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Cardiogenic shock in cancer

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Abstract
Cardiogenic shock (CS) is increasingly recognized in patients with malignancies, while cancer is independently associated with worse prognosis in CS. A number of conditions may lead to CS in cancer, including acute coronary syndromes, cardiomyopathy, takotsubo syndrome, myocarditis, pulmonary embolism, tamponade, and cardiac herniation. In these conditions, CS may be related to cancer itself or to cancer therapy, including surgery, chemotherapy, or radiotherapy. Given the significantly improved overall survival of patients with malignancies, the early recognition and proper management of CS in cancer become increasingly important. In the present paper, we review the available evidence on CS in patients with malignancies and highlight issues related to its management.

Keywords Cancer · Cardiogenic shock · Chemotherapy · Radiotherapy

Introduction

Cardiogenic shock (CS) is the most dreadful presentation of acute heart failure (HF), characterized by low cardiac output because of a cardiac cause, leading to persistent hypotension, peripheral hypoperfusion, and a vicious circle of multi-organ dysfunction with ominous prognosis [1]. Among other conditions, CS may complicate cancer and its treatment.

There are very few epidemiological data describing the relationship between cancer and CS. The prevalence of cancer in patients admitted with CS in the largest European registry was 4.8% [2]. On the other hand, the incidence and prognosis of CS in oncological patients are unknown, but the prolonged survival of cancer patients due to contemporary treatments has lately led to an increasing number of cases [3]. History of cancer was independently associated with increased mortality in patients with CS (OR 1.41, 95% CI 1.24–1.60), with metastatic cancer being one of the most important prognostic factors (OR 2.05, 95% CI 1.81–2.31) [4]. Among solid tumors, patients with colon cancer have the highest risk of developing CS, while those with lung cancer bear the greatest risk of mortality from CS [5]. Given the fact that the overall prognosis of cancer has lately been significantly improved by virtue of modern therapies, the early recognition and proper management of CS in these patients are becoming increasingly important.

Cardiogenic shock in patients with a malignant disease is preceded by different clinical entities, such as acute coronary syndrome (ACS), cardiomyopathy, takotsubo syndrome, myocarditis, thromboembolic events and pulmonary embolism, tamponade, and cardiac herniation (Fig. 1). These clinical presentations can be attributed either to cancer itself or to its therapy, including surgery, chemotherapy, or radiotherapy, in association with pre-existing cardiovascular (CV) disease or risk factors.

Cardiogenic shock related to acute coronary syndromes

Acute coronary syndromes are not rare in cancer patients due to multiple reasons: shared atherogenic risk factors, anticancer agents of different categories related to coronary vasospasm and endothelial injury, radiation of the mediastinum and the left hemithorax, mechanical phenomena of the tumor, and cancer-related factors [6]. In hematological malignancies, the incidence of ACS is 1.4% [7]. For the first 6 months after

