

The Impact of Hematologic Malignancies on the Treatment and Prognosis of Acute Coronary Syndrome

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ABSTRACT

Survival after myocardial infarction has improved but there is still a difference in clinical outcome and mortality. So far, there is very limited information on the effects of patients with an acute coronary syndrome in cancer. Although the survival after a ST-Segment Elevation Myocardial Infarction (STEMI) has improved and data demonstrates mortality 12 months after a STEMI of less than 4 percent, the cancer patients are not included in this clinical data results. As we know, cancer and cardiovascular diseases have a high incidence in elderly days, thus more cancer patients are suffering an Acute Coronary Syndrome (ACS). Patients with cancer have been excluded from most large cardiology studies and registries. Therefore, little is known about the effect of ACS in cancer patients and treatment remains empirical. Even less is known about the influence of hematological tumors on ACS. This review therefore aims to provide clinicians with an overview of how patients with a coexistence of hematologic malignancies and acute coronary syndrome have been treated in the past, what the outcomes were and what treatment might look like in the future. In ACS patients with HM myelodysplastic/myeloproliferative disorders, lymphocytic leukemia and multiple myeloma predominated. These patients were 6 years older, they were less likely to have a STEMI-constellation and more likely to have a NSTEMI. Patients with an ACS and concomitant cancer were more likely to have a previous cardiovascular disease and a worse NYHA status. A generally increased risk of relevant bleeding could not be proven. Nevertheless, fewer of these patients received an invasive therapy regimen, so it can be assumed that the poorer long-term survival could also be due to the avoidance of PCI.

Keywords: Acute coronary syndrome; STEMI; Cancer; Hematologic malignant disease; Treatment; Survival

INTRODUCTION

The treatment options for malignant diseases on the one hand and Acute Coronary Syndrome (ACS) on the other have improved significantly in recent decades, thereby increasing the survival rate and quality of life for each type of disease. Improved survival or cure from cancer not infrequently leads to a collision with atherosclerotic diseases such as Coronary Artery Disease (CAD) in the same patient. The coincidence of both diseases is relevant for the prognosis. However, the type of malignant disease is decisive for the prognosis of ACS, especially in ST-Elevation Myocardial Infarction (STEMI). There are hardly any studies on ACS and cancer. Registry data and studies on the co-

occurrence of cancer and ACS are limited. There are particularly few studies on Hematologic Malignancies (HM) and ACS. In a nationwide cohort study with data from the largest German health insurance company, around 440 thousand ACS patients were analyzed between 2010 and 2018. Of these, only 2104 patients (0.5%) also had a hematologic malignancy.

In these study myelodysplastic-/myeloproliferative disorders, lymphocytic disorders and multiple myelomas predominated among ACS patients. The prognosis here depends directly on the type of leukemia and of the type of acute coronary syndrome (STEMI vs NSTEMI). HM patients with ACS were older, sicker, less likely to have a STEMI and more likely to suffer from heart failure symptoms. Although the bleeding events among the

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patients were not significantly increased, they were less likely to receive coronary angiography and Percutaneous Coronary Interventions (PCI). Another reason of the poor overall survival could also be the reluctance to prescribe ACS drugs in line with guidelines.

Cancer incidence has steadily increased [1]. In 2022 the incidence in Germany is about 552/100000 population. The number of cancer patients suffering from hemodynamically relevant coronary artery disease has increased in the last decades [2,3]. It is postulated that the common risk factors for coronary heart disease and cancer are inflammation and oxidative stress [4]. The CANTOS trial showed that a decrease in inflammation measured in a reduction of hs CRP through the interleukin-1 β inhibitor canakinumab led to a decrease of myocardial infarction, stroke, or cardiovascular death and in particular a decrease in the incidence of cancer [5]. New specific cancer therapies (e.g., immune checkpoint inhibitors, tyrosine kinase inhibitors, immunomodulatory drugs and antibodies) improve cancer survival but sometimes carry the risk of myocardial ischemia [6]. Thus, more patients are at higher risk of suffering a myocardial infarction through a cancer-associated therapy. The risk of venous thromboembolism, cardiomyopathy, pericarditis, coronary artery disease, stroke and valvular heart disease is increased in patients with various types of cancer and not least in connection with various types of cancer therapies [7]. Survivors of cancer have a higher risk to develop a cardiovascular disease [7]. The mortality of patients with cancer and a myocardial infarction is high-almost 30% in a follow up period compared to the very low risk without a malignant disease of less than 4% in a follow up of 1 year [8,9]. Although the survival after a STEMI has improved and data demonstrates mortality 12 months after a STEMI of less than 4 percent, the cancer patients are not included in this clinical data result [9]. This review therefore aims to provide clinicians with an overview of how patients with cancer and concomitant CAD have been treated and would like to contribute how to treat the patients in future. To ensure relevance of the review, studies no older than 10 years were included.

