Complications associated with oncological therapy

- how to minimize?

Angelika Szczęśniak[1,a], Natalia Serwin[1,b], Ela Cecerska-Heryć[1,g], Anna Stangret[2,c],

Agata Mularczyk[3,d], Konrad Grzeszczak[4,e], Katarzyna Topczewska[5,f]

[1]Department of Laboratory Medicine, Pomeranian Medical University, Poland
[2]Department of Human and Clinical Anatomy, Pomeranian Medical University, Poland
[3]Department of Obstetrics and Pathology of Pregnancy, Pomeranian Medical University, Poland
[4]Department of Biology and Medical Parasitology, Pomeranian Medical University, Poland
[5]Department of Epidemiology and Management, Pomeranian Medical University, Poland

[a]https://orcid.org/0000-0002-7854-8864
[b]https://orcid.org/0000-0002-1769-2037
[c]https://orcid.org/0000-0002-2721-2121
[d]https://orcid.org/0000-0002-8273-6737
[e]https://orcid.org/0000-0002-3055-3357
[f]https://orcid.org/0000-0003-2509-8289
[g]https://orcid.org/0000-0002-7313-7193

Abstract

During cancer therapy, patients undergo long-term treatment with chemotherapists. Unfortunately, although chemotherapy effectively destroys cancer cells, its toxicity may cause many adverse effects, weakening the patient's body. Their intensity is determined by many factors, including the age of the patient, the dose and type of drugs, the efficiency of metabolism and the occurrence of coexisting diseases. The most common side effects associated with chemotherapy include: myelosuppression, anaemia, neutropenia, thrombocytopenia, thrombocytopenia, thromboembolic disease, cardiovascular disorders, hair loss, nausea, diarrhoea, mucositis, taste change or fatigue.

The complications that occur during or after chemotherapy are still a huge challenge for modern oncology. It is very important that the treatment of a patient with cancer is conducted by a team of doctors with many specializations. The individualization of treatment and the introduction of combined therapy may significantly minimize the occurrence of many serious complications, which may affect not only the quality of treatment, but also the patient life expectancy.

Key words: chemotherapy, toxicity, pain treatment, oncology, disorders

Introduction

Although chemotherapy effectively destroys cancer cells, its toxicity may cause many adverse effects and thus weaken the patient's organism. Unfortunately, chemotherapeutics do not work selectively and cause death of healthy cells too, especially those that are subject to intensive divisions.

The most susceptible are the bone marrow cells, gastrointestinal cells, reproductive organs, hair and mucous membranes (Figure 1). Cytostatics administered during chemotherapy may also destroy the cells of the heart, nervous system, lungs, kidneys and urinary bladder.

The intensity of side effects depends on many factors, including the age of the patient, the dose and type of medications taken, coexisting diseases, and the efficiency of metabolism. These symptoms may be mild or aggressive.

The most common side effects are: myelosuppression, anaemia, neutropenia, thrombocytopaenia, hair loss, nausea, diarrhoea, ulceration of the oral cavity, changes in taste or fatigue [1-5].
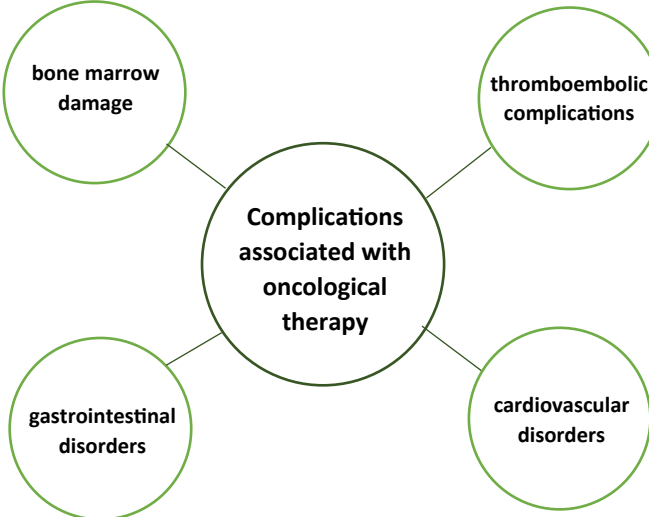
Fig. 1. Complications associated with oncological therapy

Oncological treatment is usually a complex therapeutic process. Chemotherapy is used in combination with radiotherapy, surgical treatment, as well as with nuclear medicine methods. The correct planning of all therapy stages and predicting the possibility of complications may significantly increase the effectiveness of cancer treatment.

