REVIEW ARTICLE

Modification of cardiovascular pharmacotherapy in palliative care patients with cancer: a narrative review

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KEY WORDS

cardiovascular pharmacotherapy, communication, end of life, palliative care, thromboprophylaxis

ABSTRACT

Palliative care patients with cancer are treated with many drugs, especially at the end of life. Limiting polypharmacy decreases the risk of associated adverse effects, medical errors, and harmful drug interactions. The time lag to benefit from the use of many medications used for cardiovascular diseases or their risk factors, such as hypertension and hypercholesterolemia, is frequently longer than the life expectancy of palliative care patients with cancer. It is ethically appropriate to modify, and even to discontinue, cardiovascular pharmacotherapy when there is no prospect of benefit. The decision to discontinue lipid-lowering drugs and antihypertensive drugs is rather straightforward. Antithrombotic therapy may be stopped in low-risk primary prevention but not in high-risk group. Discontinuation of drugs for heart failure may provoke exacerbation of symptoms and should be considered only in the last weeks of life.

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Introduction Palliative care is the active total care of patients whose disease cannot be cured.[1] The current population of palliative care patients consists mostly of patients with advanced cancer. In 2014, the World Health Organization adopted a resolution on early palliative care that calls for palliative care to be considered from diagnosis onwards and integrated into care for people with any condition that may lead to death in the foreseeable future, so the patient with chronic non-cancer disease (eg, heart, lung, and neurological disease) can also be considered a palliative care patient.[2] However, the focus of this paper is on palliative care patients with cancer.

The median of life expectancy of patients with advanced cancer is usually less than 2 months.[3-5] When palliative care is introduced earlier, a selected groups of patients may live longer. The median survival of patients with metastatic non–small-cell lung cancer receiving early palliative care was reported to be 11.6 months.[3]

Palliative care patients with cancer present with numerous comorbidities and are treated with multiple drugs. Adverse effects of cardiovascular drugs may become more pronounced at the end of life and negatively influence the quality of the patient's remaining life, so reconsideration of pharmacotherapy is worthwhile. The aim of this narrative review was to describe the literature regarding cardiovascular pharmacotherapy in the setting of palliative care patients with cancer, as well as to offer some recommendations for clinicians and encourage further research on this important topic.

The scope of the problem In a retrospective study of 2623 hospice patients in the United States, who received end-of-life care during their last week of life, the average number of medications administered was 10.2; 44% of patients continued antihypertensive drugs and 25% were given anticoagulants.[6]

A study of 2282 European patients with advanced cancer receiving opioids found that the mean number of administered drugs was 7.8. Drug classes that were frequently prescribed with opioids included anticoagulants (23%), diuretics (20.1%), and statins (6%).[7]

In a Swedish registry including 511 843 elderly adults in the final year before death, the proportion of individuals exposed to 10 different drugs rose from 30.3% to 47.2% in the final month of life. During the final month, the 5 most common drug classes were analgesics (60.8%),

antithrombotic agents (53.8%), diuretics (53.1%), psycholeptics (51.2%), and β-blockers (41.1%).[8] The largest increase in the number of prescribed drugs was observed among patients with cancer (the mean number of drugs per person increased from 6.7 to 10).

Palliative care patients require the use of numerous additional classes of drugs for symptom control, including analgesics, antiemetics, and anticholinergics, which may adversely interact with cardiovascular drugs.[6-8] In a large cohort of cancer patients, a potential drug interaction was identified in 27%. Most possible drug interactions (87%) involved drugs other than anticancer agents, such as warfarin and antihypertensive drugs.[9] Limiting the number of drugs at the end of life decreases the risk of associated adverse effects, medical errors, and harmful drug interactions.[10-13] These data emphasize the magnitude of the problem and raise the question of whether continuing cardiovascular pharmacotherapy is always necessary in hospice and palliative care patients.

