CARMO - Implementation of a Prospective Cardiac Monitoring Program for the Early Detection of Cardiac Dysfunction in Oncological Phase I/II Trials

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Research

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Abstract

Purpose

Cardiotoxic adverse events (AE) are challenging in the field of oncologic therapy. Age-related prevalence of cardiovascular disease and cancer itself may contribute to an increased risk of cardiac morbidity. Cardiac dysfunction impacts cardiac morbidity, survival and quality of life in cancer patients. This study established a cardio-oncological monitoring for the early detection of cardiovascular complications during experimental anti-tumour therapy.

Methods

Ninety patients referred to experimental anti-tumour therapy underwent prospective monitoring including repeat-electrocardiogram (ECG), echocardiography with speckle tracking imaging (STI), and determination of cardiac biomarkers. Changes in cardiac function were evaluated according to the Common Terminology Criteria of Adverse Events (CTCAE Version 4.03).

Results

Conventional ECG, high-sensitive troponin T, echocardiography including STI-analysis, and 24-hour Holter ECG were identified as relevant diagnostic tools. Early signs of cardiotoxicity appeared within the first 3 months after initiating anti-tumour therapy. Most frequent AEs were mitral valve disease (22%), diastolic dysfunction (15.7%), sinus tachycardia (13.8%), and increased hs-TnT (13.8%).

Conclusion

Prospective cardiac monitoring allowed early detection of cardiac dysfunction during experimental anti-tumour therapy. A multidisciplinary work-up and decision-making during cancer treatment is warranted to foster a deeper understanding of the underlying mechanisms of cardiac AEs and particularly to early detect and counteract cardiotoxicity.

Introduction

In cancer patients age-related prevalence of cardiovascular diseases, cancer itself as well as oncologic therapies result in increased and clinically relevant morbidity. Cancer is predominantly diagnosed at higher age (Eschenhagen et al. 2011), which itself represents one of the major risk factors for cardiovascular disease (Savji et al. 2013). The coincidence of oncologic and cardiovascular diseases often creates a multi-morbid patient cohort with an obvious cardiac morbidity.

Besides chemotherapeutics and the targeted agent trastuzumab, both well known as cardiotoxic drugs (Jones et al. 2009; Meinardi et al. 1999), new targeted agents can provoke severe cardiotoxic AEs (Chang et al. 2017a; Chang et al. 2017b; Michel et al. 2020). Numerous signalling pathways activated or inhibited by those innovative drugs play an overlapping role in both tumour growth and cardiac metabolism (Lal et
Inhibition of important kinases in key pathways such as the PI3K-AKT and MAPK pathways may lead to conceivable cardiotoxicity while tumour treatment proceeds successfully (Force and Kolaja 2011).

Thus far, the existing guidelines on cardiac monitoring for patients receiving cardiotoxic agents still mainly focus on chemotherapeutics or trastuzumab (Chau T. Dang 2016; Curigliano et al. 2012; Jones et al. 2009; Zamorano et al. 2016). Although the attention for cardiotoxic side effects of targeted therapies is growing and additional diagnostic tools such as cardiac biomarkers are contemplated, further research in the field of cardio-oncology is vitally important to validate the existing recommendations on the basis of clinical experience (Biersmith et al. 2020; Zamorano et al. 2016). In 2011, the European Society of Cardiology (ESC) stated explicitly that cardiac monitoring during early clinical trials is highly desirable and necessary (Eschenhagen et al. 2011). While traditional imaging-based assessment of left ventricular ejection fraction (LVEF) still has its place in cardiac monitoring, more advanced echocardiographic modalities, in particular, myocardial deformation imaging with speckle tracking imaging (STI) appears to have great potential for the early detection of cardiac AEs (Fallah-Rad et al. 2011; Sawaya et al. 2012).

