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ORIGINAL ARTICLE

Guideline-Directed Medical Therapy in Patients With Heart Failure With Reduced Ejection Fraction and Incident Cancer

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Background It has been postulated that cancer hampers the delivery of guideline-directed medical therapy (GDMT) for heart failure (HF). However, few data are available in this regard.

Methods We performed a retrospective analysis from the HF Outpatient Clinic of the IRCCS Ospedale Policlinico San Martino in Genova, Italy. All HF patients evaluated between 2010 and 2019, with a left ventricular ejection fraction <50% and at least two visits ≥3 months apart with complete information about GDMT were included in the study. We assessed the prescription of GDMT—in particular, beta-blockers (BB), renin-angiotensin system inhibitors (RASi), and mineralocorticoid antagonists (MRA)—at the time of the last HF evaluation and compared it between patients with and without incidental cancer. For those with incidental cancer, we also evaluated modifications of GDMT comparing the HF evaluations before and after cancer diagnosis.

Results Of 464 HF patients, 39 (8%) had incidental cancer. There were no statistical differences in GDMT between patients with and without incidental cancer at last evaluation. In the year following cancer diagnosis, of 33 patients with incidental cancer on BB, none stopped therapy, but two had a down-titration to a dosage <50%; of 27 patients on RASi, two patients stopped therapy and three had a down-titration to a dosage <50%; of 19 patients on MRA, four stopped therapy.

Conclusions Although HF patients with incidental cancer may need to have GDMT down-titrated at the time of cancer diagnosis, this does not appear to significantly hinder the delivery of HF therapies during follow-up.

Keywords Heart failure • Medical therapy • Guideline • Cancer • Cardio-oncology

Introduction

Therapy with beta-blockers (BB), renin-angiotensin system inhibitors (RASi) (namely angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and angiotensin receptor-neprilysin inhibitors), mineralocorticoid receptor antagonists (MRA), and, most recently, sodium-glucose cotransporter-2 inhibitors (SGLT2i) have been shown to significantly improve outcomes in heart failure (HF) with reduced left ventricular ejection fraction (LVEF) (HFrEF) [1].

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To a certain extent, these drugs are also beneficial in HF with mildly reduced LVEF (HFmrEF) [2]. The latest HF guidelines from both the European Society of Cardiology [1] and the American College of Cardiology/American Heart Association [3] advocate the use of BB, RASi, MRA, and SGLT2i with an IA class recommendation in all patients with HFrEF and suggest considering the prescription also in patients with HFmrEF.

Each single class of these drugs has an impact on HF prognosis, and their combination has shown incremental value [4,5]. Moreover, up-titration of BB and RASi to a dosage ≥50% of the target dose has been demonstrated to significantly improve prognosis [6]. As such, the achievement of guideline-directed medical therapy (GDMT) is imperative in patients with HFrEF, and possibly beneficial in HFmrEF.

Contemporary HF clinical courses are nowadays influenced by non-cardiovascular comorbidities, which may hinder the delivery of GDMT. In particular, it has been hypothesised that this could be the case when cancer is newly diagnosed in subjects with pre-existing HF [7]. However, few data are available in this regard, and real-world evidence is lacking.

Methods

All patients evaluated at the HF Outpatient Clinic of the IRCCS Ospedale Policlinico San Martino in Genova, Italy, from January 2010 to December 2019, were included in the study regardless of their vital status at the time of database completion if the following criteria were met: 1) LVEF <50%; 2) at least two visits ≥3 months apart; 3) complete information available about HF GDMT. A written informed consent to the use of anonymised clinical data for research purposes was obtained from all subjects evaluated at the study centre. Incidental cancer was defined as any malignancy diagnosed after the first visit.

We compared HF GDMT at the time of the last HF evaluation between patients with and without incident cancer. For the former (patients with incident cancer), we also evaluated the modifications of HF GDMT from the last visit before cancer diagnosis to those done in the year following cancer diagnosis. According to European Society of Cardiology HF guidelines relative to the study period [8], GDMT included BB; RASi, and MRA. A dose of BB and RASi ≥50% of the guideline-recommended one was considered as effectively up-titrated [6]. Use of loop diuretic and ivabradine was also assessed.

