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### Principles of chemotherapy

Elisabeth Åvall Lundqvist

Department of Oncology, Radiumhemmet, Karolinska University Hospital, Stockholm, Sweden

#### 1. Introduction

Chemotherapy plays a major role in the treatment of patients with gynecological malignancies. In general, chemotherapy has a smaller therapeutic window compared with drugs of other types; hence, the potential for severe adverse effects associated with chemotherapy has made appropriate patient and drug selection critical.

Before initiating treatment of any patient with a chemotherapeutic agent, the following issues should be considered:

##### Tumor characteristics:

- The primary malignant diagnosis should be verified histologically.
- The first recurrence should be verified preferably by cytology or histology. (Ideally, recurrent disease should be verified by cytology or preferably histology; it is acknowledged that this is not always possible especially in ovarian cancer.)
- The extent of disease.
- The likelihood of tumor response (e.g. type of cancer, rate of disease progression).

##### Patient characteristics:

- The patient's age.
- The patient's general state of health (performance status).
- Comorbidities (such as heart, liver, and kidney diseases).
- Previous cancer treatments (response and adverse effects).
- The patient's psychosocial status.

##### Goals of treatment:

- Cure
- Tumor control to prolong survival.
- Palliation of symptoms.

Chemotherapy should only be given to patients with a verified malignant disease and specified type of cancer. It is advisable to verify the first relapse with cytology or histology since other primary tumors may develop. Before initiation of chemotherapy the goal of treatment should be clarified. If the treatment has a curative intention (e.g. ovarian germ cell tumors) even substantial adverse effects are acceptable if the probability of cure is high. When the goal of treatment is to reduce the tumor burden to alleviate symptoms (palliative intention), treatment should be chosen so that the probability of severe adverse effects is small. In these cases, the patient-reported adverse effects should not be worse than the symptoms of disease.

Physicians who treat patients with chemotherapy need to have knowledge of tumor biology, cellular kinetics, pharmacodynamics, kinetics, and drug resistance. Tumor cells use the same pattern for cellular division and growth as normal cells and studies indicate that cell division does not occur more rapidly in cancer than in normal cells. The reason for the uncontrolled cell growth seems

to be due to loss of normal cell-cycle regulation and failure of programmed cell death (apoptosis). The time it takes for a tumor mass to double its size is referred to as the doubling time. Animal studies indicate that tumors grow exponentially when they are very small, but the rate of cancer growth slows as the tumor size increases (Gompertzian growth). There is limited information concerning the doubling time in human tumors, but in general embryonal tumors have a short doubling time (20–40 days) while adenocarcinomas and squamous cell carcinomas have relatively slower doubling times (50–150 days).

Chemotherapeutic agents have several mechanisms of action and affect cancer cells in a wide variety of ways. In general, cancer cells that are actively moving through the different phases of the cell cycle are highly chemosensitive, while cells in a resting state (G0) are relatively insensitive. Tumors consisting of cancer cells that are rapidly proliferating are therefore more responsive to chemotherapy. Patients with slowly progressive disease can live many years but, in general, their tumors are less sensitive to chemotherapy because the majority of tumor cells at each treatment cycle are in a resting phase. According to the log-kill principle, chemotherapeutic agents only kill a constant fraction of cells rather than a specific number of cells. A consequence of this hypothesis is that the chemotherapy dose should not be reduced in the case of a small tumor burden.

#### 2. Minimum requirements

##### 2.1. Administration of chemotherapy

Health professionals who prescribe, administer, and/or supervise the administration of chemotherapy should be qualified to administer chemotherapy and have acquired skills to manage its adverse effects. The administration of chemotherapy should comply with national requirements concerning occupational safety and health.

Chemotherapy can be dangerous to professionals, patients, and next of kin owing to its mutagenic, teratogenic, and carcinogenic capacity. There is also a risk of direct skin irritation or damage in case of spill. Preparation of the drugs must be performed in areas with special ventilation systems. Appropriate clothing including special gloves and gowns should be worn when preparing and administering the drugs. Separate containers to dispose of the materials used when mixing and giving the drugs are needed. The patient should be appropriately monitored and all procedures documented in writing. At the facility providing systemic chemotherapy medications, treatment of anaphylaxis should be immediately available and the staff should be trained in cardiopulmonary resuscitation. Extravasation of a chemotherapeutic agent acting as a vesicant (e.g. anthracyclines)

can cause severe tissue necrosis and calls for surgical intervention. Awareness of extravasation and improved infusion techniques through a free-flowing intravenous line and careful monitoring are important preventive measures.