Procedures used in the treatment of cancer are often very burdensome for the patient's organism. Therefore, it is very important to include supportive treatment in the therapy, the aim of which is to prevent and treat homeostasis disorders at every stage of diagnostic and therapeutic procedures, as well as to ensure the best possible quality of patient's life.

Treatment of bone marrow damage complications

Anaemia

Anemia occurs in more than half of patients during cancer treatment. The use of radiotherapy and chemotherapeutics may lead to bone marrow suppression and disorders in the production of endogenous erythropoietin, a factor stimulating the red blood cell production process, resulting in a decrease in the ability of blood to transmit oxygen.

Hemoglobin levels below the lower limit of normal (women - 12-14 g/dl; men - 14-18 g/dl) and erythrocyte deficiency cause fatigue, weakness, concentration problems, headaches and dizziness, as well as dyspnea and heart arrhythmias in oncological patients. Symptoms of anaemia may reduce the effectiveness of radiotherapy due to cellular hypoxia and hinder the continuation of chemotherapy [1].

The supplementation of iron, folic acid and vitamin B12 deficiency is important for the anaemia treatment in oncological patients [6].

Factors stimulating erythropoiesis (e.g. erythropoietin rHuEPO) and transfusions of blood or preparations containing red blood cells are also used [1, 6, 7].

Thrombocytopaenia

Thrombocytopenia is diagnosed when the platelet count falls below 150,0000/µl. Chemotherapy-related thrombocytopenia is most often caused by reduced platelet production in the bone marrow as a result of anticancer treatment or bone marrow cancer. This leads to the formation of haemorrhagic thrombocytopenic flaws, which is characterized by skin and mucosal bleeding, manifested by the formation of small petechiae most frequently on the skin of limbs, trunk, less frequently on the face and the petechiae of the oral cavity mucosa. They can also take the form of bleeding from the mucous membranes of the oral cavity and nose, urinary and sexual tract, digestive tract or bleeding to the central nervous system.

Bleeding in oncological patients may also be caused by abnormal production of coagulation factors as a result of liver damage, excessive excretion of coagulation factors in urine, abnormal renal function and no substrates for their synthesis [9].

In connection with such a broad etiology of bleeding, it is important to conduct a multidirectional analysis of the patient's condition in order to properly diagnose the cause of the pathology.

Haemorrhagic thrombocytopenic flaws may be treated with corticosteroids (prednisone), infusions of immunoglobulins and thrombopoietin receptor agonists (romiplostym and eltrombopag) [10, 11]. In more severe cases, platelet cell concentrates and recombinant human interleukin 11 (oprelvecin) are also used [3, 12].

Neutropenia

Neutrophils are the most numerous group of white blood cells of the immune system. Neutropenia means a reduction in the number of neutrophils below 1000/µl. The most common cause of neutropenia in oncological patients is abnormal production of bone marrow neutrophils due to dose-

dependent, myelotoxic action of cytostats. A decrease of neutrophils level may also be caused by radiation of large areas of bone marrow or by the suppression of normal haematopoietic cells by cancer cells.

During chemotherapy, it's very important to maintain the number of neutrophils at a horizontal level to protect the body from infection, thus allowing effective oncological treatment [9]. In the case of infections associated with neutropenia, patients are primarily treated for symptomatic infection. Growth factors of granulocytes (Filgrastim), which stimulate the growth and maturation of granulocyte stem cells and immature granulocytes, are also sometimes administered [2, 13].

Circulatory disorders

A cancer patient has a high risk of developing venous thromboembolism, which may occur even several years before the diagnosis of the disease, and during therapy. Circulatory disorders may be the result of changes associated with the underlying disease, or may be the consequence of disorders of the homeostasis of the system due to chemotherapy or radiotherapy.

Chemotherapy increases the risk of thromboembolism by over 6 times [14]. The vascular wall is damaged as a result of toxic effects of cytostatics, blood composition disorders, e.g. decreased concentration of clotting inhibitors (proteins C and S, antithrombin) and platelet activation.

