CARDIOVASCULAR COMPLICATIONS
OF CANCER TREATMENT

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I would also like to cordially thank Univ. Doz. Dr. Michael Fiegl for introducing me to statistic skills and his unconstrained support, whenever assistance or just a friendly advice was needed. Most of all, I would like to thank him for our fruitful discussions and the remarkable projects which we worked on together.

I would also like to acknowledge Univ. Prof. Dr. Günther Gastl and the Tyrolean Cancer Research Institute for giving me the opportunity to perform my PhD projects in their facilities.

My colleagues Dr. Andreas Seeber PhD, Dr. Fabian Lunger PhD, Dr. Andreas Pircher PhD and Dr. Normann Steiner PhD who also conducted their PhD thesis at Medical University of Innsbruck, always gave me great suggestions too. Over the past few years we have become close friends and launched several projects together.

A great thank you must obviously be dedicated to my family, who have supported me throughout and encouraged me to start my PhD studies. They are my loving foundation which has enabled me to enter the very competitive scientific world.

I feel obliged to express my thanks to the collaboration partners in the study centres for their great motivation to participate in an academic driven trial.

Lastly, I would like to show my appreciations to all patients and their families who were willing to take part in our clinical projects.
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ABSTRACT

Introduction. Cardiotoxicity is considered to be one of the most severe adverse effects of systemic oncological treatment as it reduces quality of life and might reduce patients’ prognosis. Present knowledge is primarily based on patients who were treated in prospective clinical trials and is focused on acute toxicities. In contrast, there is a lack of data concerning the long-term cardiotoxic effects of systemic cancer therapies. Especially data of patients treated in clinical routine is scarce. The aim of this thesis is to gain new insights into impact, risk factors and incidence of cardiovascular side effects in patients treated in real-life setting.

Methods. Different projects were conducted including retrospective analyses in large consecutive cohorts of NSCLC patients, DLBCL patients and patients treated with a non-pegylated formulation of doxorubicin, respectively. In these studies the focus was set on cardiovascular comorbidities and cardiovascular events appearing during treatment or follow-up. Moreover, a prospective multicentre, non-interventional trial was developed and has started successfully. This trial evaluates cardiovascular events in patients receiving systemic treatment in a curative intention.

Results. NSCLC patients are characterized by a considerable amount of cardiovascular comorbidities and events. Different parameters were detected which proved to be risk factors for the development of cardiovascular events. A number of cardiovascular comorbidities were significantly associated with cardiovascular events which include atrial fibrillation, myocardial infarction and cardiomyopathy.

Patients receiving non-pegylated doxorubicin showed a significant number of cardiovascular events. In these patients, cardiovascular comorbidities, chronic obstructive pulmonary disease and elevated baseline NT-pro BNP were associated with the occurrence of cardiovascular events.

In April 2016, ten centers were initiated and 273 patients have been included in the prospective trial.

Conclusion. Cardiovascular events are frequently observed in patients receiving anticancer treatment. Different clinical parameters are associated with increased risk. To strengthen the evidence of such risk factors, the results of our prospective trial are desirable.
INTRODUCTION

During the last decades constant improvements in the treatment of cancer have been achieved. Great advances were observed in many tumor entities. As a result, long term survival now is possible in many cancer patients. A big part of this success is attributable to the introduction of new potent anticancer agents. A plethora of new drugs have entered clinical routine and a multitude of promising agents are on their way to approval. Besides therapeutic efficacy, a focus in oncologic treatment is set on the side effects of the substances used. Within the different toxicities, which might arise during or after cancer treatment main concerns persist with regard to cardiotoxicity. Cardiac side effects can lead to the reduction of patients’ prognosis and quality of life. Hence, they represent one of the most severe toxicities in cancer patients.

The first studies, dealing with cardiac side effects of anticancer agents were published in the nineteen seventies. Von Hoff et al. reported on the association between the administration of anthracyclines and the development of heart failure [1, 2]. Thus, anthracyclines are the most recognized chemotherapeutic agents which are associated with cardiac side effects. Since the introduction of trastuzumab in the late 90s several clinical trials, investigating this agent have reported trastuzumab-associated cardiovascular side effects. Consequently, most literature available has focussed on cardiotoxicity of anthracyclines [1-8] and trastuzumab [9-20]. These two substances are usually associated with characteristic patterns with respect to myocardial side effects. These differences in the clinical appearance led to the definitions of type I and type II cardiotoxicity [21]. Table 1 displays the main differences between these two proposed substance-specific toxicities [12].
Table 1. Main differences between type I and type II toxicity

<table>
<thead>
<tr>
<th>Type I toxicity (anthracyclines)</th>
<th>Type II toxicity (trastuzumab)</th>
</tr>
</thead>
<tbody>
<tr>
<td>cellular death</td>
<td>cellular dysfunction</td>
</tr>
<tr>
<td>changes at myocardial biopsy</td>
<td>no typical changes at myocardial biopsy</td>
</tr>
<tr>
<td>cumulative dose related</td>
<td>no association with cumulative dose</td>
</tr>
<tr>
<td>permanent damage</td>
<td>predominantly reversible</td>
</tr>
<tr>
<td><strong>risk factors</strong></td>
<td><strong>risk factors</strong></td>
</tr>
<tr>
<td>combination with other agents</td>
<td>combination with anthracyclines and paclitaxel</td>
</tr>
<tr>
<td>age</td>
<td>age</td>
</tr>
<tr>
<td>previous cardiac disease</td>
<td>previous cardiac disease</td>
</tr>
</tbody>
</table>

Nevertheless, cardiovascular side effects have also been described for several other substances including fluorouracil [22-30], capecitabine [31-36], taxanes [37, 38], cyclophosphamide [39-41], cisplatin [42-45] and antiangiogenic agents [46-55]. Table 2 gives a brief overview of different chemotherapeutic agents which are associated with cardiac side effects and potential risk factors. A detailed review of the current knowledge is presented on pages 44-48.
Table 2. Different agents used in cancer patients, clinical appearance and risk factors of cardiotoxicity

<table>
<thead>
<tr>
<th>Agent</th>
<th>Acute cardiovascular side effects</th>
<th>Chronic cardiovascular side effects</th>
<th>Risk factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anthracyclines</td>
<td>Conduction disorders, ventricular dysfunction</td>
<td>Ventricular dysfunction, heart failure</td>
<td>Cumulative dose, combination with other agents, pre-existing cardiovascular disease</td>
</tr>
<tr>
<td>Fluorouracil</td>
<td>Anginal chest pain, ECG-abnormalities</td>
<td></td>
<td>Continuos infusion, coronary artery disease,</td>
</tr>
<tr>
<td>Taxans</td>
<td>Bradycardia, conduction disorders</td>
<td></td>
<td>Combination with anthracyclines</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>Pericarditis, acute heart failure</td>
<td></td>
<td>High-dose therapy, age, reduced ejection fraction</td>
</tr>
<tr>
<td>Cisplatin</td>
<td>Conduction disorders, ischemic events</td>
<td>Atherosclerosis</td>
<td>High cumulative dose, combination with anthracyclines, age</td>
</tr>
<tr>
<td>Trastuzumab</td>
<td>Decrease of ejection fraction</td>
<td>Heart failure</td>
<td>Combination with anthracyclines, paclitaxel, cyclophosphamide</td>
</tr>
<tr>
<td>VEGF-targeting agents</td>
<td>Hypertension, arterial thromboembolic events,</td>
<td>Heart failure</td>
<td>Age, pre-existing arterial thromboembolic events</td>
</tr>
</tbody>
</table>

Since various cardiovascular comorbidities have been linked to an increased occurrence of cardiotoxicity it might be speculated that the incidence of cardiotoxicity might be elevated in patients treated in daily routine. A report by the American Heart Association shows that one out of three American citizens above the age of twenty is affected by cardiovascular disease [56]. At least data from trastuzumab treated breast cancer patients suggests that the incidence of heart failure seems to be much higher in patients treated in clinical routine than in previous reports of the large trastuzumab pivotal trials. According to a large retrospective population-based study the cumulative incidence of heart failure was 20.1% at 5 years in patients receiving anthracycline and trastuzumab [57]. The authors state that previous clinical trials might have underestimated the magnitude of cardiotoxicity due to detection bias. Nevertheless, most real-life data regarding cardiotoxicity have come from retrospective studies. Therefore, prospective data to validate these results are warranted.
From reviewing the available literature, it appears that cardiotoxicity is a substantial side effect of many systemic therapies. However, there is a lack of knowledge regarding long term cardiovascular effects. Moreover, the incidence of cardiotoxicity is presumably higher in patients treated in daily routine since those patients are usually characterized by an increased burden of cardiovascular comorbidities compared to patients in clinical trials. This thesis focusses on cardiovascular comorbidities and cardiovascular side effects in patients suffering from malignancies who are treated in a real-life setting.
AIM OF THE THESIS

Based on the lack of knowledge regarding cardiotoxicity of systemic cancer treatment the aim of this thesis is to gain new insights into impact, risk factors and the incidence of cardiovascular side effects in patients treated in clinical routine.

A previously published review of our group provides detailed information on the current knowledge concerning cardiotoxicity. Different studies on patients treated in real life settings have been started and were successfully performed since the start of the PhD studies. A retrospective analysis in a large consecutive cohort of NSCLC patients was performed, focussing on pre-existent cardiovascular comorbidities and cardiovascular events appearing during treatment or-follow up. In collaboration with other researchers, a trial assessing cardiovascular events in patients treated with a liposomal formulation of doxorubicin was recently published. Gender aspects of cardiotoxicity were evaluated in a cohort of R-CHOP treated DLBCL patients. A substantial part of the PhD studies was dedicated to the development of a multicentre prospective trial. This trial started successfully within this period. The next section gives an overview of the different projects evaluating cardiotoxicity.
PUBLICATIONS

Review

Chemo- und Immuntherapie-induzierte Kardiotoxizität bei Tumorpatienten [58]

Florian Kocher, Michael Fridrik, Felix Keil, Gerhard Pölzl, Hellmut Samonigg and Wolfgang Hilbe

Spectrum Onkologie (2013) 4: 22-27

Applicant’s contribution

- Review of literature
- Acquisition of data
- Interpretation of data
- Preparation of manuscript

Aim of this work was to evaluate current knowledge about the specific cardiotoxic potential of various systemic therapeutic agents used in the treatment of cancer patients.