Adverse effects, weight, changes in performance status, and appropriate laboratory tests should be assessed and documented before each cycle. Quantification of adverse effects is usually done by employing toxicity scales such as the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) [1]. Adding patient-reported outcome measures (PROM) may improve the accuracy of the assessment [2]. Patient education concerning adverse effects and their intervention should be regarded as part of treatment. Chemotherapy administration safety standards have been published recently by the American Society of Clinical Oncology (ASCO)/Oncology Nursing Society [3].

### 2.2. Minimum laboratory back-up requirements to administer chemotherapy

Immediate access to a laboratory facility is needed to receive reports on at least a complete blood count (erythrocytes, leucocytes, platelets, neutrophils) and a creatinine blood test.

## 3. Common adverse effects and how they are managed

Chemotherapy-induced adverse effects are most commonly caused by damage of rapidly dividing normal cells, such as bone marrow cells, cells lining the gastrointestinal and reproductive tracts, as well as cells of hair follicles. Most chemotherapy drugs affect all these types of cells, but to varying degrees depending on, for example, the drug, dose, route of administration, and patient characteristics. Genetic variants of liver enzymes involved in drug metabolism probably account for some of the observed inter-individual differences of adverse effects, but have yet to reach clinical application.

### 3.1. Hypersensitivity reactions

Most drug reactions are mild and appear during infusion in the form of hot flushes, rash, and back pain. True allergic reactions are often more severe (e.g. shortness of breath, edema, blood pressure changes) and can even be life-threatening (anaphylaxis with cardiovascular collapse). Drugs that are more often associated with hypersensitivity reactions in the treatment of gynecological malignancies are platinum, liposomal doxorubicin, and taxanes. Despite appropriate premedication, reactions may occur during infusion with taxanes. These reactions tend to occur during the first cycles of treatment. Infusion reactions can often be treated by stopping the infusion and restarting at a slower rate. Hypersensitivity reactions associated with platinum agents occur more often during later cycles or following re-exposure, and are more often severe. Consider consultation with an allergist before rechallenge. Desensitization may be considered unless life-threatening reactions have occurred. Preparation for a possible hypersensitivity reaction should be made each time a patient is infused with chemotherapy. More specific guidelines are readily assessable, for example, the National Comprehensive Cancer Network guidelines ([www.nccn.org](http://www.nccn.org)).

### 3.2. Bone marrow/blood cells

The bone marrow is the most common site for chemotherapy-induced adverse effects. Neutropenia usually occurs 7–10 days after treatment and during these periods there is an increased risk for infectious complications. The incidence of febrile neutropenia is relatively low when using standard chemotherapy for gynecologic

malignancies. In general, there is no indication for the prophylactic use of granulocyte colony-stimulating factors (G-CSFs). In case of treatment delays due to neutropenia, the appropriate management should take the goal of the treatment into account. To keep the course interval intact, dose reduction and/or the use of prophylactic G-CSFs may be appropriate. International guidelines for G-CSF administration are readily available [4,5].

The use of erythropoiesis-stimulating agents (ESAs) to treat chemotherapy-induced anemia is debatable because of an increased risk of thromboembolic events and the association with shorter survival. However, the mechanism behind the observed association between ESAs and shorter survival in cancer patients is unclear. It is also unknown whether all patients are at risk for being harmed. ASCO guidelines recommend that ESAs may be a treatment option for patients undergoing myelosuppressive chemotherapy who have hemoglobin levels less than 10 g/dL [6]. However, the potential harms and benefits of ESAs (e.g. decreased transfusions) need to be carefully discussed with the patient, and compared with the potential harms (e.g. infections, immune-mediated adverse reactions) and benefits (e.g. rapid hemoglobin improvement) of blood transfusions.

The onset and recovery of thrombocytopenia is slightly later compared with neutropenia. There is an increased risk of hemorrhagic complications when platelet counts drop to less than 50 000/mm<sup>3</sup> and there is a particularly high risk of spontaneous bleeding once the platelet count is less than 10 000/mm<sup>3</sup>. Thrombocytopenia can be a challenging clinical problem to treat. Platelet transfusions can provide temporary relief, but often thrombocytopenia involves dose reductions or treatment delays.