Continuous variables are reported as mean with standard deviation or median with interquartile range; categorical variables are reported as percentages. Continuous and categorical variables were compared by Student's t-test and chi-squared test, respectively. Bonferroni correction was used when needed. Kaplan–Meier and univariate Cox regression analysis was used to test the association of incidental cancer with cardiovascular and non-cardiovascular mortality. Statistical analysis was carried out with SPSS version 25 (SPSS Inc, Chicago, IL, USA); significance was set at a two-sided $p<0.05$.

Results

Patients' Characteristics and HF Therapy at the Last Evaluation

The study population included 464 HF patients with LVEF <50%. Over a median follow-up of 5 (IQR, 2–7) years, cancer

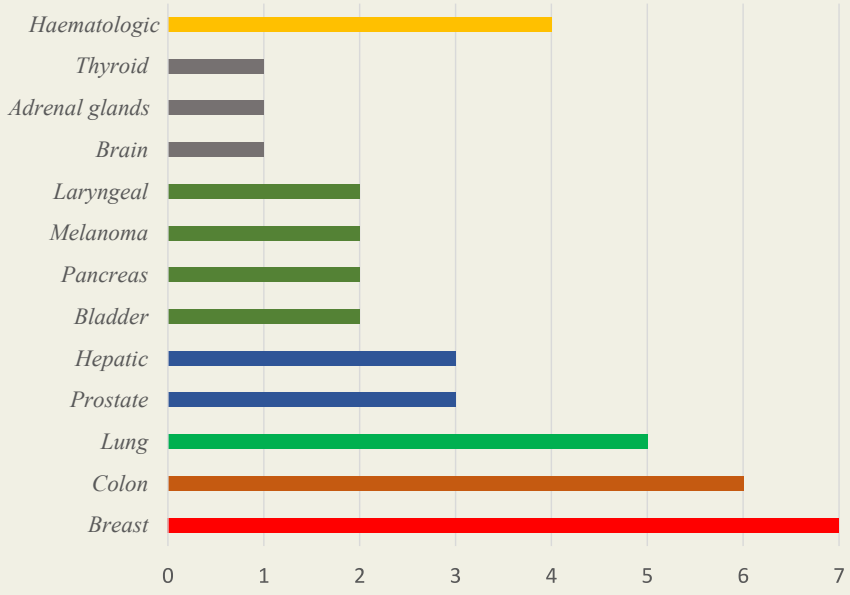

Figure 1 Types of cancer. Haematologic cancers include chronic lymphocytic leukaemia (2) and multiple myeloma (2).

Table **Characteristics and therapy of HF patients with and without incidental cancer.**

	Study cohort n=464	Non-cancer n=425	Incidental cancer n=39	P-value
Gender, n (%)				0.38
Males	325 (70)	299 (70)	26 (69)	
Females	139 (30)	126 (30)	13 (33)	
Age at HF diagnosis (years)	68±13	68±13	70±12	0.28
Age at cancer diagnosis (years)	-	-	72±12	-
Ischaemic HF aetiology	220 (47)	203 (48)	17 (44)	0.37
NYHA III/IV at last evaluation	57 (12)	50 (12)	7 (18)	0.19
Arterial hypertension	304 (66)	274 (65)	30 (77)	0.08
Dyslipidaemia	186 (40)	169 (40)	17 (44)	0.38
Diabetes mellitus	138 (30)	129 (30)	9 (23)	0.22
Chronic kidney disease	127 (27)	122 (29)	5 (13)	**0.04**[b]
Chronic obstructive pulmonary disease	78 (17)	70 (17)	8 (21)	0.32
Prior cancer	53 (11)	47 (11)	6 (15)	0.28
Atrial fibrillation	192 (44)	186 (44)	6 (38)	0.40
NT-proBNP[a] (pg/mL; median [IQR])	4,081 [1,669–7,784]	4,211 [1,701–8,010]	3,445 [1,101–5,024]	0.92
LVEF (%; mean±SD)	34±10	33±10	40±11	<**0.001**[b]
Duration of follow-up (years; median [IQR])	5 [2–7]	4 [2–7]	8 [6–17]	<**0.001**[b]
HF therapy at last evaluation, n (%)				
Beta-blockers	436 (94)	402 (95)	34 (78)	0.08
Dosage ≥50%	194 (45)	174 (43)	20 (59)	0.06
RASi	375 (81)	347 (82)	28 (72)	0.10
Dosage ≥50%	188 (50)	170 (49)	18 (64)	0.09
MRA	262 (57)	238 (56)	24 (62)	0.31
Loop diuretics	351 (76)	321 (76)	30 (77)	0.51
Ivabradine	43 (9)	41 (10)	2 (5)	0.27
ICD	72 (16)	67 (16)	5 (13)	0.50

[a]159 missing NT-proBNP values.

