

Emergency Department Management of the Cancer Patient, what we must do?

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Introduction

Medical advances have allowed that in the emergency services are met more frequently patients over 65 years and patients with chronic and devastating diseases such as cerebrovascular diseases and cancer. Epidemiology studies have shown that currently, cancer is the second leading cause of death worldwide. The increased prevalence of cancer is explained by three main factors: changes in diagnostic tests, advances in therapies for cancer and advances in diagnosis and treatment of co morbid conditions of patients. Owing to the advent of preventive strategies and early detection of disabling symptoms, the management of classic oncological emergencies has moved from the outpatient to the inpatient approach. It is mandatory that the physicians working in the emergency department become familiar with oncological diseases: Why would consult cancer patients? How the disease occurs? What its symptoms are? What it is the most practical and adequate way to reach a timely diagnosis? What are the side effects and complications of treatment and how address the family? All physicians working at the medical emergency services must be aware of the current evidence on diagnosis and treatment of the cancer patient, and they must develop skills in their care. According to WHO (World Health Organization) there are 11 million new cancer cases every year, about 80% occurring in developing countries and are related to living conditions in these countries. Of those, 30% are preventable. From 2000 to 2006 there were in Colombia 32,316 cases of cancer in men and 38,571 in women. The incidence rate, i.e., the probability of occurrence of a new diagnostic of cancer was of 186.6 and 196.6 per 100,000 inhabitants, respectively. According to WHO, approximately 71,442 new cases of

cancer are presented each year in Colombia? The most common are prostate, stomach, lung, breast, cervix and colon. Cancer incidence is estimated up to 33% in 2020 with an increasing prevalence [1].

Studies on cancer incidence in Colombia are based on three population groups: children, men and women. Leukaemia, tumors related to the central nervous system and lymphomas are the most common in children; prostate, stomach, lung, colon and rectum have the greatest incidence among men and breast, cervix, thyroid, stomach and colon are the most commonly found in women. It can be said that the cancers of stomach and colon are the most common throughout the whole population [2]. An emergency in a cancer patient usually is a severe life-threatening acute situation, directly or indirectly related to the tumour or its treatment and that can be prevented or effectively managed if promptly recognized and urgently treated. The differential diagnosis should include those emergencies that are unrelated to the cancer diagnosis. It must be remembered that an oncological emergency may be the first manifestation of a neoplasm. The subject will be develop by way of a series of questions with their answers. It will try to solve some of the questions arisen from the care of cancer patients who visit the emergency department taking into account the current evidence and the author's experience as an emergency and critical care physician.

How should we deal with the cancer patient visiting the Emergency Department?

We should be able to carry a proper and specific management approach to oncological disease, taking into account emotional and spiritual needs of the patient and

the family. We must be careful on expressing our ideas to the family and how we address it.

What are the emergencies posed by cancer patients?

Different approaches are found in the biomedical literature; nevertheless it must be proposed one that makes think of the most common emergencies and reminds those that could be overlooked:

- Classic: metabolic (tumorlysis syndrome, syndrome of inappropriate antidiuretic hormone secretion [SIADH], malignant hypercalcemia), hematologic (leukostasis, febrile neutropenia) and structural (superior vena cava syndrome, malignant spinal cord compression, intestinal obstruction and bile duct obstruction).
- Current: heart failure, respiratory failure, life-threatening bleeding, coagulopathy and sepsis.

What factors are related with increased mortality?

- Cancer status.
- Severity of acute organ failure.
- Poor performance status.
- Older age [3].

Why the cancer patient develops dyspnea?

There are some diseases that put to the cancer patient at risk to develop acute lung injury / ARDS [4]: aspiration, pneumonia, sepsis, multiple transfusions or pancreatitis. An acute respiratory failure can be precipitated by the toxic effects of radiation therapy on the chest wall and by the damage caused by the chemotherapeutic agents to the lung parenchyma [5]. The main chemotherapeutic agents involved are bleomycin, bisulfan, carmustine, cyclophosphamide, gemcitabine, methotrexate, mitomycin C and paclitaxel.

What serious metabolic alterations could occur in critically-ill cancer patients?

- Hypercalcemia.
- Hypocalcaemia.
- Hyponatremia.
- Tumor lysis syndrome.
- Metabolic disturbances related to renal failure and lactic acidosis.

