PERSPECTIVE

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Management of ischemic coronary disease in patients receiving chemotherapy: an uncharted clinical challenge

Bibhu D Mohanty¹, Sudipta Mohanty^{*2}, Yasin Hussain³, Chandrasekhar Padmaraju², Sameer Aggarwal⁴, Rebekah Gospin⁵ & Anthony F Yu⁶

Acute coronary syndrome (ACS) coinciding with active malignancy presents a unique clinical challenge given intersecting pathophysiology and treatment-related effects. There is little established clinical guidance on management strategies, rendering most treatment approaches anecdotal. We present a case highlighting the complexity of managing a patient being treated for malignancy who concurrently suffers from ACS. We then review the literature on co-management of ACS and malignancy, including reports of specific cancer therapies associated with ACS, unique features of clinical presentation and optimal use of dual antiplatelet therapy to minimize risks of bleeding and thrombosis. We also describe gaps in current literature, challenges in systematically studying the clinical intersection of these disease processes and propose alternative methodologies for further research.

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The occurrence of acute coronary syndrome (ACS) in the setting of active malignancy raises unique clinical challenges given the interplay of distinct pathophysiologic mechanisms. As simultaneous management of both pathologies has not been thoroughly studied, therapeutic decisions are largely based on anecdotal experience and may intersect to generate unexpected consequences. The rapid burgeoning of cardio-oncology as a prominent subspecialty and rising interest in forging a structured approach to patients with both cancer and cardiovascular disease are underscored by the development of new research and educational initiatives by the oncology and cardiology professional societies (e.g., the recently created Cardio-Oncology member section of the American College of Cardiology). Interdisciplinary care initiatives, to promote funding pathways, infrastructure and development of data driven guidelines, are also being called for [1]. To date, this has largely been dominated by interest in cancer-therapy-related cardiomyopathic risk and methods to estimate risk, mitigate risk, identify early subclinical signs of cardiac dysfunction and manage late cardiovascular effects in cancer survivors [2]. A growing awareness of the vascular and metabolic perturbations of oncologic therapy has led to research efforts to characterize these effects in both preclinical and clinical arenas [1,3]. However, although malignancy is known to be a risk factor for stent thrombosis – likely as a result of acquired hypercoagulability – there are no prospective data evaluating outcomes

KEYWORDS

• acute coronary syndrome
• cancer • cardio-oncology
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¹Section of Cardiology, Department of Medicine, Dartmouth-Hitchcock Medical Center, Lebanon, NH, USA

²Department of Medicine, University of California Riverside, Moreno Valley, CA 92555, USA

³Department of Medicine, Weill Cornell Medical College, NY 10065, USA

⁴Department of Medicine, University of Maryland, School of Medicine, Baltimore, MD 21201, USA

⁵Stamford Health Medical Group, Stamford, CT 06905, USA

⁶Department of Medicine, Memorial Sloan Kettering Cancer Center, NY 10065, USA

*Author for correspondence: Tel.: +1 909 618 7153; sudipta.mohanty@ucr.edu

and interactions among cancer patients treated invasively for ischemic heart disease (IHD). This knowledge gap offers an additional frontier for further research and an opportunity to improve patient outcomes. We present a case that highlights the complexities of managing both disease processes, and summarize the current literature on chemotherapy-related coronary events and discuss data relating to coronary events in cancer patients. We then present challenges that have precluded extensive study in this area and suggest avenues to pursue better fundamental and clinical understanding.

A case example

The following case highlights the challenges and limitations of our current per-patient approach to IHD management in cancer patients and provokes hypotheses that have yet to be explored. The patient is a 54-year-old man who experienced three successive acute myocardial infarctions at the same coronary anatomic site over a 4-month period likely due to unforeseen consequences of active chemotherapy in the setting of intracoronary bare metal stent (BMS) placement.

The patient had originally presented with a non-ST elevation myocardial infarction (NSTEMI) 4 months prior to our point of contact. At the time, he was thought to have stage 2 bladder cancer with a single lymph node positive for local invasion and was receiving a taxol- and gemcitabine-based chemotherapy regimen. Coronary angiography at that time revealed mid-vessel thrombosis in the dominant right coronary artery, treated with aspiration; no stenting was performed. This approach was chosen to avoid both bleeding and thrombotic concerns given concomitant diagnoses of thrombocytopenia and pulmonary embolism, respectively – thought to have arisen from chemotherapy-induced myelosuppression and malignancy-associated hypercoagulability. He had not been started on anticoagulation due to thrombocytopenia.

