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Oncological emergencies associated with gastrointestinal tumors

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Abstract

Oncological emergencies are defined as acute life-threatening conditions in cancer patients either as a result of the malignancy or as a result of its treatment. In this review, we focus on oncological emergencies associated with gastrointestinal tumors. They can be categorized by their system of origin as hematologic, neurologic or metabolic. Furthermore, we discuss mechanical emergencies such as intestinal obstruction and vena cava superior syndrome as well as acute gastrointestinal bleeding and pulmonary embolism. The patients' performance status as well as prognosis are essential during decision making for optimal treatment.

Keywords Emergency, digestive oncology, oncological emergency

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Introduction

Worldwide, cancer is the second leading cause of death and in the coming years it will probably surpass heart diseases as leading cause of death [1]. The number of some cancer cases such as small intestine, anal, liver and pancreatic cancer is still rising due to either behavioral trends (for example smoking and excess body weight) or increased detection of asymptomatic disease [1], while the incidence of other cancers such as colon cancer is decreasing thanks to the increased use of screening colonoscopy with the removal of precancerous polyps [2]. In most gastrointestinal (GI) tumor cases there has been improvement in survival rates, however for pancreatic cancer survival is still very disappointing mainly because most cases are detected at advanced stage [3].

In metastatic cancer patients, chemotherapy is being used to prolong overall survival. In colon cancer for example, median overall survival is prolonged up to more than 2 years when treated with chemotherapy and targeted agents compared to only 6 months when only best supportive care is applied [4]. The longer survival of cancer patients in combination with the increased use of different chemotherapeutic agents with potential life-threatening side effects implies that physicians working in an emergency unit need to be aware of potential oncological emergencies in order to prevent or overcome them.

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Cancer patients are at risk of a wide range of medical emergencies either related to the patient's tumor or to its treatment. Occasionally, these emergencies are the presenting symptom of a newly diagnosed cancer.

In this review we will give an overview of most common oncologic emergencies in GI Oncology as well as their treatment. While some emergencies such as bleeding and intestinal obstruction are more common in GI Oncology, we decided to describe also the less frequent emergencies associated with GI tumors, as their incidence is rising due to the longer survival of cancer patients.

Hematological emergencies

Neutropenic fever (NF)

NF is defined as fever in a neutropenic patient either one episode of above 38.3°C or a temperature above 38°C sustained for more than 1 h [5]. The definition of neutropenia is not uniform but neutropenia is usually defined as an absolute neutrophil count (ANC) below 1000 cells/μL and severe neutropenia as <500 cells/μL or an ANC that is expected to decrease below 500 cells/μL [5]. Although mortality from NF has decreased, it still remains significant with a 5% mortality rate in high-risk and 1% in low-risk patients [6]. Most patients with GI tumors treated with chemotherapy are expected to be neutropenic (<500 cells/μL) for ≤7 days which makes them less at risk for complications [5]. However, patients with comorbidities such as pulmonary and cardiovascular diseases and patients with hepatic or renal dysfunction are considered high risk for complications requiring hospitalization, regardless of the duration of neutropenia. The Multinational Association for Supportive Care in Cancer (MASCC) has developed a MASCC risk index, which is a validated tool for

estimating the risk for NF-related complications [7]. Patients with NF with a MASCC score ≥21, without clinical alarm signs, can be safely managed in the outpatient setting and are treated with a combination of oral fluoroquinolones and amoxicillin/clavulanate [8]. An alternative is the use of oral moxifloxacin [9]. High-risk patients with NF require hospitalization and treatment with intravenous antibiotics. It is important that antibiotics are started within 1 h from NF diagnosis after taking blood and urine cultures. The source of infection is only identified in about 20% of patients and most of the identified infections are believed to arise from the endogenous flora. In high-risk patients fungal pathogens are also more common than in low-risk patients. The use of colony stimulating factors (CSF) did not show any effect on the overall survival, but induced a faster recovery from fever and shorter hospital stay [10]. Most guidelines do not recommend the use of CSF for the management with NF except in patients with high-risk features such as older age, pneumonia, hypotension, sepsis and being hospitalized at the time of development of fever [11].

