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Acute coronary syndromes in patients with cancer: Recent advances

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ABSTRACT

Coronary artery disease is presently one of the leading causes of death amongst cancer survivors. The number of cancer survivors, projected to reach 26 million by 2040, presents a unique challenge in managing coronary disease in this population. Cancer patients face an elevated risk of atherosclerotic disease due to shared cardiovascular risk factors and the cardiotoxic effects of cancer therapies, predisposing them to acute coronary syndromes. Challenges in treating cancer patients presenting with acute coronary syndromes include atypical presentations, obscured symptoms, and the impact of cancer-related processes on traditional biomarkers. This review explores the complexities of acute coronary syndrome management in cancer patients, addressing challenges involved, recent advances in percutaneous strategies, pharmacology, and considerations for these high-risk individuals. The balance between invasive vs. medical strategy, technical advances in multimodal imaging, intravascular physiology, intracoronary imaging, and evolving stent options are discussed in this review, highlighting the need for tailored approaches in this complex patient population.

Key words: acute coronary syndrome, cancer

INTRODUCTION

Coronary artery disease (CAD) is presently one of the principal causes of death amongst cancer survivors [1]. Cardiovascular disease often overtakes cancer as the leading cause of mortality in cancer survivors [2] and certain cancers such as breast, thyroid, endometrial and prostate cancer are associated with a cardiovascular mortality as high as 50% [3].

With rapidly evolving screening and therapeutic innovations, the number of cancer survivors is steadily with data from 2022 suggesting that 69% of patients had survived their cancer by ≥5 years since the time of their diagnosis; whilst 47% had survived their cancer by ≥10 years [4]. It is projected that, by 2040, the number of cancer survivors will rise to 26 million, with 74% of that population being aged 65 years or more [4].

Cancer patients are at heightened risk of CAD due to a combination of factors. First, cancer populations share overlapping cardiovascular risk factors, such as smoking, obesity, diabetes and hypertension [4–7]. Second, certain cancer therapies have been shown to display cardiotoxicity, with some specific treatments predisposing to acute coronary syndromes (ACS) [7]. These specific drugs, and the pathophysiological mechanisms contributing to CAD including ACS, are highlighted in Table 1 [8]. Precipitating factors include accelerated atherosclerosis, plaque rupture (radiation therapy and vascular endothelial growth factor inhibitors); vasospasm (e.g., taxanes and vinca alkaloids); and coronary thrombosis (e.g., alkylating agents such as cisplatin, cyclophosphamide) and platinum-based treatments) [9, 10].

Most data pertaining to ACS in cancer patients relies on observational or registry studies, as cancer patients have been excluded from most major CAD randomized trials. These observational studies suggest that ACS patients with underlying cancer are at increased risks of major cardiovascular events, cardiac as well as non-cardiac mortality [9, 11]. In this review, we discuss the particular challenges associated with treating ACS in cancer patients, the recent advances made in percutaneous strategy, pharmacology, as well as future considerations when treating these high-risk populations.

CHALLENGES OF TREATING ACS IN CANCER PATIENTS

Treating ACS patients with underlying cancer comes with its own set of challenges. For instance, presentation with ACS can be atypical, with symptoms concealed by cancer itself or treatment-related side effects, and traditional biomarkers sometimes skewed by cancer-related processes [9, 12]. Patients with cancer are also at higher risk of bleeding as well as thrombotic events, such as stroke. Through the stimulation of cytokines, dysregulated platelet activity, endothelial dysfunction, oxidative stress, as well as disorders in coagulation, cancer can lead to proinflammatory, as well as prothrombotic states [10, 13]. Bleeding can also pose a

significant challenge in this group of patients, and this can be related to local tumour invasion, tumour angiogenesis, oncology therapies, or the systemic effects of the malignancy itself [12, 13]. Thrombocytopenia, which is commonly encountered in certain types of cancer, is associated with worse clinical outcomes, as reported in a study by Yadav et al. [14]. The authors pooled data from two large randomized trials and examined outcomes in 10 603 patients undergoing percutaneous coronary intervention (PCI) for ST-elevation myocardial infarction (STEMI) and NSTEMI patients. They found that thrombocytopenia was an independent predictor of mortality 12 months (hazard ratio [HR], 1.74), ischemic target lesion revascularization (HR, 1.37), and major adverse cardiac events (HR, 1.39) [14]. Thus, this is a major consideration in deciding whether to offer interventional options to this particular class of patients, and requires carefully assessing the benefits and risks associated.