After 2 months of the initial myocardial infarction, the patient presented once again with acute thrombotic occlusion at the same site in the right coronary artery. After careful deliberation, it was decided to place a BMS to reduce the possibility of target lesion re-stenosis or thrombosis while still avoiding prolonged dual antiplatelet therapy (DAPT). Unfortunately, the patient was found to have occult blood in his stool during the ensuing hospital stay. A colonoscopy was considered to identify a

bleeding source, as well as evaluate for metastasis. However, as PET-computed tomography was unrevealing and serum hemoglobin levels remained at 11.0 g/dl not requiring blood transfusions, it was decided that it would be safer to perform colonoscopy well after the patient had completed at least 1 month of DAPT with aspirin and clopidogrel. Chemotherapy was continued.

Approximately 2 months following the second myocardial infarction, on the day he was scheduled for colonoscopy after having held clopidogrel for 5 days, the patient presented with an inferior ST-elevation myocardial infarction (STEMI). Emergent cardiac catheterization revealed fresh thrombus overlying the BMS. Thrombectomy was performed without stenting, and the patient was transferred to the intensive care unit with intra-aortic balloon pump support due to hypotension and persistent chest pain.

Current experience

As demonstrated with the case above, IHD in cancer patients presents a complex scenario that remains poorly understood and unexplored. Under usual circumstances, the duration of clopidogrel received by the patient would have been more than sufficient to permit complete re-endothelialization of the BMS and prevent acute stent thrombosis. However, it is possible that the antiproliferative effects of chemotherapeutic agents being administered to the patient may have interfered with the normal endothelialization process as expected among noncancer patients receiving a BMS. After clopidogrel cessation, the stent struts were thereby vulnerable to thrombus formation. This hypothesis is further illustrated in [Figure 1](#). Differences between various stenting platforms, choice and duration of antiplatelet or procedural antithrombotic therapy, or impact of cancer or cancer treatment on endothelial repair mechanisms all remain largely unstudied with the exception of anecdotal evidence and small retrospective case series. It is well known that cardiovascular disease and malignancy are both independently leading causes of morbidity and mortality in many parts of the world. While there are minimal data on the exact prevalence of ACS in cancer patients, the aging population will presumably present a rising prevalence of both pathologies. This urgently calls for additional data to inform physicians on how to manage the challenges that lie at the intersection of these disease processes.

Figure 1. Proposed schematic cross sections of a coronary artery depicting re-endothelialization 6 weeks following stent placement in three distinct clinical scenarios. (A) Bare metal stent without chemotherapy and completion of 4 weeks of dual antiplatelet therapy (DAPT). As expected, re-endothelialization is complete. (B) Drug-eluting stent without chemotherapy and ongoing DAPT to prevent platelet aggregation. As expected, re-endothelialization is incomplete. (C) Bare metal stent in a patient receiving chemotherapy and having completed 4 weeks of DAPT. Incomplete re-endothelialization due to effects of chemotherapy reducing the efficacy of DAPT may promote early thrombus formation on exposed stent struts.

• Cancer treatment-associated myocardial infarction

There have been multiple case reports of acute coronary events precipitated by infusion of various chemotherapeutic agents [4–17]. Several mechanisms have been proposed, including vasospastic phenomena, endothelial and mitochondrial cytotoxicity, cell-cycle arrest of cardiac endothelial cells, and even release of cytokines leading to plaque rupture and platelet activation [14,15,18–21]. The variability in proposed mechanisms reflects the variability in site of action and downstream effects of cancer-specific treatment leading to ischemia. The temporal onset of ischemia also varies widely. Fluorouracil has been reported to incite events in patients with no cardiac risk factors and patients with a history of myocardial infarcts at times ranging from infusion onset [22] to minutes into therapeutic course [23] and to even several days following administration [23,24]. Vincristine has also been reported to cause this complication within hours of infusion [12]. Rituximab has also been implicated in postinfusional myocardial infarction at time points varying from infusion to several days postinfusion [21,25,26]. It has been described to cause infarcts in patients with no prior coronary artery disease, native vessel disease and patients with prior percutaneous coronary intervention (PCI) [4,21]. Successful stent placement with resolution of the acute event has allowed reinitiation of rituximab with no further events [24]. Cisplatin has caused infarcts at the time of infusion and up to weeks after the infusion, with the