According to the definition proposed by the European Association for Palliative Care, palliative care intends neither to hasten nor to postpone death.[1] The decision to modify, even to discontinue, the long-term use of medicines is difficult, requires experienced clinical reasoning, and must be based on sound prognostic data that are unfortunately hard to obtain. Cardiological emphasis on the prevention of vascular events must be balanced against the risk of dangerous drug interactions and concern for the quality of life. The problem can be analyzed with the concept of time lag to benefit, which has proved to be useful in many areas of medicine where prophylactic interventions display delayed time to benefit.[14,15] The time lag to benefit for the numerous medications used in cardiovascular diseases or risk factors, such as hypertension or hypercholesterolemia, is frequently longer than the life expectancy of a palliative care patient with cancer. The time lag to benefit is difficult to be rigorously evaluated; currently, it may be only approximated by visual inspection of the Kaplan–Meier curves.

The prognosis of palliative care patients with cancer may be evaluated with one of the available prognostic tools such as the Palliative Prognostic Index, Palliative Prognostic Score, or Prognosis in Palliative care Study models.[4,5,16]

Pharmacotherapy should be modified after identification of the patient's values and goals, reassessment of the latter, and reconsideration of therapeutic efficacy. Drug modification is more justified when the therapy is poorly tolerated. For discontinuation, suspected adverse events should be clinically important and probably related to the offensive drug. The severity of adverse effects must be balanced against the expected benefits of continued therapy. Even in this setting, the likelihood of an adverse event caused by drug discontinuation must be considered.[17] A serious cardiovascular event, such as ischemic stroke, in the last days of life may impose an enormous burden on the patient and must be prevented. Each decision on discontinuing therapy has to be tailored to the individual patient's needs and should consider each drug individually.

Other important considerations when limiting the pharmacotherapy at the end of life include impaired renal function and frailty, which are common among patients with advanced cancer.[18,19] The analysis of the large administrative database of the Department of Veterans Affairs in the United States showed that 13% of older patients with a creatinine clearance of 30 to 49 ml/min and 32% of those with a creatinine clearance of 15 to 29 ml/min received 1 or more drugs that were contraindicated or prescribed at an excessive dose given the individual's renal function. The strongest risk factor for this error was the number of drugs taken by the patient.[18] In countries where electronic health records and pharmacy reviews are available, this problem would be easier to avoid.

It is rarely possible to support the decision of therapy discontinuation with sound scientific argument, for example, the results of a randomized clinical trial. Todd et al[20] performed a systematic literature search to identify peer-reviewed observational studies investigating inappropriate drug prescription in patients with life-limiting illness. The final search yielded 19 studies. The most common classes of inappropriately prescribed medications were lipid-lowering drugs (12 studies) and antihypertensive drugs (11 studies).

Another systematic approach to decisions on limiting pharmacotherapy in palliative care was undertaken with the Delphi method by a group of geriatricians participating in the Palliative Excellence in Alzheimer Care Efforts Program (PACEP).[21] The classes of drugs were characterized as never appropriate, rarely appropriate, sometimes appropriate, or always appropriate. This classification is critically reviewed further in the text.

O'Mahony and O'Connor[22] proposed some general principles for drug prescription in patients at the end of life, including: 1) life-extending drugs are usually not appropriate; 2) drugs for primary prevention have, in general, no place in the treatment of patients at the end of life, since the time-to-benefit usually exceeds life expectancy; 3) drugs for secondary prevention require scrutiny and should be prescribed only where ongoing benefit is to be expected within a patient's life expectancy; 4) in general, prescribing more than 5 regular daily drugs to a patient with the end-of-life status should be avoided.

Cardiovascular drug classes **Statins** The largest experience regarding discontinuation of cardiovascular pharmacotherapy in palliative care is available for statins.[23] Statins are useful drugs for long-term primary and secondary prevention of cardiovascular diseases with the time lag to benefit of about 6 to 12 months.[24,25] Their usually mild adverse effects such as myalgia and

TABLE 1 Recommendations for modification of cardiovascular pharmacotherapy in palliative patients with cancer