Neutropenic enterocolitis (NE, typhlitis)

NE is a life-threatening condition caused by mucosal injury by chemotherapy in combination with profound neutropenia and impaired host defense to invasion by microorganisms [12]. The syndrome is most often associated with hematological malignancies but can also occur in patients with solid tumors receiving chemotherapy. The cause of death in these patients is usually sepsis and mortality rate is extremely high. NE must be considered in all severely neutropenic patients with fever and abdominal pain (usually right lower quadrant). A CT scan can reveal the characteristic findings such as bowel wall thickening, bowel dilatation, pneumatosis coli and mesenteric stranding. Treatment consists of broad-spectrum antibiotics (ex. piperacillin-tazobactam), nasogastric suction as well as fluid and nutritional support. In case of perforation, abscess formation or persistent bleeding, surgery is the only option.

Disseminated intravascular coagulation (DIC)

DIC is a potentially life-threatening condition, characterized by an abnormal activation of coagulation and fibrinolysis leading to thrombosis and hemorrhage simultaneously [13]. It occurs in a variety of diseases, including cancer [14]. About 10-15% of metastatic cancer patients have some evidence of DIC. It is mostly associated with acute leukemia, but can also occur in mucinous tumors such as pancreatic and gastric cancer [15]. Some patients have only a mild clinical course with consumption of coagulation factors while others present with life-threatening bleeding. Treatment consists of treating the underlying cause in combination with supportive measures such as hemodynamic support, hydration and transfusion.

Neurological emergencies

Spinal cord compression (SCC)

SCC occurs in approximately 5% of cancer patients and is most often due to extradural spread from vertebral metastases [16]. It can cause pain and irreversible loss of neurologic function. Although all tumors can cause SCC, it most often occurs in patients with cancers with a tendency to metastasize to the spinal column such as breast cancer, lung cancer, lymphoma, prostate cancer and myeloma [17]. In tumors of the digestive tract SCC is rather rare, for example only 2% of all cases with SCC had colorectal cancer as a primary tumor [17]. However, because of the increased overall survival of colon cancer patients due to the recent advances in the treatment of systemic disease and because of the poor delivery of chemotherapeutic drugs across the blood-brain barrier, chances to develop SCC secondary to vertebral metastases are likely to rise.

Pain is usually the first symptom of SCC and precedes neurologic symptoms. Prompt diagnosis and immediate treatment might impact neurological outcome. MRI is the preferred imaging modality to diagnose SCC. Treatment consists of administration of glucocorticoids [18] followed by either surgery and/or radiotherapy depending on the presence of spinal instability, radiosensitivity of the tumor and degree of SCC.

Brain metastases

Due to advances in the efficacy of systemic chemotherapy, there is an increase in the incidence of brain metastases as patients with metastatic cancer have an improved overall survival the last decades [19]. Still, in most GI tumors, such as for example colon cancer, incidence of brain metastases remains low. The clinical features of brain metastases are very variable, but most patients develop symptoms related to increased intracranial pressure, such as headache in combination with nausea and vomiting. A smaller percentage (15%) of patients develops seizures or focal neurologic dysfunction [20]. The manifestation of symptoms depends on the localization of the metastases. In rare cases patients present with stroke caused by a hemorrhage in metastases or embolization of tumor cells. For diagnosis, contrast-enhanced MRI is the preferred imaging study. Patients with signs of increased intracranial pressure should be treated with intravenous corticosteroids. Further treatment depends on the patients overall prognosis. In patients with limited extracranial disease and chemotherapeutic options, brain surgery and/or radiotherapy (whole brain or stereotactic) can be indicated. Systemic therapy is generally not adequate for brain metastases although the blood-brain barrier is not always impermeable as it is sometimes disrupted. Thus, in case of no other options and when the tumor is still chemosensitive, systemic therapy can be an option in those patients.

Some patients also develop leptomeningeal carcinomatosis, which can be confirmed by either imaging and/or evaluation of cerebrospinal fluid. The prognosis of these patients is very poor with a survival of only a few months. Sometimes intrathecal chemotherapy is given, although its superiority to systemic chemotherapy has never been established in clinical trials especially in patients with GI tumors and can therefore only be recommended in selected cases.