majority of cases in young males with germ cell tumors of the testis [27–29]. BCR–ABL-directed tyrosine kinase inhibitors such as nilotinib and ponatinib have been reported to cause acute coronary events, ranging from time of infusion to a month after therapy. Other tyrosine kinase inhibitors such as sunitinib, pazopanib and sorafenib are associated with increased arterial thrombotic events, but not specifically within the coronary circulation [30]. Stent thrombosis, the mechanism of which is inherently distinct from native-vessel ACS, has also been seen with a variety of agents. Malignancy-driven proinflammatory and hypercoagulable conditions are certainly contributory, and malignancy-specific mechanisms such as leukemic cell infiltration of coronary arteries and cardiovascular tissue are likely additional propagators of ischemia [31,32].

• Clinical presentation

A retrospective study by Yusuf *et al.* looked at 456 cancer patients diagnosed with ACS. About 85% of patients had non-ST elevation myocardial infarction versus 15% with STEMI. A third of the patients had liquid tumors. Regardless of infarct type, rates of chemotherapy use and chest radiation therapy were similar. Dyspnea rather than chest pain was the most common presenting symptom, even among STEMI patients. This may be attributable in part to pain management strategies employed for cancer-related pain that may have masked typical anginal discomfort, which interjects an important caveat to the clinical assessment of coronary ischemia

in this population [33]. A separate retrospective analysis on 275 cancer patients performed by the same group showed that over 10% of patients presenting with ACS were ultimately diagnosed with Takotsubo cardiomyopathy [34]. This distinction is important as it can allow discontinuation of low-molecular-weight heparin and P2Y₁₂ inhibitors to reduce risk of cancer-therapy-related bleeding complications.

• ACS management

There are no studies that sufficiently address the conglomerate of ACS therapies in cancer patients, and only a few small retrospective analyses have attempted to characterize outcomes of conventional medical therapy. The use of aspirin was studied in 70 patients with varying malignancies who suffered from an acute myocardial infarction at a specialized cancer hospital [35]. 27 of them were thrombocytopenic with a median platelet count of 32,000/ μ l. Among this group of patients, specifically, 7-day survival was 6% in those who did not receive aspirin versus 90% in those who did ($p < 0.0001$). No severe bleeding complications were reported. Patients with normal platelet counts also did significantly better when administered aspirin ($p < 0.0096$). A larger retrospective analysis of 456 unselected cancer patients discharged with a diagnosis of myocardial infarction were analyzed for 1-year outcomes; 70 of these patients had STEMI and only 15 underwent catheter-based intervention [33]. The overall 1-year survival rate was poor (26%; 95% CI: 22–30%). Reflecting trends in the general population, frequency of β -blocker, aspirin and thrombolytic use were greater in STEMI patients and did not differ in patients with limited versus advanced cancer. In a multivariate survival analysis, aspirin (hazard ratio [HR]: 0.77; 95% CI: 0.6–0.98) and β -blocker (HR: 0.64; 95% CI: 0.51–0.81) use were shown to be protective at 1 year, while statin and angiotensin-converting enzyme inhibitor were not. Based on these studies, it is reasonable to conclude that barring any overt contraindications, aspirin and β -blockers should be used in cancer patients as they are among the general population for the management of ACS.

• Bleeding risk

There are limited data regarding bleeding from ACS treatment in the setting of malignancy. Specifically, the ideal combination of agents to reduce thrombus formation secondary to both ACS and malignancy-driven hypercoagulability, while also minimizing bleeding risk

stemming from interaction with chemotherapeutics or impaired hematopoiesis, is unknown. Weakening of mucosal barriers, a common result of chemotherapy, may expose vessels to heightened risk with aggressive antithrombotic therapy, even without overt manifestations of hemorrhage. Additionally, secondary alterations in bone marrow and liver function may lead not only to thrombocytopenia, but also to dysfunctional platelets and clotting factors. As noted above, however, it would appear that aspirin therapy is beneficial even in ACS patients with thrombocytopenia, though the sample size tested is small.