Full text article see pages 44-48
Applicant’s contribution

- General idea
- Review of literature
- Acquisition of data
- Interpretation of data and statistical analysis
- Preparation of manuscript

Aim of this work was to evaluate the burden of cardiovascular comorbidities and the incidence of cardiovascular events during treatment or follow-up in a large unselected cohort of NSCLC patients.

Full text article see pages 49-56

Abstract

Introduction. Patients with non-small cell lung cancer (NSCLC) and cardiovascular disease often share a comparable demographic profile. The aim of this analysis was to assess the significance and prevalence of pre-existing cardiovascular comorbidity and cardiovascular events in NSCLC.

Patients and methods. 715 consecutive NSCLC patients diagnosed between 2004 and 2009 at the Medical University of Innsbruck were retrospectively assessed regarding cardiovascular comorbidities, risk factors, cancer treatment, cardiovascular events occurring after the start of treatment and outcome.
**Results.** At least one cardiovascular comorbidity was present in 462/687 (67.2%) evaluable patients. Cardiovascular events were documented in 68 patients (9.5%) with conduction disorders being the most prevalent of them (n=19) followed by cardiomyopathy (n=13), myocardial infarction (n=13), sudden cardiovascular death (n=12) need of revascularisation (n=6) and pericardial effusion (n=5). Median time between diagnosis of NSCLC and cardiovascular event was 13.9 months. Both, cardiovascular comorbidities and events showed a direct correlation with increasing age affecting up to 87.3% and 35.2% of all octogenarians in the study, respectively. Following cardiovascular comorbidities were significantly associated with cardiovascular events: atrial fibrillation, myocardial infarction and cardiomyopathy. OS was not reduced in patients experiencing a cardiovascular event compared to patients without an event.

**Conclusion.** Cardiovascular disease and cardiovascular events are frequently observed in NSCLC patients. To provide definitive recommendations on impact, prevention and screening of cardiovascular disease in NSCLC prospective trials are desirable.
Original article

Non-pegylated liposomal doxorubicin in lymphoma: patterns of toxicity and outcome in a large observational trial [60]
Ines Wasle, Gabriele Gamerith, Florian Kocher, Patrizia Mondello, Thomas Jaeger, Alois Walder, Jutta Auburger, Thomas Melchardt, Werner Linkesch, Michael Fiegl and Michael Mian

Applicant´s contribution

- Acquisition of literature
- Review of literature
- Interpretation of data
- Preparation of manuscript

Aim of this work was to evaluate cardiovascular toxicities in patients receiving non-pegylated liposomal doxorubicin. Liposomal doxorubicin seems to induce less cardiotoxicity compared to conventional doxorubicin. Therefore, this agent is mainly used in patients where anthracycline cardiotoxicity is considered to be a relevant side effect or in patients with pre-existing cardiovascular comorbidities.

Full text article see pages 57-65

Abstract

Introduction. The anthracycline doxorubicin plays a major role in the treatment of lymphoproliferative disorders. However, its use is often limited due to cardiac toxicity, which seems to be much less in the liposomal non-pegylated formulation (Myocet®). The aim of this study was the evaluation of efficacy and toxicity of Myocet®
containing treatment regimens, with a focus on cardiotoxicity during treatment in lymphoma patients.

**Patients and methods.** 326 consecutive patients, treated between March 2008 and December 2013 in 11 Austrian and 1 Italian cancer centers, were retrospectively assessed. Patients’ baseline, and treatment related parameters were obtained by reviewing hospital records.

**Results.** Median age was 74 years (range 26-93). The most common histology was DLBCL (60%), followed by FL (13%) and MCL (8%). At least one cardiovascular comorbidity was present in 72% of patients. Most common grade 3/4 toxicities were hematologic, namely leukopenia, neutropenia, thrombocytopenia and febrile neutropenia in 44%, 40%, 17% and 16%. Overall, 43 patients suffered a cardiac event (any grade) with most patients developing congestive heart failure. Parameters significantly associated with severe cardiac events (grade 3 – 5) were the presence of cardiovascular comorbidities, chronic obstructive pulmonary disease and elevated baseline NT-pro BNP. Treatment response after first line Myocet®-containing therapy was ≥58% among all entities (range 58%-86%) and therefore comparable to those of conventional therapeutic regimens.

**Conclusion.** Herein, we provide a detailed toxicity profile of Myocet®-containing chemotherapy regimens. Despite the high rate of patients with preexisting comorbidities, the number of adverse events was encouraging. However, these results need to be confirmed in a prospective randomized trial.
Is gender a risk factor for secondary cardiovascular events in R-CHOP treated DLBCL patients? [61]

Florian Kocher, Andreas Volgger, Wolfgang Willenbacher, Michael Fiegl and Wolfgang Hilbe
Accepted ÖGHO Frühjahrstagung 2015

Applicant’s contribution

- General idea
- Review of literature
- Acquisition of data
- Interpretation of data and statistical analysis
- Preparation of abstract

Aim of this analysis was to prove whether gender is a risk factor in anthracycline treated patients suffering from diffuse large B-cell lymphoma. We conducted this analysis since some studies in childhood cancer survivors have reported an increased risk of cardiotoxicity in women [62, 63]. Despite the previous reports gender did not prove to be a risk factor with regard to cardiotoxicity.

Poster see page 66

Abstract

Introduction. Cardiotoxicity is a well-known late effect of anthracycline treatment. Some studies indicate that women are at increased risk to develop cardiac side effects following anthracycline treatment. These results were deduced from studies investigating survivors of childhood cancers. Prompted by these findings we investigated the impact of gender on the development of cardiovascular events in a consecutive cohort of DLBCL patients treated with R-CHOP.
**Methods.** 184 patients diagnosed with DLBCL between 2000 and 2012 at Medical University of Innsbruck were included. Parameters of most interest were pre-existent cardiovascular comorbidities (all grades) and cardiovascular events (heart failure, conduction disorders, acute coronary syndrome, valvular replacement) appearing during treatment or follow-up.

**Results.** Mean age at diagnosis was 60.2 in women (n=99; 53.8%) and 55.9 years in men (n=85, 46.2%) (p=0.076), respectively. Both genders were characterized by a comparable burden of cardiovascular comorbidities (women 53.1%, men 46.9%, p=0.170). The mean administered cumulative dose of anthracycline was similar (women 284 mg/m², men 296 mg/m²; p=0.383) Overall, 14 women (16.5%) and 9 men (9.1%) developed a secondary cardiac event (p=0.179). Distribution of different cardiovascular events (p=0.141) and time to cardiovascular event (5-year EFS; women 82.5%, men 95.6%; p=0.124) was comparable between the groups. Appearance of a cardiovascular event was not associated with reduced overall survival (p=0.474).

**Conclusion.** Our data indicate that cardiovascular events are considerable complications in DLBCL patients. In our series gender did not prove to be a risk factor with respect to cardiotoxicity. Nevertheless, adequately powered prospective studies are needed to validate our results.
Prospective Trial

Long-term cardiotoxicity in patients treated with chemotherapy and/or targeted Drugs, a prospective non interventional trial [64]

Florian Kocher, Stephan Dobner, Bernhard Föger, Michael Fiegl, Michael Fridrik, Günther Gastl, Michael Hubalek, Alois Lang, Andreas Petzer, Ewald Wöll and Wolfgang Hilbe on behalf of the CACOCA studygroup

Applicant´s contribution

- Development of study protocol
- Development of case report form
- Development of informed consent
- Organisation of study meetings
- Submission to ethics committee
- Submission to Austrian regulatory agency
- Initiation of study centres
- Monitoring of study centres
- Patient recruitment
- Development of an electronic trial database
- Trial presentation at several meetings
- Data acquisition

In April 2012 a task force consisting of representatives of the „Österreichische Gesellschaft für Hämatologie und Onkologie“ (ÖGHO) stated that there is a lack of current knowledge regarding cardiotoxicity. Hence, research addressing cardiovascular side effects would be desirable. Encouraged by this statement we performed an extensive literature research to gain a comprehensive view on this field of research. After review of literature we concluded, that patients treated in clinical routine have not been investigated so far. Patients treated in clinical trials often represent selected cohorts since they are often characterized by a good physical performance. Nevertheless, pre-existing cardiovascular comorbidities are associated with the occurrence of cardiotoxicity. Thus, especially unselected patients should be included to gain representative data. To improve the level of evidence of such an
investigation the trial should be performed in a prospective way using standardized diagnostic procedures. Moreover, a large number of patients should be recruited to determine the definite impact of cardiotoxicity. Prompted by these considerations we developed a multicentre, prospective non-interventional trial to elucidate the incidence of cardiotoxicity in a real-life setting. The aim of this investigator initiated trial is to prospectively document cardiotoxic effects in curatively treated patients. After completion of data collection we intend to generate a risk score for the detection of patients with increased risk for cardiotoxicity.
CACOCA trial
(cardiovascular complications of cancer treatment)

Study design
- Multicentre
- Prospective
- Non interventional

As one aim is to evaluate patients in clinical routine the study is designed as a non-interventional trial. Consequently, patients who are included in the study must be treated with already approved agents. Only standardized evaluations which usually are a part of clinical routine work-up are used as diagnostic tools. This approach certainly enables many centres to take part in this project since only well-established examinations are used.
Inclusion criteria

- Diagnosis of breast cancer, non-small cell lung cancer (NSCLC), colorectal cancer or lymphoma.
- For solid tumours: completion of curative intervention (surgery, radiotherapy) and qualification for adjuvant systemic therapy (chemotherapy or monoclonal antibodies or kinase inhibitors). In breast cancer patients neoadjuvant treatment is permitted.
- For lymphomas: stage and histology must offer the option of a curative intent of the systemic therapy.
- Eastern Cooperative Oncology Group (ECOG) Score of 0-2 qualifying for systemic treatment.
- Age ≥18 years.
- Written informed consent that is consistent with ICH-GCP guidelines.