Hence, cardiac dysfunction that develops during or after completion of cancer therapy is a growing health concern that should be addressed in a multidisciplinary setting. For every oncologic patient a baseline cardiovascular risk assessment is essential. Monitoring patients for subclinical cardiotoxicity is crucial for the prevention of symptomatic heart failure (HF). Detecting a decrease in LVEF after cancer therapy represents a late finding, and beyond that is considered to predict poor prognosis. Therefore, early markers of cardiac injury have to be actively explored. STI and increased cardiac serum biomarkers (e.g. high-sensitive troponins (hs-TnT)) are possible candidates for this purpose. A tailored plan for the management of cardiotoxicity should represent the future strategy to prevent heart failure. Decisions must balance the anti-tumour efficacy of the treatment with its potential cardiotoxicity. Patients developing cardiac dysfunction should be treated in accordance with established guidelines within an interdisciplinary set-up of oncologic and cardiologic specialists.

That in mind the development of a comprehensive cardiovascular (CV) monitoring schedule with periodic screening for cardiac AEs before, during and after anti-tumour treatment seems to be overdue. We here present results of a sustained and extended prospective CV monitoring program (CARM0) for patients receiving oncologic agents with potential cardiotoxic side effects in the frame of clinical phase I/II trials.

**Methods**

Between October 2011 and November 2015 90 patients with diverse advanced malignancies being referred to phase I/II anti-tumour treatment at the Comprehensive Cancer Center Mainfranken were included into CARM0 after they gave written informed consent. The study was performed in accordance with the Declaration of Helsinki and approved by the ethics committee of the University of Würzburg (EK #69/2011). Patients’ characteristics are summarized in Table 1. In the frame of our study, cardiologic baseline assessment was followed by a pre-defined and systematic cardiologic work-up (Table 2).
accompanying the anti-tumour therapy. CARMO included conventional 12-lead ECG and (24-hour) Holter ECG, echocardiography including STI, cardiac serum biomarkers (hs-TnT, NT-proBNP), and, if indicated, cardiac magnetic resonance imaging (cMRI). Cardiologic re-evaluation including cardiac imaging and STI for the detection of (subclinical) cardiotoxicity was performed at months 3 and 6 of oncologic treatment. Detected cardiac AEs were graded using the Common Terminology Criteria of Adverse Events (CTCAE 4.03) (SERVICES et al. 2010).

Statistical Analysis

A frequency analysis test was performed for all detected AEs after 3 and 6 months. Clustered bar diagrams depict the frequency of AEs detected by the different diagnostic tools at both timepoints. To illustrate the difference between the frequency of AEs after 3 and 6 months of experimental drug therapy we compared the mean value of AEs per patient at both timepoints. Paired t tests served to compare the mean values of global longitudinal strain (GLS) at baseline and after 3 months of experimental drug therapy. Statistical analysis was performed using IBM SPSS Statistics 22/23. A p-value with \( p < 0.05 \) was considered statistically significant.

Results

Patient demographics and baseline cardiovascular evaluation: Ninety patients were included into the CARMO study. The median age was 64.5 years (range 55 – 73), with 61% being male patients. Among study participants the clinically relevant cardiac morbidity rate was 50%, with at least one pre-existing cardiac disease (Table 1). The kind of malignancies and their respective treatments are summarized in supplemental Table 1.

Re-evaluation after 3 months: Re-evaluation after 3 months of anti-tumour therapy was possible in 51 patients. Twenty patients were screening failures for participation in the respective oncologic trial and 19 patients were withdrawn from oncologic treatment because of disease progression. Table 3 provides an overview on detected cardiac AEs. Sinus tachycardia (7/51 patients, 13.8%), elevation of hs-TnT (7/51 patients, 13.8%) and QT-prolongation (6/51 patients, 11.8%) were the most frequent AEs. Twenty-four hour Holter ECG detected 7 sinus tachycardias whereof 6 were treatment-emergent AEs. One patient treated with a MEK inhibitor (MEKi) combined with docetaxel had hs-TnT levels of 56.4 pg/ml (CTCAE grade 3) while clinical symptoms (angina pectoris) as well as ECG signs of myocardial ischemia were lacking. In two patients pre-existing coronary heart disease aggravated during the first 3 months of oncologic drug therapy (one NSTEMI with hs-TnT >3000 pg/ml; one acute coronary syndrome (ACS) with hs-TnT 7.3 pg/ml). Methods used to detect cardiac dysfunction are shown in Fig. 1a.