Historically, cancer patients with significant thrombocytopenia were deferred from antiplatelet therapy, and therefore also deferred from potential clinical benefits of coronary intervention, which require antiplatelet therapy. In several series of patients, Yusuf *et al.* have looked at safety and bleeding risk with utilization of antiplatelet therapy in the setting of malignancy with thrombocytopenia. Their work suggests that beyond platelet count alone, the cause of thrombocytopenia might modulate bleeding risk from antiplatelet therapy. This implicates an interaction between platelet function and count. Specifically, in cancer patients experiencing ACS with and without thrombocytopenia, aspirin improved short-term survival without an excess in bleeding [36]. Expanding these data, the Society for Cardiac Angiography and Interventions recently published an expert consensus statement to provide focused guidance when treating these patients. They suggested reduced platelet count thresholds for cardiovascular therapies, recommending aspirin initiation in patients with platelet counts $>10,000/\text{ml}$ and DAPT initiation (with aspirin and clopidogrel) if platelet counts are $>30,000/\text{ml}$. Prasugrel, ticagrelor and IIB–IIIA inhibitors have not been studied with platelet counts $<50,000/\text{ml}$ [37]. The American Society of Clinical Oncology practice guidelines on platelet transfusion in cancer patients recommend prophylactic transfusion prior to cardiac catheterization in the following two scenarios: platelet count $<20,000/\text{ml}$ plus high fever, leukocytosis, rapid fall in platelet count or other coagulation abnormalities, or platelet count $<20,000/\text{ml}$ in solid tumor patients receiving chemotherapy for bladder cancer, gynecologic malignancies, colorectal tumors, melanoma or necrotic tumors [38].

• Ischemia & thrombosis

The Dutch Stent Thrombosis Registry is one of the few large studies to demonstrate a critical intersection between IHD management and malignancy [39]. In over 21,000 patients receiving BMS and drug-eluting stent, only DAPT cessation at varying time points of 30 days (HR: 36.35; $p < 0.0001$), 30–180 days (HR: 4.63; $p < 0.0122$), 180–365 days (HR: 5.87; $p < 0.0043$) and stent undersizing (HR: 13.39; $p < 0.0001$) was a stronger independent risk factor for stent thrombosis than active malignancy (HR: 4.50; $p < 0.0001$), as seen in **Figure 2**. The authors do not address this association, which perhaps speaks to the complexity of this issue and lack of any concrete grounding on which to formulate discussion.

The recently published DAPT trial tested 30-month DAPT compared with a conventional 12-month regimen following PCI in a

prospective randomized fashion [40]. The trial demonstrated significant reduction in stent thrombosis, myocardial infarction, and major adverse cardiovascular and cerebrovascular events among patients in the prolonged treatment arm. However, all-cause mortality was higher (2.0 vs 1.5%; $p = 0.05$). Since cardiac deaths were nearly the same in both arms, this increased mortality was due to an excess of death from noncardiovascular causes (48 vs 22 deaths; $p = 0.002$) – most notably from cancer. This unexpected link to malignancy led to a firestorm of questions regarding trial design, presentation of data, randomization and thienopyridine safety. Clopidogrel, in particular, was used in the majority of patients with cancer-related death. This finding should not come as a complete surprise, however, given that multiple randomized trials in the past have also shown similar correlations of increased

Figure 2. Independent risk factors for stent thrombosis. A comparison of the total group of patients with stent thrombosis with all matched-control subjects. Represented by HR and 95% CI.

ASA: Acetyl salicylic acid; CAD: Coronary artery disease; DES: Drug-eluting stent(s); DM: Diabetes mellitus; HR: Hazard ratio; LVEF: Left ventricular ejection fraction; PAD: Peripheral artery disease; PCI: Percutaneous coronary intervention; TIMI: Thrombolysis in myocardial infarction.

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noncardiovascular deaths among cancer patients receiving prolonged thienopyridine therapy [41].