These four types of malignancy were included since the incidence of these entities are rather high and therefore facilitates patient recruitment. Since it is intended to provide data on long-term cardiotoxicity only patients in whom a curative treatment approach is followed are included.

Exclusion criteria

- Any concomitant serious illness or organ system dysfunction in which the decision of a curative intervention is not reasonable in the opinion of the investigator.
- Female patients, who are pregnant.
- Patients unable to comply with the protocol in the opinion of the investigator.

Only patients in whom a curative treatment is contraindicated due to other serious illnesses are excluded. In contrast to previous clinical trials even patients with a high burden of cardiovascular comorbidities are included.
Study visits

Eligible patients will be monitored at study entry (eg. chemo naive state), after third cycle of chemotherapy and at 12, 36 and 60 months after start of first chemotherapy cycle. These time points enable a detection of acute cardiac toxicities and even possible long-term cardiac effects of cancer treatment.

**Figure 4.** Time points of study visits.
Study procedures

At study visits (i.e. cardiac check-ups), patients are examined with respect to their oncological treatment, cardiovascular risk profile, cardiovascular performance and quality of life. Different diagnostic features are used to gain a comprehensive view on the patient’s cardiovascular status.

Table 3. different examinations during study period

<table>
<thead>
<tr>
<th>Examinations at Cardiac Check up</th>
<th>1st CC</th>
<th>2nd CC</th>
<th>3rd CC</th>
<th>4th CC</th>
<th>5th CC</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Time after start of first CTx</strong></td>
<td></td>
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<tr>
<td>Within 21 days after Inclusion and prior to CTx</td>
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<tr>
<td>After 8-15 days after 3rd CTx cycle</td>
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<tr>
<td>After 12 months (±30 days)</td>
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<td>After 36 months (±30 days)</td>
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<tr>
<td>After 60 months (±3 months)</td>
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<tr>
<td><strong>Patient Data</strong></td>
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<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
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<tr>
<td><strong>Documentation anticancer treatment</strong></td>
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<td>X</td>
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<tr>
<td><strong>Concomitant diseases</strong></td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
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<tr>
<td><strong>Concomitant medication</strong></td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
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<tr>
<td><strong>Lifestyle/physical performance questionnaire</strong></td>
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<td>X</td>
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<tr>
<td><strong>Family history questionnaire</strong></td>
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<td>X</td>
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<tr>
<td><strong>QOL-questionnaire</strong></td>
<td>X</td>
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<td>X</td>
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<tr>
<td><strong>Laboratory values</strong></td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
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<tr>
<td><strong>Electrocardiography</strong></td>
<td>X</td>
<td>X</td>
<td>X</td>
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<tr>
<td><strong>Echocardiography</strong></td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td><strong>Cardiac disorders</strong></td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>
Oncological treatment

Oncologic treatment is under the discretion of the treating physician. The used substances with the respective dosage are documented.

Cardiac risk factors

Cardiac risk factors are evaluated during physical examinations and at patient’s history taking. The focus is set on different cardiovascular comorbidities and other diseases with increased risk for cardiac events (eg. diabetes). Moreover, cardiac co-medication is documented at each study visit. Patient’s smoking history, sport behaviours and family history of cardiac diseases is evaluated via a pre-specified questionnaire.

Cardiac function

Cardiac function is measured by standardized use of electrocardiography [ECG] and echocardiography. ECGs are collected and are centrally analysed to minimize interobserver variability. Echocardiography is performed at each centre according to the centres guidelines.

Laboratory values

Routinely assessed laboratory values like C-reactive protein, lactate-dehydrogenase or liver-specific parameters are documented. Other laboratory values of special interest are the lipid profile, NT-pro BNP and troponin levels.
Physical performance

Physical performance is estimated using the Duke Activity Status Index-questionnaire [65]. This questionnaire has been developed to assess patient’s functional capacity. Moreover, the results can be converted to an estimation of patient’s metabolic equivalent [MET score]. Another tool which provides information on the physical performance of the patient is the well-established New York Heart Association functional classification [NYHA score] [66]

Quality of life

Since an adequate quality of life is a main goal in oncologic treatment and might be impaired due to cardiotoxicity the quality of life is assessed using the EORTC-QLQ C30 questionnaire (version 3.0) [67]. This questionnaire is a validated instrument and is widely used in oncologic trials.
**Primary endpoint**

The primary endpoint of the study is the incidence of major cardiovascular events after the start of systemic treatment. Major cardiovascular events are defined according to CTC AE criteria (Version 4) [68] and include cardiac diseases with severe acute symptoms and/or require an invasive intervention or cardiovascular death. Similar definitions were used in the large breast cancer trials. This approach facilitates the comparison of these results with other clinical trials that reported on cardiotoxicity.

**Secondary endpoints**

Secondary endpoints include the incidence of minor cardiac events (defined as symptomatic cardiovascular events), quality of life assessment, NT pro-BNP alterations, LVEF decrease, changes in cardiovascular performance (NYHA, Duke activity status index)
## Definition of minor and major cardiac events

1 CTC-AE Grade 2 vs. 3-5; 2 CTC-AE Grade 3 vs. 4-5

<table>
<thead>
<tr>
<th>Condition</th>
<th>Minor Event</th>
<th>Major Event</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coronary Artery disease¹</td>
<td>Minor or moderate symptoms or progressive angina; cardiac enzymes normal; hemodynamically stable</td>
<td>Symptomatic, unstable angina and/or acute myocardial infarction, cardiac enzymes abnormal, hemodynamically stable or unstable and/or need of intervention (e.g. revascularisation: PCI, CABG)</td>
<td>Death</td>
</tr>
<tr>
<td>Valvular dysfunction²</td>
<td>Minor or moderate symptoms; severe regurgitation or stenosis by imaging; symptoms controlled with medical intervention</td>
<td>Severe symptoms or life-threatening consequences and/or intervention indicated (e.g. valve replacement, valvuloplasty)</td>
<td>Death</td>
</tr>
<tr>
<td>Conduction disorder¹,³</td>
<td>ECG alterations and minor or moderate symptoms</td>
<td>Severe symptoms or life-threatening consequences and/or intervention indicated (e.g. pacemaker implantation)</td>
<td>Death</td>
</tr>
<tr>
<td>Heart failure¹</td>
<td>Symptoms with mild to moderate activity or exertion</td>
<td>Severe with symptoms at rest or at minimal activity or exertion; intervention indicated or life-threatening consequences (e.g. continuous IV therapy or mechanical hemodynamic support or cardiac transplantation)</td>
<td>Death</td>
</tr>
<tr>
<td>Pericardial effusion²</td>
<td>Effusion with physiologic consequences</td>
<td>Severe symptoms or life-threatening consequences and/or intervention indicated (e.g. Pericardiocentesis)</td>
<td>Death</td>
</tr>
</tbody>
</table>

³ Conduction Disorders: AV-Block, Atrial Fibrillation/ Flutter, LBBB, RBBB
Sample size estimation

Considering the high variability of reported cardiovascular side effects ranging between 0% and 30% it is impossible to perform a valid power calculation. Moreover, data of patients in real-life setting is widely lacking. Therefore, it is estimated that approximately 10% of all included patients will develop a major cardiovascular event within the study period of 5 years. Our goal is to include 1000 patients all over Austria in this trial. Hence, approximately 100 major events will be recorded. It is estimated that this number of events is sufficient to perform valid statistical analyses.
### Milestones CACOCA trial

<table>
<thead>
<tr>
<th>Milestone</th>
<th>12 Q3</th>
<th>12 Q4</th>
<th>13 Q1</th>
<th>13 Q2</th>
<th>13 Q3</th>
<th>13 Q4</th>
<th>14 Q1</th>
<th>14 Q2</th>
<th>14 Q3</th>
<th>14 Q4</th>
<th>15 Q1</th>
<th>15 Q2</th>
<th>15 Q3</th>
<th>16 Q1</th>
<th>16 Q2</th>
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<tr>
<td>Review of literature</td>
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<td>Submission to ethics committee</td>
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<td>Initiation visits</td>
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<tr>
<td>Monitoring</td>
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<td>Data acquisition</td>
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</tbody>
</table>

- **08/12** start with protocol development and search for cooperating centres
- **09/12** study meeting Salzburg: discussion of study design and definition of participating centres
- **10/12** study meeting Innsbruck: presentation of the preliminary case report form (CRF) and definition of cardiovascular endpoints
- **01/13** study meeting Vienna: presentation of preliminary protocol, case report form and informed consent
- **02/13** submission of protocol to local ethics committee of the Medical University Innsbruck and Austrian regulatory agency
- **03/13** approval of the study by the local ethics committee with restrictions
- **04/13** CACOCA launch meeting Linz
- **04/13** poster presentation of trial design at “ÖGHO Frühjahrstagung” in Linz
- **06/13** poster presentation of trial design at “Pneumoupdate” in Iglis
- **07/13** final approval of study protocol by ethics committee
- **08/13** start of initiation visits of the participating centres
- **09/13** first patient included
Current status

so far 10 centres in Austria have been initiated

- Department of Internal Medicine V, Medical University Innsbruck
- Department of Obstetrics and Gynecology, Medical University Innsbruck
- Department of Internal Medicine, KH Zams
- Department of Internal Medicine, LKH Bregenz
- Department of Internal Medicine, LKH Feldkirch
- Department of Internal Medicine I, BHS Linz
- Department of Internal Medicine III, AKH Linz
- Department of Internal Medicine, KH Kufstein
- Department of Internal Medicine III, Hanusch Krankenhaus Wien
- Department of Internal Medicine I, Wilhelminenspital Wien
Recruitment has started in 7 participating centres. In April 2016, 273 patients have been included in the trial.