Drug classes	Predicted survival of 2–12 months	Predicted survival of less than 2 months
Statins	Discontinue if no vascular event in the last year	Discontinue
ACEIs and ARBs in hypertension	Modify the dose	Discontinue gradually if normotensive
β-Blockers in hypertension	Modify the dose	Discontinue gradually if normotensive
Diuretics in hypertension	Modify the dose	Discontinue gradually if normotensive
α-Blockers in hypertension	Discontinue	Discontinue
ACEIs and ARBs in heart failure	Modify the dose when hypotensive	Modify the dose or discontinue when hypotensive
β-Blockers in heart failure	Modify the dose when hypotensive	Modify the dose or discontinue when hypotensive
Diuretic in heart failure	Modify the dose	Modify the dose
Digoxin	Continue	Discontinue
Spironolactone or eplerenone in heart failure	Continue	Continue
Amiodarone	Continue if tolerated	Discontinue if poorly tolerated
Sotalol, propafenone, flecainide	Continue if effective and tolerated	Discontinue if poorly tolerated
β-Blockers in arrhythmia	Modify the dose when hypotensive	Modify the dose when hypotensive
ASA in primary prevention	Discontinue	Discontinue
ASA in secondary prevention	Continue	Continue in the absence of bleeding
Clopidogrel, prasugrel, or ticagrelor	Continue for 12 months after acute coronary syndrome and after drug-eluting stent implantation	Continue for 12 months after acute coronary syndrome and after drug-eluting stent implantation if there is no bleeding
Heparins in primary prevention	Initiate only in bedridden patients	Do not initiate
Heparins in secondary prevention	Continue for 6 months after thromboembolic event	Continue for 6 months after thromboembolic event
VKAs	Continue if a CHA_2DS_2-VASc score >4 and in the presence of mechanical prosthetic heart valve	Continue if a CHA_2DS_2-VASc score >4 and in the presence of mechanical prosthetic heart valve
NOACs	Continue if a CHA_2DS_2-VASc score >4	Continue if a CHA_2DS_2-VASc score >4

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ASA, acetylsalicylic acid; NOAC, novel oral anticoagulant; VKA, vitamin K antagonist

impaired exercise performance are often exacerbated in elderly patients and those at the end of life.[26] Discontinuation of statins has already become a common practice in patients with advanced cancer.[23] Recently, this approach has been validated in a randomized trial that included 381 patients with advanced life-limiting illness.[27] There was no difference in the number of deaths during 60 days (23.8% in the group discontinuing statin vs 20.3% in the group continuing statin). The quality of life was better for the group discontinuing statin therapy. Importantly, the generalization of these results is limited by the fact that one of the exclusion criteria was the opinion of the treating physician that the patient had active cardiovascular disease or a sufficient risk of active cardiovascular disease to require ongoing therapy with statins, so it is probable that patients with a recent cardiovascular event were not included. In the Swedish registry, there was a minimum decrease in the statin prescription rate in the last year of life from 18% to 16% in the last month.[9]

There are a few reasons to continue statins in patients with advanced life-limiting illness, and such decisions should be tailored to the individual patient's needs. However, if acute coronary syndrome occurred recently and statins are well tolerated, they should be continued until the last weeks of life (TABLE 1).

Antihypertensive drugs The time lag to benefits from the therapy of high blood pressure (BP), mostly the reduction of the incidence of ischemic stroke, is approximately 6 to 12 months, regardless of the drug class.[3,28,29] Continuation of antihypertensive therapy in palliative care patients is questionable because an epidemiological study demonstrated an attenuated or inverse association between higher BP and mortality at older age.[30] In the last 12 to 24 months of life, a decline in systolic BP is observed, with the values being 15 mm Hg lower at the end of this period than at the beginning.[31]

Frailty is a common finding in older people with cancer and is frequently associated with polypharmacy.[32] There is evidence that among frail and slower-walking adults, neither elevated systolic nor diastolic BP was associated with mortality.[33] Frailty is a recognized risk factor for mortality in patients with advanced cancer, but there are no data on the relation of BP to prognosis in palliative care patients with cancer.[34]

