Severe intestinal ischemia during chemotherapy for small cell lung cancer

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Practice points

- In cancer patients, thromboembolic events (TEE) are frequent.
- Guidelines for the prevention of cardiovascular complications in cancer patients are available.
- Cisplatin-based chemotherapy is known to increase the risk of TEE.
- Intestinal ischemia is a rare complication in cancer patients treated with chemotherapy.
- When acute abdominal pain develops in a patient treated for cancer, intestinal ischemia must be considered.
- An overall assessment of cardiovascular risk factors and a risk assessment for venous TEEs are imperative before starting systemic anticancer therapy.

Thromboembolic events (TEEs) are frequent in cancer patients, especially venous thrombosis. Arterial thrombosis is less frequent. Chemotherapy increases the risk of these TEEs. Although TEEs are often reported, intestinal ischemia is a rare complication in cancer patients treated with chemotherapy. Here we describe a rare case of a patient with small cell lung cancer, who developed intestinal ischemia during treatment with cisplatin-etoposide chemotherapy. Shock and multiple organ failure developed and an urgent laparotomy with total colectomy was necessary. This case and review of the literature show that overall arterial TEEs are not as infrequent and may rarely manifest as intestinal ischemia. A cardiovascular assessment before the start of anticancer therapy is therefore imperative for cancer patients.

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Thromboembolic events (TEE) are frequent in cancer patients, especially venous thrombosis [1]. Arterial thrombosis is less frequent [2,3]. Chemotherapy is known to increase the risk of TEEs, venous as well as arterial [1–2,4–5]. Although TEEs are often reported, intestinal ischemia is a rare complication in cancer patients treated with chemotherapy [1,6–7]. Here we describe a case of a patient with small cell lung cancer (SCLC) who developed intestinal ischemia during treatment with cisplatin-etoposide chemotherapy.

Case report

A 66-year-old male patient was diagnosed with a locally advanced SCLC (TNM staging cT3N0M0) in August 2016. This diagnosis was made after the patient developed a paraneoplastic dermatomyositis. He had a history of prostate cancer, treated with radical prostatectomy and adjuvant local radiotherapy in 1999. In 2002, he underwent a surgical closure of a perforated peptic ulcer. He suffered from cluster headache and bilateral frozen shoulder syndrome. He had a known dyslipidemia, treated with statins. Besides statins, his medical treatment comprised methylprednisolone, omeprazole, amitriptyline, lormetazepam, low molecular weight heparin (LMWH) in prophylactic dose and iron and magnesium supplements. He was an active smoker at the time of diagnosis of his SCLC, with 50 pack years, and was treated for chronic obstructive pulmonary disease with long-acting bronchodilators. There was no known history of arterial hypertension, diabetes or obesity. A treatment with concurrent chemoradiotherapy was proposed, with four cycles of cisplatin-etoposide and thoracic radiotherapy starting from the second cycle.

Figure 1. Abdominal CT scan showing bowel distention and atherosclerosis of the aortic and iliac arteries.

The first cycle of cisplatin-etoposide was completed without any major toxicities, besides an uncomplicated grade 4 neutropenia. However, on day 2 of cycle 2, the patient, still hospitalized for chemotherapy administration, developed subacute abdominal pain with nausea and vomiting, but without diarrhea. Blood pressure was 144/75 mmHg, heart rate 76/min, oxygen saturation 96% while breathing ambient air, temperature of 36.4°C. On clinical examination, there was tenderness in the hypogastric region. There was no rebound tenderness. Peristalsis was present. White blood cell count was $6.02 \times 10^9/l$, neutrophilic count $5.1 \times 10^9/l$, hemoglobin 13.6 g/dl, platelets $591 \times 10^9/l$, C-reactive protein was 2.6 mg/l. Other routine laboratory findings were normal. Abdominal x-ray showed bowel distention, without signs of intestinal obstruction. There was no sign of perforation either. Alizapride was administered. Only a couple of hours later the patient developed an acute abdomen with signs of shock: unmeasurable blood pressure, weak pulse, loss of conscience. Arterial blood gas showed a metabolic acidosis with elevated lactate levels. The patient was transferred to the emergency room for hemodynamic stabilization. Abdominal CT scan was performed, without intravenous contrast because of iodine contrast allergy. CT scan showed dilation of the entire colon, suspect for intestinal ischemia. Further, diffuse atherosclerosis of the aortic artery as well as the iliac arteries was visible on computed tomography (Figure 1). The patient's clinical status deteriorated with development of a septic shock and multiple organ failure. Twelve hours later, after hemodynamic stabilization, an urgent laparotomy was performed. Inspection of the bowel revealed transmural ischemia of the entire large intestine, with spontaneous perforation of the sigmoid colon. A total colectomy was performed. The intestinal ischemia was most likely caused by a thrombosis of the mesenteric arteries.