**Preliminary results**

To give a first brief overview, baseline characteristics of patients who have been recruited so far are presented. Up to now, data entry into the electronical database has been entirely performed for patients treated at Medical University of Innsbruck (Department of Internal Medicine, Department of Obstetrics and Gynecology). In other study centers electronical data acquisition is still ongoing. **Table 4** displays baseline characteristics of the so far recruited patients in the two study centres in Innsbruck.
Table 4. Baseline characteristics

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>All patients</strong></td>
<td>105</td>
<td></td>
</tr>
<tr>
<td>Age mean (range), years</td>
<td>52.2 (20-93)</td>
<td></td>
</tr>
<tr>
<td>BMI mean (range)</td>
<td>25.7 (15.8-41.8)</td>
<td></td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>90</td>
<td>85.7</td>
</tr>
<tr>
<td>Male</td>
<td>15</td>
<td>14.3</td>
</tr>
<tr>
<td><strong>Tumor type</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Breast</td>
<td>75</td>
<td>71.4</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>26</td>
<td>24.8</td>
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<td>Colorectal</td>
<td>1</td>
<td>1.0</td>
</tr>
<tr>
<td>NSCLC</td>
<td>3</td>
<td>2.9</td>
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<tr>
<td><strong>NYHA</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not applicable</td>
<td>101</td>
<td>96.2</td>
</tr>
<tr>
<td>I</td>
<td>4</td>
<td>3.8</td>
</tr>
<tr>
<td><strong>Concomitant disease</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>24</td>
<td>22.9</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>2</td>
<td>1.9</td>
</tr>
<tr>
<td>Stroke / TIA</td>
<td>2</td>
<td>1.9</td>
</tr>
<tr>
<td>Diabetes</td>
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<td>2.9</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>9</td>
<td>8.6</td>
</tr>
<tr>
<td>Peripheral arterial disease</td>
<td>2</td>
<td>1.9</td>
</tr>
<tr>
<td>Chronic kidney disease</td>
<td>2</td>
<td>1.9</td>
</tr>
<tr>
<td>COPD</td>
<td>6</td>
<td>5.7</td>
</tr>
<tr>
<td><strong>Concomitant medication</strong></td>
<td></td>
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<tr>
<td>ACE - Inhibitor</td>
<td>8</td>
<td>7.6</td>
</tr>
<tr>
<td>Angiotensin II receptor</td>
<td>10</td>
<td>9.5</td>
</tr>
<tr>
<td>blocker</td>
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</tr>
<tr>
<td>Beta blocker</td>
<td>9</td>
<td>8.6</td>
</tr>
<tr>
<td>Aldosterone antagonist</td>
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<td>1.9</td>
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<tr>
<td>Calcium channel blocker</td>
<td>5</td>
<td>4.8</td>
</tr>
<tr>
<td>Diuretics</td>
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<td>5.7</td>
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<tr>
<td>Amiodarone</td>
<td>2</td>
<td>1.9</td>
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<tr>
<td>Statins</td>
<td>10</td>
<td>9.5</td>
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<tr>
<td>Ivabradin</td>
<td>2</td>
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<tr>
<td>Single antiplatelet therapy</td>
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<td>6.7</td>
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<td>Double antiplatelet therapy</td>
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</tr>
<tr>
<td>Anticoagulant therapy</td>
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<td>2.9</td>
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<tr>
<td>Diabetes medication</td>
<td>2</td>
<td>1.9</td>
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<tr>
<td><strong>Laboratory values (mean)</strong></td>
<td></td>
<td></td>
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<tr>
<td>Total Cholesterol mg/dl</td>
<td>200.3 (85-297)</td>
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</tr>
<tr>
<td>Triglycerides mg/dl</td>
<td>121.0 (38-449)</td>
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<tr>
<td>HDL mg/dl</td>
<td>57.4 (3-90)</td>
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<tr>
<td>LDL mg/dl</td>
<td>123.3 (14-218)</td>
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<tr>
<td>LDH U/L</td>
<td>198.4 (101-549)</td>
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<tr>
<td>Troponine ng/L</td>
<td>3.7 (0-123.8)</td>
<td></td>
</tr>
<tr>
<td>NT pro-BNP ng/L</td>
<td>163.7 (0-1819)</td>
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</tr>
</tbody>
</table>
Periodical reports

Since the start of the project we have published different abstracts and posters at meetings to provide periodical updates on the current status of the trial.

ÖGHO-Frühjahrstagung 2013, Linz
Long term cardiotoxicity in patients treated with chemotherapy and/or targeted drugs, a prospective non interventional trial.


Pneumo-Update 2013, Innsbruck/Igls
CACOCA-Trial: Long-term cardiotoxicity in patients treated with chemotherapy and/or targeted drugs, a prospective non interventional trial.

Pneumologie 2013; 67 - P27

ÖGHO Frühjahrstagung 2014, Innsbruck
Update CACOCA Trial (Cardiovascular Complications of Cancer Treatment). A prospective non-interventional trial.

Memo Volume 7, Issue 1 Supplement p 8. Abstract K09

Pneumo-Update 2014, Innsbruck/Igls
Update CACOCA Trial (Cardiovascular Complications of Cancer Treatment). A prospective non-interventional trial.

Pneumologie 2014; 68 - P20
ÖGHO Frühjahrstagung 2015, Salzburg
Cardiovascular Complications of Cancer Treatment: Update CACOCA Trial

Memo Volume 8, Issue 1 Supplement p 9. Abstract K10
DISCUSSION

Although many substances are associated with cardiovascular side effects, there is a lack of awareness regarding cardiotoxicity within the physicians´ community. It seems that physicians often underestimate cardiovascular side effects of antineoplastic agents. A possible explanation might be that in most patients the focus of treatment is set on therapeutic efficacy rather than toxicity which might arise years after curation. Prior cancer patients are then usually no longer managed by their oncologists. Thus, there might be a missing link between the initial induction of detrimental effects to the cardiovascular system (e.g. chemotherapeutic treatment) due to the different medical specialities involved (oncologist, cardiologist).

We performed an extensive review of literature to evaluate the current knowledge with regard to cardiotoxicity [58]. In this review we give a detailed overview of cardiovascular side effects of frequently used systemic cancer treatments. It was recognized there is a paucity of data addressing cardiotoxicity in real-life settings.

Prospective evaluations of cardiotoxicity are mainly based on clinical trials [5, 14, 30, 35, 39, 42, 51]. However, patients in clinical trials certainly do not mirror patients treated in clinical routine. Usually such cohorts represent preselected patients with good performance status and absence of severe comorbidities. Moreover, most oncological studies exclude patients with cardiovascular diseases. Similarly, malignancies are an exclusion criteria in most cardiologic al trials. However, it has to be considered that both cardiovascular disease and malignancies are attributable for the highest burden of disease worldwide [69]. In light of increasing life-expectancy, the impact of both clusters of disease will rise, as both are associated with increasing age. This fact was nicely illustrated in a study evaluating the prevalence of cardiovascular disease and cancer appearing in American physicians. This study found a strong correlation between cardiovascular comorbidities, cancer and increasing age (Figure 3.) [70].
Some cardiovascular comorbidities have already been linked to an increased occurrence of cardiotoxicity [6, 11, 16, 44]. However, pre-existing comorbidities like coronary artery disease were only detected as potential risk factors in retrospective trials [29]. Again this can partly be explained by the exclusion of patients with serious cardiovascular diseases in prospective clinical trials.

In a retrospective study evaluating a large consecutive cohort of NSCLC patients we showed that those patients are characterised by a high burden of cardiovascular comorbidities [59]. It revealed that at time of diagnosis the majority of NSCLC patients (67.2%) were affected by at least one cardiovascular comorbidity. In addition, this study provided a detailed overview of distinct cardiovascular comorbidities, laboratory patterns and cardiovascular co-medication present at diagnosis of NSCLC. A considerable proportion of cardiovascular events appearing in the course of disease or in the follow-up period were detected. In our analysis 9.5% of all patients developed a cardiovascular event after diagnosis of NSCLC. This corresponds to a rate of 4.4 events per 100 patient years. Age proved to be an important risk factor for the development of CV events. Of all octogenarians included in the study, 35.2% were affected by a CV event. Of note, in this work different
cardiovascular comorbidities which proved to be risk factors for the development of cardiovascular events were identified. In our analysis cardiovascular comorbidities like atrial fibrillation, previous myocardial infarction and cardiomyopathy were associated with the development of cardiovascular events.

In cooperation with scientific colleagues, an analysis of lymphoma patients receiving a liposomal formulation of doxorubicin was performed [60]. A goal of this study was to evaluate the efficacy and toxicity profile of this agent. In previous publications it has been shown that this substance is associated with a more favourable risk profile with regard to cardiotoxicity compared to conventional anthracyclines [71-75]. Consequently, liposomal formulations of doxorubicin are mainly used in patients where cardiovascular side effects might be a matter of concern. In our trial we analysed treatment related toxicities of the respective patients, especially focussing on cardiovascular side effects. The detected cardiovascular side effects reflected the expected spectrum with congestive heart failure being the most prevalent. Even though the profile of cardiovascular events seemed to be considerable it has to be taken into account that patients receiving non-pegylated liposomal doxorubicin mostly represent a patient collective with a high burden of cardiovascular risk factors or comorbidities. Again, in this study we could detect certain risk factors which were associated with the occurrence of cardiovascular events (chronic obstructive pulmonary disease, general cardiovascular comorbidity and elevated NT-pro BNP levels).

A study investigating survivors of childhood cancer reported an increased occurrence of cardiotoxicity in female patients who received anthracycline-based treatment [59]. To evaluate whether gender is a risk factor for cardiotoxicity we performed an analysis in R-CHOP treated patients suffering from diffuse large B-cell lymphoma. Interestingly, this study did not find an association of cardiotoxicity and female gender [61]. However these findings have to be interpreted cautiously due to a limited number of patients included.

Even though cardiac side effects are nowadays evaluated in clinical trials, the main focus is set on acute cardiac adverse events rather than long-term effects. Therefore, there might be a blind spot regarding long term cardiac events since they are not assessed in the follow-up period. Long-term cardiotoxicity is mostly reported in retrospective trials [3, 44]. There is a paucity of data that prospectively evaluated
cardiovascular events. Even though we were able to identify several risk factors in different patient settings, adequately powered prospective studies are needed to validate the impact of certain risk factors and possible long-term cardiotoxic effects. After extensive research of literature a multicentre trial was planned evaluating patients in a real-life setting. Different meetings were conducted to attract centres to participate in this academic driven trial. A study protocol and various study materials were developed to achieve the approval of the ethics committee and the Austrian regulatory agencies. The first patient was subsequently included in September 2013. So far 134 patients have been included in 10 participating centres [64].