Active malignancy, which is defined as a diagnosis within the previous 12 months or ongoing active cancer therapy including surgery, chemotherapy, or radiotherapy, is considered one of the major criterion for high bleeding risk, as outlined by the Academic Research Consortium for High Bleeding Risk [15, 16]. In a study by Raposeiras-Roubin et al. [17], 1 in 13 post-discharge bleeding events noted in ACS patients was associated with a new cancer (positive predictive value for cancer diagnosis of post discharge bleeding = 7.7%), affecting mainly the gastrointestinal, genitourinary and bronchopulmonary systems [18].

Moreover, radiation-induced CAD (RICAD), which results from both direct and indirect effects of radiation exposure, is the second most frequent cause of morbidity and mortality amongst patients exposed to radiotherapy for breast cancer and Hodgkin’s lymphoma [16]. RICAD has been shown to have a predilection for ostial epicardial coronary lesions, typically involving the left main stem or proximal left anterior descending coronary artery, possibly because these vessels lie more anterior/central to the mediastinum, in a distribution which is more exposed to radiation [18]. In this group of patients, the relative risk of mortality, from myocardial infarction (MI), is roughly double that found in the general population. Treating patients with RICAD can sometimes prove challenging, as the lesions involved can be resistant to treatment, in view of their fibrotic nature, heavy calcification, and negative remodelling, as demonstrated on intravascular ultrasound [19]. These patients are at high risk for surgical revascularization despite having an indication for it because of concern for bleeding, poor sternal wound healing and increased morbidity associated with prior chest radiation [20]. PCI amongst patients with RICAD has been shown to be associated with worse outcomes, compared to propensity-match patients, with radiation exposure noted to correlate with higher all-cause mortality [21, 22].

REVASCULARISATION FOR ACS IN CANCER PATIENTS

The last few years have seen a shift in the revascularisation strategy adopted in ACS patients with concomitant cancer, moving from a traditionally conservative to a more invasive approach. With the introduction of third-generation drug-eluting stents (DES) and data favoring shorter antiplatelet therapy duration, the new European Society of Cardiology (ESC) guidelines recommend an invasive strategy with coronary angiography and PCI in "patients with cancer presenting with ST-elevation MI (STEMI) or high-risk non-ST elevation ACS (NSTE-ACS), with life expectancy ≥6 months", or if their ACS is complicated by acute complications, such as cardiogenic shock malignant arrhythmias, or pulmonary edema [23]. This framework comes as retrospective data [23] suggests better outcomes in cancer patients treated invasively for ACS, compared to a conservative approach. A recent propensity-matched study [24] in STEMI patients with cancer suggested that, despite its lower use, the treatment effect of primary PCI was similar to that observed in the no-cancer group. Another study by Balanescu et al. [25], concluded that cancer patients undergoing PCI for acute MI (AMI) had better overall survival rates, compared to patients treated medically, with the most benefit seen when angiography was undertaken within 3 days of admission. However, it is important to note that cancer patients with AMI are a heterogenous group of patients with varying risk-benefit profiles and clinical outcomes. We have previously demonstrated that AMI patients with lung cancer were associated with the highest in-hospital mortality and MACE while those with colon cancer were associated with highest risk of bleeding [26]. Additionally, patients with known metastatic disease, who are admitted with an ACS, have been shown to fare worse following PCI, as opposed to having a more conservative strategy [27].