Re-evaluation after 6 months: After 6 months 36/90 patients were still on anti-cancer therapy while 15 patients had terminated their treatment mainly due to tumour progression. Two ventricular tachycardias (CTCAE grade 2, 2/36 patients) were detected during 24h Holter ECG monitoring. Levels of hs-TnT increased in one patient under MEKi/docetaxel combinatory treatment, however, without any chest pain, ECG abnormalities and/or changes in LVEF (hs-TnT at 3 months: 56.4 pg/ml; hs-TnT at 6 months: 82.7
Conventional ECG, hs-TnT, echocardiography, and 24h Holter ECG monitoring detected most AEs after 6 months of treatment (Table 3; Fig. 1b). Compared to the 3 months follow-up examination less cardiac AEs were detected at 6 months.

In summary, our study detected a total of 24 AEs of at least grade 2 after 3 months of anti-cancer treatment. Cardiac AEs were diagnosed by conventional ECG (sinus tachycardia, sinus bradycardia) and 24h Holter ECG (sinus tachycardias, intermittent atrial fibrillation, atrial ectopies). Abnormalities in echocardiograms (AE ≥ grade 2) did not result in direct intervention(s) or a modification of medical treatment. The data obtained 6 months after initiation of anti-cancer therapy showed similar results. Only two ventricular tachycardias detected by 24h Holter ECG monitoring led to a modification of medical therapy. The remaining AE ≥ grade 2 (mitral valve insufficiency, two partial respiratory insufficiencies, hs-TnT >50 pg/ml without symptoms of angina or changes in ECG) did not result in direct intervention(s) or a modification of medical treatment. In total four patients had to be hospitalised due to cardiologic AEs. Two of those were detected in the frame of the CARMO program (2h ECG: signs of perimyocarditis, at the 3 months-visit: instable angina). One patient was hospitalized shortly after the 3 months-visit because of lung oedema and NSTEMI. Another patient showed a hemiparesis at an oncological study visit. The cardiologic work-up revealed a cardiac embolus as the most likely cause of the neurologic event.

STI: Out of all echocardiograms, 51 echocardiograms at baseline and 48 echocardiograms after 3 months of experimental cancer therapy fulfilled the quality criteria for STI analysis (Suppl. Table 2). Compared to baseline measurements there was no significant decrease in GLS values after 3 months of experimental cancer therapy (p = 0.412).

The findings in a subgroup of patients treated with a MEKi/docetaxel combinatory treatment clearly demonstrate the additional value of STI for the detection of (subclinical) cardiotoxicity, as absolute LVEF values remained within a normal range (Suppl. Table 3, Fig. 2 a-d). Two patients showed hs-TnT and particularly GLS values clearly out of the normal range which fortunately returned to a normal range about one year after cessation of docetaxel while continuing MEKi monotherapy (Fig. 2 c-d). These results underscore the necessity of a longer follow-up and also point towards a possible reversibility of the detected cardiotoxicities.

Discussion

Due to increasing cardiotoxic effects of (novel) oncologic drugs the need for expertise and clinical data in the field of cardio-oncology is growing continuously (Caspi and Aronson 2019; Lopez-Sendon et al. 2020; Michel et al. 2020; Prisco et al. 2014). The implementation of the CARMO program intended to improve early detection of cardiac AEs in order to increase patient safety during oncologic treatment and to unmask potential cardiotoxicity of the applied targeted therapies.