Modern BP-lowering drugs are usually well tolerated, but all of them, especially α-blockers, often cause hypotension, mostly postural.[35] Orthostatic hypotension is frequently a disabling symptom posing the risk for a dangerous fall. Debilitated patients at the end of life are susceptible to hypotension, so continuation of antihypertensive therapy must be carefully evaluated. In most

patients, discontinuation of such therapy will result in an asymptomatic return of BP to pretreatment levels.[36] In a systemic review of studies on the withdrawal of antihypertensive drugs, 38% of patients remained below the threshold for the inititation of hypertension treatment at 6 months.[37] When the therapy is withdrawn abruptly, a small minority of patients may experience withdrawal (or discontinuation) syndrome, characterized by a rapid return or overshoot of BP with the signs and symptoms of sympathetic overactivity and associated with an increased short-term risk of cardiovascular and cerebrovascular events, including pulmonary edema.[38]

The indications for and potential benefits of antihypertensive medications should be evaluated in all patients under palliative care and discontinued if the expected benefit is minimal. In most instances, antihypertensive drugs can be safely reduced or discontinued in these patients. A gradual discontinuation of antihypertensive drugs under BP control may be done safely. Another option is to consider a significant drug dose reduction (TABLE 1). The PACEP has classified β-blockers, calcium channel antagonists, angiotensin-converting enzyme inhibitors (ACEIs), and angiotensin receptor blockers as sometimes appropriate, while α-blockers, as rarely appropriate in palliative care.[21]

Drugs for heart failure Multiple drugs are used in heart failure (HF) and polypharmacy is common. Among nursing home residents with HF, a regular use of 5 or more medications was reported in 77%.[39]

ACEIs, angiotensin receptor blockers, and β-blockers are recommended for symptomatic patients with HF and reduced ejection fraction to reduce the risk of hospitalization and death.[40] Spironolactone or eplerenone is also recommended in all symptomatic patients (despite treatment with an ACEI and a β-blocker) with HF and reduced ejection fraction to reduce mortality and hospitalization rates.[40] Their hypotensive effect is usually weaker than that of ACEIs and β-blockers. The common side effects of spironolactone include drowsiness, lethargy, confusion, headache, fever, ataxia, fatigue, anorexia, dyspepsia, nausea, vomiting, and peptic ulcers.[41] Eplerenone is better tolerated.

The time lag to benefit (ie, reduced hospitalizations for HF) of all the above classes of drugs is approximately 1 month, so their discontinuation may exacerbate HF symptoms within the same period and should rather be avoided.[42-44] The real risk of HF exacerbation is greater than the possible risk of polypharmacy. Hypotension is frequently a limitation for using HF drugs in palliative care patients with cancer. Dose reduction may lower the preventive efficacy of these drugs. They should be continued in early palliative care, but in the last weeks of life, patients may not live long enough to experience HF exacerbation after drug withdrawal, so the medications may be discontinued and possible congestion may be treated with an increased dose of a diuretic (TABLE 1).

Diuretics are recommended to improve symptoms and exercise capacity in patients with congestion.[40] There is no evidence of their long-term benefit, but their withdrawal may cause symptomatic fluid retention.[45] Frail patients, especially those at the end of life, who are on diuretics can benefit from dose adjustment, as they usually become dehydrated due to limited fluid intake (TABLE 1).

Digoxin may be considered in symptomatic patients with HF in sinus rhythm to reduce the risk of hospitalization, but its effect is weak.[40] On the other hand, digoxin—if only not overdosed—is usually well tolerated.[40] The only argument for discontinuation of digoxin is to limit polypharmacy.

Antiarrhythmic drugs The most prevalent arrhythmia in elderly patients, namely, atrial fibrillation (AF), is treated pharmacologically to control either heart rhythm or ventricular rate.[46]

One of the potent drugs used for the above indications is amiodarone. Doctors caring for patients on amiodarone must be aware of its multiple adverse effects. Some are well recognized, such as thyrotoxicity and pulmonary toxicity, but the less known ones, such as nausea, anorexia, constipation, and neurotoxicity, are quite prevalent and often more troublesome.[47] Because of a long half-life, the discontinuation of amiodarone will not immediately terminate the effect of the drug. After a few weeks, a new onset of AF and tachycardia may occur, which may both negatively impact the quality of life.