TECHNICAL ADVANCES

Multimodality imaging

Since it was first coined in 2013 [28], there has been growing interest and research surrounding the syndrome of myocardial infarction with non-obstructive coronary artery disease, (MINOCA). MINOCA [29] is defined as the triad of acute MI (positive cardiac biomarker and corroborative clinical evidence of infarction), non-obstructive coronaries on angiography (i.e., no coronary stenosis 50%), and the absence of clear specific cause for the acute presentation. A study by Stepien et al. [30] demonstrated that patients with MINOCA were found to have higher rates of concurrent cancer, compared to patients with MI and obstructive CAD (MI-CAD). Cancer was also noted to correlate with less favourable survival in both groups of

patients. Furthermore, takotsubo cardiomyopathy (TC) is common amongst cancer patients, with a reported prevalence of cancer amongst TC ranging between 6%–28% [31–34]. Multimodal imaging is key in these instances, in order to distinguish a potential presentation of TC, from other conditions. Transthoracic echocardiography, for instance, has the ability to detect typical appearances of TC, (which include apical ballooning with severe hypokinesia/akinesia of the apical and mid-ventricular segments), although a coronary angiogram or computed tomography scan is necessary to differentiate it from anterior MI associated with atherosclerotic obstructive CAD. The last decade has seen a dramatic expansion of the use of cardiac magnetic resonance imaging (CMR) in patients with MINOCA, which is a key tool [35] for detecting late gadolinium enhancement, thus localizing the site and pattern of myocardial injury and helping to differentiate between ischemia, myocarditis and infiltrative processes [36]. CMR can also risk stratify patients admitted with MINOCA, with strongest reported predictors [36] of mortality having been shown to be a CMR diagnosis of cardiomyopathy and ST-elevation at the time of presentation. In patients with cancer who present with ambiguous symptoms, non-invasive imaging such as those described above, are being increasingly used in modern practice, in order to inform diagnosis and management, and also avoid invasive procedures or anticoagulants in high-risk patients, where imaging can clinch the diagnosis.

Vascular access

The last decade has seen radial vascular access emerge as the access of choice in both ACS and elective patients undergoing PCI. Radial access [37] has been shown to be associated with lower all-cause mortality and major bleeding, compared with femoral access in numerous randomised controlled trials [38, 39]. In cancer patients at higher risk of bleeding and vascular complications, this is particularly important, as radial approach favours prompt ambulation, whilst reducing bleeding risks. Where the radial artery is small in calibre or susceptible to spasm, ultrasound guidance [39], the use of hydrophilic sheaths, and anticoagulation can increase the success and reduce complications of radial artery cannulation [40].

Intravascular physiology and imaging

In the last decade, physiological assessment of coronary lesions has emerged as gold standard adjunctive tools to conventional coronary angiography in guiding PCI decisions. In cancer patients presenting with ACS and found to have intermediate bystander coronary lesions, fractional flow reserve can be very valuable in identifying haemodynamically significant

stenoses in non-culprit vessels [41, 42], thus assisting operators in decision-making pertaining to whether those stenotic lesions should be treated with PCI. In recent times, intracoronary imaging has emerged as a critical resource in PCI, although there still remains considerable geographical and hospital/physician-level variability [43, 44]. In cancer patients, the addition of intravascular imaging can prove extremely valuable in identifying patients with intermediate lesions, where acceptable minimum lumen areas, can allow for the safe postponement of revascularization [45, 46]. For example an minimum lumen areas ≥6 mm was deemed a safe cut-off for deferring revascularization in left main lesions [47]. This approach can be of particular value in cancer patients with left main stem disease, where the benefits of percutaneous intervention must be balanced with risks conferred by the cancer burden and associated bleeding.

In patients undergoing PCI, intracoronary imaging, such as intravascular ultrasound or optical coherence tomography (OCT), plays a crucial role in defining vessel architecture [48], by detecting and quantifying coronary atheroma, thrombus, and calcium burden [49]. Moreover, intracoronary imaging aids in assessing stent expansion and malapposition, whilst minimizing periprocedural complications including stent edge dissection and stent thrombosis. Recent consensus position statements from the European Association of Percutaneous Coronary Interventions underscore the pivotal role of imaging in guiding and optimizing stent implantation [49–51]. The PROTECT-OCT Registry [52] showcased the utility of OCT in cancer patients undergoing PCI, allowing operators to identify high-risk patients based on criteria such as uncovered stent struts, stent underexpansion, malapposition, and in-stent restenosis. Consequently, OCT imaging facilitates the identification of cancer patients at low-thrombotic risk, who may safely discontinue dual antiplatelet therapy (DAPT) prematurely to undergo cancer-related surgery [52].