Mechanical emergencies

Superior vena cava (SVC) syndrome

SVC syndrome results from a mechanical obstruction of the blood flow through the SVC. This can be caused either by external compression of the SVC by an adjacent tumoral process or by thrombosis within the SVC. Although most commonly SVC syndrome is caused by lung cancer (75% of cases) and non-Hodgkin lymphoma it can rarely also occur in other solid tumors with mediastinal lymph node metastases [21]. The symptoms of facial swelling, dyspnea and distended neck veins depend upon the rate at which obstruction of the SVC occurs and thus the time for development of venous collaterals. In case of airway obstruction of laryngeal edema urgent treatment is indicated. Chest CT is the mainstay of diagnosis. Treatment depends upon the type of cancer, prognosis and whether or not the patient was already pretreated. In case tumors present with SVC syndrome, a histological diagnosis is obligatory to define the best treatment plan. In chemotherapynaïve patients in whom a rapid clinical response is expected (for example germ cell tumors or lymphoma), chemotherapy can be the first choice. In other patients, either radiotherapy or endovenous stenting are valuable alternatives. Corticosteroids are often used in conjunction with radiotherapy to decrease edema. When SVC syndrome is caused by an extensive thrombosis, either catheter-directed thrombolysis or mechanical thrombectomy is the preferred choice of treatment [22].

Intestinal obstruction

GI tumors can often cause mechanical small bowel obstruction either by intrinsic or extrinsic compression. Especially some tumors, e.g. located in the colon, pancreas and stomach, are more likely to disseminate in the peritoneum and subsequently cause mechanical obstruction. Tumors can also impair bowel motility by invasion of the celiac plexus. There are no guidelines on the role of palliative surgery versus medical management. However, we feel that in the absence of urgent indications for surgery (such as perforation, bowel infarction), preference should be given to medical treatment including GI decompression using a nasogastric tube, adequate hydration and controlling nausea and vomiting. A randomized, doubled blind, placebo-controlled phase III study also showed efficacy of the somatostatin analog lanreotide in patients with inoperable bowel obstruction resulting from peritoneal carcinomatosis [23]. Palliative surgery should only be considered in selected patient with limited metastatic disease. In most metastatic cancer patients palliative surgery is associated with high mortality [24]. In cases with isolated gastric outlet or colonic obstruction, endoscopic stent placement should be considered although there is a risk of stent migration, re-occlusion or bowel perforation.

Acute GI bleeding

Bleeding is a frequent complication of GI tumors and may result from tumor invasion, treatment response, vessel damage or from systemic processes such as DIC. Patients can present with either hematemesis or melena. Risk factors include the use of chemotherapeutic agents which can cause hematological toxicity such as thrombopenia and the use of anti-angiogenic agents such as sunitinib and bevacizumab, associated with increased bleeding tendency [25]. In patients with a hepatocellular carcinoma, spontaneous rupture can occur resulting in hemoperitoneum and hemorrhagic shock. Predisposing factors are subcapsular location, large size of the tumor, portal hypertension, and tumor necrosis [26]. Furthermore, a lot of cancer patients are treated with low molecular weight heparins due to an increased risk of thrombosis, which on the other hand can increase the risk of bleeding.

The treatment needs to be individualized depending on the underlying cause and risk benefit ratio of the treatment. Endoscopic interventions, involving the injection of sclerosing agents into the bleeding vessels, are an option when feasible. Often, however, there is diffuse bleeding of the tumor which cannot be stopped by local injection (Fig. 1). In these cases palliative hemostatic radiotherapy can be considered. Emergency surgery or transcutaneous arterial embolization can be considered but only in selected cases.

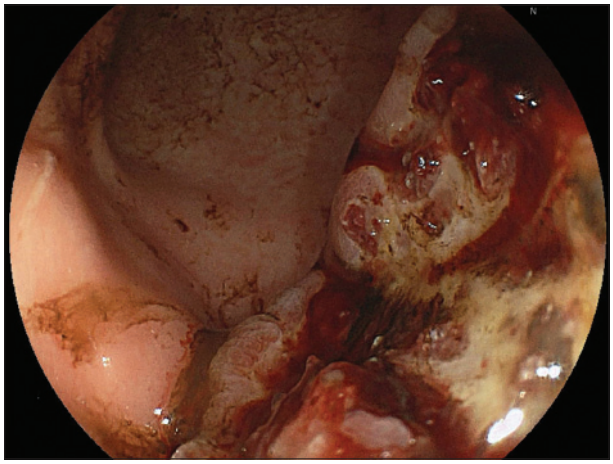

Figure 1 Endoscopic image of an ulcerating and diffuse bleeding adenocarcinoma of the stomach