Besides the current ambiguity with respect to the incidence and possible risk factors of cardiotoxicity in patients treated in real-life setting, there is a lack of evidence in detection, prevention and surveillance of cardiovascular events appearing after systemic therapy. Today, the most used tools to monitor cardiovascular function in cancer patients are echocardiography, clinical examination and electrocardiography. Many physicians tend to use LVEF to estimate of cardiac function prior to the use of anthracyclines. However, it has to be considered that echocardiography shows a strong variability in repeated measurements even within the same investigator. Studies report that the intra as well as the inter-observer variability range between 10 to 30% [76]. In some clinical studies multi gated acquisition scans (MUGA) were used to assess the cardiac function [16, 18, 77, 78]. Even though this examination provides objective results it does not seem to be a feasible option in clinical routine due to high costs, exposure to radiation and the need of specialized centres. Electrocardiography is often used prior to the administration of chemotherapeutics. However, to the best of our knowledge there are currently no guidelines, which recommend a modification of antineoplastic treatment, based on therapy naïve electrocardiographic abnormalities.

Within the on-going prospective trial we hope to gain new valid data to demonstrate whether or not certain examinations are suitable to detect cardiotoxicity in asymptomatic state. Finally we aim to develop a risk score based on different parameters which may predict the probability of cardiovascular events upon systemic treatment. The final results of the trial are expected in 2021. The large number of participating centres and the encouraging number of included patients certainly reflect the feasibility of our study protocol.
In conclusion our findings give detailed insights with regard to the cardiovascular burden of patients affected by cancer and its association with cardiovascular events. In the future, results from our prospective trial might provide further evidence to the association of clinical characteristics, systemic therapies involved, cardiotoxicity and the feasibility of preclinical detection.
REFERENCES

68. National Cancer InstituteCommon Terminology Criteria for Adverse Events v4.0 NCI, NIH, DHHS. 2009; NIH publication # 09-7473.
APPENDIX PUBLICATIONS
Zur **Evaluierung kardialer Langzeitschäden** wurde auf Initiative der ÖGHO eine multizentrische, prospektive, nichtinterventionelle Studie initiiert.

In dieser Studie werden Patienten im **adjuvanten Therapiesetting über 5 Jahre** bezüglich ihres kardiovaskulären Status, Risikofaktoren, körperlicher Leistungsfähigkeit und Lebensqualität untersucht.

Im Gegensatz zu vorangegangenen Studien sind in dieser Beobachtung **Patienten mit vorbestehender Herzerkrankung nicht exkludiert**, um das tatsächliche Patientenkollektiv, wie es im klinischen Alltag auftritt, besser abbilden zu können.

Nähere Informationen unter **CACOCA-office@i-med.ac.at**

**Das unterschätzte Risiko**

**Chemo- und immuntherapieinduzierte Kardiotoxizität bei Tumorpatienten**

**Übersicht Kardiotoxizität**

Die Bedeutung kardiovaskulärer Nebenwirkungen durch systemische Therapien wird in der Hämatologie und Onkologie vielfach unterschätzt. Dies kann zum einen dadurch bedingt sein, dass in einer historischen Betrachtung vor allem in einer palliativen Situation die Erfassung der Wirksamkeit antineoplastischer Substanzen im Vordergrund stand, zum anderen fand bei einer per se limitierten Lebenserwartung eine potenziell später auftretende kardiale Toxizität im Rahmen einer Tumorprogression meist wenig Beachtung.


führen Struktur (Tab. 1), der Symptomatik wie auch nach dem Zeitpunkt des Auftretens einteilen. Es können sowohl das Reizbildungs- und Leitungssystem als auch das Gefäßsystem, das Myokard, die Herzklappen oder das Perikard durch eine Tumorthерapie in Mitleidenschaft gezogen werden. Klinisch können kardiale Schädigungen entweder als EKG-Veränderungen (Arrhythmien, QT-Verlängerung, Bradykardie, Blockbilder), Herzinsuffizienz, Stenokardien (Vasospasmen), thrombembolischen, Hypertonie, Klappen- und chronischen Toxizitäten. Störungen des Reizbildungs- und Leitungssystems (EKG-Veränderungen, Bradykardie, Arrhythmie) oder Vasospasmen (Angina pectoris/Myokardinfarkt) sind häufig frühe Ereignisse und meist reversibel. Spättoxizitäten manifestieren sich entweder innerhalb der ersten zwei Jahre nach Beginn der Therapie und präsentieren sich zum Beispiel als Abnahme der linksventrikulären Pumpfunktion (LVEF) und erlauben somit eine Vereinheitlichung der Definitionen.


<p>| Tab. 1: Strukturelle kardiale Schädigungen in Abhängigkeit der verwendeten Therapien |</p>
<table>
<thead>
<tr>
<th>Geschädigte Struktur</th>
<th>Therapie</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myokard</td>
<td>Anthrazykline, RTx, Trastuzumab, Zyklophosphamid, Sunitinib</td>
</tr>
<tr>
<td>Gefäßsystem</td>
<td>5-FU, RTx, Cisplatin, Bevacizumab, Sorafenib</td>
</tr>
<tr>
<td>Reizleitungssystem</td>
<td>Anthrazykline, Taxane, Cisplatin, RTx</td>
</tr>
<tr>
<td>Klappen</td>
<td>RTx</td>
</tr>
</tbody>
</table>

RTx = Strahlentherapie; 5-FU = Fluorouracil

Abb. 2: Zeitliches Auftreten von Kardiotoxizität

Tab. 1: Strukturelle kardiale Schädigungen in Abhängigkeit der verwendeten Therapien

Abb. 3: Zentren und Studienablauf CACOCA-Trial
13 Zentren in ganz Österreich fand im Sommer 2013 statt. Zentren, die nähere Informationen erhalten wollen oder an einer Teilnahme interessiert sind, haben die Möglichkeit, sich per E-Mail (CACOCA-office@i-med.ac.at) an die Studienzentrale zu wenden (Abb. 3).


Das langfristige Ziel muss sein, die Lebensqualität der Patienten zu erhalten und noch vor einer Senkung der Leistungsfähigkeit die Behandlung zu adaptieren, um einer möglichen Langzeitkardiotoxizität entgegenzuwirken. Im folgenden Abschnitt möchten wir die kardiotoxische Potenz häufig verwendeter antineoplastischer Substanzen näher beleuchten.

### Kardiotoxizität bei häufig verwendeten Substanzen

#### Anthrazykline


#### Anthrazykline

<table>
<thead>
<tr>
<th>Therapie</th>
<th>Akut</th>
<th>Subakut</th>
<th>Spät</th>
<th>RF</th>
</tr>
</thead>
<tbody>
<tr>
<td>RTx Perikarditis</td>
<td>Arteriosklerose, CMP, Klappenveränderungen, Reizleitungsstörungen</td>
<td>Dosis, Alter, Strahlenfeld, Kombination mit kardiotoxischen Substanzen, kardiale Vorерkrankungen</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anthrazykline Arrhythmie</td>
<td>ventrikuläre Dysfunktion, HI</td>
<td>hohe kumulative Dosis, junge und alte Patienten, mediastinale RTx, weibliches Geschlecht, kardiovaskuläre Vorерkrankungen</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5-FU Angina pectoris, EKG-Veränderungen, Takotsubo-CMP</td>
<td>KHK, mediastinale RTx, Kombination mit Cisplatin, Dosis, Langzeitinfusion</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Taxane Reizbildungs- und -leitungsstörungen (v. a. Bradykardie)</td>
<td>Kombination mit Anthrazyklinen</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zyklophosphamid Perikarderguss; CMP</td>
<td>Hochdosistherapie</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Cisplatin Reizleitungsstörungen; Ischänie; Hypertonie</td>
<td>Arteriosklerose</td>
<td>hohe kumulative Dosis, Kombination mit Anthrazyklinen, Alter, mediastinale RTx</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trastuzumab LVEF-Senkung</td>
<td>Herzinsuffizienz (v. a. in Kombination mit Anthrazyklinen)</td>
<td>Kombination mit Anthrazyklinen, Paclitaxel, Zyklophosphamid</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bevacizumab</td>
<td>Hypertonie, thromboembolische Ereignisse</td>
<td>kumulative Dosis, Therapiedauer</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sunitinib LVEF Senkung</td>
<td>Hypertonie, HI</td>
<td>kardiovaskuläre Vorерkrankungen</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sorafenib Hypertonie</td>
<td>kardiale Ischämie</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

RF – Risikofaktoren; RTx – Strahlentherapie; CMP – Kardiomyopathie; HI – Herzinsuffizienz; KHK – koronare Herzkrankheit; LVEF – “left ventricular ejection fraction”

Tab. 2: Übersicht über therapieinduzierte kardiale Nebenwirkungen und assoziierte Risikofaktoren


Antimetabolite

Taxane

Alkylanzien und Platinverbindungen

Monoklonale Antikörper
Trastuzumab ist zurzeit bezüglich der kardialen Sicherheit einer der am besten evaluierten monoklonalen Antikörper. Kardiotoxische Effekte äußern sich meist durch asymptomatiche Abnahme der

[graph](https://example.com/graph.png)

**INFO-BOX**

**Sorafenib**

Sorafenib interagiert direkt mit dem RAF-MEK-ERK-Signalweg und hat dadurch entscheidenden Einfluss auf die Funktion des Gefäßsystems. Aus der Inhibierung der VEGF- und FGF-Signaltransduktion resultiert ein proapoptotischer Effekt an Endothelzellen. Weitere Anzeichen von kardiovaskulärer Nebenwirkungen vorliegen; SORAFENIB-Arm zeigt (3 % vs. < 1 %).