[b]Bold indicates statistically significant result.

Abbreviations: HF, heart failure; NYHA, New York Heart Association; NT-proBNP, N-terminal prohormone of brain natriuretic peptide; LVEF, left ventricular ejection fraction; SD, standard deviation; RASi, renin-angiotensin system inhibitor; MRA, mineralocorticoid antagonist; ICD, implantable cardioverter defibrillator.

was newly diagnosed in 39 patients (8%); the types of cancer are reported in Figure 1. Patients with incident cancer had a lower prevalence of chronic kidney disease (13% vs 29%, p=0.04), a higher LVEF (40±11 vs 33±10, <0.001) and a longer follow-up (median, 8 [IQR, 6–17] vs 4 [IQR, 2–7] years, p<0.001) as compared with those without (Table). In the overall population, 94% of patients were prescribed BB, and 81% with RASi, with 45% and 50% taking a dosage ≥50%, respectively. Moreover, 57% of the patients were taking MRA, 76% loop diuretics, and 9% ivabradine; and, 16% had received an implantable cardioverter defibrillator. There were no statistically significant differences in the prescription of GDMT, ivabradine and loop diuretic at the last evaluation in patients with and without incident cancer. The proportion of subjects on BB and RASi was numerically lower in the cancer vs the non-cancer group, but there was a trend for a more common use of doses ≥50% of the target in cancer than in non-cancer patients (Table).

Changes in HF Therapy

Of the 39 patients with incident cancer, median time from first HF evaluation to cancer diagnosis was 4 (IQR, 2–8) years; and median time from cancer diagnosis to last HF evaluation was 4 (IQR, 2–8) years. None of the incidental cancer patients received anthracyclines as part of their anti-cancer treatment; 30 received a combination of surgery with/without radiotherapy or hormone therapy, three received a platinum-based regimen, two bortezomib-melphalan-prednisone, two cyclophosphamide, one rituximab and bendamustine, and one an immune checkpoint inhibitor. Chest radiotherapy was performed in four cases of breast cancer.

At the time of cancer diagnosis, 33 were prescribed BB and 27 with RASi, with 21 (64%) and 15 (56%) taking a dosage ≥50%, respectively. Moreover, 19 patients were taking MRA, 27 loop diuretics, and three ivabradine. In the following year, none of the cancer patients stopped BB, but two had a

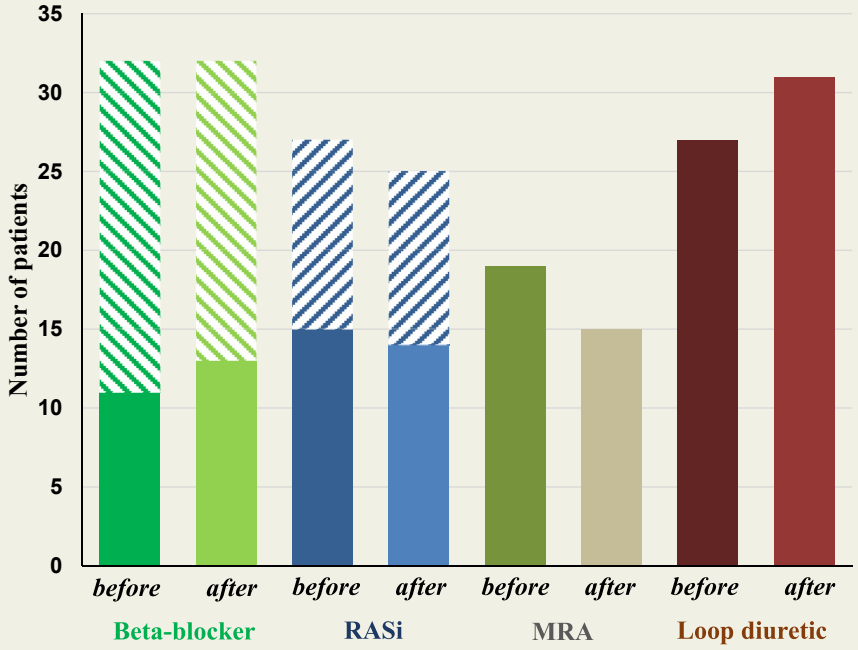

Figure 2 Prescription of GDMT before and after cancer diagnosis. The Y-axis shows the number of patients. The X-axis shows the HF class of drugs; for each, the first column presents the number of patients receiving that therapy before cancer diagnosis, and the following column is the number of patients receiving that therapy in the year after cancer diagnosis. For BB and RASi, dashed parts of the columns represent patients with drug dosage ≥50%.
Abbreviations: RASi, renin-angiotensin system inhibitor; MRA, mineralocorticoid antagonist; GDMT, guideline-directed medical therapy; HF, heart failure; BB, beta blocker.