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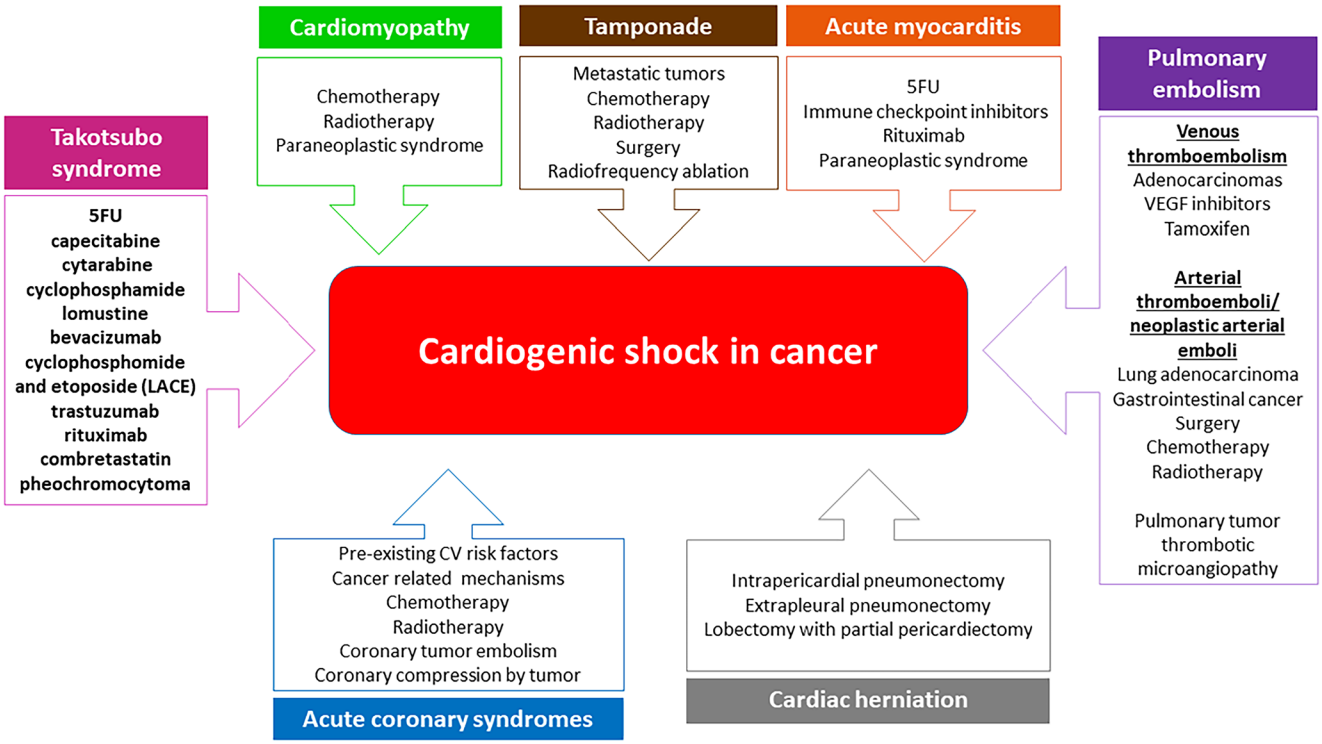

Fig. 1 Pathophysiological mechanisms of cardiogenic shock in cancer

cancer diagnosis, the risk of arterial thromboembolism is two-fold higher compared with that of similar patients without cancer, including an increased risk of ACS. This risk declines a year after cancer diagnosis and is thereafter associated with cancer stage [8]. Patients with ACS and a history of cancer are at increased risk of complications during hospitalization, with CS being the most serious of them (OR 1.44, 95% CI 1.09–1.92) [9, 10]. Interestingly, the increased early mortality of patients with cancer suffering a ST-elevation myocardial infarction is related to CS and anemia rather than to chemotherapy, radiotherapy, or the underuse of advanced treatments, such as mechanical circulatory support [11].

Atherosclerosis and cancer share many risk factors, including age, obesity, smoking, and sedentary life. Antimetabolites and small tyrosine kinase inhibitors (TKIs) are the most common chemotherapeutics to cause ACS, with 5-fluorouracil and nilotinib being the most representative ones [6, 12] (Table 1). Other anticancer agents that have also been associated with ACS include alkylating agents, anthracyclines, antimicrotubule agents, monoclonal antibodies, and aromatase inhibitors [13]. The time interval in which myocardial ischemia occurs varies; fluoropyrimidines, bevacizumab, and TKIs are associated with ACS during infusion or within few days while taxanes, interleukin-2, and interferon may lead to ACS later, even years, after therapy [14]. Radiation-induced coronary artery disease (CAD) develops early compared with the general population in survivors from childhood or adolescence malignancies, while in adult cancer patients, the mean time interval is 82 months since radiation therapy. The risk of developing CAD increases by 7.4% per Gy of radiation, with no lower safe threshold. As expected, the distribution of coronary lesions is associated with the location of radiotherapy, with left main and right coronary artery and ostial lesions being more common. Radiation of the left hemithorax in left breast cancer patients is associated with medial to peripheral lesions in the left anterior descending artery. Cardiac tumors can compress [15] or embolize coronary arteries [16–18]. Among solid tumors, lung, gastric, and pancreatic cancers are associated with increased risk of thromboembolic events, including ACS complicated by CS [19]. Among hematological malignancies, polycythemia vera, essential thrombocythemia, and acute promyelocytic leukemia also pose an increased risk of thromboembolism and ACS [19]. Cancer-related factors that predispose to ACS and thus CS include hypercoagulable and pro-inflammatory state, thrombocytopenia and paraneoplastic disease.

