Risk factors and prevention of anthracycline-related heart failure

Summary of Ph.D. Thesis

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LIST OF PUBLICATIONS

This doctoral thesis is based on the following publications:

I. **Fogarassy G**, Vathy-Fogarassy Á, Kenessey I, Kásler M, Forster T. Risk prediction model for long-term heart failure incidence after epirubicin chemotherapy for breast cancer - A real-world data-based, nationwide classification analysis. Int J Cardiol 2019; 285: 47-52. *IF: 3.229*

II. **Fogarassy G**, Fogarassyné Vathy Á, Kováts T, Hornyák L, Kenessey I, Veress G, Polgár C, Forster T. Analysing the risk factors of doxorubicin-associated heart failure by a retrospective study of integrated, nation-wide databases. [Doxorubicin kezeléshez kapcsolódó szívelégtelenség kialakulásának rizikótényezői a hazai országos adatbázisok integrált, retrospektív elemzése alapján]. Orv Hetil 2020; 161: 1094-1102. [*Hungarian] IF: 0.497*

III. **Fogarassy** G, Vathy-Fogarassy Á, Kenessey I, Veress G, Polgár C, Forster T. Prevention of cancer therapy-related heart failure, is it really possible? A population-based study. J Cardiovasc Med (Hagerstown). *Accepted for publication on 21st August 2020. IF: 1.225*

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INTRODUCTION

The evolving, more and more potent anticancer biological and chemotherapies put patients at increased risk of adverse cardiac effects. These deteriorative effects may corrupt the survival benefit. Consequently, the importance of cardiovascular mortality is growing among cancer patients.

Regarding cancer therapy-related dilated cardiomyopathy, the application of anthracyclines remained a relevant factor. However, this adverse effect was shortly revealed after their introduction to therapy in the late 1960s, anthracyclines have yet been frequently used in cancer therapy because of their effectivity against a wide range of malignant tumours. The most frequently applied members of this class are doxorubicin, epirubicin. Myocyte injury and the subsequent dilated cardiomyopathy is the most important limiting factors during this therapy. The principal mechanism of cardiotoxicity is now considered to be triggered by the formation of topoisomerase 2β-anthracycline complexes resulting in impaired mitochondrial function. In the anthracycline-damaged mitochondria, iron-dependent reactive oxygen species generation is induced, which leads up to amplified mitochondrial dysfunction and consequent apoptosis. Traditionally, anthracycline-related heart failure was considered mainly irreversible. However, as it was recently revealed, if detected and treated early, at least partial reversibility of left ventricular deterioration can be achieved in the vast majority of patients. The left ventricular deterioration manifests itself in a delayed manner but commonly within the first year after the termination of anthracycline chemotherapy. Nevertheless, presumably due to the lack of systematic and prolonged echocardiography follow-up during and after cancer therapy, severe, irreversible anthracycline-related heart failure is not an infrequent phenomenon in every day clinical practice.

The incidence of anthracycline-related cardiomyopathy is highly dependent on their cumulative doses. Albeit they can be administered relatively safely while kept under a threshold cumulative dose, the excessive doses raise the risk exponentially. Furthermore, in smaller previous studies, other influencing factors were also confirmed as associated with anthracycline-related heart failure: older age (>65), black race, more advanced cancer stage and pre-existing cardiovascular disorders. Nonetheless, in these early studies much higher cumulative anthracycline doses were applied than in the practice nowadays. Besides, new anticancer protocols have come into practice, therefore, these previous, simple risk-prediction models are no longer effective.

To avoid the potentially irreversible consequences of cancer-therapy-related cardiomyopathy, it would be reasonable to start preventive therapy in patients characterized by elevated heart failure risk. Nevertheless, we have only limited evidence-based data on the effective preventive approach, hence it has not yet been widely adopted in clinical practice.

Dexrazoxane, which decreases mitochondrial iron level during anthracycline treatment and diminishes intramyocardial reactive oxygen species production, is supposed to decrease heart failure occurrence. Meanwhile, its use remained equivocal, as it was associated with severe side effects and a nonsignificant trend to reduce anticancer efficacy.