All studies were registry studies; the majority had a retrospective design. Large parts of the statistical evaluation (e.g., comorbidities, prognosis and mortality) originate from a large dataset of compulsory insurance data from the largest German health insurance fund [10,11]. Following the statistics on cancer cases in Germany by the Robert Koch society, we investigated on a large real-world cohort the following groups of Hematological Malignancies (HM): Hodgkin's disease, leukemia, multiple myeloma and non-Hodgkin's lymphoma.

LITERATURE REVIEW

Acute Coronary Syndrome (ACS) and cancer in generally

There is clear evidence that patients with a malignant disease have a higher risk to develop a severe CAD and thus the occurrence of a ST-Elevation Myocardial Infarction (STEMI) or a Non-ST-Elevation Myocardial Infarction (NSTEMI) in elderly patients with malignant diseases is higher compared to the

general population [10]. The probability of a pre-existing cardiovascular disease, a previous PCI and a progress of the disease (3-vessel disease) was more likely. Chronic kidney disease was also more common [10]. Patients with an ACS and cancer were more likely to experience Major Adverse Cerebral and Cardiovascular Events (MACCE), such as death or ischemic stroke, cardiogenic shock and inpatient resuscitation. Drug-Eluting Stents (DES) was used less frequently and BMS were favored, most likely because of an expected increased risk for cancerous bleeding. On the other hand, thromboembolic events in cancer patients are also common. Deep vein thrombosis and pulmonary embolism are generally the second leading cause of cancer death [10].

In median the patients with ACS and HM were six years older. In the whole study population of 439,716 ACS patients STEMI:NSTEMI occurred in a proportion of 35%:65%. In contrast the STEMI patients in concomitant HM were only 18.2% and the vast majority was NSTEMI patients. The patients with a HM and ACS had a worse NYHA-stage, more frequent heart failure, more right heart failure and atrial fibrillation [12]. Also comorbidities such as diabetes mellitus, arterial hypertension and psychiatric disorders were more prevalent. However, this was not the case in obesity, nicotine abuse and dyslipidemia [13].

In a nationwide cohort study of Lange et al., the 8-year survival rate of 20%-41.2% in acute STEMI in skin, prostate, colon, breast, urinary tract, lung and other cancers. The hematologic malignancies were summarized under the heading of other cancers [10]. That study showed that a Peripheral Artery Disease (PAD), pre-existed metastases, a lung cancer and a stroke were independent risk factors of a worse outcome.

PAD, renal insufficiency and previous dialysis were more frequent in cancer patients. Accordingly, to the pre-existing diseases (CAD, PAD, stroke, heart failure) of vast patients with HM one therapy with OAC or PAI were more likely. Statins, beta-blockers and ACE-I or ARBs were more likely in the medication history of these patients. Overall fewer patients with an ACS and a HM underwent an invasive strategy, such as corona angiography and PCI [14]. When it came to coronary treatment and intervention the use of bare metal stents Implantation was higher in comparison to the implantation of Drug eluting stents. The implantation of bare metal stents requires a less aggressive platelet inhibition. This type of stents was probably used more often because of reduced risk of bleeding. As far as Coronary Artery Bypass Graft (CABG) was concerned, the rate was equally distributed.

Hematological malignancies incidences and risk of coronary heart disease

The incidence of leukemia was 14.1 per 100000 population in the EU 2020 [11]. Patients with an ACS and current HM were about 0.5%. Conversely 1.4% of HM patients suffer an ACS [12]. In a large Swedish registry patient with HM had a higher risk to suffer an ACS in the first 6 months after diagnosis. The incidence risk for Coronary heart disease was 2.81 [13]. Chronical lymphocytic leukemia accounts the largest proportion

with over 70%, followed by Chronical myeloid leukemia (16%), acute myeloid leukemia (10.5%) and acute lymphocytic leukemia (1.7%). Statistically the incidence of multiple myeloma was 7.5/100000 in EU in year 2020. The standardized incidence risk for a coronary heart disease was significantly higher in the 6 months after diagnosis and remained significantly higher in the first 10 years after diagnosis [13]. The incidence of Non-Hodgkin's lymphoma was reported with 18.3/100000, the incidence of Hodgkins lymphoma with 2.7/100000. The risk for a coronary heart disease was higher in the first six months after diagnosis of a Non-Hodgkin's lymphoma, but decreased after that 6-month period. The risk of developing coronary heart disease was not higher in patients with Hodgkin's lymphoma [15].