down-titration to a dosage <50%; two patients stopped RASi and three had a down-titration to a dosage <50% (Figure 2). Four (4) patients stopped MRA, four were initiated on loop diuretics, and one stopped ivabradine. No implantable cardioverter defibrillator was implanted after cancer diagnosis. In no cases was HF therapy variations deemed related to anticancer therapy delivery and neither was anticancer therapy changed in relation to HF therapy modifications. Reasons for down-titration or stop of therapy were hypotension or fatigue.

Evaluating variations of GDMT from baseline to last evaluation in patients without incident cancer (n=425), of the 402 patients on BB, 19 had them prescribed, and 62 had them up-titrated during follow-up, whereas in six, BB were stopped and in 11 down-titrated. Of the 347 patients on RASi, 45 had them prescribed and 46 up-titrated during follow-up, whereas in 22, RASi were stopped and in 40, down-titrated. Of the 238 patients on MRA, 53 had them prescribed but 55 stopped during follow-up. Of the 41 patients on ivabradine, 14 had it prescribed and 19 stopped during follow-up; and, of the 321 patients on loop diuretics, 30 had them prescribed, but 40 stopped during follow-up.

Prognosis

At Kaplan–Meier analysis, survival free from non-cardiovascular death (Figure 3) was worse in patients with incident cancer versus without incident cancer (p log=0.03), whereas survival free from cardiovascular death (Figure 4) was similar in those with incident cancer (p log=0.15). At univariate Cox regression analysis, adjusted for prescription of combined BB, RASi, and MRA therapy, incident cancer was associated with non-cardiovascular death (odds ratio [OR] 3.5; 95% confidence interval [CI] 1.2–10.3; p=0.03), but not with cardiovascular death (OR 1.8; 95% CI 0.8–4.0; p=0.15).

Discussion

Cancer is an emerging comorbidity of HF [8,9]. Limited data from clinical trials suggest that patients with HF and incident cancer are treated akin to those who do not develop cancer [9]. However, real-life evidence about the patterns of HF therapy in cancer patients is lacking. This is critical, as it is speculated that the occurrence of cancer may cause symptoms and alterations that render HF GDMT poorly tolerated. This may be the result of cancer itself, but also of the interaction of HF and anticancer drugs [10–12].

Our analysis of patterns of HF medication prescription did not highlight statistically significant differences in GDMT between patients with and without incident cancer, although we cannot exclude that some trends we observed could have been significant if the sample size had been bigger. It is also notable that, when we evaluated the

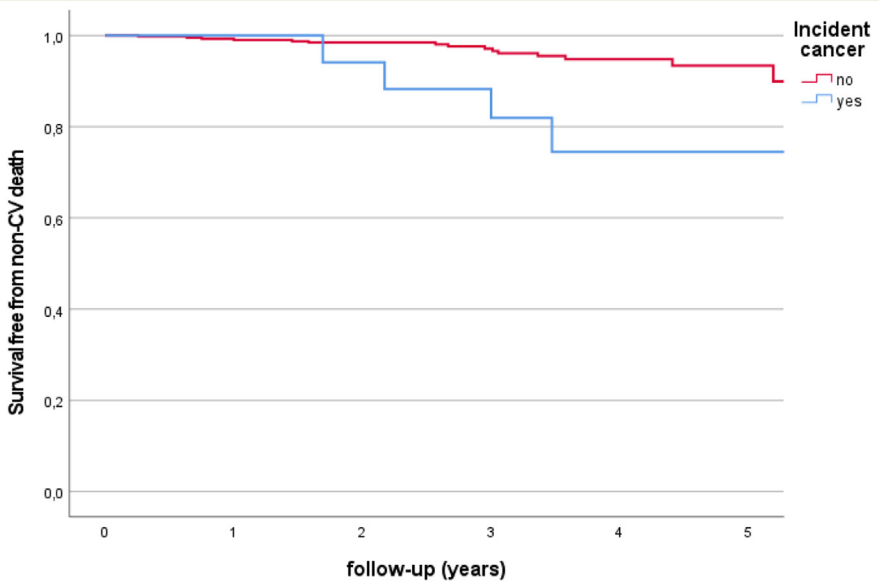

Figure 3 Kaplan–Meier curves for non-CV mortality according to the presence of incident cancer.
Abbreviation: CV, cardiovascular.