The CARMO baseline assessment comprises the current recommendations of the European Society of Medical Oncology (ESMO) (Curigliano et al. 2012; Curigliano et al. 2020) and the ESC (Zamorano et al. 2016). A baseline assessment of cardiovascular risk factors, pre-existing co-morbidities, prior cardiotoxic
oncological treatment and the baseline status of cardiac performance can identify patients at risk for cardiac AEs. Of note, the cardiac morbidity rate (at least one pre-existing cardiovsacular disorder) of the patients included into CARMOMO was 50%. Thus, careful baseline evaluation of tumour patients entering anti-cancer treatment should be a pre-requisite for subsequent oncologic treatment decisions. In addition to the ESMO (2012) and ESC recommendations the CARMOMO program included a 24h Holter ECG monitoring and STI. By 24h Holter ECG monitoring we detected most of the treatment-emergent cardiac AEs followed either by direct intervention(s) or a change in medical treatment. That in mind and with respect to the occurrence of cardiac arrhythmias in cancer patients (Guglin et al. 2009; Hersh et al. 1986) the need for a 24h Holter ECG monitoring as part of future monitoring programs becomes evident. Additional STI analyses may help to identify subclinical changes in cardiac function and represent a promising measure for the early detection of asymptomatic cardiac AEs. In addition, STI may represent a useful early diagnostic tool to predict a further deterioration of LVEF (Thavendiranathan et al. 2014); however, the cut-off values for clinically relevant changes in strain values remain to be defined.

On the basis of our CARMOMO study conventional 12-lead ECG, echocardiography, the serum biomarker hs-TnT and 24h Holter ECG were identified as the most important cardiac monitoring tools able to detect clinically relevant AEs as well as subclinical changes in cardiac function 3 and 6 months after initiation of anti-cancer therapy. It might be debated whether the chosen time intervals between the cardiologic assessments were appropriate and reasonable. Since the current recommendations are merely based on expert opinions (Zamorano et al. 2016), the ESC recommends to schedule the intervals between the different visits on the basis of the individual risk profile of a given oncologic patient. More precise recommendations were published in 2010 and 2012 by the ESMO suggesting cardiologic assessments at intervals of 12 weeks (after 3, 6 and 9 months) (Bovelli et al. 2010; Curigliano et al. 2012). Our CARMOMO program set up in 2011 is in full accordance with the ESMO recommendations and demonstrates for the first time that a defined cardiac monitoring program is feasible and reliably detects cardiac AEs as well as subclinical changes in cardiac function at defined time points (in our case 3 and 6 months after initiating anti-cancer drug therapy).

However, the timing and the composition of the cardiac work-up may be discussed as our results are suggestive of a change in cardiac function especially during the first 3 months of experimental anti-cancer therapy (Suppl. Fig. 1). A closer meshed cardiac monitoring in the first weeks of experimental anti-cancer treatment might prevent hospitalisation, detect AEs at an earlier stage and, consequently, could prevent the aggravation of pre-existing cardiac disorders. Since most AEs implicating direct intervention(s) or a modification of the current medical treatment were detected by conventional (and/or 24h Holter) ECG, additional examinations at earlier timepoints might have detected treatment-emergent cardiac arrhythmias at an earlier stage. Additional measurements of hs-TnTs and echocardiography including STI analysis at these timepoints might in the future even contribute to detect (subclinical) changes in cardiac function, to reveal (novel) cardiotoxic drug effects, and to more precisely identify patients at risk for clinically relevant cardiac events.
STI- respectively GLS-measurements hold promise to represent the future method of choice for the early detection of cardiotoxicity (Ali et al. 2016; Plana et al. 2014; Santoro et al. 2017). Several studies showed a decrease in GLS values under chemotherapy irrespective of changes in global LVEF (Fallah-Rad et al. 2011; Sawaya et al. 2011; Sawaya et al. 2012), inferring that STI might in fact represent a more sensitive diagnostic tool for the detection of very early changes in cardiac function. This brings up the possibility to timely initiate cardioprotective drug therapy comprising ACE inhibitors and/or beta-blockers to prevent or counteract a clinically relevant reduction in LVEF (Curigliano et al. 2020; Lynce et al. 2019; Negishi et al. 2018). Though CARMOMO did not find a significant decrease in GLS after three months of experimental anti-cancer treatment compared to baseline, STI measurements revealed potential cardiotoxicity in a small number of patients treated with MEKi and taxanes. Thus, STI analysis seems to be capable to detect early (subclinical) cardiotoxicity thereby allowing to initiate cardioprotective drug therapy already at early stages of cardiac dysfunction.

