Treatments in Patients with Cancer and Cardiac Diseases

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15.1 Introduction

The incidence and the prevalence of both cardiovascular and the neoplastic diseases are increasing, as are the therapeutic possibilities and survival. Thus, identifying the best cardiovascular care in a patient ready to start an antineoplastic treatment is becoming a rather common problem.

The coexistence of two different diseases may rise several problems:

- The presence of the tumor might worsen the cardiac status
- The antineoplastic treatments might directly or indirectly worsen the preexisting cardiac problems or may limit the cardiac therapeutic options.
- There are pharmacological interactions between cardiac and antineoplastic drugs
- The prognosis of either cardiac or neoplastic disease might influence the therapeutic choices

These points will be analyzed in summary here (for more details go to the relative chapters).

15.1.1 Risk of Worsening of Cardiac Status Due to the Tumor

- Several tumors induce a hypercoagulable status and might increase the risk of thromboembolism [1, 2]. In patients with atrial fibrillation (AF), history of deep vein thrombosis, and/or pulmonary embolism, mechanical prosthetic cardiac valves anticoagulant therapy should be optimized and followed strictly unless actively bleeding.
- A change in the anticoagulant strategy may be required in particular cases: oral anticoagulants (OA) may be less effective in patients with bowel disease, or—on the other hand—be less tolerated in case of bleeding. Low molecular weight heparins (LMWH) are the first choice in treatment and prophylaxis of venous thromboembolism in cancer, since they are more effective and safe compared to OA. To date, there are insufficient evidence to recommend NOACs in cancer patients [3–5]. (See also Chap. 6: "Thromboembolic disorders")

In patients with chronic AF or mechanical prosthetic valves, LMWH at dosage of 100 UI/kg twice a day should be considered as the optimal alternative to OA until the cancer has been cured.

- New onset or recurrence of AF is rather common in lung cancer patients, mostly after thoracic surgery, and affects negatively the clinical outcome.
  - ECG and possible Holter monitoring are useful to early detection of arrhythmias. In patients at high risk (clinical history of recurring AF, enlarged left atrium, depressed left ventricular function), antiarrhythmic prophylaxis may be necessary. Unless contraindicated in patients with thyroid dysfunction or by drug–drug interactions, beta-blockers and amiodarone are the preferred agents.
- Severe anemia (as observed in some **hematologic** malignancies or in solid tumors with severe bleeding) may decompensate a patient with ischemic heart disease or a patient with dilated cardiomyopathy. Secondary tachycardia may also cause angina or precipitate heart failure in patients with both systolic and diastolic dysfunction.
  - Try to correct anemia as far as possible.

- Persistent sinus tachycardia should be treated if not well tolerated: low dose beta-blockers (bisoprolol, starting with 1.25 mg once a day and carefully titrating the dose according to blood pressure) or ivabradine (5 to 7.5 mg twice a day) in case of hypotension are useful.

15.1.2 Antineoplastic Treatments Interfering with the Cardiovascular Function

- Several antineoplastic treatments are associated with an increased risk of thromboembolism, which may be life-threatening [6].
  - Patients with other thrombosis risk factors should receive appropriate prophylaxis [7].
- Some antineoplastic drugs (as platinum, for instance) require the infusion of large amount of fluid to prevent nephrotoxicity. **In patients with dilated cardiomyopathy, or with diastolic dysfunction, the volume overload may precipitate acute decompensation and pulmonary edema.**

In patients with left ventricular dysfunction, a careful balance of fluid loads is necessary.

- Some antineoplastic treatments may cause an electrolyte imbalance (even indirectly, because of emesis, or of bone or tumor lysis) or may prolong the QT interval. In patients with a clinical history of arrhythmias or with ischemic heart disease, this might be harmful.
  - Baseline routine examinations in any neoplastic patient should include an ECG; cardiologic evaluation should be asked if it is abnormal.
  - In patients at risk, the possibly precipitating factors (anemia, electrolyte changes…) should be prevented or promptly corrected.
- Following abdominal surgery or antineoplastic treatments inducing prolonged emesis, some patients may be unable to take regularly their prescribed cardiologic drugs.
  - Oncologists and surgeons should ask a cardiologist's consult before therapy in any case there is such a risk. Some treatments (lipid lowering drugs, acetylsalicylic acid, anticoagulants in patients with recurring atrial fibrillation but in sinus rhythm, drugs with very long blood half-life as amiodarione, for instance) may be temporarily discontinued; other treatments should be changed from oral to transdermal, intravenous route, or rectal (i.e., aspirin 300 mg). It is better to plan the change some days in advance, in order to assess its efficacy.