Metabolic emergencies

Hypercalcemia

Hypercalcemia is the most common metabolic emergency in cancer patients, occurring in approximately 20-30% of patients [27]. Most common tumor types associated with hypercalcemia are breast, kidney and lung cancer, and multiple myeloma, although it also occurs in digestive tumors such as esophageal cancer [28]. Patients with hypercalcemia of malignancy often have a bad prognosis. Hypercalcemia occurs either by osteolytic metastases or by tumor production of calcitriol (1,25-dihydroxyvitamin D) or parathyroid hormone-related peptide. Clinically, patients are often asymptomatic until reaching high levels. Then neurologic changes occur such as fatigue, muscle weakness, stupor and coma. Hypercalcemia may also cause cardiac abnormalities such as arrhythmias, heart block and even cardiac arrest [29]. GI symptoms include anorexia, nausea, vomiting, ileus, constipation, and, in rare cases, pancreatitis. Often patients complain of polyuria and polydipsia due to inability of concentrating the urine, and, as the hypercalcemia persists, progressive renal insufficiency occurs (caused by calcium deposits in the kidney).

Aggressive treatment should be initiated as quickly as possible depending on the severity of the hypercalcemia. In general, patients with calcium >14 mg/dL (3.5 mmol/L) require therapy with volume expansion with isotonic saline to maintain sufficient urine output. For short-term management (in the first 48 h), calcitonin can be used which increases renal calcium excretion an decreases bone resorption via interference with osteoclast function [30]. Furthermore, biphosphonates (preferably zoledronic acid) should be administered for longer term control of hypercalcemia [31], with a maximum effect after 2-4 days. Since bisphosphonates are potentially nephrotoxic, caution is warranted when used in patients with impaired renal function. Dose reduction in combination with adequate hydration may minimize the risk. As a last option, hemodialysis is an effective treatment.

Syndrome of inappropriate secretion of antidiuretic hormone (SIADH)

SIADH occurs in approximately 1-2% of cancer patients. It should be suspected in any cancer patient with hyponatremia in combination with hypo-osmolality and high urine osmolality. It results from ADH-induced retention of ingested water. Ectopic production of ADH by a tumor is most often associated with lung carcinoma (especially small cell) but can also occur in other tumors such as head and neck cancer and rarely in GI tumors such as esophageal, gastric, pancreatic, and colon cancer [32]. Antineoplastic drugs such as cisplatin are also well known to cause hyponatremia by a mechanism that may involve SIADH. Clinical symptoms depend on the level of hyponatremia and the rapidity of onset. Symptoms include changes in mental status, apathy, fatigue, headache, seizures and ultimately coma. Management involves control of the underlying tumor as well as fluid restriction of 500 mL to 1 L/day. In severe cases patients can be treated with hypertonic saline by slow infusion at a rate to increase the serum sodium level by 0.5-1.0 mEq/L/h. Sometimes isotonic saline is used as an alternative, however the electrolyte concentration of the administered fluid has to be greater than the concentration in urine, otherwise isotonic saline will not be effective and will even lead to further lowering of the serum sodium [33]. Loop diuretics are only recommended when urine osmolality is more than twice the plasma osmolality thereby increasing water excretion.

Pulmonary thromboembolism (PTE)

Patients with cancer are in a hypercoagulable state and thus more likely to develop venous thromboembolisms [34]. The risk is further increased by the administration of chemotherapy. Thrombotic events are even the second leading cause of death in cancer patients. The risk of thrombosis varies by cancer type and is especially high in pancreatic, gastroesophageal, brain, and lung cancer [35]. Acute PTE is very common in cancer patients, with a highly variable clinical presentation from no symptoms to shock or sudden death. The most common presenting symptom is dyspnea at rest. Treatment should focus on stabilizing the patient and start of anticoagulation, as untreated PTE is associated with a mortality of around 30%. The benefit of anticoagulation should always be weighed against the risks such as in patients with bleeding or with limited life expectancy. Low molecular weight heparins are the treatment of choice in cancer patients, especially when treated with chemotherapy. Newer oral anticoagulants have not been studied in cancer patients. When anticoagulation is contraindicated, such as in cases of bleeding or low platelets, the placement of a vena cava filter may be considered.

Concluding remarks

Cancer patients are at increased risk of a wide variation of medical emergencies, either by the effect of the tumor itself or by the antineoplastic treatment. The recognition of these emergencies by clinicians as well as the knowledge of their treatment is critical. Some emergencies occur more frequently in patients with GI tumors, such as bleeding and intestinal obstruction, while others are less frequent, but nevertheless important to recognize. Patients' performance status and prognosis are essential during decision making for optimal treatment.

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