Stent options

The preferred stent strategy when treating cancer patients in the past involved bare metal stents (BMS), to enable a shorter duration of DAPT. Recent randomized controlled trials have highlighted the superiority of new, third generation DES [53, 54] over BMS in patient groups at high bleeding risk, especially when long-term DAPT therapy is not a viable option. The new stent platforms, including the polymer-free and carrier-free, umirolimus-coated BioFreedom stent, have been reported, in the LEADERS FREE trial, to outperform BMS with a shortened duration of DAPT (1 month) [55]. Moreover, the ONYX-one study [56] demonstrated that, amongst patients at significant risk of bleeding, a 1-month DAPT regimen following PCI with

zotarolimus-eluting stents, was comparable to the use of polymer-free drug-coated stents in terms of safety and adverse outcomes. In addition, the TWILIGHT study [57] revealed that among high-risk patients treated with PCI who had completed 3 months of DAPT therapy, ticagrelor monotherapy was associated with a lower incidence of significant bleeding compared to ticagrelor plus aspirin, without an increased risk of death, stroke, or myocardial infarction. Thus, a major progress made in treating cancer patients is the feasibility of shorter DAPT therapy with the third-generation stent technology. Finally, drug-eluting balloons (DEB) represent a relatively new technology which enables treatment of in-stent restenotic lesions, but also de-novo lesions in small (≤2.75 mm) vessels [58, 59], as well as bifurcation lesions [60]. Such a strategy can be particularly useful in cancer patients at exceedingly high bleeding risk, as DAPT following DEB can be stopped after 4 weeks. Studies such as PEPCAD NSTEMI [61] have demonstrated that DCBs for the treatment of *de novo* lesions were non-inferior to BMS or DES, although larger trials with DES as comparator are needed.

Antiplatelet therapy and secondary prevention

In line with the previous discussion, several trials have demonstrated the safety and feasibility of shorter duration DAPT regimes in cancer patients at high bleeding risk. In addition to the TWILIGHT study [57], the MASTERDAPT subanalysis [62] looked at the effect of 1- or ≥3-month DAPT in high bleeding risk (HBR) patients treated with sirolimus stents for complex PCI (defined as one of: multivessel PCI; ≥3 stents/lesions; long stent length, bifurcation disease etc.). It was found that abbreviated DAPT was associated with lower bleeding complications compared with standard DAPT (HR, 0.64; 95% CI, 0.42–0.9), whilst not being associated with significantly increased risks of ischemic events [62]. The STOPDAPT-2 trial [63], which compared 1 month of DAPT followed by clopidogrel monotherapy, to standard 12 month DAPT, showed the shortened DAPT regime to meet criteria for both non-inferiority and superiority, with significantly reduced rates of cardiovascular and bleeding events [58]. In light of these findings, current ESC guidelines [64] recommend considering an abbreviated DAPT regime (1 month DAPT) in patients at high bleeding risk (class IIb), and de-escalalation of $P2Y_{12}$ inhibitors (e.g., from ticagrelor to clopidogrel), in order to reduce bleeding propensity. In high-risk cancer patients, these recommendations, together with a careful assessment of thrombotic vs. bleeding risks, are very useful when deciding length of DAPT regime. Whilst undertaking such risk assessments, it will be essential to first define HBR patients, as per the Academic Consortium Consensus document [16]. According to this document, HBR is defined as Bleeding Academic Research Consortium, BARC 3 or 5 bleeding risk of ≥4% at 1 year or a

risk of intracranial haemorrhage of ≥1% at 1 year. The consensus document also defines 20 clinical criteria, which are further divided into major criteria (e.g., long-term oral anticoagulation, severe renal failure with eGFR <30 ml/min/1.73 m^2, anemia with Hb <11 g/dl, active malignancy, liver cirrhosis with portal hypertension); and minor criteria (e.g., age ≥75 years, long-term use of non-steroidal anti-inflammatory drugs) [16].