15.1.3 Pharmacological Interactions Between Cardiac and Antineoplastic Drugs

The pharmacological interactions may be due to both a metabolic interaction (drugs metabolized by inhibitors or substrates of Cytochrome p450 [CYP450]) or to a cumulative side effect.

Metabolic Interactions

The association of a drug metabolized by the CYP 450 and a substrate, inhibitor, or inducer of the same cytochrome may be dangerous and require dose adjustments).

- Almost all the tyrosine kinase inhibitors (TKI) are ***metabolized*** by **the CYP450 3A4**, as several cardiac drugs (amiodarone, apixaban, diltiazem, edoxaban, flecainide, losartan, prasugrel, ranolazine, rivaroxaban, most statins excluding pravastatin and rosuvastatin, verapamil).
- Verapamil, diltiazem, amiodarone, and imatinib are ***inhibitors*** of CYP 450 3A4
- Other oncologic drugs (docetaxel, paclitaxel, imatinib, irinotecan, ondansetron, sirolimus, tamoxifen, paclitaxel, vincristine) and cardiac drugs (all the calcium channel blockers, atorvastatin, lovastatin, simvastatin) are ***substrates*** of CYP450 3A4.

In ◘ Table 15.1, the major interaction between the most used oncologic and cardiovascular drugs are summarized. However, many other interactions—not considered in this text—may be possible. There are several regularly updated sites to check interactions, as: www.drugs.com/drug_interaction.php

In ◘ Table 15.2 , are described antineoplastic drugs with low risk of cardiac toxicity

Cumulative Effects

QT interval may be prolonged by drugs commonly used in oncology (TKI, arsenic trioxide, bortezomib, ondansetron, tamoxifen, tacrolimus) and by several cardiac drugs (amiodarone, dronedarone, flecainide, furosemide, indapamide, nicardipine, ranolazine, quinidine, sotalol).

- The use of two or more drugs prolonging the QT interval may lead to severe, even life-threatening ventricular arrhythmias, as torsade de pointes and ventricular fibrillation.
- However, some drugs (as octreotide and the antiemetics dolasetron and granisetron) prolong the QT interval without inducing arrhythmias; with some other drugs the arrhythmic risk is limited to the higher doses or to the presence of a genetic predisposition.

A frequently updated, useful site to check drugs which may prolong the QT interval and related the arrhythmic risk is: www.qtdrugs.org

- Some TKI, as Sunitinib and thalidomide, may cause **bradycardia**, which may be severe and symptomatic in combination with cardiac drugs with the same effect, as beta-blockers and transdermal clonidine
  - In case of severe bradycardia, consider reduction/changes of cardiovascular drugs. In extreme cases, a pacemaker implantation might be indicated in order to continue the therapy.
- Lenalidomide given together with statins may increase the risk of **rhabdomyolisis**.
- Clopidrogrel, commonly used in coronary artery disease, especially with drug-eluting stents, has hepatic metabolism but in cancer patients with liver failure the efficacy has not been well established.
- Prasugrel without the same problem has major risk of bleeding.

15.2 Practical Approach to the Patient with Cardiovascular Disease

Any cardiac disease may be adversely influenced by different antineoplastic treatment side effects (◘ Fig. 15.1). As a general rule, a patient with known heart disease, before starting an antineoplastic therapy, should have his cardiac problem reassessed, and his/her therapy optimized (◘ Table 15.3).

Table 15.1 Pharmacological Interactions Between Cardiac and Antineoplastic Drugs

	Drug	Sunitinib	Sorafenib	Axitinib	Regorafenib	Pazopanib	Imatinib	Nilotinib	Erlotinib	Dasatinib	Everolimus	Others
Diuretics	Furosemide	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	
	Torasemide	NO	NO				A+	A+		NO		
	Hydroclorotiazide	NO	NO	NO	NO	NO					NO	
	Spironolacton	NO	NO									
B-blockers	Metoprolol	AE*§	NO				***A+***	A+		***P+***		
	Bisoprolol	AE*§	NO				***A+***	A+		***A+***		
	Carvedilol	AE*§	NO				A+	A+		A+		
	Atenolol	AE*§	NO	NO	NO	NO	NO	NO		NO	NO	
	Nebivol	NO	NO	NO	NO	NO	II	NO		NO	NO	
	Sotalolol	AE#	AE#			AE#		***A+ AE#***				
Ace-inhibitors	Enalapril	NO	NO	NO	NO	NO	A+P+	A+		P+	NO	
	Ramipril	NO	NO	NO	NO	NO	NO	NO		NO	NO	
	Lisinopril	NO	NO	NO	NO	NO	A+			P+	NO	
	Quinapril	NO	NO	NO	NO	NO					NO	
Sartanes	Losartan	NO	A-	II	II	II	A-P+	A+		A+P+	II	
	Candesartan	NO	NO	NO	NO		NO	NO		NO	NO	
	Telmisartan	NO	NO	NO	NO						NO	
	Olmesartan	NO	NO	NO	NO						NO	
	Irbesartan	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	