Cardiogenic shock related to cardiomyopathy

Cardiomyopathy (CM)-associated ventricular dysfunction and HF is another clinical presentation which can lead to CS in patients with malignancies. In these patients, CM may often result from cancer therapies [13]. Among them, anthracyclines represent the traditional prototype of chemotherapy causing

Table 1 Anticancer medications associated with acute coronary syndromes (ACS)

Medication	ACS incidence
Antimetabolites	
5-Fluorouracil	0.1–19%
Capecitabine	0.02–10%
Small tyrosine kinase inhibitors (TKIs)	
Nilotinib	2–25%
Sorafenib	1–2%
Sunitinib	1–13%
Pazopanib	2–10%
Antimicrotubule agents	
Paclitaxel	0.2–4%
Vinblastine	< 5%
Alkylating agents	
Cisplatin	0.2–12%
Antitumor antibiotics	
Bleomycin	< 3%
Monoclonal antibodies	
Bevacizumab	1–6%
Ramucirumab	1.5–2%
Rituximab	Rare
VEGF inhibitors	
Aflibercept	3%
Hormone therapy	
Aromatase inhibitors	1–2%
Anti-androgens	2–5%
Estrogen/nitrogen mustard	1–3%
Gonadotropin-releasing hormone agonists	1–5%
Gonadotropin-releasing hormone antagonists	< 1%
Topoisomerase inhibitors	
Etoposide	1–2%
Biologic response modifiers	
Interferon Interleukin-2	Up to 21%

CM, mainly with a dilated phenotype [20]. According to a large Italian cohort of cancer patients receiving doxorubicin mainly for breast cancer or hematological malignancies, cardiotoxicity, in the form of left ventricular ejection fraction decline of more than 10% points to an absolute value below 50%, occurred in 9% of cases, including 2% of cases with HF of New York Heart Association class III or IV [21]. Interestingly, the majority of cases occurred soon after chemotherapy, with a median time to CM onset of 3.5 months, which stresses the importance of close echo monitoring during and the first months after doxorubicin therapy. Besides anthracyclines, anticancer agents, including classical and novel chemotherapeutics and targeted therapies, have been associated with ventricular dysfunction and HF [20] (Table 2). In addition, chest irradiation may lead to restrictive CM several years or decades after exposure [13].

Cardiogenic shock related to takotsubo syndrome

In the most recent consensus document about takotsubo syndrome, cancer and chemotherapy are listed among its physical triggers [22], while this is also true for surgical procedures [23]. The incidence of takotsubo in cancer patients is approximately 10% [24]. According to a small study [23], the most common severe complication in patients with takotsubo was CS requiring inotropic agents in 20% of patients [23]. Interestingly, these patients were able to resume cancer treatment relatively early, after a median time of 20 days. In this study, none of the patients experienced recurrence of takotsubo syndrome and this risk is generally low, even with chemotherapy rechallenge [25].