The prognosis of these patients will depend on early diagnosis, cancer status or progression, co morbidities and the presence of organ dysfunction at the time of diagnosis. Encephalopathy is the main clinical

manifestation of metabolic disorders and may vary from confusion to coma. The neurological examination rarely shows any neurological focal sign [6]. The clinical presentation of metabolic encephalopathy many times is unspecific. Lethargy, polydipsia, dyspnea, cyanosis, jaundice, abnormal respiratory rate, muscular weakness, hyporreflexia/hyperreflexia, heart rhythm disorders (related to hypokalaemia, hypercalcemia or hypomagnesaemia) would be always looked for; they could be paramount to identify the source of metabolic disorder. The definitive diagnosis is achieved by mean of the diagnostic tests. Hypercalcemia is the most common metabolic emergency in these patients; it occurs most often in the cancer of the lung (27.3%), breast (25.7%), myeloma (7.3%), and head and neck (6.9%) [7]. Hypercalcemia is due to increased mobilization of calcium from bone and to his tubular decreased excretion by the kidney. Immobilization, dehydration, anorexia, nausea and vomiting, replacement hormonal therapies and thiazide diuretics can strengthen these mechanisms. A low chlorine serum (<100 mEq/L) suggests hypercalcemia associated with cancer. Measurement of parathyroid hormone levels is not necessary for diagnosis, but it could be useful to understand the mechanism of hypercalcemia. High levels are associated with increased risk of recurrent hypercalcemia within 14 days [8]. Intravenous hydration, loop diuretics, bisphosphonate therapy, calcitonin and dialysis have been used to treat it.

The tumorlysis syndrome occurs because of the lysis of a large number of malignant cells due to apoptosis or by the action of chemotherapy and radiotherapy. The rapid release of intracellular elements in amounts that exceed the capacity of renal excretion causes metabolic disorders and organ dysfunction. Its rate incidence ranges from 33% to 42% on different series [9]. It is more frequently seen in patients with acute lymphoblastic leukaemia and Burkitt's lymphoma after initiation of chemotherapy, but it can also be spontaneous in other types of tumors with high proliferation rate, large or marked sensitivity to chemotherapy and in patients with chronic lymphocytic leukaemia, acute myeloid leukaemia and multiple myeloma.

The severity of the syndrome is enhanced by extensive pre-existing disease and kidney disease. The signs and symptoms are nonspecific and can start spontaneously: generally, the patients have recently started chemotherapy (inside of 12 previous hours), urine output may decrease and the patient may show symptoms of uraemia or volume overload, seizures or arrhythmias. Are required two or more of the followings to the diagnosis: uric acid >8 mg/dL, potassium > 6.0 mEq/L, phosphorus

>4.5 mg/dL and corrected calcium <7.0 mg/dL [10]; increased creatinine, cardiac arrhythmias, seizures and death are common manifestations. Optimal treatment includes adequate hydration, administration of loop diuretics, allopurinol for 3 days before chemotherapy in patients at high risk (WBC > 100,000, lactate dehydrogenase > 2 times the reference value) and rasburicase [11]. Because hyperphosphatemia is harder to correct than hyperuricemia, alkalisation of the urine should be avoided. Patients with tumor lysis syndrome should be admitted to hospital for cardiac monitoring.

Which cancer patients more likely will develop venous thromboembolism?

- Gastric cancer.
- Pancreatic cancer.
- Lung cancer.
- Acute promyelocytic leukaemia.

Mucin-secreting tumors are associated with increased risk of blood clots.

Which are the cardiovascular and pulmonary emergencies in cancer patients?

The most common cardiac emergencies in cancer patients are those related to metastasis and toxicity associated with chemotherapeutic agents. Malignant pericardial effusion is a factor of poor prognosis, especially if it is greater than 350 mL. When it is present, the survival is usually less than one year [12]. Patients with lung cancer, hematologic cancer such as mediastinal lymphoma, melanoma or those who are being treated with chemotherapeutic agents such as cyclophosphamide and cytarabine are at risk of pericardial effusion. Malignant pericardial effusion is due mainly to metastatic cancers. Primary tumors of the pericardium are rare and mesothelioma is the most common. Chemotherapeutic agents such as doxorubicin, epirubicin, bevacizumab and dasatinib have an well known adverse effect on cardiac function, leading to cardiac dysfunction, impaired conduction and arrhythmias. Pericardial effusion can be asymptomatic. The classic findings of Beck's triad rarely are seen in a same patient. Most patients complain of dyspnea and chest discomfort. Tachycardia and paradoxical pulse may be present. As little as 100 mL of liquid in the pericardic sac can produce the clinical picture of pericardial tamponade. Pericardiocentesis with previous evaluation with ultrasonography of the pericardium is the treatment of choice. The superior vena cava syndrome is caused by an obstruction on the veins returning from the head, neck and upper extremities to the right atrium of the heart. Around 95% of cases is caused by primary or metastatic tumors. Clinical

manifestations consist on dilation of superficial veins of the chest, facial plethora and oedema in the upper limbs. Stridor, hoarseness, dysphagia, syncope and headache at the base of the skull can suggest a critical condition. Cancers typically associated with superior vena cava syndrome are lung, breast, mediastinal lymphoma, lymphoblastic lymphoma, thymoma, and germinal cell tumour [13]. Diagnosis is typically achieved by means of a selective venography, but Computed Tomography (CT) and Magnetic Resonance Imaging (MRI) are preferred by their easy access and availability [14]. The superior vena cava syndrome requires prompt diagnosis for timely treatment that includes endovascular stents, radiation and chemotherapy directed at the underlying cause.