However, there are some limitations of the CARMOMO study. First, the study-echocardiograms were obtained by different (albeit experienced) physicians which might have resulted in some interobserver variability. To minimize interobserver (and intraobserver) variability, a structured training and certification of echotechnicians might optimize the cardiac imaging process and evaluation. NT-proBNP is a well evaluated biomarker in HF (Ponikowski et al. 2016). However, until now studies validating BNP as a biomarker for the detection of cardiotoxic side effects of oncologic drugs are lacking (Stevens and Lenihan 2015). Due to a missing classification regarding natriuretic peptides in the CTCAE and the lack of data defining cut-off values CARMOMO did not detect any AEs on the basis of changes in NT-proBNP values. Second, blood pressure monitoring is part of current cardiac monitoring recommendations (Zamorano et al. 2016). Some studies identified arterial hypertension as a risk factor for the development of cardiotoxic AEs under anti-cancer treatment (Kotwinski et al. 2016; Pinder et al. 2007). Against the background that targeted anti-cancer drugs as e.g. VEGF inhibitors can induce or lead to an aggravation of (pre-existing) arterial hypertension (Izzedine et al. 2009; Milan et al. 2014), systematic measurements of blood pressure at the different time points should be part of future monitoring programs.

In conclusion, cancer patients are generally at risk of clinically relevant cardiotoxicity. Thus, the implementation of extended cardiac monitoring programs such as CARMOMO are strongly recommended especially in phase I/II trials with anti-cancer drugs in order to optimize early detection of cardiac dysfunction, to obtain a deeper understanding of the possible mechanisms causing cardiotoxicity and to elaborate cardioprotective treatment strategies. In this regard, an interdisciplinary cooperation between oncologists and cardiologists is indispensable to improve the care of cancer patients. Future programs should foster a multidisciplinary work-up in larger patient cohorts with the aim to reach a level of significance for some of the hypotheses outlined here as a basis for evidence-based cardiac monitoring recommendations for early clinical cancer trials.

**Declarations**

**Funding**
There was no funding.

**Conflicts of interest**

Conflict-of-interest disclosure: R.C.B. has consulted for Amgen, Novartis and GeMoaB. R.C.B. has received honoraria from Amgen, Novartis, GeMoaB, Cellex, Molecular Partners. R.C.B. has served for Amgen, Novartis, GeMoaB, Cellex, and Molecular Partners in advisory boards. M.E.G. has served on advisory boards for Amgen, GeMoAb and Roche, or has received honoraria or travel support from Novartis, Roche, Bristol-Myers Squibb (BMS) and Janssen-Cilag, outside the submitted work. B.S. is on the advisory board or has received honoraria from Incyte, Novartis, Roche, Bristol-Myers Squibb (BMS) and MSD Sharp & Dohme (MSD), research funding from Pierre Fabre Pharmaceuticals, BMS and MSD and travel support from Novartis, Roche, BMS, Pierre Fabre Pharmaceuticals, MSD and Amgen, outside the submitted work. V. G. received travel support from Novartis, Pierre Fabre Pharmaceuticals, BMS and MSD and has received speakers honoraria from BMS, outside the submitted work. C.S. and R.J. declare no competing financial interests. C.M. reports speakers honoraria from Amgen and Tomtec, a travel grant from Orion Pharma and Alnylam, and participation in Advisory and Patient Eligibility Boards sponsored by AKCEA, Alnylam, and EBR Systems outside the submitted work. M.C. has received speakers honoraria from Pfizer.