Other drugs used for rhythm control in AF are flecainide, propafenone, and sotalol.[46] Similarly to amiodarone, they prolong the QT interval, which may pose the risk of fatal arrhythmia when administered with other QT-prolonging drugs like methadone or haloperidol. They are markedly less effective than amiodarone. Common adverse effects of flecainide are dizziness, light-headedness, anxiety, and insomnia,[48] while those of propafenone include blurred vision, dizziness, fatigue, and postural hypotension.[49] The adverse effects of sotalol are visual and hearing impairment.[50]

Antiarrhythmic drugs are sometimes continued even when they are not effective. However, it is important to remember that it is difficult to maintain the sinus rhythm in debilitated patients at the end of life. The withdrawal of the above antiarrhythmic drugs rarely results in the return of arrhythmia. In that case, the strategy of rate control may be safely introduced.[51] Antiarrhythmic drugs are rarely necessary in palliative care of cancer patients, so they may be stopped especially in the last weeks of life (TABLE 1).

A ventricular rate of 110 bpm is recommended in the 2016 European Society of Cardiology guidelines for the management of AF as the target for heart rate control therapy.[51] The first-line drugs to be used for rate control in AF are

β-blockers and digoxin. The use of β-blockers in palliative care may be sometimes limited because of their hypotensive effect. The discontinuation of β-blockers, if ever considered, should be gradual because of the risk of rebound tachycardia. The effect of digoxin on the heart rate is rather weak, and the drug may be stopped to limit polypharmacy.

Antithrombotic drugs Acetylsalicylic acid (ASA) is the most common drug used for primary and secondary prevention of cardiovascular diseases. Its safety profile is well established. The most common adverse events are dysphagia and minor bleedings. The risk of severe bleeding is elevated in patients with thrombocytopenia and locally advanced cancers, as well as in those older than 75 years.[52] If the bleeding is hard to control, the discontinuation of ASA may help, but it may take a few days until its effect wears off. The use of ASA along with nonsteroidal anti-inflammatory drugs, which are step 1 in the analgesic ladder, reduces the efficacy of ASA and increases the risk of gastrointestinal bleeding.[53]

The decision to continue ASA in palliative care should be based on whether it is used for primary or secondary prevention. Because the use of ASA in primary prevention in the general population is not widely accepted, it is even more debatable in palliative care where the goals of treatment shift away from prevention.[54] On the other hand, the use of ASA benefits patients for many years after acute coronary syndrome and ischemic stroke, and its discontinuation is dangerous particularly in patients with recent acute coronary syndrome and recent ischemic stroke.[55] The PACEP has reached no consensus on the use of ASA in palliative care.[21]

Dual antiplatelet therapy (DAPT), which consists of clopidogrel, prasugrel, or ticagrelor in addition to ASA, is recommended for 12 months after acute coronary syndrome or after implantation of the first-generation drug-eluting stent.[56] In the few patients who currently receive bare metal stents, the obligatory duration of DAPT is only 1 month in stable patients but still 12 months in those after acute coronary syndrome.[56] Recently, the European Society of Cardiology Working Group on Thrombosis defined 2 therapeutic modalities that are associated with a high risk of thrombosis: percutaneous coronary intervention with newer-generation drug-eluting stent when the risk is elevated for up to 30 days, and biovascular scaffolds when the risk is elevated for up to 12 months. The recommendation was to continue DAPT in this group despite the high risk of bleeding.[57] In the Swedish registry, antiplatelet therapy was prescribed in 44% of patients without evidence of its withdrawal in the last month of life.[9]

Oral anticoagulation therapy with vitamin K antagonists (VKAs) or novel oral anticoagulants (NOACs) is recommended for all patients with nonvalvular AF with a CHA_2DS_2VASc score of 2 or higher.[47] The use of VKAs in palliative care patients with cancer is limited by the difficulty in maintaining stable international normalized ratio and by an unpredictable dietary intake of vitamin K due to anorexia, nausea, or vomiting.[58] VKAs are involved in numerous drug-to-drug interactions. There are few data from randomized trials on the efficacy and safety of NOACs in patients with AF and cancer.[59]