There are two hypotheses that may explain the association of cancer with takotsubo syndrome. The first concerns the decrease of threshold for stressful stimuli after cancer diagnosis while the second suggests that chronic inflammatory state observed in cancer increases cardiac adrenoreceptor sensitivity due to excess levels of inflammatory mediators [26]. What actually triggers takotsubo syndrome in cancer patients seems to be multifactorial, including a combination of cancer, surgical stress, acute complications of cancer, and cardiac or extracardiac side effects of cancer therapy [27]. Heterogeneous classes of anticancer agents (Table 3), such as antimetabolites, alkylating agents, monoclonal antibodies, and tyrosine kinase inhibitors, have been reported to cause takotsubo syndrome and CS with the common pathogenetic mechanisms being global reversible endothelial injury, arterial thrombosis, and alterations in molecular control of vascular smooth muscle tone [28].

Paragangliomas and pheochromocytomas are rare neuroendocrine tumors which can cause catecholamine-induced myocardial dysfunction in 8–11% of patients that may in turn be complicated with CS [29], while the incidence of CS per se in these patients is 2% [30]. Several cases of classical and inverted takotsubo syndrome and CS have been reported in relatively young patients suffering from these malignancies [31–34]. Most of them survived with inotropes, with intra-aortic balloon pump (IABP), or with extracorporeal membrane oxygenation (ECMO) [35, 36].

Table 2 Anticancer agents most frequently associated with cardiomyopathy (reprinted from reference 19)

Class	Drug example	Cardiomyopathy incidence
Anthracyclines	Doxorubicin	3–48%
Alkylating agents	Cyclophosphamide	7–28%
Antimicrotubule agents	Docetaxel	2–13%
Monoclonal Ab	Trastuzumab	1–20%
Tyrosine kinase inhibitors	Sunitinib	3–19%
Proteasome inhibitors	Carfilzomib	11–15%

Cardiogenic shock related to myocarditis

Myocarditis represents another clinical scenario that may lead to CS in cancer. Several classes of anticancer agents have been associated with myocarditis, often of fulminant presentation. The antimetabolite 5-fluorouracil has been related to an inflammatory response, with apoptosis of myocardial and endothelial cells that mimic toxic myocarditis [37, 38]. Rituximab has also been shown to cause viral myocarditis and CS through hypogammaglobulinemia [39, 40]. Myocarditis has further been recently associated with immune checkpoint inhibitors (ICIs) [35–37]. Ipilimumab, atezolizumab, and nivolumab, despite belonging to different categories (CTLA-4, antiPD-L-1, antiPD-1, respectively), have all been associated with myocarditis, that is often fulminant, leading to CS [41–43], indicating a class-effect of these agents. ICI-related myocarditis occurs early—within few weeks—after treatment onset and although is generally rare, observed in less than 1% of cases, is often lethal, with an overall mortality rate of 50%. Besides cancer therapy, paraneoplastic syndromes may also cause myocarditis, including catecholaminergic myocarditis in patients with pheochromocytoma [29, 35], eosinophilic myocarditis in lung adenocarcinoma or eosinophilic leukemia [44], and giant-cell or lymphocytic myocarditis in lymphoma, sarcoma, lung cancer, and thymomas [40, 41].

Cardiogenic shock related to pulmonary embolism

Cardiogenic shock related to pulmonary embolism (PE) may be caused by either venous thromboembolism or arterial thromboembolism, including neoplastic arterial thromboembolism. The incidence of thromboembolic events in oncological patients is generally 15% [45], with an estimated 6 to 7-fold higher risk than that in the general population [46]. PE events, particularly of venous origin, are more frequent in patients with adenocarcinomas, including colorectal, pulmonary, pancreatic, and ovarian cancer, as well as in brain tumors, myelomas, and lymphomas [47]. Risk factors include demographics, clinical and laboratory characteristics, as well as treatment options, such as surgery [48], percutaneous cryoablation [49] chemotherapy with tamoxifen [50] or bevacizumab [51], hormonal therapy, and transfusions [13]. Risk factors for neoplastic arterial emboli are related to surgery, cancer localization, cardiac and intravascular involvement, neoplasm subtype, and stage of the disease [52]. Neoplastic emboli may be the first presentation of a malignancy [52]. Lung adenocarcinoma followed by gastrointestinal neoplasia is the most common source of emboli [52], while case reports of emboli from myxomas, renal cell carcinoma, breast cancer, non-Hodgkin lymphoma, and choriocarcinoma [52] have been published.