**Der Studienstart mit 13 Zentren in ganz Österreich fand im Sommer 2013 statt. Zentren, die nähere Informationen erhalten wollen oder ebenso an einer Teilnahme interessiert sind, haben die Möglichkeit sich per E-Mail (CACO-CA-office@i-med.ac.at) an die Studienzentrale zu wenden.**

Eine umfassende Version dieses Beitrags inklusive ausführlicher Literaturverweise findet sich online auf www.medmedia.at.
Cardiovascular Comorbidities and Events in NSCLC: Often Underestimated but Worth Considering

Florian Kocher,1,2 Michael Fiegl,1 Michael Mian,1,3 Wolfgang Hilbe1,4

Abstract

Patients with non–small-cell lung cancer (NSCLC) and cardiovascular (CV) disease often share a comparable demographic profile. This retrospective analysis of CV comorbidities, risk factors, CV events, and outcome in a large consecutive NSCLC cohort found that preexisting CV comorbidities and development of CV events are frequently observed in NSCLC patients. For recommendations on impact, prevention, and screening of CV disease in NSCLC, prospective trials are warranted.

Introduction: Patients with non–small-cell lung cancer (NSCLC) and cardiovascular (CV) disease often share a comparable demographic profile. The aim of this analysis was to assess the significance and prevalence of preexisting CV comorbidities and events in NSCLC. Patients and Methods: A total of 715 consecutive NSCLC patients diagnosed between 2004 and 2009 at the Medical University of Innsbruck were retrospectively assessed regarding CV comorbidities, risk factors, cancer treatment, CV events occurring after the start of treatment, and outcome. Results: At least one CV comorbidity was present in 462 (67.2%) of 687 evaluable patients. CV events were documented in 68 patients (9.5%), with conduction disorders being the most prevalent (n = 19), followed by cardiomyopathy (n = 13), myocardial infarction (n = 13), sudden CV death (n = 12), need of revascularization (n = 6), and pericardial effusion (n = 5). Median time between diagnosis of NSCLC and CV event was 13.9 months. CV comorbidities and events both showed a direct correlation with increasing age, affecting up to 87.3% and 35.2% of all octogenarians in the study, respectively. The following CV comorbidities were significantly associated with CV events: atrial fibrillation, myocardial infarction, and cardiomyopathy. Overall survival was not reduced in patients experiencing a CV event compared to patients without an event. Conclusion: CV disease and events are frequently observed in NSCLC patients. To provide definitive recommendations on impact, prevention, and screening of CV disease in NSCLC, prospective trials are desirable.

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Keywords: Cardiovascular comorbidities, Cardiovascular events, NSCLC, Outcome, Risk factors

Introduction

It is estimated that lung cancer and cardiovascular (CV) disease together account for approximately 18.9 million annual deaths worldwide.1,2 Thus, these 2 diseases represent a substantial global burden of disease. Many cancer patients and patients with CV disease share a comparable demographic profile. Indeed, a prospective cohort study investigating the incidence of CV disease and cancer in American physicians reported a direct correlation between increasing age and these 2 clusters of diseases.3 Therefore, it is evident that a high proportion of cancer patients is affected by CV comorbidities and that many patients with severe CV diseases have cancer. Moreover, nicotine consumption certainly is one of the most important risk factors in lung cancer and CV disease.

Besides demographic coincidences and mutual risk factors, antineoplastic treatment by itself might induce adverse CV events. Cardiotoxic adverse effects have been reported in various substances frequently used in the treatment of non–small-cell lung cancer (NSCLC). In addition, a number of patient and treatment related factors (eg, preexisting CV disease, high dosage, combination of substances) might increase the risk of CV events.4,7 Furthermore,
radiotherapy, which often represents an additional treatment option in lung cancer, has a cardiotoxic potential if the heart is involved in the radiation field.8,9

As a result of continuous advances in the treatment of NSCLC, disease-specific survival has constantly increased. Today, a considerable proportion of patients can experience curative treatment or long-term survival. The probability for the development of CV disease in those patients is thus increasing.

In recent years, CV safety of newly established substances has evolved as a major issue in modern drug development. However, it needs to be considered that the incidence of CV events during treatment may be much higher in routine use than reported as a result of patient selection in pivotal trials. Incorporating the demographic profile of NSCLC and CV comorbidity the occurrence of CV events may be an underestimated factor in these cancer patients. Furthermore, treatment of NSCLC may trigger CV events. Consequently, an assemblage of both aspects might provide new insights on CV events during the course of NSCLC.

To our knowledge, data on CV comorbidities and CV events in NSCLC patients are lacking. The aim of our analysis was to assess the prevalence and significance of preexisting CV comorbidity and CV events occurring after diagnosis.

Patients and Methods
The medical files of 715 consecutive NSCLC patients diagnosed between 2004 and 2009 at the Medical University of Innsbruck and affiliated hospitals were retrospectively analysed. The last data update was performed in July 2014. Data acquisition was performed based on a prespecified protocol. It included the following: baseline characteristics, including CV comorbidities and risk factors present at diagnosis; lung cancer—specific treatment and outcome; and CV events occurring after the start of treatment.

Patients were documented within our institution’s comprehensive lung cancer project, Twenty-Year Retrospective of Lung Cancer (TYROL). This registry focuses on the clinical characteristics of lung cancer patients treated in daily routine.10-12 Relevant data were collected using the hospitals’ electronic database and microfilm documentation. We estimated that >95% of patients recruited at the participating institutions were documented in this registry. The TYROL study was approved by the institutional review board/ethics committee of Medical University of Innsbruck.

CV Comorbidities, Risk Factors, and Events
Patient charts were reviewed in regard to CV comorbidities, risk factors, and events. An extensive list of parameters was assessed, including general comorbidities (renal impairment, stroke/transient ischemic attack, peripheral vascular disease, diabetes, chronic obstructive pulmonary disease [COPD]); clinical risk factors (body mass index, smoking status); laboratory values (total cholesterol, high-density lipoprotein [HDL], low-density lipoprotein [LDL], triglycerides); CV comorbidities (hypertension [any grade], myocardial infarction, previous need of revascularization of coronary arteries [balloon dilatation, coronary artery bypass graft, stenting], conduction disorders [pacemaker implantation, atroventricular block, bundle branch block], atrial fibrillation, cardiomyopathy, coronary heart disease [CHD; angina pectoris, myocardial infarction, silent myocardial ischemia], valvular disease [insufficiency or stenosis of grade II or higher, valvular replacement]); and CV co-medication (β-blocker, angiotensin-converting enzyme inhibitor, cardiac glycosides, anticoagulant, antiplatelet therapy, calcium channel blocker, diuretic agent, amiodarone, statin, nitro, angiotensin receptor blocker). The following cardiologic diseases were defined as severe CV events (first event counted): sudden CV death; cardiomyopathy; manifest CHD with need of revascularization of the coronary arteries; nonmalignant pericardial effusion; myocardial infarction; and conduction disorders with severe symptoms and the need of intervention.

Chi-square test was used to compare categorical variables. The incidence of CV events was presented as percentage and as event rate per 100 patient-years. Event-related data (CV event-free survival [CV-EFS], defined as time from diagnosis of NSCLC until last follow-up or the occurrence of a CV event, and overall survival [OS], defined as time from diagnosis until last follow-up or death), were estimated by the Kaplan-Meier method. The log rank test was used for comparison of categorical factors on CV-EFS and OS. Univariate analysis was used to determine which baseline and treatment related parameters were associated with CV-EFS and OS. Cox regression analysis was performed in order to identify comorbidities that independently influenced OS or CV-EFS. In all analyses, a P value of ≤.05 was considered to be statistically significant. All analyses were performed by SPSS software, version 20.0 (IBM, Armonk, NY).

Results
Baseline Characteristics
In total, 715 consecutive patients were included. Median age at diagnosis of NSCLC was 64.6 years, and 481 patients (67.3%) were male. Most patients were diagnosed as having stage IV disease

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of all patients</td>
<td>715</td>
</tr>
<tr>
<td>Age median (range), years</td>
<td>64.6 (34-94)</td>
</tr>
<tr>
<td>Male sex</td>
<td>481 (67.3%)</td>
</tr>
<tr>
<td>Stage</td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>171 (23.9%)</td>
</tr>
<tr>
<td>II</td>
<td>63 (8.8%)</td>
</tr>
<tr>
<td>IIIA</td>
<td>79 (11.0%)</td>
</tr>
<tr>
<td>IIIB</td>
<td>108 (15.1%)</td>
</tr>
<tr>
<td>IV</td>
<td>294 (41.1%)</td>
</tr>
<tr>
<td>Histology</td>
<td></td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>392 (54.8%)</td>
</tr>
<tr>
<td>Squamous</td>
<td>216 (30.2%)</td>
</tr>
<tr>
<td>Adenosquamous</td>
<td>14 (2.0%)</td>
</tr>
<tr>
<td>Large cell</td>
<td>38 (5.3%)</td>
</tr>
<tr>
<td>Other</td>
<td>55 (7.7%)</td>
</tr>
<tr>
<td>PS (n = 593)</td>
<td></td>
</tr>
<tr>
<td>0-1</td>
<td>456 (76.9%)</td>
</tr>
<tr>
<td>2</td>
<td>113 (19.1%)</td>
</tr>
<tr>
<td>3</td>
<td>24 (4.0%)</td>
</tr>
</tbody>
</table>

Abbreviation: PS = performance status.
## Table 2  Comorbidities, Laboratory Patterns, and CV Co-Medication at Diagnosis