(continued)

Table 15.1 (continued)

	Drug	Sunitinib	Sorafenib	Axitinib	Regorafenib	Pazopanib	Imatinib	Nilotinib	Erlotinib	Dasatinib	Everolimus	Others
Calcium-channel antagonists	Verapamil	***Ø AE*§***	II	II (P+)	II (P+)	***Ø P+***	***ØP+***	A+P+	***ØP+***	***A+P+***	***Ø P+***	**+ Ibrutinib:P+ Ø**
	Diltiazem	***Ø P+ AE*§***	II	II (P+)	II (P+)	***Ø P+***	***ØA+P+***	P+		***Ø P+AE§A+***	***Ø P+AE§***	**+ Ibrutinib:P+ Ø**
	Nifedipine	AE*	II	II (P+)	II	II	***A+***	A+		***A+***	II	
	Amlodipine	AE*	II	II (P+)	II	II	A+	A+		A+	II	
	Lacedipine	II	II	II (P+)	II	II					II	
	Nicardipine	II	II								Ø **P+**	
	Ranolazine	***AE#***	***AE#***	II (P+)	II	***AE#***		***AE#***		***AE#***	II	
Lipid-lowering drugs	Simvastatine	NO	A+				***A+P+***	***A+P+***	**Ø^^**	***A+P+***	**A+**	**+ Lenalidomide: rabdomyolysis**
	Atorvastatin	NO	A+				***A+***P+	A+	**Ø^^**	A+P+		**+ Lenalidomide: rabdomyolysis**
	Pravastatin	NO	NO	NO	NO	NO	NO	NO	**Ø^^**	NO	NO	**+ Lenalidomide: rabdomyolysis**
	Rosuvastatin	NO							**Ø^^**			**+ Lenalidomide: rabdomyolysis**
	Ezetimibe	NO	NO	NO	NO	NO					NO	
	Gemfibrozil	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	
	Fluvastatin	NO	NO	NO	NO	NO	NO	NO	NO	NO	NO	**+ Lenalidomide: rabdomyolysis**

Antiplatelets, anticoagulants	Aspirin	NO	A+				NO	NO	&			**+ Ibrutinib: AE &; + Sirolimus: renal failure**
	Clopidogrel	NO	NO	NO	NO		A+	A+		A+	NO	**+ Ibrutinib: AE** &
	Ticlopidine				**AE** &					**AE**		**+ Ibrutinib: AE** &
	Acenocumarol	NO	A+				A+	A+				**+ Ibrutinib: AE** &
	Ticagrelor				**AE** &							**+ Ibrutinib/ Cabozantinib: AE** &
	Prasugrel											**+ Ibrutinib/ Cabozantinib: AE** &
	Warfarin	II	II				A+	A+	&	A+		**+ Ibrutinib: AE** &
	Heparin	NO	NO				A+			P+		**+ Ibrutinib: AE** &
	Dabigatran	NO	NO	NO	**Ø AE** &	NO	NO	NO		**Ø AE** &	NO	**+ Ibrutinib: AE** &
	Rivaroxaban				**AE** &					**AE** &		**+ Ibrutinib: AE** &
	Apixaban									**AE** &		**+ Ibrutinib/ temsirolimus: AE**&
	Digoxin	EA#	A-				***A-***	**AE #**		***AE#***		

(continued)

Table 15.1 (continued)

	Drug	Sunitinib	Sorafenib	Axitinib	Regorafenib	Pazopanib	Imatinib	Nilotinib	Erlotinib	Dasatinib	Everolimus	Others
Anti-arrhythmics	Amiodarone	***AE# P+***	***AE# P+***	II	***AP+***	AE#	***A+P+***	**A+ AE #**		**A+ AE #**	II	
	Dronedarone	***Ø AE#***	***Ø AE#***			***Ø AE#***		**A+ AE #**			Ø **AE#**	**+ Ibrutinib:P+**
	Propafenone	***AE#***	***AE#***	II	II			**A+ AE #**			II	
	Flecainide	***AE#***	***AE#***	II	II			**A+ AE #**			II	