Except for enalapril demonstrated effective in terms of heart failure prevention for very high-risk cancer patients treated with high dose chemotherapies and showing early troponin elevation, none of the preventive cardiovascular medications have been tested in a long-term, high-volume, randomized controlled trial regarding the rate of incident cancer therapy-related cardiomyopathy. In the published small randomized controlled trials, the preventive angiotensin-blocking and statin treatment exhibited some beneficial effects on left ventricular ejection function, but with beta-blockers, controversial results were revealed.

AIMS

Since a comprehensive heart failure risk prediction model has been unavailable so far for anthracycline-treated patients,

(i) we aimed to introduce up-to-date heart failure risk prediction models, which reflect the contemporary protocols and integrate not only the patients' clinical characteristics but also the additional risk attributable to other anticancer therapies.

By more precise and tailored heart failure risk prediction, we intended to support the clinical decisions during anthracycline therapy. For patients characterized by elevated heart failure risk, preventive strategies might be considered. Given that so far, no convincing evidence-based data have been recorded on the clinical benefit of the wide-spread use of preventive medication against cancer therapy-related heart failure,

(ii) we sought to evaluate the potential preventive ability of concomitant cardiovascular medications against anthracycline-related heart failure.

MATERIAL AND METHODS

A retrospective study by integrating Hungarian nation-wide, real-world, anonymized databases was conducted. The merged dataset consisted of the Hungarian National Cancer Registry and the administrative databases of the National Health Insurance Fund, namely the in- and outpatient healthcare databases and the database of the pharmacy medicine dispensation records. The studied database covered the period between 1st January 2004 and 31st December 2016. Exclusively patients free from previous heart failure/dilated cardiomyopathy and anticancer therapies were enrolled. To ensure a long enough period for collecting the exclusion criteria, we did not enrol patients from the first three years of the database. The heart failure endpoint was defined by the coincidence of the administration of loop diuretics or potassium-sparing diuretics and the assignment of I50 International Classification of Diseases diagnosis code (heart failure) at hospital discharge or in autopsy reports.

By multivariable binary logistic regression executed on the data of the eligible breast cancer patients treated with anthracyclines (doxorubicin or epirubicin), we calculated odds ratios for the heart failure event. Pre-existing conditions, cancer stage and cumulative doses of the applied anticancer drugs were considered in the analysis.

Given that the epirubicin cohort was large enough for internal validation, the database was randomly split in a 70/30 ratio, the majority became the derivation cohort used to calculate heart failure score points, and the minority the validation cohort.

For the analysis to explore the preventive ability of the concomitant cardiovascular medication against chemotherapy-related heart failure, a broader population, the patients diagnosed with primary breast or colorectal carcinoma and treated with any biological or chemotherapy were selected. Anthracycline-treated patients were assessed as a prespecified subgroup in this study.

By applying multivariable logistic regression, a propensity score for the assignment of the cardiovascular therapies was calculated in order to use it for selecting the comparable treated and untreated cohorts. Propensity score matching was performed using the nearest neighbour method. The time to the first heart failure event in the treated and the matched control groups was compared using the Cox proportional-hazards model.

All the statistical analyses were done using IBM SPSS Statistics Version 23 (Armonk, NY). Probabilities of <0.05 were considered significant.

RESULTS

In the Hungarian breast cancer population treated with anthracyclines and free from previous heart failure, the overall cumulative incidence of heart failure was 6.9% in the epirubicin-treated cohort (8068 patients) during 3–10 years of follow-up and 6.2% during 3–9 years of follow-up in the doxorubicin-treated cohort (3288 patients).