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>n</th>
<th>%</th>
<th>3-Year CV-EFS (%)</th>
<th>3-Year OS (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>715</td>
<td>—</td>
<td>88.6</td>
<td>49.6</td>
</tr>
<tr>
<td><strong>Baseline Characteristics</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age ≥ 70 years</td>
<td>223/715</td>
<td>31.2</td>
<td>83.7(^a)</td>
<td>39.6(^c)</td>
</tr>
<tr>
<td>PS ≥ 2</td>
<td>137/593</td>
<td>23.1</td>
<td>90.7(^a)</td>
<td>26.0(^c)</td>
</tr>
<tr>
<td><strong>CV Comorbidities</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>320/687</td>
<td>46.6</td>
<td>88.4</td>
<td>52.2</td>
</tr>
<tr>
<td>Coronary heart disease</td>
<td>82/687</td>
<td>11.9</td>
<td>87.0</td>
<td>50.0</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>54/687</td>
<td>7.9</td>
<td>69.1(^b)</td>
<td>37.8(^c)</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>48/687</td>
<td>7.0</td>
<td>78.5(^b)</td>
<td>45.1</td>
</tr>
<tr>
<td>Previous revascularization</td>
<td>46/687</td>
<td>6.7</td>
<td>85.1</td>
<td>60.4</td>
</tr>
<tr>
<td>Cardiomyopathy</td>
<td>36/687</td>
<td>5.2</td>
<td>65.8(^b)</td>
<td>26.5(^c)</td>
</tr>
<tr>
<td>Conduction disorders</td>
<td>33/687</td>
<td>4.8</td>
<td>72.8</td>
<td>62.3</td>
</tr>
<tr>
<td>Valvular disease</td>
<td>25/687</td>
<td>3.6</td>
<td>100</td>
<td>59.6</td>
</tr>
<tr>
<td><strong>General Comorbidities</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>COPD</td>
<td>375/681</td>
<td>55.1</td>
<td>89.5</td>
<td>50.0</td>
</tr>
<tr>
<td>Diabetes</td>
<td>95/686</td>
<td>13.8</td>
<td>88.0</td>
<td>54.5</td>
</tr>
<tr>
<td>Stroke/TIA</td>
<td>76/677</td>
<td>11.2</td>
<td>87.4</td>
<td>37.7</td>
</tr>
<tr>
<td>PVD</td>
<td>72/667</td>
<td>10.8</td>
<td>89.2</td>
<td>39.7</td>
</tr>
<tr>
<td>Renal impairment</td>
<td>48/681</td>
<td>7.0</td>
<td>76.7</td>
<td>17.2(^c)</td>
</tr>
<tr>
<td><strong>Clinical Risk Factors</strong></td>
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<td></td>
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<tr>
<td>Smoking history</td>
<td>482/563</td>
<td>85.6</td>
<td>88.8</td>
<td>48.4</td>
</tr>
<tr>
<td>Body mass index ≥ 25</td>
<td>240/570</td>
<td>42.1</td>
<td>89.4</td>
<td>56.8</td>
</tr>
<tr>
<td><strong>CV Co-medication</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antiplatelet</td>
<td>163/352</td>
<td>46.3</td>
<td>86.8</td>
<td>47.1</td>
</tr>
<tr>
<td>ACE inhibitor</td>
<td>148/352</td>
<td>42.0</td>
<td>83.6</td>
<td>55.7</td>
</tr>
<tr>
<td>Beta blocker</td>
<td>124/394</td>
<td>35.2</td>
<td>86.3</td>
<td>51.1</td>
</tr>
<tr>
<td>Diuretic agent</td>
<td>101/352</td>
<td>28.7</td>
<td>81.1(^b)</td>
<td>47.9</td>
</tr>
<tr>
<td>Statin</td>
<td>139/654</td>
<td>21.3</td>
<td>94.7</td>
<td>58.3</td>
</tr>
<tr>
<td>Calcium channel blocker</td>
<td>74/352</td>
<td>21.0</td>
<td>85.3</td>
<td>63.0</td>
</tr>
<tr>
<td>Angiotensin receptor blocker</td>
<td>56/352</td>
<td>15.9</td>
<td>87.9</td>
<td>44.6</td>
</tr>
<tr>
<td>Cardiac glycoside</td>
<td>25/352</td>
<td>7.1</td>
<td>65.3(^b)</td>
<td>38.7(^c)</td>
</tr>
<tr>
<td>Nitro</td>
<td>24/352</td>
<td>6.8</td>
<td>79.6</td>
<td>44.5</td>
</tr>
<tr>
<td>Anticoagulant</td>
<td>21/352</td>
<td>6.0</td>
<td>87.8</td>
<td>71.9</td>
</tr>
<tr>
<td>Amiodarone</td>
<td>5/352</td>
<td>1.4</td>
<td>100</td>
<td>53.3</td>
</tr>
<tr>
<td><strong>Laboratory Values</strong></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Hemoglobin &lt; 12 mg/dL</td>
<td>57/382</td>
<td>14.9</td>
<td>91.4</td>
<td>37.2(^c)</td>
</tr>
<tr>
<td>Leukocytes &gt; 15 g/L</td>
<td>30/383</td>
<td>7.8</td>
<td>85.7</td>
<td>24.8(^c)</td>
</tr>
<tr>
<td>LDH elevated ≥ 240 U/L</td>
<td>70/363</td>
<td>19.3</td>
<td>72.7(^b)</td>
<td>26.4(^c)</td>
</tr>
<tr>
<td>CRP &gt; 1 mg/dL</td>
<td>188/378</td>
<td>49.7</td>
<td>84.4(^c)</td>
<td>44.8(^c)</td>
</tr>
<tr>
<td>Triglycerides ≥ 180 mg/dL</td>
<td>104/427</td>
<td>24.4</td>
<td>87.7</td>
<td>47.2</td>
</tr>
<tr>
<td>Cholesterol &gt; 250 mg/dL</td>
<td>40/429</td>
<td>9.3</td>
<td>100</td>
<td>41.8</td>
</tr>
<tr>
<td>HDL &lt; 40 mg/dL</td>
<td>61/221</td>
<td>27.6</td>
<td>92.3</td>
<td>40.6(^c)</td>
</tr>
<tr>
<td>LDL ≥ 180 mg/dL</td>
<td>10/200</td>
<td>5.0</td>
<td>100</td>
<td>23.3(^c)</td>
</tr>
</tbody>
</table>

Abbreviations: ACE = angiotensin-converting enzyme; COPD = chronic obstructive pulmonary disease; CRP = C-reactive protein; CV = cardiovascular; EFS = event-free survival; HDL = high-density lipoprotein; LDH = lactate dehydrogenase; LDL = low-density lipoprotein; OS = overall survival; PS = performance status; PVD = peripheral vascular disease; TIA = transient ischemic attack.

*Data were not always available, as indicated.

\(^{a}\)Significantly reduced CV-EFS of the respective parameter.

\(^{b}\)Significantly reduced OS of the respective parameter.
CV Events in NSCLC

(n = 294; 41.1%), followed by stage I disease (n = 171; 23.9%). Adenocarcinoma was the most frequent histologic subtype (n = 392; 54.8%). A favorable Eastern Cooperative Oncology Group [ECOG] performance status [PS] (0 or 1) was documented in 456 (76.9%) of 593 evaluable patients (Table 1).

Comorbidities, Laboratory Patterns, and CV Co-Medication at Diagnosis

Numbers and percentages of all relevant parameters are displayed in Table 2. Briefly, at least one CV comorbidity was present in 462 (67.2%) of 687 evaluable patients. The most common CV comorbidity was hypertension, which occurred in 46.2% of patients, followed by CHD (11.9%), atrial fibrillation (7.9%), myocardial infarction (7.0%), and previous revascularization (6.7%). Most prevalent general comorbidities were COPD and diabetes, at 55.1% and 13.8%, respectively. A history of smoking was documented in 482 (85.6%) of 536 patients, with a median of 40 pack-years. A total of 240 (42.1%) of 570 evaluable patients had a body mass index above 25 kg/m² and therefore were considered overweight. The majority of patients (352 of 659 evaluable cases, 53.4%) were treated with CV co-medication, mostly with antiplatelet therapy, commonly used antihypertensive combinations, or both. Of note, only 202 (64.7%) of 320 patients in whom hypertension was present at the time of NSCLC diagnosis were receiving antihypertensive medication. Blood pressure measured at time of diagnosis was available for 202 patients. In these patients, a blood pressure of ≥ 140/90 mm Hg was documented in 33.2% (n = 67). Of those 67 patients, 33 patients (49.3%) were receiving an antihypertensive drug combination. Alterations in the lipid profile were observed in a considerable number of proportion of patients, with HDL < 40 mg/dL in 27.6% and cholesterol ≥ 250 mg/dL in 9.3%.

Incidence and Description of CV Events

During a median follow-up time of 12.9 months, 68 CV events were documented. This corresponds to an incidence of 9.5% and 4.2 severe CV events per 100 patient-years. Median time to event was 13.9 months (Figure 1). The following CV events occurred during the observational period: conduction disorders (n = 19, 27.9%), cardiomyopathy (n = 13, 19.1%), myocardial infarction (n = 13, 19.1%), sudden CV death (n = 12, 17.6%), need of revascularization (n = 6, 8.8%), and pericardial effusion (n = 5, 7.4%).

NSCLC Diagnosis, CV Comorbidities, CV Events, and Age

Patients were divided by age at diagnosis. Distribution of prevalence of CV comorbidities showed a direct correlation with increasing age and ranged between 31.7% in patients younger than 50 years and 87.3% in octogenarians. Most patients were diagnosed with NSCLC in their 60s (34.0%). Interestingly only 8.8% and 7.7% of NSCLC patients were diagnosed at age < 50 years and ≥ 80 years, respectively. As expected, the incidence of CV events was highest in patients diagnosed when they were older than 80, affecting 35.2% of patients (Figure 2A).

Baseline Parameters and CV Events

There were significant associations of baseline characteristics and CV events (Table 2). The presence of CV comorbidity (myocardial infarction, atrial fibrillation, cardiomyopathy), intake of CV medication (cardiac glycosides, anticoagulants), and renal impairment were significantly associated with an increased incidence of CV events.

CV Comorbidities/Events and Different Treatment Intent

Patients were divided into 3 groups according to their primary treatment intent. A curative treatment approach (radical operation, radiochemotherapy with curative intent) was followed in 325 patients. A total of 306 patients received up-front palliative treatment, and 84 patients received best supportive care (BSC) only. CV comorbidities varied between groups. Detailed comparisons of baseline characteristics, comorbidities, and laboratory features are displayed in Table 3. As expected, patients in the BSC only group were characterized by a high burden of comorbidities.