***A* active interactions** (the oncologic drug alters the cardiovascular drug metabolism), *AE* addictive effect, Hypothetic= possible interaction (according to pharmacokinetics) but never reported so far, *NO* no interaction, *P* passive interaction (the oncologic drug metabolism is altered by the cardiovascular drug).
+ increases the concentration or effect of the drug; – reduces the concentration or effect of the drug
* Increases PR interval at ECG (possible atrio-ventricula block)
§ Bradicardia
# Increases QT interval at ECG (possible ventricular arrhythmias)
& Hemorrhagic risk
In bold the most frequent or clinically relevant interactions
Ø = dangerous interaction (black box warning)

Table 15.2 Antineoplastic drugs with low risk of cardiac toxicity

Drug	Use in oncology	Cardiotoxicity	Warnings
Citarabine	AML and other lymphoproliferative diseases.	At the usual dosage, very rare cases of arrhythmias have been reported; cardiomyopathy with fatal consequences has been described only when cytarabine is used at high dosage, in autologous staminal cell transplant.	Hematological, pulmonary, CNS, gastrointestinal toxicities
Gemcitabine	Bladder, lung, pancreatic, breast, and ovarian cancer	Cardiac toxicity is described as not common or rare. It can be used for all patients except for those with severe heart failure.	Pulmonary, hepatobiliary, gastrointestinal, and hematological toxicity
Vinorelbine	NSCLC, breast cancer	Only few cases of angina, myocardial infarction, and ECG abnormalities have been reported. It may cause respiratory distress which can mimic heart failure.	Pulmonary, gastrointestinal, and hematological toxicity
Carboplatin	NSCLC, breast, ovarian, endometrial cancer	Cardiovascular events, such as heart attack, have been seldom reported	Hematological toxicity, neurotoxicity. It should not be administered in case of kidney injury or immunosuppression
Chlorambucil	CLL, follicular lymphoma.	Cardiac events never reported	Gastrointestinal and bone marrow toxicity
BCNU	Brain cancer, multiple myeloma, Hodgkin disease, Non-Hodgkin lymphoma	Rare cases of cardiac events	Pulmonary, gastrointestinal, hematological, hepatic, kidney, testicular toxicity.
DTIC	Melanoma, Hodgkin disease, sarcoma.	Cardiac events never reported	Hematological toxicity, hepatic veno-occlusive disease, and hepatic necrosis
Bleomycin	Testicular cancer, Hodgkin disease.	Moderately increased MI risk at young ages has been described, probably because it is used with other drugs.	Lung fibrosis.

(continued)

Table 15.2 (continued)

Drug	Use in oncology	Cardiotoxicity	Warnings
Etoposide	SCLC, testicular cancer, high grade neuroendocrine tumors	Arrhythmias and myocardial ischemia are not common. Congestive heart failure has been reported in high-dose therapies	Gastrointestinal and hematological toxicity
Fludarabine	CLL, follicular lymphoma	Arrhythmias and heart failure rarely reported	Hematological and gastrointestinal toxicity
Methotrexate	Breast cancer	Pericarditis and pericardial effusion are very rare; hypotension is rarely reported.	
Mitomycin C	Different types of cancer such as breast cancer or colon cancer	Cardiac events not reported	Hematological and gastrointestinal adverse events
Oxaliplatin	Colon and pancreatic cancer	Cardiac events not reported	Neurological and gastrointestinal toxicity
Topotecan	Ovarian and cervical cancer, SCLC	Cardiac events not reported	Hematological toxicity

AML acute myeloblastic leukemia, *CLL* chronic lymphocytic leukemia, *SCLC* small cell lung carcinoma
Very common ≥1/10
Common from ≥ 1/100 to <1/10
Not common from ≥ 1/1000 to <1/100
Rare from ≥1/10,000 to <1/1000

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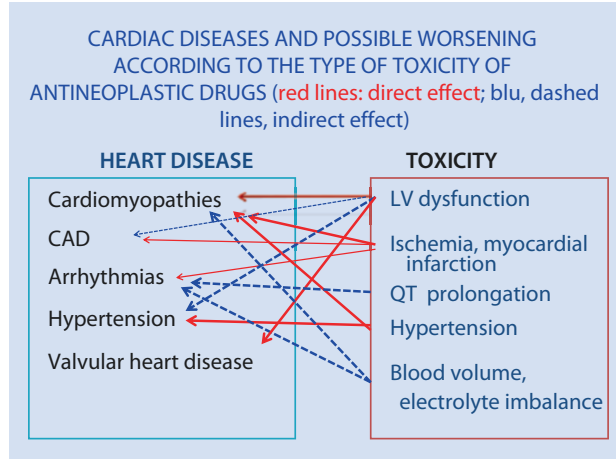