The distribution frequency of 2104 ACS patients with an ACS and a concomitant HM in one retrospective cohort study of Lange et al., in descending order was as follows: Myelodysplastic and myeloproliferative disease (27.7%), lymphocytic leukemia (24.8%), multiple myeloma and malignant plasma cell neoplasms (22.4%), chronic myeloid leukemia (8.8%), aggressive lymphoma (5.9%), indolent lymphoma (5.1%), Hodgkin's lymphoma (3.5%), and myeloid leukemia (1.9%) [10].

Bleeding risk and prevalence of multi morbidity diseases

The bleeding complications are not clear in the few studies, which exists. Mohamed, et al., found no increased risk of bleeding in patients with hematologic cancer compared to ACS patients without cancer [14]. In contrast, using a large, Swedish database on ACS and cancer, Velders, et al., demonstrated that the risk for severe, life-threatening bleedings or nonfatal bleeding complications was higher in patients with leukemia compared with other cancer [15].

HM patients did not have a relevant increase in bleeding complication; this has also been shown in ACS patients with leukemia in the U.S [14]. Similar to data from the U.S., Lange et al., observed a higher risk of renal failure in HM patients and ACS [10]. Since the NSTEMI with HM patients are suffering from multi morbidity diseases (atrial fibrillation, diabetes and hypertension) a vast therapeutically concept is required and a more aggressive invasive regime. The higher average age at the time of infarction can be seen as an independent risk factor. Another reason of the poor overall survival could be the less prescription of the four common guidance compliant medications which has a high recommendation in patients who survived an ACS [16].

Accordingly, to the studies significant higher risk of severe bleeding advents are controversial and not clear. If further studies cannot show a significant higher bleeding risk in future this would justify a more progressive invasive management of infarction in these patients.

Coronary angiography and percutaneous coronary intervention in HM

Coronary angiography and percutaneous coronary intervention have been performed frequently in patients with leukemia [12,14]. In a small retrospective study by Park, et al., in which only 25% underwent coronary angiography, one third had an intracoronary thrombus, and half of the patients had severe three-vessel or left main coronary disease. Approximately 75% of ACS patients were treated with drugs alone [12].

A primary PCI was performed 2%-6% less frequently [10]. The use of bare-metal stents, which require a shorter phase of dual platelet inhibition, was higher than drug-eluting stents, probably due to consideration of the higher risk of bleeding in cancer patients [10].

Patients with leukemia had a higher risk of MACCE and increased all-cause mortality compared with ACS patients without malignancy [14,15]. Furthermore acute myeloid leukemia was associated with approximately three times the risk of an ACS and four times the risk of death compared with patients without an ACS. It could also been shown that the risk of hospitalization for heart failure in patients with an ACS and concomitant HM was higher [15]. The fact that many patients with an ACS and AML tend to thrombocytopenia, less than 50% of non-interventional patients received an antiplatelet agent or anticoagulants [12]. This might explain the worse outcome in these patients.

Lange et al., showed that a STEMI affect the survival rate for most cancers, with the exception of lung cancer [10]. Generally, less than 50% of patients with an acute STEMI and concomitant cancer disease got an invasive strategy for the further therapy although an invasive therapy was an important predictor of better survival in these patients [10]. In all cancer forms generally concurrent cancer more often leads to a conservative medical management strategy and worse clinical outcomes in STEMI patients [10].

DISCUSSION

Specific HM-treatments and cardiovascular side-effects

Tumor therapies can as well induce an ACS e.g., alkylating agents, antimetabolites, anti-microtubule agents, antibiotics, hormonal therapies, monoclonal antibodies and Tyrosine kinase inhibitors [16-18]. Radiation therapy used for certain types of tumors in the chest can damage the vascular walls and lead to thrombosis, plaque formation and fibrosis [19-21]. Thus, mediastinal fibrosis, aortic valve disease, and coronary artery disease are also consequences of such chest irradiation [21-27].

The following chemotherapeutic agents are used for various types of lymphoma and can cause angina, vasospasm, and ACS: Vinblastine, bleomycin, and rituximab [28]. Rituximab can also induce takotsubo cardiomyopathy [29]. TKI therapy in multiple myeloma resulted in progression of coronary artery disease and ACS [30]. However, the risk of cardiovascular events is higher with

second-(dasatinib, nilotinib, or bosutinib) and third (ponatinib) generation TKIs than with imatinib, the first generation TKI [31]. Unfortunately, the TKIs are also associated with thrombocytopenia [31]. Antitumor antibiotic treatment with bleomycin for non-Hodgkin's and Hodgkin's lymphomas can cause angina, vasospasm, and ACS [32]. Cyclophosphamide, part of the CHOP treatment protocol (Cytoxan, hydroxyrubicin (Adriamycin), Oncovin (Vincristine), Prednisone (chemotherapy regimen), can cause left ventricular dysfunction, heart failure, myocarditis, pericarditis, arterial thrombosis, arrhythmias such as bradycardia, atrial fibrillation, and supraventricular tachycardia [33].