Continuation of oral anticoagulation in palliative care patients with cancer should be thoroughly considered due to the increased bleeding risk discussed above. Importantly, discontinuation of VKAs in patients with AF is associated with a 1.5-fold higher risk of ischemic stroke.[60] Because of the discomfort related to regular blood testing and higher risk of bleeding, a switch from VKAs to NOACs in palliative care patients may be considered.[61] Discontinuation of any oral anticoagulant therapy is acceptable only in low to moderate thromboembolic risk defined as a CHA_2DS_2VASc score of 4 or lower.[57] Mild renal dysfunction and frailty are not contraindications to NOAC therapy.[61] Oral anticoagulation therapy with VKAs is obligatory in high-risk patients with mechanical prosthetic heart valve and should usually be continued.[57]

Heparins are used in the prophylaxis and treatment of venous thromboembolism (VTE), which is a common life-threatening disease in palliative care patients with cancer. However, the available experience of VTE treatment in the setting of palliative care is limited. A case series has been reported of 62 patients with advanced malignancy on long-term treatment with low-molecular-weight heparin (LMWH), which was self-administered by 74% of patients.[61] Minor bleedings occurred in 8.1% of patients, while no major bleeding events were observed. No patient developed heparin-induced thrombocytopenia.[62]

The problem of thromboprophylaxis in palliative care is complex and difficult to interpret, considering the concept that palliative care intends neither to hasten nor postpone death.[2] Chambers[63] argued against the introduction of thromboprophylaxis to palliative care, because palliation is the alleviation of symptoms without necessarily eradicating their cause. In contrast, prophylaxis is the preemptive attempt to prevent symptoms that might never arise anyway.[63] A stronger argument is the lack of evidence on the medical benefit in this population, as reflected in the guidelines.[64-66]

Cancer is a strong risk factor for VTE. Numerous palliative care patients are bedridden, which is another significant risk factor for VTE. The guidelines for thromboprophylaxis in patients with cancer are inconsistent. For instance, the American College of Chest Physicians limits prophylaxis to cancer patients who are bedridden with an acute medical illness (grade 1A).[64] The International Society of Thrombosis and Hemostasis recommends prophylaxis in cancer patients only when they are treated with chemotherapy.[65] Finally, the American Society of Clinical Oncology

recommends thromboprophylaxis in most hospitalized patients but not in ambulatory patients with cancer.[66] Palliative care patients cared for at home often do not fulfill any of the above criteria, so the decision to introduce thromboprophylaxis in ambulatory palliative care patients is not supported by scientific evidence or practice guidelines. Palliative care patients with cancer tolerate LMWH injections well, much better than they do compression stockings.[67] They are also satisfied with the protection that the treatment offers against a life-threatening event.

There are strong arguments for continuing the treatment of VTE in palliative care with heparins or oral anticoagulants for 3 to 6 months after a VTE event; however, only selected palliative care patients should receive thromboprophylaxis with LMWH, especially when they are at the end of life. A sort of a compromise approach is to offer thromboprophylaxis with LMWH to palliative care patients who are bedridden (TABLE 1).

Principles of ethics and communication Discontinuation of a drug that is no longer beneficial is ethically appropriate, and such a decision is even more justified when the drug is potentially harmful. The fundamental principles of palliative care are mutual trust and good communication, so the decision to stop any medication must be thoroughly explained and shared with the patient.[68-70] Patients must acknowledge their limited prognosis and lack of benefit from continuation of therapy. It is particularly important to address any feelings of abandonment that the patient may experience when the therapy is discontinued. Patients often regard polypharmacy as the evidence that their treating physician is dedicated to their care.[71] The comfort and safety of the patient is always the primary goal. To avoid any legal problems, the shared decision as to therapy discontinuation must be documented in medical records.

Summary The priority in palliative care is to maintain the quality of life, while less emphasis should be placed on avoiding the polypharmacy itself. Each decision on discontinuing therapy needs to balance the life expectancy of the patient against the time lag to drug benefit. Primary prevention drugs are the first to be discontinued. High-quality research in this area and a precise evaluation of the risk of polypharmacy in comparison with the risk of drug withdrawal is strongly encouraged.

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