Fig. 15.1 Cardiac diseases (*left column*) at risk to be worsened/decompensated by some anticancer treatments' side effects (*right column*). *CAD* coronary artery disease, *LV* left ventricle

Table 15.3 General rules to be followed by the cardiologist in evaluating a patient undergoing anticancer therapy

1. Basal assessment of cardiologic problem
Severity (even second level tests)
Clinical impact (symptoms, mandatory drugs…)
Comorbidities (renal failure, diabetes, etc.)
Stratify the risk of progression
2. Optimize pharmacological therapy
Optimal blood pressure
Correct electrolyte imbalances
Check for drug interactions
Prefer potentially cardioprotective drugs
3. Consider possible non-pharmacological interventions
At short term
At medium term

15.2.1 Dilated and/or Hypokinetic Cardiomyopathies (CMP)

Cardiac function or symptoms may be worsened:
- By treatments which may impair left ventricular function (as anthracyclines, trastuzumab, tyrosine kinase inhibitors)
- By treatments requiring a large volume overload (as platinum)
- By any treatment which cause an increase in heart rate (either directly or causing severe anemia)

The oncologist may prevent/reduce the risk, when prescribing some antineoplastic therapies:
- Anthracyclines: the cardiac damage may be reduced by the association of prolonged infusions, dexrazoxane, of refracted reducing dose or use of liposomal formulations.
- TKI should be used—if possible—at lower dosage
- Anemia should be treated with erythropoietin

The cardiologist should check a baseline left ventricular function and optimize the cardiologic therapy before starting and follow up the patient frequently during the antineoplastic treatment.
- **Anthracyclines**: if at baseline echocardiogram shows any systolic or diastolic dysfunction, follow the suggestions above (CMP).
- **Anti-VEGF**: have a baseline and regular follow-up echocardiograms.

After an acute coronary syndrome or revascularization, the risk/benefit ratio of starting immediately or postpone for some weeks a required anti-VEGF therapy should be evaluated in the single patient; in either case, a close symptomatic monitoring should be done at least for the first 3 months if possible.

Table 15.4 Drugs preferred in the hypertensive patient undergoing anticancer treatments according to the possible side effects

Antineoplastic drug	Possible side effects	Cardiac drugs of choice
Anthracyclines, trastuzumab	Left ventricular dysfunction	ACE inhibitors or ARB, Beta-blockers
Fluoropyrimidines	Ischemia	Calcium channel blockers (amlodipine, nifedipine, diltiazem)
Bevacizumab	Hypertension, endothelial dysfunction, reduced NO production	Nebivolol, ACE inhibitors or ARB, Beta-blockers, Diuretics
Anti-VEGF TKI	Hypertension, Left ventricular dysfunction, CYP450 interaction	ACE or ARB inhibitors (no Losartan), Beta-blockers (Nebivolol and Atenolol preferred), Diuretics
Taxanes	Tachycardia, edema	Beta-blockers, Diuretics

ACE angiotensin converting enzyme, *ARB* angiotensin receptor blockers, *TKI* tyrosine kinase inhibitors, *VEGF* vascular endothelial growth factor

- **Fluoropyrimidines**: have a stress test before starting CT and adjust medical therapy (or consider revascularization) if positive; start first course at 50–75 % of regular dose; check side effects with ECG, visit and possibly stress test the last day of first course (see also Chap. 11, "Cardiac ischemia")

15.2.2 Hypertension

In patients with hypertension, a cardiologic evaluation and possibly some changes in chronic therapy should be planned before antineoplastic therapies, according to the possible side effects (Table 15.4).

- Before starting therapies with anti-VEGFR, the blood pressure should be optimized.
- If the antineoplastic treatments may cause bradycardia (as sunitinib, sorafenib, 5-fluorouracil) avoid verapamil, diltiazem (which may also interfere with the TKI), and strong beta-blockers.
- Have an echocardiogram before starting therapies with anthracyclines or trastuzumab: if hypertensive CMP is detected, follow the same rules above mentioned. Moreover, amongst the antihypertensive drugs, choose those with a protective effect on the myocardium (ACE-inhibitors, beta-blockers).

15.2.3 Coronary Artery Disease (CAD)

A baseline cardiologic evaluation should be planned before any possibly cardiotoxic antineoplastic therapy. Further interventions will be planned according to the possible cardiotoxicity of each antineoplastic agent.

Treatment Options for Chronic CAD

Treatment options for chronic CAD are: medical treatment in patients with stable angina; revascularization in patients with severe CAD and unstable or severe angina. The choice depends on the severity of cancer status [8].