A cancer patient has a high risk of developing venous thromboembolism, which may occur even several years before the diagnosis of the disease, and during therapy. Circulatory disorders may be the result of changes associated with the primary disease, or may be the consequence of disorders of the homeostasis of the system due to chemotherapy or chemotherapy.b radiotherapy.

Chemotherapy increases the risk of thromboembolism by over 6 times [14]. The vascular wall is damaged as a result of toxic effects of cytostatics, blood composition disorders and platelet activation. As a result of these changes, thrombi forms inside the deep veins, hindering or preventing proper

blood flow. In some patients, this is manifested by pain, swelling, tenderness or redness of the skin area [15].

The treatment of venous thromboembolism and its complications in the course of cancer is mainly based on prevention. Pharmacological treatment includes aspirin, low molecular weight heparins (dalteparin, enoxaparin sodium, tinzaparin, hyperparin, bemiparin), unfractionated heparins, oral anticoagulants (warfarin), factor Xa inhibitors (fondaparinux, rivaroxaban) and direct thrombin inhibitors (dabigatra) [15-17].

Gastrointestinal disorders

Induced nausea and vomiting chemotherapy (CINV)

Nausea and vomiting are very common side effects of both chemotherapy and radiotherapy. Although they do not cause life-threatening conditions, they significantly reduce the quality of life of patients. Increased occurrence of vomiting may lead to water-electrolyte balance disorders and long-term eating disorders.

CINVs usually occur in two phases. The acute phase occurs within 1-2 hours after chemotherapy administration and may last up to 24 hours, while the delayed phase after 24 hours [4].

The mechanism of vomiting pathophysiology is mainly based on the release of serotonin from enterochromafilic cells in the gastric and intestinal mucosa. This process is induced by free radicals formed after chemotherapy. Serotonin interacts with 5-HT3 receptors located in the intestinal wall to stimulate the vomiting reflex. In addition, chemotherapeutic agents directly affect the receptors in the central nervous system, stimulating the center responsible for inducing vomiting [4, 18].

The basic principle of recommended antiemetic treatment is prophylaxis, based on taking an optimal dose of antiemetic drugs before the administration of chemotherapeutic. Due to the highest therapeutic index, the most commonly used antivomiting drugs are serotonin receptor antagonists (granisetron,

ondansetron, dolasetron, tropisetron). Drugs from this group act on 5-HT3 receptors, effectively suppressing the early phase of CINV [19]. Another group of drugs are NK-1 receptor inhibitors (aprepitant), used both for early and late vomiting. In case of aggressive chemotherapy regimens (cisplatin, decarbazin, high-dose cyclophosphamide), corticosteroids (dexomethasone) are used [20].

Mucositis

Oral and/or gastrointestinal mucositis is a frequent consequence of cancer treatment. The frequency of inflammatory symptoms is strongly dependent on the type and dose of drugs used. In 20-50% of patients undergoing standard doses of chemotherapy and 75% of patients on high dose chemotherapy, inflammation of mucous membranes is observed. Symptoms associated with mucositis reduce the quality of life of patients and may cause water-electrolyte disorders as a result of malnutrition and/or malabsorption. The intensification of these symptoms often makes it necessary to discontinue the planned treatment and reduces the chances of recovery [21].

In relation to mucositis, in addition to active treatment, prevention efforts aimed at reducing the risk of complications play are very important. Preventive measures include ensuring adequate nutrition, stopping the use of alcohol and tobacco, thorough treatment of lesions of the oral cavity and teeth before starting anticancer treatment, as well as maintaining proper oral and dental hygiene during therapy. In selected cases, non-steroidal anti-inflammatory drugs, antibiotics and antifungal agents are also used prophylactically [5].

The treatment of inflammatory changes primarily involves the administration of broad-spectrum or targeted antibiotics and antifungal medicines. In addition, analgesics, including opioids, benzidamines, glutamines and oral cryotherapy are also used [5, 21].

Cardiovascular disorders

Cardiovascular complications are a group of serious disorders resulting from chemotherapy in about 10% of patients [22]. They may contribute to increased morbidity and mortality in patients who have undergone oncological treatment. Symptoms of cardiovascular disease appear after a longer period of time, even several decades after anticancer treatment [23, 24]. Chemotherapy-related cardiotoxicity includes mainly myocardial dysfunction, left ventricular failure, ischaemic heart disease, arterial hypertension, coronary heart disease, cardiac arrhythmias, peripheral vascular diseases and stroke [23-25].