**Ethics approval**

The study was performed in accordance with the Declaration of Helsinki and approved by the Ethics Committee of the University of Würzburg (EK #69/2011).

**Consent to participate**

Informed consent was obtained from all individual participants included in the study.

**Consent for publication**

All authors consented to the submitted version of the manuscript.

**Availability of data and material**

Data were provided from study site les, from patients’ treating oncologists, and from general practitioners as well as from the tumour registry of the Comprehensive Cancer Center Mainfranken (Würzburg, Germany) and the German Heart Failure Center (DZHI, Würzburg, Germany). All data are archived and available at the Early Clinical Trial Unit, University Hospital Würzburg.

**Code availability**

Not applicable

**Authors’ contributions**
Contribution: V.G., C.S. and M.E.G. designed the research; V.G., C.S., D.L. and M.E.G. performed the research; V.G., C.S., D.L., M.C., C.M. and M.E.G. analyzed the data; V.G. and M.E.G. wrote the manuscript and all authors reviewed and contributed to its final version.

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**Tables**

**Table 1 Patients´ characteristics, medical history and cardiac risk profile at baseline**
| Characteristics                                      | Patients (n = 90) |
|-----------------------------------------------------|------------------|
| Age median (Q.25 – Q.75) (years)                    | 64.5 (55-73)     |
| Sex, n (%)                                          |                  |
| female                                              | 35 (39)          |
| male                                                | 55 (61)          |
| **CVRF**                                            |                  |
| Arterial Hypertension, n (%)                        | 39 (43.3)        |
| Diabetes mellitus, n (%)                            | 10 (11.1)        |
| Hyperlipidaemia, n (%)                              | 8 (8.9)          |
| Hyperuricaemia, n (%)                               | 4 (4.4)          |
| **Pre-existing cardiological diseases**              |                  |
| Coronary artery disease, n (%)                      | 13 (14.4)        |
| Myocardial infarction, n (%)                        | 7 (7.8)          |
| History of revascularisation, n (%)                 | 9 (10)           |
| History of bypass surgery, n (%)                    | 1 (1.1)          |
| Heart failure, n (%)                                | 4 (4.4)          |
| - NYHA I                                            | 1 (1.1)          |
| - NYHA II                                           | 2 (2.2)          |
| - NYHA III                                          | 1 (1.1)          |
| Arrhythmia, n (%)                                   | 5 (5.5)          |
| **Oncological pre-treatments**                      |                  |
| Mean number of lines (range)                        | 2.31 (± 1.98)    |
| Anthracyclines, n (%)                               | 22 (24.4)        |
| Mediastinal/thoracic Radiation, n (%)               | 30 (33.3)        |

Table 2 Schedule of diagnostic procedures at baseline, during and/or after anti-tumour treatment
| Visit | Timepoint | ECG | Holter ECG | Echocardiography + STI | Biomarker |
|-------|-----------|-----|------------|-----------------------|-----------|
| 1     | Baseline¹ | x   | x          | x                     | x         |
| 2     | 2 h¹/²    | x   |            |                       |           |
| 3     | 7 d¹/²    | x   |            |                       |           |
| 4     | 28 d¹/²   | x   |            |                       |           |
| 5     | 3 mo¹/²   | x   | x          | x                     | x         |
| 6     | 6 mo¹/²   | x   | x          | x                     | x         |

ECG, electrocardiogram; STI, speckle tracking imaging; h, hour; d, day; mo, months; ¹CmRT, cardiac magnet resonance imaging, optional; ²time after start of treatment