### 3.3. Nausea and vomiting

Patients rate nausea/vomiting as one of the most distressing adverse effects following chemotherapy. The incidence and severity of chemotherapy-induced nausea/vomiting are affected by several factors, including the specific chemotherapeutic agents used, as well as dosage, schedule, and route of administration. The risk is increased among women and patient-related factors such as age under 50 years; previous motion sickness and/or morning sickness during pregnancy; prior chemotherapy emesis or anesthesia emesis; and anxiety. Alcoholism decreases the risk of emesis. Chemotherapy-induced nausea/vomiting is classified as acute or delayed. Acute-onset emesis usually occurs within a few minutes to several hours and commonly resolves within the first 24 hours after drug administration. Delayed-onset emesis develops more than 24 hours after chemotherapy administration and generally peaks 48–72 hours after administration. Depending on the specific chemotherapy used, it can last for up to 7 days.

The goal of antiemetic therapy is to prevent nausea/vomiting; therefore, antiemetic therapy should be initiated before chemotherapy administration. The choice of antiemetic used is based on the emetogenic potential of the chemotherapy, prior experience with antiemetics, and patient risk factors. The emetogenicity of chemotherapy is classified in 4 categories according to the percentage of patients not receiving antiemetic prophylaxis who experience acute emesis: highly emetogenic agents (≥90% risk of acute emesis); moderately emetogenic agents (30%–90% risk); low emetogenic agents (10%–30% risk); and minimal emetogenic agents (<10% risk). ASCO guidelines for the use of antiemetics have recently been updated [7]. The key recommendation for patients receiving highly emetic chemotherapy regimens is a 3-drug combination of neurokinin 1 (NK1) antagonist, serotonin 5-HT<sub>3</sub> receptor antagonist, and dexamethasone. For moderate emetic regimens, the recommendation is a 2-drug combination of palonosetron and a corticosteroid. If palonosetron is not available, it may be substituted by a first-generation 5-HT<sub>3</sub> antagonist. A single

8-mg dose of dexamethasone before chemotherapy is suggested for low emetogenic chemotherapy agents and no routine prophylactic antiemetics are recommended for minimal emetogenic agents. For patients receiving combination chemotherapy, antiemetic treatment is chosen according to the agent with the highest degree of emetic risk. Oral and intravenous 5-HT<sub>3</sub> antagonists have equivalent efficacy when used at appropriate doses. For selected patients unable to swallow, the transdermal route may be of value. For patients with anticipatory emesis (occurring before the patient receives chemotherapy), the most active antiemetic regimens appropriate for the chemotherapy used should be chosen initially. If anticipatory emesis occurs, behavioral therapy is suggested. The incidence of anticipatory emesis varies between 18%–57%, and nausea is more common than vomiting.

Acupuncture point stimulation may be of some benefit [8], especially if modern antiemetic drugs are not available. Electroacupuncture may reduce chemotherapy-induced acute vomiting. Self-administered acupressure can be taught to patients to help protect against acute nausea, but no effect has been demonstrated for acute vomiting or delayed emesis. In addition, adjustment of eating habits, such as small frequent meals, may alleviate nausea/vomiting. Other potential causes of emesis also need to be considered, such as bowel obstruction, dyspepsia, brain metastasis, electrolyte imbalance, and uremia.

Patients treated with chemotherapy may experience weight loss due to loss of appetite, changes to sense of taste (e.g. metallic), sore mouth, diarrhea, and constipation. Contributing factors may be pain, psychological factors, and poor performance status. Weight should be monitored before each chemotherapy cycle. In case of weight loss exceeding more than 10% for adults, appropriate investigation and directed therapy should be initiated and a dietary consultation is recommended.

### 3.4. Alopecia

Hair loss, or the fear of it, is one of the most troublesome adverse effects of chemotherapy. Many chemotherapy agents do not induce complete hair loss, but make the hair thin, fragile, and easily broken. The effects usually begin within 2–3 weeks after initial chemotherapy, but for taxanes, which often lead to complete alopecia, onset is quicker. Hair grows back after treatment in almost all cases, and a full head is seen after 3–6 months. During regrowth, the hair may have altered color and structure. Proper pretreatment information about the risk of hair loss, prescription of wigs when appropriate, and tips for headwear and creation of new eyebrows and lashes may be helpful and provide a feeling of control. There is some evidence that scalp cooling can reduce hair loss during treatment with some chemotherapy agents [9]. However, it should not be used if there is a high risk of cancer cells surviving in the blood vessels of the scalp, such as certain hematological malignancies.