Upon consideration of additional data and detailed review, the US FDA concluded that definitive statements on the effect of DAPT on malignancy could not be drawn due to aspects of study design, enrollment and missing data. Additionally, they reported that although both clopidogrel (relative risk [RR] = 1.2) and prasugrel (RR = 1.3) were associated with an excess of solid cancer events, point estimates of increased risk were not significant as the study was heavily underpowered to detect such a difference. They also acknowledged that the rate of cancer events in the noncardiovascular death group was consistent with census data from the CDC which showed cancer to be the dominant cause of death (49%) among those in a similar age group. Based on the information we have at this time, antiplatelet treatment recommendations cannot be modified, particularly as thienopyridine use has not been clearly implicated in malignancy risk through numerous prior trials with tens of thousands of patients. However, this certainly remains a wholly unanswered question and represents an area ripe for further investigation from both a mechanistic and clinical standpoint.

• IHD & intracoronary radiation therapy

While radiation therapy is typically more germane to the discussion of malignancy, the possibility of intracoronary radiation therapy (IRT) to treat IHD has been evaluated extensively. In-stent restenosis (ISR) still represents a significant problem after PCI, with recurrence rates reportedly ranging from 7 to 37% and a recurrence rate after treatment for ISR >30%. IRT for ISR involves treatment of the entire lesion site with a β -emitting (electrons generated from phosphorous 32, strontium/yttrium 90 or rhenium 188) or γ -emitting (photons from iridium 192) radiation source via either a transiently indwelling coronary catheter or a radioactive stent platform. Controversy still surrounds which radiation source provides greater efficacy. However, the preponderance of data suggests that β -radiation provides lower intravascular indwelling times and lower radiation exposure to personnel and patients [42].

Current American Heart Association guidelines do not support the use of IRT for restenosis, instead favor drug-eluting stent placement as the best available option [43]. Placebo-controlled trials show marked short-term

(<6 months) reduction in restenosis rate, need for repeat revascularization and major adverse cardiac events. However, on long-term follow-up (6–48 months), IRT results in more target lesion revascularization, target vessel revascularization and thrombosis [44]. Additionally, complications such as late thrombosis and the edge restenosis have been noted [45–48], potentially attributable to therapy missing full geographic coverage of the restenotic segment [49]. Triggers may include delayed re-endothelialization, unhealed dissection, inadequate antiplatelet therapy and the use of additional stents [50]. There is no established role for use of this technology in patients with acute ischemia and concurrent malignancy. However, IRT reminds us of the potential to develop novel therapeutic approaches where seemingly unrelated pathologies intersect.

• Novel PCI therapies

Bioresorbable stents (BRS) and drug-coated balloons (DCB) have been under study for the last decade as potential solutions to late lumen loss, thrombotic events related to the implanted stent materials and prolonged DAPT. BRS have been in use in Europe for approximately 5 years, and DCBs have been used in peripheral intervention. ABSORB II was the first randomized controlled trial to directly compare biodegradable and standard drug eluting stents. About 501 patients with myocardial ischemia were enrolled in the study and randomized to receive the Absorb everolimus-eluting BRS or the Xience everolimus-eluting cobalt–chromium stent. The Absorb BRS showed noninferiority in composite end points of adverse cardiac events, myocardial infarction and clinically indicated target lesion revascularization [51]. This was followed by the ABSORB III trial, a larger study of 2008 patients with more complex and multivessel disease. Noninferiority of the Absorb BRS on the same composite end points was again demonstrated [52]. This served as the basis of the FDA's recent approval of BRS on 5 July 2016. Of note, patients with malignancy were excluded from both studies. However, as evidenced by the case above, it stands to reason that these options may hold considerable potential in patients with active malignancy and chemotherapy, especially if DAPT presents higher risk of bleeding. These new developments should spark curiosity in the safety and efficacy of novel management approaches to ACS, particularly for cancer patients in whom

antiplatelet therapy often poses a major clinical dilemma. For example, in the acute setting, a patient on active chemotherapy may be treated solely with DCB angioplasty with more durable stent-based therapy performed later in a staged fashion once chemotherapy is completed. Certainly, more investigation is required in this field, as demonstrated by two recent meta-analyses which suggest increased stent thrombosis among BRS [53,54] and the even larger ABSORB IV trial currently underway to evaluate different end points, including symptoms and quality of life.