Surgery was complicated by leakage of the pancreatic duct with abdominal collection formation and sepsis. Several abdominal drains were placed. Besides abdominal collections, his stay at the intensive care unit was marked by prolonged mechanical ventilation, temporary tracheotomy, pneumonia, renal failure and critical illness polyneuropathy. After 5 weeks in the intensive care unit, the patient was transferred to the pulmonology ward.

Because of this event of major intestinal ischemia during intravenous cisplatin-etoposide administration, the decision was made to omit chemotherapy and solely continue thoracic radiotherapy, because of his locally advanced SCLC, without metastatic lymph nodes or distant metastases. Local thoracic radiotherapy (10 fractions of 3 Gray) was completed in January 2017. However, in March 2017, only 2 months after radiotherapy, progressive disease with new pleural metastases developed. After discussion with the patient and his family, a policy of best supportive care was agreed upon.

Table 1. Thromboembolic events described in the current literature.

Study (year)	Number of patients	Cancer treatment	Total number of TEE, n (%)	Arterial TEE, n (%)	Intestinal ischemia, n	Deaths by TEE, n (%)
Yun-Gyoo <i>et al.</i> (2015)	277	Cisplatin or carboplatin doublet	30 (11%)	7 (2.5%)	Unknown	Unknown
Mellema <i>et al.</i> (2014)	784	Cisplatin or carboplatin doublet	69 (8.8% overall) 55 (8% in cisplatin) 8 (5% in carboplatin)	24 (3% overall)	0	13 (1.7%)
Proverbs-Singh <i>et al.</i> (2012)	8216	Cisplatin or noncisplatin	Unknown	34 (0.67% in cisplatin) 21 (0.47% in noncisplatin)	Unknown	Unknown
Khorana <i>et al.</i> (2007)	4466	Unknown	Unknown	8 leading to death	1 (leading to death)	13 (9.2% of all deaths)
Numico <i>et al.</i> (2005)	108	Cisplatin–gemcitabin	19 (17.6%)	10 (9%)	0	4 (3.7%)

TEE: Thromboembolic event.

Discussion

We described the acute occurrence of intestinal ischemia in a lung cancer patient treated with intravenous cisplatin chemotherapy. We estimated that the intestinal ischemia was associated with the treatment with cisplatin.

In our case, the patient developed intestinal ischemia 24 h after administration of cisplatin. It seems that cisplatin at least partially contributed to the ischemia. An arterial thrombosis and/or a cisplatin-induced vasospasm probably caused the intestinal ischemia. Because of iodine allergy, an abdominal angiography was not performed. Besides cisplatin, atherosclerosis due to dyslipidemia (though treated with statins) and smoking were a risk factor for arterial thrombosis, as well as the lung cancer itself, which predisposes to TEEs.

Cancer is associated with an altered hemostasis [8]. Cancer cells promote a hypercoagulable state through various mechanisms [8]. Thromboembolism thus frequently occurs, in up to 18% of patients treated for cancer, depending on series. However, arterial thromboembolic complications are less frequent than venous thromboembolism [1,2]. Chemotherapy and other anticancer drugs (e.g., targeted therapies) [5] are known risk factors for the development of TEE and other cardiovascular complications [5,9].

Khorana *et al.* performed a prospective observational study of causes of death in 4466 patients receiving chemotherapy [1]. In 13 out of 141 (9.2%) deceased patients, TEE was the cause of death. Arterial thromboembolism accounted for eight deaths (5.6%).

In a review and meta-analysis of 38 trials and patients, Proverb-Singh *et al.* described a higher relative risk of an arterial TEE for cisplatin-based chemotherapy versus noncisplatin-based chemotherapy [10]. However, this difference was not significant [10].

In lung cancer, arterial TEEs during treatment seem frequent [2–3,11]. In a retrospective analysis by Mellema *et al.*, 784 patients with NSCLC treated with platin-based chemotherapy were evaluated, 24 arterial TEEs (3% of patients) were described during treatment [11]. Yun Gyoo *et al.* noted 7 arterial TEEs in 277 patients (2.5%) treated for SCLC [2]. Cisplatin was associated with a higher risk of TEE in comparison with carboplatin or other chemotherapeutic agents in this study [2]. In a prospective study of 108 patients with NSCLC treated with cisplatin and gemcitabin, Numico *et al.* mentioned 10 arterial thromboembolisms (9%) [3]. This is summarized in Table 1.

Overall, intestinal ischemia is a rare complication of chemotherapy [1,6–7,11]. In the series of Khorana *et al.*, one case of intestinal ischemia, leading to death, was described [1]; as in the series of Mellema *et al.*, there was no case of intestinal ischemia [11]. Few case reports may be found in the literature. Kanat *et al.* described a fatal ischemic bowel necrosis in a patient with NSCLC treated with cisplatin and docetaxel [6]. In this case, the intestinal ischemia was attributed to docetaxel. Another case report described an ischemia of the jejunum in a patient with a laryngeal carcinoma, treated with cisplatin, docetaxel and 5-fluorouracil [7]. In a Japanese case report, a 74-year-old patient with a metastatic melanoma, developed intestinal ischemia, the day after the administration of carboplatin–paclitaxel [12].