In order to reduce the risk of cardiovascular complications, every patient with planned chemotherapy should undergo meticulous cardiological evaluation. Prophylactic administration of drugs such as angiotensin-converting enzyme inhibitors and β-adrenolytic drugs in these patients is not justified. Only in cases of diagnosis of coexisting cardiovascular diseases should be used drugs appropriate for the specific disorder [22].

Pain treatment

During chemotherapy, pain affects 30-50% of patients. Later on, the disease affects up to 90% of patients. The aetiology of pain in these patients is very extensive. It is the result of complex pathological processes, including both cellular, tissue and systemic changes caused by the growing cancer tissue, changes associated with the progressive disease, disorders resulting from anticancer treatment, or coexisting diseases.

If analgesic therapy is appropriate in chemotherapy patients, it is very important to identify the factors that cause pain, determine the location and radiation of pain, pain intensity, also the factors that relieve and intensify it. The efficacy and tolerance of existing treatment should also be considered as well.

The Numerical Rating Scale (NRS) (Fig. 2) is currently the standard used to assess pain severity and monitor pain management efficacy [26].

0	1	2	3	4	5	6	7	8	9	10
no pain	mild pain			moderate pain			severe pain			worst possible pain

Fig. 2. The Numerical Rating Scale NRS.

It is assumed that in patients with effective analgesic management, the severity of pain measured using the NRS scale should be ≤ 3 [27, 28].

The treatment of pain in oncology is based on pharmacotherapy. The analgesic drug and dosage should be selected individually for each patient depending on the type of pain, in accordance with the analgesic ladder (Fig. 3) - defined by the WHO (World Health Organization) - a three-stage scheme of the intensity of pharmacological treatment depending on the level of pain perception [29, 30]. Every next step of the scheme represents a higher potential for analgesic effect.

severe pain
on the NRS scale: 7-10

Strong opioid drugs:
morphine, fentanyl, buprenorphine, oxycodone, methadone

± non-opioid analgesics
± koanalgetics

ineffectiveness of the drug
or increasing pain

moderate pain
on the NRS scale: 4-6

Weak opioid drugs:
codeine, tramadol, dihydrocodeine

± non-opioid analgesics
± koanalgetics

ineffectiveness of the drug
or increasing pain

minor pain
on the NRS scale: 1-4

Non-opioid analgesics:
paracetamol, metamizol, non-steroidal antiinflammatory drugs
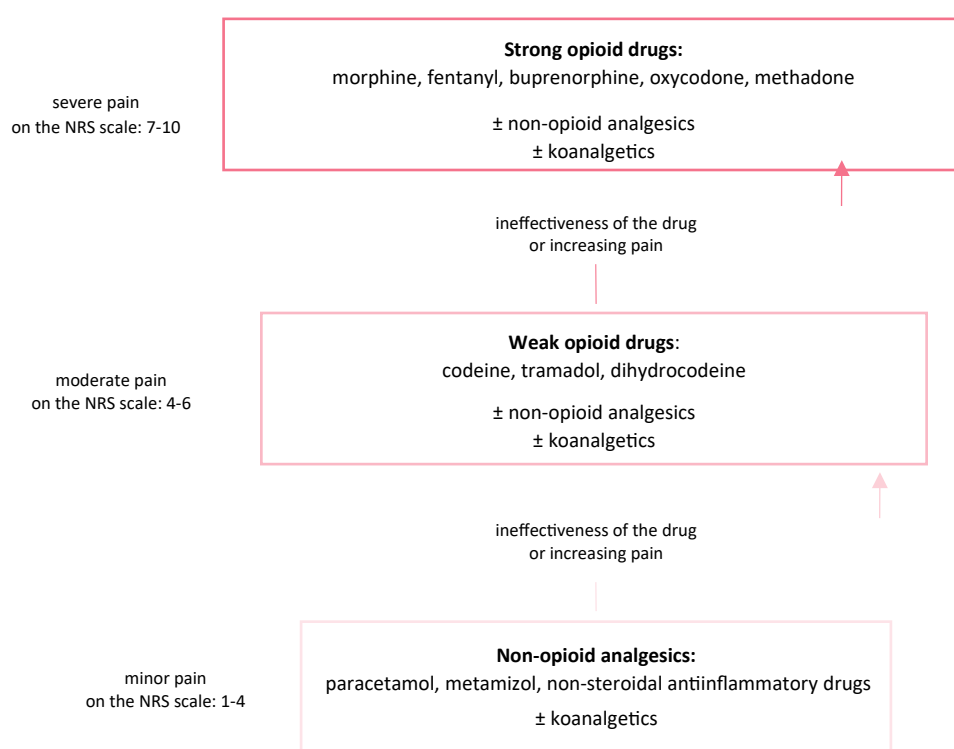
± koanalgetics