- Revascularization with surgical coronary artery by-pass grafting (**CABG**) may be considered in patients with good cancer prognosis. Using of extracorporeal circulation considers the possibility of spread of the tumor, bleeding, and infections
- Percutaneous angioplasty (**PTCI**) may be preferred in patients with aggressive cancer. It may be performed with different techniques:
  - Dilatation without stenting (POBA). It is suitable in limited anatomic conditions only
  - Dilatation with implant of bare metal stent (BMS). It requires dual antiplatelet treatment for 4 weeks
  - Dilatation with implant of drug-eluting stent (DES). It requires dual antiplatelet treatment for one year. For the use of antiplatelets agents in cancer patients, see below the paragraph about acute coronary syndromes. Second and third generation DES appear to have comparable risk of stent thrombosis compared with bare metal stents with less restenosis and should be considered in the majority of the cancer patients.
- In case of **neoplasms requiring surgery and CAD requiring revascularization**, the timing of treatments should be planned on an individual basis, considering various options: staged approach (surgical treatment of neoplasm followed by revascularization or vice versa) or combined approach (cardiac and cancer surgery at the same session) [9].

Treatment Options for CAD with Acute Coronary Syndrome (ACS)

Treatment options for CAD with ACS are: medical treatment, thrombolysis, and catheter-based revascularization.

- Often the more aggressive strategy is not given to cancer patients, either because a concern about the cancer prognosis, cancer-related or unrelated comorbidities, including thrombocytopenia. Each decision should be taken on a individual basis, and poor cancer prognosis, renal or hepatic failure, or other severe comorbidities (like sepsis or cachexia) will trigger a more conservative approach.
- **A rather frequent condition which can be observed in cancer patients and should be discussed in detail is thrombocytopenia. It should be considered that:**
  - Thrombocytopenia does not protect from thrombosis, because platelets may be larger and more adhesive to the vascular surface.
  - Actually AMI has been reported in patients who have thrombocytopenia that is associated with various conditions and occurs in up to 39 % of patients who have both thrombocytopenia and cancer.
  - In a retrospective study of 2007, therapy with ASA was associated with a significantly improved 7-day survival after ACS in cancer patients, with or without thrombocytopenia, and not associated with more severe bleeding [10].
  - There are no large studies to assess the safety of antiplatelet or fibrinolytic agents in thrombocytopenic cancer patients, but several cases published in the literature report that their use may be relatively safe [11].

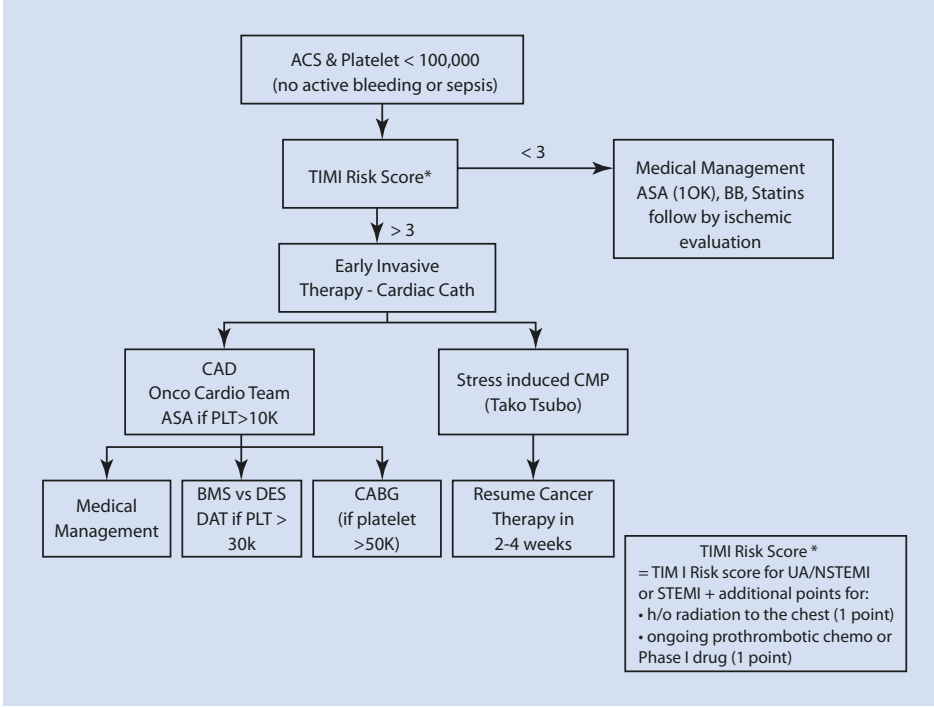

Fig. 15.2 Suggested operative flowchart in presence of Acute Coronary Syndrome (ACS) in thrombocytopenic patients. *ASA* acetylsalicylic acid, *BB* beta-blockers, *BMS* bare metal stent, *CABG* coronary artery by-pass graft, *CAD* coronary artery disease, *CMP* cardiomyopathy, *DAT* dual antiplatelet therapy, *DES* drug-eluting stent, *NSTEMI* non-ST elevation myocardial infarction, *STEMI* ST elevation myocardial infarction, *UA* unstable angina. Reproduced with permission from Iliescu CA, Iliescu GD, Marmagkiolis K. Myocardial Ischemia and Acute Coronary Syndrome in Cancer Patients. In: OncoCardiology, 2015.