Because of the high incidence of TEE in cancer patients, risk stratification models have been developed [13]. Khorana *et al.* developed a predictive model for venous thromboembolism (VTE) based on:

- Cancer site: very high risk of VTE in pancreatic and gastric cancer, high risk in lung, bladder, testicular, gynecologic cancer and lymphoma;
- Prechemotherapy platelet count 350,000/mm³ or more;

- Prechemotherapy leucocyte count more than 11,000/mm³;
- Hemoglobin level less than 10 g/dl or the use of red blood cell growth factors;
- BMI 35 kg/m² or more [13].

High-risk patients, identified by this score, are recommended to be treated with prophylactic LMWH [13]. Based on the Protecht study, Verso *et al.* proposed to add treatment with cisplatin or carboplatin and/or gemcitabine as additional risk factors for VTE [14].

The cardiac toxicity of cisplatin in particular is well described [4,9–11], which includes angina pectoris and acute myocardial infarction, hypertension, arrhythmias, myocarditis, cardiomyopathy and congestive heart failure [5,9]. As mentioned above, platin-based therapy has been shown to increase the risk of thrombotic events, venous and arterial, in cancer patients [9].

The underlying mechanism of vascular toxicity of cisplatin is the induction of endothelial damage [4,5]. This damage of the vascular intima predisposes to thrombosis [9]. Therefore, injury of endothelium and endothelial dysfunction are the key mechanisms of altered vasoreactivity with these drugs [5]. Cisplatin might elevate the levels of von Willebrand factor, induce vasospasm and trigger antiangiogenic activity [9]. Deickman *et al.* showed an increase of von Willebrand factor during the course of cisplatin-based chemotherapy in patients treated for a germ cell tumor [15]. Furthermore, cisplatin levels may remain detectable for years after therapy and as a consequence also the risk for acute ischemic events [5].

Since a substantial number of cancer patients may develop cardiovascular events and TEEs during chemotherapy, it is important to identify those at large risk for these complications [1,5]. The prevalence of cardiovascular disease in the general population is high [5,16]. An assessment of baseline cardiovascular risk factors before initiation of cancer therapy is therefore necessary [5].

The guidelines of the European Society of Medical Oncology recommend a baseline clinical evaluation of cardiovascular risk factors and comorbidities. An ECG and echocardiography before initiating chemotherapy are advised [17]. The Society for Cardiac Angiography and Intervention proposed an algorithm (an Society for Cardiac Angiography and Intervention expert consensus statement) to define and assess the cardiovascular risk and to optimize modifiable cardiovascular risk factors [18]. Based on signs and symptoms of cardiovascular disease and based on the planned treatment, further investigations are proposed. Furthermore, treatment of arterial hypertension and pre-existing coronary artery disease are recommended [18].

Recently, the ABCDE approach was proposed for all patients with cancer [16]. This principle has been used in breast cancer and prostate cancer patients before [16]. In ABCDE approach, A stands for awareness, assessment, aspirin; B stands for blood pressure control; C for cholesterol lowering, cigarette cessation; D stands for diet, dose of chemotherapy, diabetes management; and E stands for exercise, echocardiography [16].

The patient described in this case report, had known cardiovascular risk factors, in other words, dyslipidemia (treated with statins) and a smoking history. However, the patient was not treated with aspirin. An echocardiography at the time of diagnosis showed a structurally normal heart with a normal left ventricle ejection fraction. In Khorana's risk stratification model for VTE, the patient had a score of 1 point because of the presence of lung cancer, with no elevated platelet count or elevated leucocyte count prechemotherapy, normal hemoglobin levels and a BMI of 23.5 kg/m². This score of 1 point is considered an intermediate risk [13]. The patient was indeed treated with a prophylactic dose of LMWH.

The hypercoagulable state in lung cancer, an underlying atherosclerosis due to dyslipidemia and smoking, and finally, the administration of cisplatin most probably caused the intestinal ischemia in this patient.

As mentioned above, TEEs are thus frequent in cancer patients. However, TEEs in the intestinal arterial circulation in particular are rather rare. One should always be very cautious for this diagnosis, when abdominal pain develops in cisplatin-treated (lung) cancer patients.

Conclusion

A rare case of acute intestinal ischemia in a patient with SCLC treated with cisplatin-etoposide chemotherapy was described. Cardiovascular complications may occur during cancer treatment. Venous TEEs are frequent and well known in patients receiving chemotherapy, but one must keep in mind that overall, arterial TEEs are not as infrequent and may manifest as rare complications as shown in this case. An overall assessment and treatment of cardiovascular risk factors and risk assessment for VTE before the start of systemic anticancer therapy are therefore imperative for cancer patients.

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Informed consent disclosure

The authors state that they could not obtain verbal and written informed consent from the patient for the inclusion of their medical and treatment history within this case report, because the patient already died previous to the manuscript writing. However, informed consent was obtained from the widow of the patient and is written down in his (electronic), medical file.

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