Challenges to clinical study & potential solutions

Randomized trial data to inform decision making in this setting are nonexistent. There are a number of factors that would make it practically impossible to design a study to determine optimal IHD management in the setting of active malignancy. Malignancy manifests in a vast multitude of permutations specific to location, organ or organ system involved, degree of progression, and the interplay of genetic and environmental factors that promote a unique natural history. There would be no way to generalize the impact of malignancy on the degree of systemic hypercoagulability, tumor-specific biochemical mediators, effects on endothelial function or plaque integrity, response to the systemic impact of myocardial ischemia or the interaction of cancer therapies with specific antiplatelet and anticoagulant agents used during treatment of myocardial ischemia. From the perspective of primary PCI, the clinical response to specific features of different stent platforms would also vary across malignancies. Examples include the drug released, scaffolding structure and material, maneuverability, interaction with angiogenic cytokines and downstream rates of thrombosis or restenosis. A well-designed prospective trial with defined criteria and parameters would simply fail to capture the inherent variability in the subject matter, and, in turn, would yield little meaningful information.

• Alternative methodologies

As an effective alternative, the development of registries comprising data on patients being actively treated for both malignancy and IHD would permit identification of clinically important patterns. Organizing a database of this kind

to yield meaningful output would certainly be a complex enterprise given the breadth of data, but still maybe within the processing ability of modern information systems. To reduce noise, albeit at the loss of some degree of resolving power, drugs or cancers can be included selectively. For example, only chemotherapeutics that impact vascular endothelium or angiogenesis or drugs known to cause nonvascular myocardial toxicity (i.e., anthracyclines) can be followed. Alternatively, specific cardiac medications can be followed in selected cancer populations to look at impact on outcomes. Yet another approach maybe to include only cancers, most often known to intersect with coronary disease due to similar risk profiles (i.e., smoking as a prominent risk factor for lung cancer and coronary disease).

The studies on aspirin and β -blockers discussed earlier, albeit small, retrospective and hampered by considerable confounding factors, serve as foundational attempts to characterize patterns in patient data, and will open the doors to further study. The rise of collaborative efforts with cardiovascular specialists in dedicated cancer hospitals will undoubtedly facilitate development of such registries.

• A role for intravascular imaging?

The selective use of intravascular imaging modalities may aide in better understanding the nature of coronary occlusion and response to intervention during malignancy. Intravascular ultrasound has long been used to characterize vascular wall composition, thrombus burden, adequacy of stent deployment and residual disease burden. Optical coherence tomography offers exceptional intima-medial and luminal resolution with similar instrumental profile. Near-IR spectroscopy employs IR-derived chemograms to selectively identify the extent of lipid content in the arterial wall. Although operators may hesitate to use additional devices when treating patients with underlying malignancy, use of these devices in well-trained hands is safe, efficient, and can certainly inform important treatment decisions on a case-by-case basis. In the setting of malignancy, these tools may be able to distinguish classic myocardial infarction, which manifests following rupture of unstable, lipid-laden plaque, from less common causes such as emboli, plaque fissuring or irregularity, and endothelial injury or dysfunction. An example of the clinical impact of such

information was demonstrated in a small optical coherence tomography-guided study showing that acute myocardial infarction may feasibly be treated by thrombus aspiration alone, without stent placement [55] – an option that may be an extremely appealing treatment strategy in cancer patients. Furthermore, Ito *et al.* have shown using intravascular ultrasound that thrombus formation rather than atherosclerotic plaque precipitated the hindrance of coronary flow in two patients treated with cisplatin for advanced gastric cancer and a non-small-cell adenocarcinoma of the lung [56].

• Rise of a new field

The ‘Heart Team’ approach has gained considerable popularity in conjunction with the development of structural intervention, bringing cardiologists, surgeons and other involved disciplines together for more deliberative and patient-centric decision making in complex cases. The growth of cardio-oncology has forged a similar pathway. Oncologists, cardiologists and care-related staff are working together to facilitate improvement in mutual understanding of the clinical issues at play in this population. While the impact of Heart Team on outcomes is debated, it is true in almost any deliberative context that having the maximal amount of information from multiple contributing sources will likely be of benefit to the patient.

There is also growing interest in the formalization and establishment of cardio-oncology clinical and research programs among fellows and early career faculty [57]. This has remained largely in the realm of secondary cardiomyopathy, which offers an expansion of academic opportunity in the study of management of coronary ischemia during malignancy.