Fig. 3. The analgesic ladder defined by the WHO.

On each step of the analgesic treatment ladder we can include the coanalgesics (adjuvants). These drugs enhance the analgesic effect, and are also used to treat the side effects of medicines from other groups used in the treatment of pain. Coanalgesics are also effective in the therapy of neuropathic pain when the lack of efficacy of classical analgesics is observed [30, 31].

Summary

Complications occurring during or after chemotherapy are still a great challenge for modern medicine. It is very important that the treatment of oncological patient is carried out by a team of multidisciplinary doctors. The individualization of treatment and the introduction of combined therapy may significantly minimize the occurrence of many serious complications, and thus may affect not only the quality of patients' life, but also their life expectancy.

Acknowledgements

References

1. Radziwon P, Krzakowski M, Kalinka-Warzocha E, Zaucha R, Wysocki P, Kowalski D, et al. Anemia in cancer patients — Expert Group recommendations. 2017;3.
2. Dale D. Current management of chemotherapy-induced neutropenia: the role of colony-stimulating factors. Semin Oncol 2003;30:3-9.
3. Schiffer CA, Bohlke K, Delaney M, Hume H, Magdalinski AJ, McCullough JJ, et al. Platelet Transfusion for Patients With Cancer: American Society of Clinical Oncology Clinical Practice Guideline Update. J Clin Oncol 2018;36:283-299.
4. Rapoport BL. Delayed Chemotherapy-Induced Nausea and Vomiting: Pathogenesis, Incidence, and Current Management. Front Pharmacol 2017;8.
5. Rubenstein EB, Peterson DE, Schubert M, Keefe D, McGuire D, Epstein J, et al. Clinical practice guidelines for the prevention and treatment of cancer therapy-induced oral and gastrointestinal mucositis. Cancer 2004;100:2026-46.
6. Busti F, Marchi G, Ugolini S, Castagna A, Girelli D. Anemia and Iron Deficiency in Cancer Patients: Role of Iron Replacement Therapy. Pharmaceuticals 2018;11.
7. Bormanis J, Quirt I, Chang J, Kouroukis CT, MacDonald D, Melosky B, et al. Erythropoiesis-stimulating agents (ESAs): do they still have a role in chemotherapy-induced anemia (CIA)? Crit Rev Oncol Hematol 2013;87:132-9.
8. de Putter R, Geboes K, De Man M, Van Belle S. Treatment of anemia in patients with solid tumors receiving chemotherapy in palliative setting: usual practice versus guidelines. Acta Clin Belg 201;73:251-256.
9. Benichou C, Solal Celigny P. Standardization of definitions and criteria for causality assessment of adverse drug reactions. Drug-induced blood cytopenias: report of an international consensus meeting. Nouv Rev Fr Hematol 1991;33:257-62.
10. Soff J, Bussel J. TPO-mimetics for chemotherapy-induced thrombocytopenia: timing matters. Leuk Lymphoma 2018:59:2763-2764.
11. Zhang X, Chuai Y, Nie W, Wang A, Dai G. Thrombopoietin receptor agonists for prevention and treatment of chemotherapy-induced thrombocytopenia in patients with solid tumours. Cochrane Database Syst Rev 2017;11:Cd012035.
12. Wilde MI, Faulds D. Oprelvekin: a review of its pharmacology and therapeutic potential in chemotherapy-induced thrombocytopenia. BioDrugs 1998;10:159-71.
13. Lyman GH, Allcott K, Garcia J, Stryker S, Li Y, Reiner MT, Weycker D. The effectiveness and safety of same-day versus next-day administration of long-acting granulocyte colony-stimulating factors for the prophylaxis of chemotherapy-induced neutropenia: a systematic review. Support Care Cancer 2017;25:2619-2629.
14. Heit JA, Silverstein MD, Mohr DN, Petterson TM, O'Fallon WM, Melton LJ. Risk factors for deep vein thrombosis and pulmonary embolism: a population-based case-control study. Arch Intern Med 2000;160:809-15.
15. Singh G, Rathi AK, Singh K, Sharma D. Venous thromboembolism in cancer patients - magnitude of problem, approach, and management. Indian J Cancer 2017:54:308-312.
16. Ay C, Pabinger I, Cohen AT. Cancer-associated venous thromboembolism: Burden, mechanisms, and management. Thromb Haemost 2017;117:219-230.
17. Donnellan E, Khorana AA. Cancer and Venous Thromboembolic Disease: A Review. Oncologist 2017;22:199-207.
18. Navari RM. The safety of antiemetic medications for the prevention of chemotherapy-induced nausea and vomiting. Expert Opin Drug Saf 2016;15:343-56.
19. Aapro M. 5-HT(3)-receptor antagonists in the management of nausea and vomiting in cancer and cancer treatment. Oncology 2005;69:97-109.
20. de Wit R, Herrstedt J, Rapoport B, Carides AD, Carides G, Elmer M, et al. Addition of the oral NK1 antagonist aprepitant to standard antiemetics provides protection against nausea and