- A retrospective study from MD Anderson Cancer Center published in 2012 showed that the patients treated with catheter-based reperfusion had a significantly better outcome; a significant advantage in survival was also given by beta-blockers, aspirin, and statins [12].
- Approaches to the treatment of AMI in thrombocytopenic patients might be better directed toward the evaluation of platelet function than toward platelet count, and the risk–benefit equation of invasive procedures and antithrombotic therapies may need to take this information into account [11].
- An operative flowchart for thrombocytopenic patients with ACS is reported in Fig. 15.2.

Patients with acute coronary syndrome and a cancer with medium-long term good prognosis should be treated according to the current guidelines for non-cancer patients. Changes in the treatment strategy may be necessary in particular cases, but thoughtfully weigh the risk and benefit.

In case of urgent surgery after PCI, intravenous tirofiban can be administered and clopidogrel restarted with dose of 300 mg.

- Cancer patients with bare metal stents (BMS) appear to have a sevenfold increase in risk of stent thrombosis compared to general population with the majority of events in patients on dual antiplatelet therapy (DAPT) [13].

- As cancer is a prothrombotic state, one might think that more potent antiplatelet therapies now available (Prasugrel, Ticagrelor) would be a better therapeutic option for this patient population. The advent of an oral reversible P2Y12 inhibitor (Ticagrelor), with rapid onset of action and offset of antiplatelet effect within 2–3 days, would allow better flexibility in the management of all types of patients with acute coronary syndromes.
  - The TRITON-TIMI 38 was a head-to-head trial to assess the efficacy and safety of the experimental antiplatelet agent prasugrel vs. standard care with clopidogrel on top of aspirin. Besides ischemic protection at expense of bleeding disadvantage, **prasugrel-treated patients experienced a three times higher rate of colonic neoplasms than with clopidogrel, and this difference was significant.** The gastrointestinal bleeding preceded the diagnosis of colonic neoplasms only in half of the patients.
  - More delicate platelet inhibition and shorter exposure to oral antiplatelet agents will prevail. We have used Ticagrelor in cancer patients with multivessel stenting, but larger clinical trials with different dual antiplatelet therapy combinations are needed to prove the superiority of one specific regimen [14].

15.2.4 Arrhythmias

- **Atrial fibrillation**: before starting therapies with drugs which could impair LV function, obtain a ventricular rate <80/m' and check regularly heart rate during chemotherapy; beta-blockers are the preferred drugs if anthracyclines are used. Thromboembolic prophylaxis and effective stroke prevention with oral anticoagulation should be prescribed, but the balance between thromboembolic and bleeding risk and the possible drug interactions must be evaluated (See Chaps. 6 and 7)
- **Bradycardia**: be careful when using fluoropyrimidines (mostly with 5-FU), sunitinib, and sorafenib. Obtain ECGs and possibly Holter monitoring during at least the first course of therapy, to assess the tolerability.
- **Ventricular arrhythmias**: check blood K+ and Mg++ (and correct with supplements if low) before starting CT and during the treatment in case of prolonged emesis; have regular ECG and possibly Holter monitoring when using fluoropyrimidines, platinum, or drugs which can prolong the QT interval. Consider also the possibility of underlying cardiac ischemia.

15.2.5 Valvular Heart Disease

The approach differs in patients with native valve disease and patients with prosthetic valves.

Native Valve Disease

Assess the entity of the dysfunction, the clinical impact, the possibility of progression.

- **Mild dysfunction** usually does not require any change in planned therapies
- **Moderate dysfunction** should be evaluated in prospect, considering the possible indication of cardiac surgery on the medium term, the planned time to be spent in antineoplastic treatments, and the prognosis of the tumor. The risk of an urgent cardiac surgery in a patient under chemotherapy may be very high. If CT is not urgent,

anticipating cardiac surgery, with insertion of a biologic valve which will not require lifelong anticoagulation, might be the best choice, mostly in patients with low grade tumors.