Furthermore, secondary prevention occupies as important a role in cancer patients as in non-cancer patients. Thus, unless there are specific contraindications, consideration should be made regarding starting patients on drugs with established impact on survival post ACS, such as for instance angiotensin-converting enzyme inhibitors, beta-blockers and statins. In addition, lifestyle modification, wherever possible, should also be encouraged, in the form of healthy diet, smoking cessation, and increased physical activity.

CONCLUSION

In conclusion, the intricate interplay between CAD and cancer poses substantial challenges in the management of cancer survivors. With the increasing prevalence of both conditions, there is a pressing need for nuanced approaches to address the unique considerations of ACS in this population. As emphasised by a previous expert comment by Leszek et al. [65]. The interplay between CAD and oncology remains very nuanced, and extremely important when considering therapeutic options in this category of patients. For this reason, a multidisciplinary approach, including cardiology and oncology, or a specialized cardio-oncologist if available, together with radiologists, surgeons, and, if required, gastroenterologists, should help not only in selecting treatment based on comorbidity and risk, but also in monitoring for any potential complications related to treatment. The development of new stent technology, as well as innovations in intravascular imaging and pharmacology, have shown promise in improving outcomes for cancer patients presenting with ACS. Post ACS care of these patients must involve collaborative efforts between cardiologists and oncologists to develop patient-specific strategies that optimize cardiovascular outcomes without compromising cancer treatment.

Article information

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Table 1. Cancer drugs and their cardiovascular effects [8]

Cardiovascular pathophysiological effect	**Cancer drug**
Acute thrombosis	Alkylating agents e.g., cisplatin, cyclophosphamide VEGF inhibitors e.g., bevazicumab
Atherosclerosis acceleration	Tyrosine kinase inhibitors e.g., nilotinib
Vasospasm	Vinca alkaloids e.g., vincristine, vinblastine Anti-microtubule agents e.g., paclitaxel Antimetabolites e.g., gemcitabine, 5-FU
Endothelial dysfunction	Interferon-α

Abbreviations: VEGF- valcular endothelial growth factor; 5FU- 5-fluorouracil

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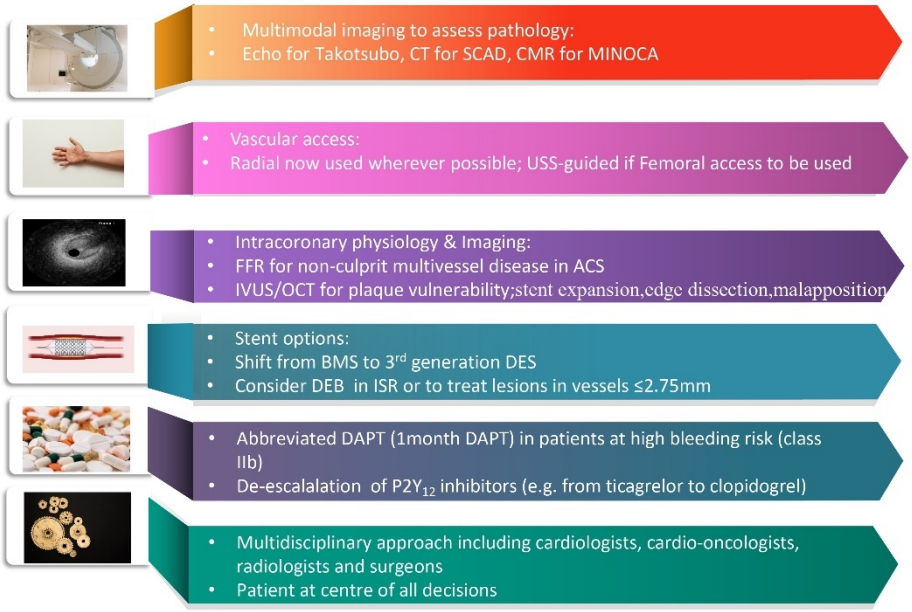

Pathophysiology of increased CVD in cancer survivors