vomiting during multiple cycles of cisplatin-based chemotherapy. J Clin Oncol 2003;21:4105-11.

21. Clarkson JE, Worthington HV, Furness S, McCabe M, Khalid T, Meyer S. Interventions for treating oral mucositis for patients with cancer receiving treatment. Cochrane Database Syst Rev 2010;Cd001973.

22. Perez IE, Taveras Alam S, Hernandez GA, Sancassani R. Cancer Therapy-Related Cardiac Dysfunction: An Overview for the Clinician, Clin Med Insights Cardiol 2019;13.

23. Curigliano G, Cardinale D, Suter T, Plataniotis G, de Azambuja E, Sandri MT, et al. Cardiovascular toxicity induced by chemotherapy, targeted agents and radiotherapy: ESMO Clinical Practice Guidelines. Ann Oncol 2012;23(7):155-66.

24. Curigliano G, Cardinale D, Dent S, Criscitiello C, Aseyev O, Lenihan D, et al. Cardiotoxicity of anticancer treatments: Epidemiology, detection, and management. CA Cancer J Clin 2016;66:309-25.

25. Ewer MS, Lippman SM. Type II chemotherapy-related cardiac dysfunction: time to recognize a new entity. J Clin Oncol 2005;23:2900-2.

26. Breivik H, Borchgrevink PC, Allen SM, Rosseland LA, Romundstad L, Hals EK, et al. Assessment of pain. Br J Anaesth 2008;101:17-24.

27. Chien CW, Bagraith KS, Khan A, Deen M, Strong J. Comparative responsiveness of verbal and numerical rating scales to measure pain intensity in patients with chronic pain. J Pain 2013;14:1653-62.

28. Hjermstad MJ, Fayers PM, Haugen DF, Caraceni A, Hanks GW, Loge JH, et al. Studies comparing Numerical Rating Scales, Verbal Rating Scales, and Visual Analogue Scales for assessment of pain intensity in adults: a systematic literature review. J Pain Symptom Manage 2011;41:1073-93.

29. Ripamonti CI, Santini D, Maranzano E, Berti M, Roila F. Management of cancer pain: ESMO Clinical Practice Guidelines. Ann Oncol 2012;23(7):139-54.

30. Wordliczek J, Kotlinska-Lemieszek A, Leppert W, Woron J, Dobrogowski J, Krajnik M, et al. Pharmacotherapy of pain in cancer patients - recommendations of the Polish Association for the Study of Pain, Polish Society of Palliative Medicine, Polish Society of Oncology, Polish Society of Family Medicine, Polish Society of Anaesthesiology and Intensive Therapy and Association of Polish Surgeons. Pol Przegl Chir 2018;90:55-84.

31. Forbes K. Pain in patients with cancer: the World Health Organization analgesic ladder and beyond, Clin Oncol (R Coll Radiol) 2011;23:379-80.