assess renal function deterioration. In addition, it is necessary to ensure the euvolemia in patients to be treated by high-dose cisplatin and saline diuresis of at least 100 ml/hour prior to, during and after the administration of cisplatin (saline diuresis: ~ 1% NaCl concentration of urine, pre-and posthydration with saline infusion on the day before chemotherapy and following cisplatin treatment (total of 3.5-4.0 liters during 3-4 hours). Keeping the proper hydration recommended guarantees prolonged cisplatin treatability of lung cancer patients.

Nurse's advice regarding the prevention of nephrotoxicity may be that patients should increase fluid intake 1-2 days before cisplatin treatment and on the day of chemotherapy. It is important to keep the prescribed infusion velocity.

Summary

Palliative chemotherapy for lung cancer may have several side effects. Effective prevention and appropriate management pose a major challenge for clinicians, nurses and patients. Involving patient and family members, and addressing the therapy-related difficulties they may face can contribute to the efficacy of the complex treatment. Considering that during

lung cancer chemotherapy dozens of other medications (many of these given by injections) are needed, it is essential for the physicians and nurses to make their patients aware of the drugs they take to prevent certain complications and symptoms. As many patients are old, have co-morbidities influencing cognitive function or vision, support for medication dosing and administration from family members or health care providers is strongly needed. A drug diary is also suggested for cancer patients to record daily medication used beside chemotherapy of lung cancer.

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