Heart failure was induced by the higher anthracycline cumulative doses, the threshold doses were 709 mg/m^2 for epirubicin and 400 mg/m^2 for doxorubicin (odds ratio: 1.758; p=0.039; odds ratio: 2.27; p=0.008; respectively). The prominent contributing factor in elevated heart failure incidence was the higher age, even over 40 years in the epirubicin cohort (for category 40–49, odds ratio: 2.19; p=0.035) and over 50 years in doxorubicin cohort (for category 50–59, odds ratio: 2.97; p=0.005). The risk rose sharply with older age in both the epirubicin and the doxorubicin cohort; for patients over 70 years, the odds ratios were as high as 9.3 and 5.78, respectively. Cancer stage with regional spread (odds ratio: 1.257; p=0.061) seemed to have some impact on the development of heart failure, nevertheless, the advanced stage with distant metastases (odds ratio: 2.327; $p=1.13*10^{-10}$) exhibited high importance for provoking heart failure.

The presence of capecitabine (pyrimidine-analogue) in the protocol was confirmed as a weighty risk factor for heart failure in both the epirubicin and the doxorubicin cohorts (odds ratio: 2.507; $p=3.39*10^{-9}$ and odds ratio: 2.52; $p=7.49*10^{-6}$, respectively). Except for the 5-fluorouracil in combination with epirubicin, the additional treatments with other pyrimidine-analogues were also associated with higher heart failure risk. For metastatic breast cancer, bevacizumab, an anti-vascular endothelial growth factor monoclonal antibody is ofter administered, we have confirmed an elevated heart failure risk associated with it, as well (odds ratio in epirubicin cohort: 2.48; in doxorubicin cohort: 1.96; $p<0.05$ at both) In addition to anthracycline therapy, docetaxel exhibited a cumulative dose-dependent effect to induce heart failure (higher risk over 510 mg/m^2; odds ratio: 1.279 vs. 1.586; $p<0.05$ at both). When adding to doxorubicin therapy, carboplatin was also associated with a higher risk (odds ratio: 1.85; $p<0.05$).

Thanks to the larger cohort, in the epirubicin study a detailed risk assessment was achievable for the clinical characteristics, of which diabetes mellitus (odds ratio: 1.642); hypertension (odds ratio: 1.356); coronary artery disease either with previous myocardial infarction/revascularization (odds ratio: 1.886) or without them (odds ratio: 1.295); and

previous stroke (odds ratio: 1.704) were confirmed as factors associated with higher heart failure risk (for all, $p< 0.05$).

Based on the results from the epirubicin study, we constructed a risk prediction score derived from regression coefficients, which was able to classify heart failure risk over a wide range (2–30%) in the validation cohort and to identify the elevated risk for heart failure (score points≥ 9) with good sensitivity (0.79) and acceptable specificity (0.65).

In the research exploring the methods of heart failure prevention in cancer patients, our results confirmed the concomitant ACEi/ARB medication able to induce a preventive effect (hazard ratio: 0.809; p=0.032). This effect was more pronounced in the cohort with elevated baseline cardiovascular risk, compared to those without (hazard ratio: 0.707; p=0.032; hazard ratio: 0.805; p=0.117; respectively). No significant interaction was observed between the preventive effects of ACEi/ARB therapy and the presence of anthracyclines in the chemotherapy.

Statin preventive medication also exhibited an effect against the development of cancer therapy-related heart failure (hazard ratio: 0.748; p= 0.038). The preventive effect against heart failure was homogeneous irrespective of the baseline CV risk (p for interaction = 0.245). The benefit seemed much more pronounced at higher statin doses, compared to that seen at lower doses (hazard ratio: 0.722; p=0.234; hazard ratio: 0.928; p=0.729, respectively). The subgroup treated with anthracycline or platinum or capecitabine mostly benefitted from statins (hazard ratio: 0.66; p=0.032), while at patients treated without anthracyclines no benefit was found (hazard ratio: 0.917; p=0.628).

Nebivolol was identified as the only beta-blocker that may induce preventive effect against chemotherapy-related heart failure. However, this association showed merely a borderline significance and was detected exclusively in anthracycline- or capecitabine-treated patients (hazard ratio: 0.584; p=0.069).