**Table 3 Cardiac adverse events 3 and 6 months after initiation of targeted anti-tumour treatment**
| Adverse Events                          | Patients (n = 51/90) | Patients (n = 36/90) |
|----------------------------------------|----------------------|----------------------|
|                                        | reevaluation after   | reevaluation after   |
|                                        | 3 months             | 6 months             |
|                                        | All Grades | Grade ≥ 2  | All Grades | Grade ≥ 2  |
| Acute coronary syndrome                | 2 (0.9)   | 2 (3.9)    | 0 (0)      | 0 (0)      |
| Aortic valve disease                   | 4 (7.8)    | 1 (2.0)    | 2 (5.6)    | 0 (0)      |
| Atrial fibrillation                    | 1 (2.0)    | 1 (2.0)    | 0 (0)      | 0 (0)      |
| Chest pain – cardiac                   | 2 (3.9)    | 2 (3.9)    | 0 (0)      | 0 (0)      |
| Conduction disorder                    | 2 (3.9)    | 0 (0)      | 1 (2.8)    | 0 (0)      |
| Mitral valve disease                   | 11 (21.6)  | 2 (3.9)    | 4 (11.1)   | 0 (0)      |
| Myocardial infarction                  | 1 (2.0)    | 1 (2.0)    | 0 (0)      | 0 (0)      |
| Palpitations                           | 1 (2.0)    | 0 (0)      | 0 (0)      | 0 (0)      |
| Pulmonary valve disease                | 1 (2.0)    | 0 (0)      | 0 (0)      | 0 (0)      |
| Sinus bradycardia                      | 3 (5.9)    | 1 (2.0)    | 1 (2.8)    | 0 (0)      |
| Sinus tachycardia                      | 7 (13.8)   | 6 (11.8)   | 0 (0)      | 0 (0)      |
| Supraventricular tachycardia           | 5 (9.8)    | 1 (2.0)    | 0 (0)      | 0 (0)      |
| Trikuspidal valve disease              | 8 (15.7)   | 1 (2.0)    | 5 (13.9)   | 1 (2.8)    |
| Ventricular arrhythmia                 | 1 (2.0)    | 0 (0)      | 0 (0)      | 0 (0.0)    |
| Ventricular tachycardia                | 0 (0)      | 0 (0)      | 2 (5.6)    | 2 (5.6)    |
| Diastolic dysfunction                  | 8 (15.7)   | 2 (3.9)    | 1 (2.8)    | 0 (0)      |
| High-sensitive Troponin T²             | 7 (13.8)   | 2 (3.9)    | 3 (8.3)    | 1 (2.8)    |
| Prolonged QT interval                  | 6 (11.8)   | 0 (0)      | 1 (2.8)    | 0 (0)      |
| Pulmonary hypertension                 | 5 (9.8)    | 2 (3.9)    | 0 (0)      | 0 (0)      |
| Hypoxia                                | 3 (5.9)    | 0 (0)      | 2 (5.6)    | 2 (5.6)    |

151/90 patients reached 3 months reevaluation and 36/90 patients 6 months reevaluation

²AE linked to each other
Figure 1

Number of cardiac adverse events detected depending on diagnostic tool after three and six months of treatment. AE, adverse event; ECG, electrocardiogram; Echo, echocardiography; STI, speckle tracking imaging; BGA, blood gas analysis
Figure 2

LVEF and GLS in patients #23, #29, #36 and #55 during treatment with MEKi and docetaxel. LVEF, left ventricular ejection fraction; GLS, global longitudinal strain. Cut-off value was -17% in accordance with the results published by Sugimoto et al. (95% CI for normal strain: -17.2 to -27.7) (Sugimoto et al. 2017). LVEF, left ventricular ejection fraction; GLS, global longitudinal strain; BL, baseline
Figure 3

Course of LVEF, TnT-hs and GLS in patients #29 and #36 during treatment with MEKi and docetaxel. LVEF, left ventricular ejection fraction; GLS, global longitudinal strain. LVEF, left ventricular ejection fraction; TNT-hs, high-sensitive Troponin T; GLS, global longitudinal strain; BL, baseline