### 3.5. Peripheral neuropathy

Chemotherapy-induced peripheral neuropathy is a major dose-limiting adverse effect of chemotherapy drugs commonly used in gynecological malignancies, such as platinum and taxane. Peripheral neuropathy typically occurs in 30%–40% of patients and can begin during or after the end of treatment. The symptoms, including pain, numbness/tingling, sensory loss, and functional impairment, are often only partially reversible and the neuronal damage can be permanent. The risk of peripheral neuropathy is related to the chemotherapeutic drug, cumulative dose, and the concomitant use of several neurotoxic agents. The risk is also associated with patient characteristics such as age and pre-existing neuropathy (e.g. alcohol, diabetes induced, vitamin B12

deficiency, and hypothyroidism). There is currently no evidence-based pharmacological agent that can efficiently prevent or treat chemotherapy-induced peripheral neuropathy [10]. Therefore, early detection of symptoms before they interfere with function and activities of daily life is the best way to prevent the condition becoming disabling. Dose modification or even withdrawal of taxane may be necessary in platinum–taxane combination therapy. Patient needs include appropriate shoes and awareness of potential hand and foot injuries due to reduced neurosensitivity.

### 3.6. Sexual dysfunction, reproduction, and pregnancy

Sexual dysfunction is a common and distressing problem among women treated for gynecological malignancies. The reason is multifactorial and includes decreased interest in sex and physical problems such as dyspareunia and vaginal dryness. Although treatment-induced sexual dysfunction is caused mainly by previous surgery and/or radiotherapy, chemotherapy can affect the vaginal mucosa leading to dryness and superficial bleeding. In addition, vaginal infections such as fungus or herpes may be reactivated. Sexual dysfunction needs to be actively addressed and management may include lubricants, hormone replacement therapy, vaginal dilators, and sexual counseling when appropriate. Patient education is important and should include information that there is no medical reason for not engaging in sexual activity during the chemotherapy treatment period.

The risk of chemotherapy-induced permanent ovarian insufficiency and infertility depends on patient age, drug dose, and specific chemotherapeutic agent. The risk increases from 30 years of age and is pronounced among women older than 40 years, especially after treatment with alkylating agents. Women younger than 30 years who receive platinum-based chemotherapy will often have temporary amenorrhea, but ovarian function commonly recovers. It is important that patients use effective contraception during and up to 1 year after completion of chemotherapy. Women who have not completed childbearing and are at risk of infertility should discuss germ cell preservation options with the medical team. The research field within female fertility preservation is rapidly changing, and no longer results in a significant delay in the initiation of cancer treatment.

Chemotherapy has potential mutagenic, teratogenic, and carcinogenic effects for the embryo depending on chemotherapy agent, dose, and gestational stage. Gynecologic cancer during pregnancy is challenging and should be managed by a multidisciplinary team. Both the maternal prognosis and the risk for the fetus need to be taken into account. Chemotherapy should be avoided during the first trimester but selective agents, such as platinum, can be administered with reasonable safety during the second and third trimester without an excessive increased risk for the fetus [11,12]. Delivery should be postponed preferably until after 35 weeks of pregnancy. However, long-term follow-up is limited and prospective studies are lacking. Breastfeeding should be avoided during chemotherapy treatment.

### 3.7. Other adverse effects

Some of the chemotherapy agents that are used to treat gynecological malignancies are recognized for their potential nephrotoxic effects. These are cisplatin, ifosfamide, cyclophosphamide, and methotrexate. Renal function should be monitored before every cycle and adequate hydration given before and after treatment to maintain adequate diuresis. Mannitol should be administered if indicated. Cognitive impairment and fatigue are other more general adverse effects that can affect women during and after chemotherapy.

Healthcare professionals should be educated and trained in assessing and managing adverse effects. Patient and next of kin education about the acute and late adverse effects of chemotherapy should be an integral part of cancer treatment. Cancer rehabilitation should start at cancer diagnosis.

### Conflict of interest

The author has no conflicts of interest to declare.

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