Which are the emergencies related to bleeding and coagulopathy in cancer patients?

Such emergencies are common in the emergency department. Staff caring requires skills and abilities for treat the patient, since most often those conditions are life-threatening. Growth or invasion of the tumor can promote bleeding; this also can be presented as an adverse reaction to chemotherapy or radiotherapy. Coagulopathy and disseminated intravascular coagulation are common causes of gastrointestinal bleeding. Another major causes of gastrointestinal bleeding are peptic ulcer, anastomotic ulcer, hemorrhagic gastritis and esophagitis. Compression of the site is the first therapeutic manoeuvre to stop the bleeding, when it is possible. Blood components or clotting factor concentrates should be indicated to correct anemia and coagulopathy and failing to stop bleeding should encourage the performance of an endovascular technique to control the hemorrhage or promote an operative exploration.

How to assess the death risk of cancer patients?

There is not an ideal tool to assess the risk or severity of the disease in cancer patients. Nevertheless, another scales extrapolated from another group of patients can be use [15]. APACHE-II scale underestimates mortality in patients with cancer. Its accuracy is lower in them. Groger et al. have proposed a probability of mortality model. It includes variables such as intracranial mass effect, allogeneic bone marrow transplantation and recurrence or disease progression. Its use is recommended by experts but has not yet been validated externally [16]. The cancer treatment may put the patient at risk of gastrointestinal bleeding and bone marrow suppression. Severe thrombocytopenia, decreased wound healing and perforated ulcer are mentioned effects owing to bevacizumab. There are three tools for predicting the probability of biochemical recurrence of the most prevalent cancer in men in Colombia, prostate cancer: the

University of California and San Francisco Cancer of the Prostate Risk Assessment (CAPRA) [17], the nomogram of Kattan et al. [18] (1998) and nomogram of Stephenson et al. [19] (2006). All three have been validated in the United States, Europe and Asia. In the different studies they have achieved adequate performance, none superior to each other.

Which are the emergencies related to chemotherapy?

- Tumor Lysis Syndrome.
- Reactions to infusions of antibodies.
- Haemolytic Uremic Syndrome.
- Febrile neutropenia.
- Pulmonary infiltrates.
- Typhlitis (inflammation of the caecum).
- Hemorrhagic cystitis.
- Extravasation of the chemotherapeutic agent.
- Anaphylactic reactions to chemotherapeutic agent.

The use of systemic chemotherapy has increased by 60% since 2005, benefiting many patients [20]. Emergencies often seen related to chemotherapy are: febrile neutropenia, dehydration and shock secondary to nausea and emesis, diarrhea, Mucositis and electrolyte disturbances. Emesis can be graded from 1 to 4; a patient with more than 6 to 10 episodes for one day must be evaluated and treated in an emergency department or a unit of oncological care. Emetogenicity of chemotherapeutic agents may depend on the mode of action of the agent and on the sensitivity of the same patient. Carmustine, cisplatin, cyclophosphamide, dacarbazine, mecloretamida and estreptozocin are the agents who that more likely can produce emesis. If emesis of the patient is not related to the use of chemotherapy in the past 48 hours, other diagnoses to explain nausea and emesis should be looked for. 5-HT₃ antagonists are used by prophylaxis or treatment alone or with steroids. As emesis, diarrhea is a serious complication of chemotherapy; it can result in death if not treated properly. The main agents that cause diarrhea are 5-fluorouracil, capecitabine, irinotecan and oxaliplatin. Diarrhoea induced by chemotherapy is primarily secretory and may have an exudative component. It can be classified as early diarrhea, <24 hours after administration of chemotherapy. It is the most common type and is dose dependent. Their pathophysiological mechanism is reversible inhibition of acetylcholine. Late diarrhea, > 24 hours after administration of chemotherapy is not mediated by cholinergic system. Its aetiology is multifactorial and comes of damage to the intestinal mucosa. Diarrhoea can be classified into 5 degrees, according to National Cancer Institute [21].

Grade 1: depositions increase less than 4 stools above baseline; Grade 2: 4-6 depositions increase above baseline; Grade 3: Increased 7 or more depositions on the baseline; Grade 4: life - threatening diarrhea and grade 5: death. Diarrhoea is complicated when classified in grade 3 or 4 or when presented with one of the followings: moderate to severe abdominal pain, vomiting grade ≥ 2 , decrease in functional status, fever, sepsis, neutropenia, bleeding or dehydration.