changes in GDMT at the nearest HF visit before and after cancer diagnosis, we found a tendency to a reduced use of RASi and MRA and a reduced use of up-titrated BB and RASi. Thus, the present study suggests that, in tertiary centres caring for HF, GDMT for HFrEF (and HFmrEF) may be down-titrated in single cases, but overall is maintained over time. This way of managing HF when it is complicated by cancer implies an integrated follow-up of HF patients, dedicated to their bidirectional cardiovascular and non-cardiovascular (i.e., oncological) needs [13,14], which is desirable, but might be complex to pursue in real-world clinical practice. In this perspective, a 'holistic' cardio-oncology approach may prove particularly effective, as it represents the optimal scenario which involves care for HF patients living with cancer, and not only for patients with cardiotoxicities [15,16]. Moreover, such a dynamic and

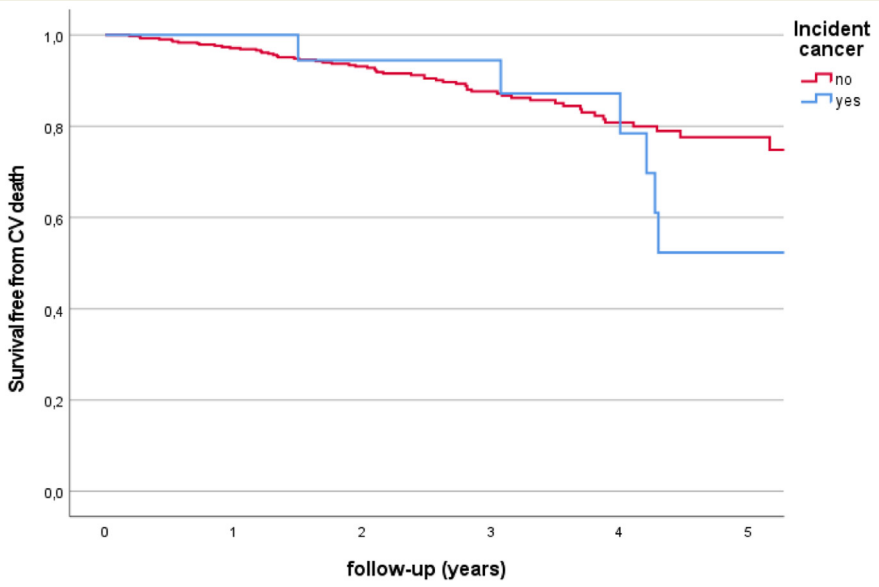

Figure 4 Kaplan–Meier curves for cardiovascular mortality according to the presence of incident cancer.
Abbreviation: CV, cardiovascular.

dedicated follow-up of HF patients may also serve to constantly optimise therapy, avoiding clinical and therapeutic inertia [17].

Finally, in line with the absence of significant differences in GDMT over the entire follow-up, we found that incident cancer was not associated with cardiovascular mortality. On the contrary, at univariate Cox regression analysis, it appeared associated with non-cardiovascular mortality, again highlighting the significant impact of non-cardiovascular comorbidity in the contemporary course of HF.

Some shortcomings of our analysis should be acknowledged. First, it is a single-centre, retrospective study with a small sample, as already commented upon, and our results should thus be considered only as hypothesis-generating. Second, we examined data regarding years of practice before the implementation of SGLT2i, hence we could not explore the impact of incident cancer on all components of current GDMT for HF. However, to our knowledge, this is the first study to assess real-world trends in HF therapy prescriptions in patients with incident cancer.

In conclusion, in patients with HFrEF and HFmrEF from a contemporary cohort of a tertiary centre, incident cancer was associated with individual and transient changes in the prescription patterns of GDMT.

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Conflicts of Interest

PA received speaker and/or advisor fees from AstraZeneca, Boehringer Ingelheim, Bayer, Daiichi-Sankyo, Janssen, Merck Sharp & Dohme, all outside the submitted work. The other authors have no conflicts of interest to disclose.

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