DISCUSSION

Our study was the first comprehensive, nation-wide, real-world data analysis that defines the effect of common comorbid conditions, concomitant medications, cancer stage and chemotherapy cumulative doses together in terms of the likelihood of cancer therapy-related heart failure.

In the large anthracycline-treated breast cancer population, the overall long-term cumulative incidence of heart failure was 6.9% in the epirubicin cohort and 6.2% in the doxorubicin cohort. These data are in good agreement with the previously published results. Above the cumulative threshold dose (for epirubicin 709 mg/m^2, for doxorubicin 400 mg/m^2) a significant increase was found in heart failure incidence. Since anthracyclines were mostly administered under these doses, the development of cardiomyopathy was mainly influenced by other factors.

Previous papers showed that after anthracycline chemotherapy, heart failure risk rose at patients over 65 years. Our data indicate that age affects heart failure incidence even for patients over 40 years, and the risk of heart failure increases rapidly with age. The higher age was confirmed as the outstanding contributing factor in heart failure risk elevation. As awaited, we found higher heart failure risk at advanced cancer stage with distant metastases, as well.

Besides the higher age and advanced cancer stage, the presence of capecitabine was the most important contributing factor to the higher heart failure risk in both the epirubicin and the doxorubicin cohorts. Fluoropyrimidine analogues, like capecitabine, gemcitabine, 5-fluorouracil, are well-known provoking factors for acute coronary syndromes. However, our study was the first to explore thoroughly their importance to cause heart failure when combined with anthracyclines.

In terms of taxanes when administered after anthracyclines, a potential effect to promote heart failure was already known, which got affirmation from our epirubicin study for docetaxel but not for paclitaxel. Moreover, a cumulative dose-dependent effect of docetaxel for initiating heart failure was also observed in our study.

Trastuzumab, the well-known ErbB2 receptor antagonist antibody was not associated with an elevated heart failure risk in our long-term analysis, probably thanks to the obligatory echocardiography monitoring prescribed during this therapy and the rapid reversibility of the trastuzumab-related systolic dysfunction. Contrarily, for bevacizumab, an anti-vascular endothelial growth factor monoclonal antibody, administered for metastatic breast cancer, an

elevated heart failure risk was observed in both cohorts. Presumably, its common side effect, the hypertension may be involved in promoting heart failure.

As expected, diabetes mellitus, hypertension and coronary artery disease were proven associated with higher heart failure risk. Moreover, our study confirmed that the previous stroke was also an independent predictor for cancer therapy-related heart failure.

As a protective agent, the ability of dexrazoxane to reduce heart failure risk was not found in our research.

Radiotherapy treatment did not cause an elevated heart failure risk. Presumably, modern radiation therapies, which are carried out in respect of heart protection, do not have an impact on heart failure development.

The suggested risk-score-point model can differentiate heart failure risk over a wide range (2–30%). Using the threshold score (≥9), an elevated heart failure risk can be identified with good sensitivity and acceptable specificity.

The analysed, real-world dataset represents the current therapeutical practise, therefore, the derived models are suitable to assess the long-term heart failure risk of a patient treated with doxorubicin or epirubicin. By means of this, surveillance, preventive strategies and cancer therapies can be individualized to improve the outcome. Optimal echocardiography follow-up scheduling during and after anthracycline therapy is crucial to ensure that the dilated cardiomyopathy is diagnosed in an early stage when at least partial reversibility can be achieved.

Since we have only limited evidence-based data on the effective preventive approach against chemotherapy-related heart failure, this strategy has not yet been adopted in clinical practice. Our propensity score matching-based analysis performed in the unselected breast or colorectal cancer patients treated with any chemo- or biological therapy shed light on this important topic. As confirmed, the concomitant ACEi/ARB and statin medications were associated with a significantly lower risk of incident heart failure.

A previous randomized trial established the preventive ACEi medication administered to patients especially prone to dilated cardiomyopathy, characterized by early troponin positivity, as having a beneficial effect against chemotherapy-induced cardiomyopathy.