In cancer patients it is always important to evaluate the aetiology of diarrhea because there is an increased risk of infectious complications due to increased permeability of the intestinal barrier, bacterial translocation and growing risk of sepsis by gram-negative bacilli [22]. Typhlitis or neutropenic enterocolitis are the most common complications in patients with leukaemia who are receiving induction therapy. These gastrointestinal complications can occur even in other tumors treated with chemotherapy at high doses. Ischemic colitis, pseudo membranous colitis and Clostridium-difficile immune-mediated enter colitis must be looked for. As basic pharmacological measures for treatment are used loperamide, octetide, atropine, budesonide and probiotics [23]. There are no recommendations for prophylaxis for diarrhea.

Mucositis may occur between the fifth and tenth day after chemotherapy and may coincide with the onset of neutropenia. The physician should be well aware and not underestimate this finding. Even though febrile neutropenia can be seen as an emergency of an infectious complication, it is more commonly seen as an effect of cytotoxic therapy. It is considered an emergency because it was found that in patients with fever and bacteraemia becoming neutropenic after chemotherapy, mortality reached up to 50% at 48 hours of admission [24]. Nadir of neutropenia in many patients occurs between 5-10 days after last dose of the chemotherapy, especially with these agents used in hematological malignancies. Some risk factors are: rapid fall on neutropenia, prior exposure to chemotherapy, immunosuppressant by drugs, previous increases in alkaline phosphatase, bilirubin or transaminases, decreased glomerular filtration rate and cardiovascular co morbidities. Anthracyclines, taxanes, topoisomerase inhibitors, gemcitabine, vinorelbine and cyclophosphamide are the chemotherapeutic agents that have the higher risk of neutropenia [25]. In a minority of cases of patients with febrile neutropenia it can be identified an infectious agent. Gram-positive cocci is the germs isolated in most cases. A deeper consideration about clinical manifestations, risk stratification, diagnostic criteria and treatment of patients with febrile neutropenia may be found in the clinical practice

guidelines [26,27]; talk about each of these points would unnecessarily lengthen this review.

Which are the most common surgical emergencies in cancer patients?

- Mechanical obstruction [28].
- Organ perforation.
- Pathological fractures.

What neurological emergencies can be found in patients coming to the emergency department?

- Malignant compression of spinal cord.
- Increased intracranial pressure.
- Seizures.

Compression of the spinal cord of cancer aetiology is considered an emergency. It needs to be treated quickly to obtain a prompt relief of pain and to preserve neurological function. As a rule, any tumor could generate compression of the spinal cord, but breast, prostate and lung tumors frequently cause this type of emergency. Near to 5 to 20% of patients come to the emergency department with compression of the spinal cord as the first manifestation of an oncological disease [29]. Timely detection of disease is the main prognostic factor of neurological recovery of the patients. Clinical presentation may vary depending on the severity, location and duration of compression [30]. The most common symptom is low back pain. Sometimes it can be the first sign of malignancy as in non-Hodgkin lymphomas or multiple myeloma. The diagnostic imaging of choice is MRI, which has a sensitivity of 93% and specificity of 97%. Plain radiographs would not be used because they may have false negatives up to 17% [31]. The management of these patients requires the use of glucocorticoids, surgery and radiotherapy [32].

Increased intracranial pressure secondary to malignancy (cerebral herniation, carcinomatous meningitis) is a devastating picture, requires timely diagnosis and prompt treatment. Most intracranial lesions of malignant origin are met mainly as metastatic tumors secondary to lung (20%), kidney (10%), melanoma (7%) and breast (5%) cancer [33]. This type of metastases are the most common complications of all cancers [34]. Not treated patients have a survival rate of approximately 4 weeks [35]. MRI offers better diagnostic performance and with the newest techniques is useful for planning surgical approach when it be considered appropriate. Glucocorticoids are first-line treatment as they reduce brain swelling around the tumor and decrease its mass effect [36].

Which are the most common hematologic emergencies?

Hyper viscosity syndrome: It refers to the clinical consequences derivated from an increased blood viscosity as a result of increased proteins, especially immunoglobulin's (Macroglobulinemia Waldenström, multiple myeloma). The classic triad consists on neurologic abnormalities, visual alterations and bleeding.

Leukostasis: is a hyperleukocytosis with values greater than 100,000 cells/mL. It is associated with respiratory failure and intracranial hemorrhage. Mortality reaches 40% if is not recognized and treated early.

Which cancer patients should arrive at the Intensive Care Unit?

- Patients with specific aims in life (marriage, birth, graduation).
- Patients with good life expectancy and adequate oncological prognosis.
- Patients who consider or are comfortable with their quality of life (quality of life model Ferrell) [37,38].

The ICU must be considered as a bridge to achieve these aims.

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