A specific subtype of pulmonary artery tumor embolism is pulmonary tumor thrombotic microangiopathy (PTTM), a rare cause of PE in cancer with ominous prognosis [50, 51]. Its histological characteristics include intimal and medial fibromuscular thickening, with accumulation of carcinomatous cells in the residual lumen of the small arteries and arterioles to form a tumor emboli [53, 54]. This causes pulmonary hypertension, respiratory failure, right heart failure, CS, and death. Cases of PTTM and CS in patients with different neoplasms have been reported in the literature, including colon [55], breast [56], gastric [57, 58], cervical [59], and ovarian cancer [60].

Cardiogenic shock related to cardiac tamponade

The most serious manifestation of pericardial involvement in cancer is cardiac tamponade. It is the potentially lethal component of neoplastic pericarditis, associated with very poor prognosis [61]. Cancerous cells can invade the pericardial space directly or through blood and lymphatic metastases [62]. Primary tumors such as pericardial sarcoma, intrapericardial paraganglioma, mesothelioma, and metastatic tumors from lung, breast, esophageal, and cervical cancer, and also lymphoma and leukemia have all been associated with cardiac tamponade and CS [63–65]. Cardiogenic shock related to tamponade has further been reported due to mediastinitis [66], thoracoscopic surgery [67], radiofrequency ablation [68], radiotherapy [69], and very recently as a side effect of certain anticancer drugs, such as dabrafenib and trametinib [70], bortezomib [71], nivolumab [72], and busulfan [69] (Table 4).

Table 3 Anticancer agents most commonly associated with takotsubo syndrome–induced cardiogenic shock

Anticancer agent class/regimen	Drugs
Antimetabolites	5-Fluorouracil, capecitabine, cytarabine
Alkylating agents	Cyclophosphamide
Monoclonal antibodies	Trastuzumab, rituximab, bevacizumab
Tyrosine kinase inhibitors	Axitinib, sunitinib, ibrutinib
LACE	Lomustine, cytarabine, cyclophosphamide, etoposide
R-CHOP	Rituximab, prednisone, doxorubicin, cyclophosphamide, vincristine

Cardiogenic shock due to cardiac herniation

Cardiac herniation, a rare but potentially life-threatening complication occurring after surgery involving the pericardium, may be responsible for CS in patients with malignancies. It involves protrusion and/or rotation of a part of the heart through an ignored or inadequately closed pericardial sac defect [73, 74]. Intrapericardial pneumonectomy, extrapleural pneumonectomy, and lobectomy with partial pericardiectomy are the main types of operations in cancer patients associated with cardiac herniation [73]. It usually occurs within the first 24 h postoperatively, but it is possible to develop even months later [75]. The incidence of herniation is equal on the right and left side, but the pathophysiologic mechanism responsible for hemodynamic failure is different. Torsion of the superior and inferior vena cava is the main mechanism on the right side. At the left side, the left ventricular apex can rotate through the pericardial defect and become strangulated, with resultant CS due to impairment of mechanical filling and emptying of the left ventricle. The severity of the clinical presentation is associated with the level of strangulation [74].