Pharmaceutical treatments of an acute coronary syndrome

HM patients appeared to benefit from therapy to a similar extent as patients without a HM. In the reality HM patients had a lower

myeloma cell line, in which statin therapy have an apoptotic effect [25]. Beta Blocker (BB) is still a highly recommended drug therapy in the guidelines of an ACS, though in patients with a HM no positive effect could be shown (Table 1).

CONCLUSION

The mortality of ACS patients increased by HM with the exception of Hodgkin's disease regardless of older age. One different distribution of the various leukemia types was found for the ACS patients compared to the normal population. Patients with ACS and HM were less likely to have a dyslipidemia and obesity. The oral medication therapy of a lipid lowering therapy with statins or a BB did not show a positive effect. Patients with a HM do not always receive the recommended standard medication with a platelet activation inhibitor or an oral anticoagulant due to their low platelet count.

Author	Year	Study design	Patients	ACS/ STEMI/ NSTEMI	NPL	PCI	Periods	Endpoints	Year
Mohamed, et al., [14]	2020	Retrospective, Registry study	6,750,878	100%; 35,1/ n.i.	100%, leukemia	42,9% vs 28,2 %	2004-2014	MACCE and bleeding	2020
Lange, et al., [10]	2022	Retrospective, Registry study	175,262	n.i./100%/ n.i.	Solid tumours-/HM (n=27,213; 15,5%)	2%-6%, 1% less than normal	2010-2017	All cause mortality	2022
Lange, et al., [24]	2023	Retrospective, Registry study	439,716	100%; 18,2% vs 81,8%	n=2104 (0,5 %), Hematolog. Malignancies	44,30%	2010-2018	In hospital mortality, 1-year mortality, MACCE and bleeding	2023
Park, et al., [12]	2019	Retrospective, Registry study	5300	1%,4%; 0,189% vs 1,075%	100%, Hematolog. Malignancies	35,30%	2004-2014	In hospital mortality, 1-year mortality	2019
Gudatti, et al., [13]	2016	Retrospective, Registry study	49,515	100%; 32,24 vs 67,76%	100% (Metastatic disease)	STEMI 24,9%; NSTEMI 9%, 6%	2000-2009	In hospital mortality	2016
Velders, et al., [3]	2020	Registry study	175,146	100%/ 35.6%/n.i.	9,30%	48%	2001-2014	All cause mortality	2020

Table 1: Mortality, MACE, and re-infarction/death comparison between STEMI and NSTEMI patients with and without HM.

prescription rate for all medications recommended in the guidelines of the European society of cardiology [14]. Statins did not show a positive effect in HM patients, neither in the STEMI nor in the NSTEMI collectives.

In the past studies of patients with a multiple myeloma there has been reported about a statin sensitive and a statin-insensitive

Thus, a reason of the poor overall surveillance could be the less prescription of the four common guidance compliant medications, which has a high recommendation in patients who survived an ACS. Therefore, the patients should be prescribed all four medications to benefit in long terms.

Of note, two studies showed that bleeding events were not higher overall in patients with a hematologic malignancy. It should therefore be seriously questioned whether a more aggressive invasive procedure would not be better for these patients in terms of prognosis.

Statistically, the in-hospital mortality, the 30-day and 90-day mortality were higher in ACS patients with HM. However, there was no evidence of increased in hospital, after 30-day and 90-day mortality in STEMI patients. One year after an ACS, the rate of death was almost twice as high in patients with HM for both STEMI and NSTEMI. Except of Hodgkin's lymphoma, patients with ACS and HM had lower survival rates.

In summary, the long-term survival of NSTEMI patients in general and with concomitant HM is worse compared to the STEMI study population.

The studies suggest that cancer-specific complications such as bleeding and thromboembolism should no longer be specified as a general exclusion criterion for an interventional approach. Better stent technologies, techniques for precise monitoring of PCI outcomes, and experience with dual antiplatelet therapy also provide hope that more high-risk patients can receive invasive coronary therapy. However, it would also be desirable if a prospective PCI study could confirm the advantages of the new stent technologies with shorter required dual platelet inhibition also for malignancy patients with increased bleeding risk.

However, CAD treatment of patients with advanced and complex cancers will remain the subject of individual decisions. It is not only in these particularly difficult cases that joint decision making between the treating cardiologists, oncologists, and primary care physicians is necessary in the best interest of the patient.

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