- **Severe dysfunction** usually requires cardiac surgery, which should be planned possibly before the antineoplastic treatment. In case of patients with severe aortic stenosis requiring urgent major abdominal or gynecological surgery for cancer, balloon aortic valvuloplasty may be used as bridge therapy [15]. In patients with expected survival more than 2 years, Transcatheter Aortic Valve Replacement (TAVR) can be considered.

There is a concern about the risk that cardiac surgery with extracorporeal circulation might favor the metastatic spread in solid tumors or worsen the prognosis in hematologic tumors [16, 17]. This risk has not been confirmed in the most recent studies [18–20].

A joint evaluation by the oncologist and the cardiologist (including careful assessment of severity, prognosis, and treatment options of each disease) is necessary to plan the best therapeutic approach in the individual patient.

Prosthetic Valves

- **Biologic valves** have no particular problem, beside the risk of bacterial endocarditis in case of severe depression of immunity defenses.
- **Mechanical valves** require chronic oral anticoagulation, which should be continued—if possible—even during chemotherapy. The ***oncologist*** should use—if possible—drugs less likely to induce thrombocytopenia, which do not interfere with oral anticoagulants and which do not cause emesis. If these drugs cannot be avoided, or if there is any risk of bleeding, LMWH may be used as an alternative.

LMWH must be prescribed at dose of 100 Units/kg twice a day. It should be taken in mind that the thrombosis of a mechanical prosthetic valve requires few days and is a life-threatening event. Proper and constant anticoagulation is mandatory. If blood platelets are reduced to <75,000/ml and there is a risk of bleeding, the dose of LMWH may be reduced but always given every 12 h.

15.2.6 Varicose Veins

Some antineoplastic treatments, as tamoxifen, fluoropirimidines, and anti-VEGFR, may increase the risk of deep vein thrombosis.

- Consider mechanical and/or pharmacological prophylaxis
- Suggest regular physical activity (walking, cycling)

15.2.7 Patients with Cardiac Implantable Electronic Devices (CIED) Who Need Radiotherapy

Radiotherapy may impair the function (signal interference, memory data loss or parameter reset) of these devices, even if they are not included in the radiation field, because of scatter radiation. The consequences may be asymptomatic or cause even severe symptoms:

- **Pacemakers (PM)** are generally implanted for advanced heart block and symptomatic bradycardia. If the patient is "***pacemaker dependent***," the loss of PM function may cause severe symptoms.
- **Internal Cardioverter Defibrillator (ICD)** are implanted in patients with an increased risk of life-threatening ventricular arrhythmias. If it detects tachyarrhythmias, it delivers an electric shock to revert the rhythm. A dysfunction of an ICD may cause both inappropriate (i.e., in absence of dangerous arrhythmias) shock deliveries and failure of shock delivery in presence of life-threatening arrhythmias.

The risk of clinically relevant complications depends mostly on:

1. Cumulative dose of radiation received by the device
2. Pacing-dependency of the patient

In a recently published study, proximity of the radiation treatment field to the device did not predict for malfunction (actually, the malfunction rates were higher with treatments to the abdomen and pelvis region), and the use of neutron-producing radiation (>10 MV) was the principal risk factor for device malfunction [21].

15.3 Practical Approach to the Patient with Cardiac Implantable Electronic Devices [22, 23]

15.3.1 Before Starting Radiotherapy

- Inform the treating cardiologist and inform the patient
- Evaluate if patients is pacing-dependent. If so, evaluate if there are medical approaches which can reduce this condition (i.e., reduce digitalis, beta-blockers, or other drugs causing bradycardia)
- If ICD, check if anti-tachycardia therapy can be switched off by magnet
- Plan a device check-up if the last one was done > 3 months before starting radiotherapy

15.3.2 During Radiotherapy

- *If the dose is <2 Gy:*
- *PM in patient not pacing dependent:* Monitor heart rate during radiotherapy
  - **ICD**: program tachycardia therapy off or use magnet
- *If the dose is 2 to 10 Gy and patients is pacing dependent:*
  - Crash cart present during RT
  - Weekly check-up of the device
  - Have an external pacing device (external defibrillator for patients with ICD) ready
  - Alert the cardiologist to be able to intervene within 10 min
- **If the dose is estimated to exceed 10 Gy** consider device relocation and discuss the indications for radiation therapy device-related risks. If the treatment is necessary:
  - Monitor ECG during each treatment session
  - Crash cart present during RT

- Have an external pacing device (external defibrillator for patients with ICD) ready
- Alert cardiology to be able to intervene within 10 min
- Check-up within 24 h of each treatment session by a pacemaker technician

15.3.3 After Radiotherapy

CIEDs need to be interrogated 1, 3, and 6 months after the last RT due to the risk of latent damage.

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