Conclusion & future perspective

The management of acute IHD among cancer patients remains a poorly studied area, bereft of data barring a few observational analyses. The CDC currently lists heart disease and cancer as the two leading causes of death in the US population [58]. As the two pathologies will likely continue to intersect with greater frequency, it is only a matter of time before this sobering statistic garners greater social and clinical attention.

Patients with cancer have traditionally been left out of clinical trials in ACS for the inherent

confounding effect on outcomes, which makes them such a challenge to manage. The need of the hour, however, calls for a scientific approach to understand how to manage these patients, especially before the concomitant incidence outpaces our ability to coherently treat such illness. Breaking with past enrollment conventions, studies should be performed specifically targeting patients with cancer. Randomized trials may be challenging to orchestrate given the complexity of cancer, which is a broad categorization for numerous unique pathologies. However, considerable preliminary information may be derived from registries and prospective observational data. Presently, even this information is sparse in the literature.

The Heart Team concept that has recently regained prominence in cardiology is starting to formulate in the cardio-oncology sphere as well. A field borne of collaborative enterprise and driven largely by delayed cardiac sequelae of childhood cancer therapy and oncotherapy-related cardiotoxicity, cardio-oncology will continue to grow as dedicated centers and subspecialists increase. We anticipate that increased conversation among cardiologists, oncologists, pharmacists, basic scientists, medical device engineers, statisticians, clinical trialists and industry experts will yield a more selective approach to ACS management based on the type of chemotherapy being used, the type of underlying malignancy and with consideration for drug–drug interactions. Newer *ex vivo* and *in vivo* imaging technologies will allow us to visually analyze clinically pertinent intersections, and newer stent technologies will likely play a role in reducing the effects of concomitant disease as well. Rather than being rigidly uniform or inconsistently anecdotal with our recommendations regarding antithrombotic management and interventional strategies, patient-specific recommendations can be made to optimize outcomes.

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EXECUTIVE SUMMARY**Cancer treatment-associated myocardial infarction**

- Case reports have correlated various chemotherapeutic agents including fluorouracil, vincristine, rituximab and cisplatin with acute coronary events.
- Temporal onset of myocardial ischemia in these reports varies widely.
- Acute coronary syndrome (ACS) has been documented in the context of various malignancies in all degrees of cardiovascular risk. Multiple mechanisms have been proposed.

Clinical presentation

- ACS in cancer patients predominantly presents as non-ST elevation myocardial infarction (85%), and dyspnea appears to be the primary presenting symptoms.

ACS management

- Small retrospective analyses on ACS in cancer patients have shown that aspirin reduces mortality without increasing bleeding risk, even in patients with thrombocytopenia. Data also suggest that β -blockers may have a mortality benefit as well.

Bleeding risk

- Limited data and expert consensus suggest that aspirin and clopidogrel can be given safely at lower platelet counts in select patients to minimize thrombotic complications without significantly increasing cancer- or chemotherapy-related bleeding complications.

Ischemia & thrombosis

- Data from large patient registries have established active malignancy as a strong independent risk factor for stent thrombosis.
- There are some data to suggest prolonged thienopyridine therapy correlating with increased noncardiovascular death in cancer patients. However, limitations in the data do not allow for definitive conclusions nor provide grounds for modification in antiplatelet treatment recommendations.

Ischemic heart disease & intracoronary radiation therapy

- Current American Heart Association guidelines do not support the use of intracoronary radiation therapy for coronary restenosis given good short-term but poor long-term outcomes.

Novel percutaneous coronary intervention therapies

- The US FDA has recently approved bioresorbable stents given noninferiority to drug-eluting stent. These novel therapies have not been studied in the context of ACS in patients with active malignancy and should be prime targets for future research.

Challenges to clinical study & potential solutions

- There are many practical barriers to studying ACS in cancer patients via randomized controlled trials.
- Alternative methodologies include the development of registries for both ischemic heart disease and malignancy to help identify important clinical patterns; the use of intravascular imaging to study the *in vivo* pathophysiology underlying a unique combination of diseases and facilitate patient-specific decision making; and the adoption of the 'Heart Team' approach to increase interdisciplinary collaboration.

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