Our results showed that the wide-spread use of ACEi/ARB preventive medication administered during pharmaceutical anticancer therapies induced effective prevention against incident heart failure. No interaction was observed between the preventive effects of ACEi/ARB medication and the presence of anthracyclines in the chemotherapy. The patients

characterized as having higher CV risk (DM, previous myocardial infarction, myocardial revascularization, stroke, peripheral artery disease) mostly benefitted from this therapy. The potential explanation for the preventive effect of ACEi/ARB medication observed in patients of probably normal left ventricular ejection fraction might be a result of elevated intracardiac tissue ACE activity induced by chemotherapy.

Our results confirmed the statin therapy as unequivocally associated with lower heart failure risk, the subgroup treated with anthracycline or platinum or capecitabine mostly benefitted from statins. The preventive effect against heart failure was homogeneous irrespective of the baseline CV risk. Hence, it should not only be considered for the very high cardiovascular risk patients but also for those with a moderately elevated risk for the development of heart failure. Reactive oxygen species-mediated oxidative processes play important roles in the anthracycline-induced cardiomyopathy, presumably, their antioxidative properties make statins able to prevent left ventricular function deterioration. More intense statin therapy (simvastatin ≥40mg, atorvastatin ≥30mg, rosuvastatin ≥15mg) showed association with a greater reduction in heart failure risk than less-intense therapies.

Concerning the preventive ability of beta-blockers against the cancer therapy-related deterioration of left ventricular ejection fraction, controversial data were published. Our results did not provide evidence supporting the beneficial preventive effect of beta-blockers against incident heart failure in this population. Cardioprotection was neither confirmed at high CV risk subgroup nor anthracycline-treated subgroup. Nevertheless, lower risk of heart failure was identified of borderline significance for nebivolol administered to patients treated with anthracycline or capecitabine. This potential beneficial effect of nebivolol may be a consequence of its nitric oxide-restoring property.

Our propensity score matching based results may be considered as a paradigm for future randomized clinical studies in the field of the prevention against cancer therapy-related cardiotoxicity.

CONCLUSIONS FROM THE NEW OBSERVATIONS

(i) By multivariable, real-world data analysis, I confirmed, that at anthracycline-treated patients, the paramount contributing factors besides the cumulative anthracycline dose in elevated heart failure incidence were the higher age, even over 50 years and the advanced cancer stage with distant metastases.

(ii) I established that among the additional anticancer therapies, capecitabine was the most prominent contributing factor to the higher heart failure risk.

(iii) I confirmed that bevacizumab, an anti-vascular endothelial growth factor monoclonal antibody was associated with a notably elevated heart failure risk.

(iv) I revealed that in addition to anthracycline therapy, docetaxel exhibited a cumulative dose-dependent effect to induce heart failure.

(v) I established diabetes mellitus, hypertension, coronary artery disease (especially with previous myocardial infarction or revascularization) and previous stroke as relevant conditions associated with a higher risk for anthracycline therapy-related heart failure.

(vi) Using the results from the multivariable analysis, I constructed a risk-prediction score that was able to classify the anthracycline-related heart failure risk over a wide range (2–30%) and to identify the patients of elevated heart failure risk with good sensitivity (0.79) and acceptable specificity (0.65).

(vii) By a propensity score matching-based analysis, I found that the wide-spread used, concomitant ACEi/ARB medication is able to induce a preventive effect against the development of cancer therapy-related heart failure, which was more pronounced at elevated baseline cardiovascular risk.

(viii) I established that the statin medication exhibited a beneficial effect in the prevention of cancer therapy-related heart failure, which was irrespective of baseline cardiovascular risk and stronger with higher statin doses.

(ix) The results of my analysis pointed out that the subgroup that mostly benefitted from statins was the one treated with anthracycline or platinum or capecitabine.

(x) I found that none of the beta-blockers but nebivolol exhibited results suggesting an association (borderline significance) with a lower risk for the development of cancer therapy-related heart failure, which could be detected exclusively in anthracycline- or capecitabine-treated patients.

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