Specific issues in the treatment of cardiogenic shock in cancer

Cardiogenic shock treatment in cancer is a therapeutic challenge. Overall, it does not differ from that in the general population. Ensuring hemodynamic stability of the patient is the first priority but ultimately treatment of the underlying cause of CS will increase substantially the chances of survival. Advanced treatment measures, such as mechanical circulatory support (MCS) with extracorporeal membrane oxygenation (ECMO) [74] and/or ventricular or biventricular assist devices (VAD), should be included in the therapeutic armory of cancer patients with refractory CS [75]. The use of MCS maybe justified not only in patients with good life expectancy [28, 76–78], but also in patients with anthracycline-induced CM and contraindications to heart transplantation, as there are reports confirming improvement of CS and successful weaning from VAD [79–82].

The treatment of CS due to specific types of myocarditis, such as fulminant myocarditis by ICIs, includes immunosuppressive agents, mainly glucocorticoids, while further agents such as immunoglobulin, antithymocyte globulin, tacrolimus, mycophenolate, or infliximab have further been suggested [76].

The therapeutic options for pulmonary embolism and CS due to PTTM are limited and the prognosis is extremely poor with the vast majority of patients dying rapidly after the development of symptoms. Endothelin receptor antagonists, inhaled nitric oxide and prostacyclin analogues used in pulmonary arterial hypertension, can reduce pulmonary pressure acutely, but their long-term effectiveness is limited [77]. Corticosteroids [78] and the PDGF-receptor inhibitor imatinib in selected cases of PTTM with tumor overexpression of PDGF as in some gastric malignancies [79] and bevacizumab [80] may also improve prognosis.

In CS due to NCT, the first therapeutic goal is to treat tamponade urgently, so pericardiocentesis is imperative as soon as possible. Complications are rare and the immediate success rate is > 95%, but recurrences may occur [81]. The other two therapeutic goals involve prevention of recurrent episodes and/or treatment of the local or systemic neoplastic disease to prolong survival. For prevention of recurrences, extended drainage, surgical or percutaneous balloon pericardiostomy, sclerosing local therapy, and local and/or systemic chemotherapy or radiation therapy (RT) (external or with intrapericardial radionuclides) are available. Bleomycin or thiotepa are used as local therapy, as well as platinum and mitoxantrone [82]. Local measures are more effective when combined with systemic chemotherapy. The clinical outcome is different according to the underlying malignancy with patients with lymphoma or leukemia to have a fair survival after diagnosis of NCT with systemic chemotherapy compared with patients with lung or breast cancer [61].

Cardiogenic shock due to cardiac herniation is an urgent condition and its timely diagnosis requires high clinical suspicion. Mortality is 50% if identified and treated immediately and 100% if diagnosed later or not detected [74]. Open surgery with closure of the pericardial defect and restoration of the herniated heart to its normal position is the only appropriate treatment.

In this context, it should be stressed that the role of established cardio-oncology clinics and services is quite

Table 4 Causes of cardiac tamponade-induced cardiogenic shock

Category	Typical example
Primary tumors	Pericardial sarcoma Intrapericardial paraganglioma Mesothelioma
Metastatic tumors	Lung cancer Breast cancer Esophageal cancer Vaginal adenocarcinoma Cervical cancer Lymphoma
Anticancer agents	Dabrafenib, trametinib Bortezomib Nivolumab Busulfan
Radiotherapy	Mediastinal irradiation for lymphoma Left breast irradiation
Thoracoscopic surgery	Lung cancer
Radiofrequency ablation	Hepatocellular carcinoma
Mediastinitis	Gastric cancer

important for the identification of high-risk patients who require close monitoring during cancer therapy as well as the timely diagnosis and effective management of patients with CV complications, including CS [83].

Conclusions

Cardiogenic shock in patients with cancer is not extremely rare, caused by cancer itself, chemotherapy, radiotherapy, or surgery. It can follow different clinical entities, like acute coronary syndrome, cardiomyopathy, takotsubo syndrome, myocarditis, pulmonary embolism, tamponade, or cardiac herniation. It is associated with ominous prognosis and its treatment apart from the generally applied measures includes specific therapeutic options according to the specific cause.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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