Within the curative, the palliative, and the BSC cohorts, 38 (11.7%) of 325, 24 (7.8%) of 306, and 6 (7.1%) of 84 severe CV events were documented, respectively. Table 4 displays the different types of CV events according to treatment intent. Considering the imbalance of follow-up between the groups due to varying survival, the event rate per 100 patient-years was calculated. Patients without adequate antineoplastic treatment had the highest event rate, with 15.0 events per 100 patient-years, followed by palliatively treated patients, with 7.3, and patients treated with curative intent, with 3.1 events per 100 patient-years. When compared to the curative cohort, CV events were significantly increased in the palliative (P = .001) and the BSC (P < .001) cohorts.

Different CV Events and Temporal Appearance

Certain types of CV events showed varying temporal appearance after diagnosis of NSCLC. Median time interval between start of treatment and the occurrence of a CV event was shortest in patients experiencing a pericardial effusion (n = 4, median 5.2 months), followed by CV death (n = 11, 7.1), myocardial infarction (n = 12, 8.4), cardiomyopathy (n = 11, 14.1), conduction disorders (n = 18, 18.9), and need of revascularization (n = 5, 60.6) (Figure 2B).
CV-EFS, OS, and CV Comorbidities, Co-Medication, and Other Patient-Related Factors

Baseline parameters, displayed in Table 2 and described in the Methods, were tested for significant outcome differences, namely CV-EFS and OS. The presence of age ≥ 70 years, ECOG performance state ≥ 2, elevated lactate dehydrogenase (LDH), elevated C-reactive protein, general presence of CV comorbidity, atrial fibrillation, myocardial infarction, cardiomyopathy, intake of CV co-medication, diuretic agents, and cardiac glycosides were associated with a significantly shorter CV-EFS (Table 2).

Factors associated with an unfavorable OS were age ≥ 70 years, ECOG PS ≥ 2, elevated LDH, elevated C-reactive protein, elevated leukocytes, hemoglobin < 12 mg/dL, atrial fibrillation, cardiomyopathy, renal impairment, cardiac glycoside intake, reduced HDL, and increased LDL (Table 2).

In order to identify those factors with an independent impact on CV-EFS (n = 505 patients) and OS (n = 580 patients), parameters were included in a multivariate Cox regression model. For CV-EFS, atrial fibrillation (hazard ratio [HR], 2.82; 95% confidence interval [CI], 1.11-7.21; P = .030), myocardial infarction (HR, 2.99; 95% CI, 1.44-6.21; P = .003), and cardiomyopathy (HR, 2.95; 95% CI, 1.33-6.55; P = .008) emerged as independent prognostic factors. For OS, ECOG PS ≥ 2 (HR, 3.09; 95% CI, 2.39-3.99; P < .001) and renal impairment (HR, 2.52; 95% CI, 1.69-3.77; P < .001) proved to be independent prognosticators.

OS and CV Events

Because severe CV events might be associated with premature death, we analyzed survival of different treatment intents with regard to the presence or absence of CV events. Notably, in none of

Table 3 Comorbidities According to Treatment Approach

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>BSC Only</th>
<th>Curative Intent</th>
<th>Palliative Intent</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>84</td>
<td>325</td>
<td>306</td>
<td></td>
</tr>
<tr>
<td><strong>Baseline Characteristics</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age ≥ 70 years</td>
<td>51/84</td>
<td>60.7</td>
<td>74/325</td>
<td>22.8</td>
</tr>
<tr>
<td>PS ≥ 2</td>
<td>46/64</td>
<td>71.9</td>
<td>31/274</td>
<td>11.3</td>
</tr>
<tr>
<td><strong>CV Comorbidities</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Hypertension</td>
<td>42/78</td>
<td>53.8</td>
<td>452/318</td>
<td>47.8</td>
</tr>
<tr>
<td>Coronary heart disease</td>
<td>13/78</td>
<td>16.3</td>
<td>40/318</td>
<td>12.6</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>12/78</td>
<td>15.4</td>
<td>89/291</td>
<td>6.3</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>3/78</td>
<td>3.8</td>
<td>33/181</td>
<td>7.2</td>
</tr>
<tr>
<td>Previous revascularization</td>
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<td>1.3</td>
<td>54/178</td>
<td>8.2</td>
</tr>
<tr>
<td>Cardiomyopathy</td>
<td>13/78</td>
<td>16.7</td>
<td>14/318</td>
<td>4.4</td>
</tr>
<tr>
<td>Conduction disorders</td>
<td>8/78</td>
<td>10.3</td>
<td>7/291</td>
<td>5.7</td>
</tr>
<tr>
<td>Valvular disease</td>
<td>6/78</td>
<td>7.7</td>
<td>4/291</td>
<td>3.4</td>
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<td></td>
<td></td>
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<tr>
<td>COPD</td>
<td>42/75</td>
<td>55.3</td>
<td>173/316</td>
<td>54.9</td>
</tr>
<tr>
<td>Diabetes</td>
<td>12/78</td>
<td>15.4</td>
<td>49/317</td>
<td>15.5</td>
</tr>
<tr>
<td>Stroke/TIA</td>
<td>19/75</td>
<td>25.3</td>
<td>31/311</td>
<td>1.0</td>
</tr>
<tr>
<td>PVD</td>
<td>15/75</td>
<td>20.0</td>
<td>26/305</td>
<td>8.5</td>
</tr>
<tr>
<td>Renal impairment</td>
<td>9/76</td>
<td>11.8</td>
<td>14/315</td>
<td>4.4</td>
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<td><strong>Clinical Risk Factors</strong></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Smoking history</td>
<td>49/60</td>
<td>81.7</td>
<td>216/294</td>
<td>85.0</td>
</tr>
<tr>
<td>Body mass index ≥ 25</td>
<td>14/47</td>
<td>29.8</td>
<td>123/268</td>
<td>45.9</td>
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<td><strong>Laboratory Values</strong></td>
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<td></td>
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<tr>
<td>Hemoglobin &lt; 12 mg/dL</td>
<td>17/52</td>
<td>32.7</td>
<td>22/186</td>
<td>11.8</td>
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<tr>
<td>Leukocytes &gt; 15 g/L</td>
<td>9/53</td>
<td>17.0</td>
<td>6/186</td>
<td>3.2</td>
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<tr>
<td>LDH elevated ≥ 240 U/L</td>
<td>17/48</td>
<td>35.4</td>
<td>15/176</td>
<td>8.5</td>
</tr>
<tr>
<td>CRP &gt; 1 mg/dL</td>
<td>59/51</td>
<td>76.5</td>
<td>74/185</td>
<td>4.0</td>
</tr>
<tr>
<td>Triglycerides ≥ 180 mg/dL</td>
<td>7/39</td>
<td>17.9</td>
<td>51/189</td>
<td>27.0</td>
</tr>
<tr>
<td>Cholesterol &gt; 250 mg/dL</td>
<td>2/39</td>
<td>5.1</td>
<td>12/192</td>
<td>6.2</td>
</tr>
<tr>
<td>HDL &lt; 40 mg/dL</td>
<td>9/22</td>
<td>40.9</td>
<td>23/100</td>
<td>23.0</td>
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<tr>
<td>LDL ≥ 180 mg/dL</td>
<td>1/18</td>
<td>5.6</td>
<td>5/194</td>
<td>1.1</td>
</tr>
</tbody>
</table>

Abbreviations: COPD = chronic obstructive pulmonary disease; CRP = C-reactive protein; CV = cardiovascular; HDL = high density lipoprotein; LDH = lactate dehydrogenase; LDL = low density lipoprotein; PS = performance status; PVD = peripheral vascular disease; TIA = transient ischemic attack.

aData were not always available, as indicated.
the groups (BSC only, palliative intent, curative intent) was a significant survival disadvantage in patients experiencing a CV event observed (Figure 2C). Median survival after CV events (excluding CV death) was 23.3 months. Patients experiencing a cardiomyopathy had the shortest postevent survival (5.8 months), followed by pericardial effusion (8.1 months), conduction disorders (23.3 months), need of revascularization (23.5 months), and myocardial infarction (median not reached) (Figure 2D).

**Discussion**

In this study, we focused on a detailed analysis of CV disease in NSCLC patients. A large cohort (n = 715) of consecutive NSCLC patients was included, and the incidence and prevalence of CV events were assessed. The results showed that patients with a history of CV events had a significantly reduced survival compared to those without. The median OS was 113.3 months for patients with no CV events, 113.0 months for those with CV events and palliative intent, and 7.7 months for those with CV events and BSC only. The survival curves for different CV events are provided in Figure 2D.
retrospectively assessed to evaluate the presence of CV comorbidities and risk factors present at diagnosis of NSCLC. Moreover, severe CV events occurring after start of NSCLC treatment were documented. Finally, all parameters and risk factors were correlated with both CV-EFS and OS to delineate prognostic factors for CV events and survival.

At diagnosis of NSCLC, the majority of patients (67.2%) presented with at least one CV comorbidity. This circumstance is also reflected in the high proportion of patients treated with CV co-medication (53.4%).

By incorporating data of large observational studies and considering age and smoking status, our cohort seems to be characterized by an increased prevalence of the respective diseases (hypertension, atrial fibrillation, CHD, myocardial infarction). The same observations have been made in regard to general comorbidities (COPD, peripheral vascular disease, diabetes, stroke). Additionally, the high proportion of patients with a history of smoking (86.4%) certainly reflects the usual prevalence of nicotine abuse in NSCLC patients but is markedly elevated compared to the general population.

Altogether, 68 patients developed a severe CV event after diagnosis of NSCLC. This corresponds to an incidence of 9.5%, or 4.4 CV events per 100 patient-years. It is worth noting that patients who did not receive antineoplastic treatment had the highest incidence of CV events, with 15.0 events per 100 patient-years. This circumstance can certainly be explained by an accumulation of CV risk factors in this cohort (eg, increased age, CV comorbidities), which rendered those patients ineligible for antitumoral treatment in most cases. As expected, patients treated with palliative intent were characterized by a less favorable risk factor profile than those treated with curative intent. Because of the disparities of the groups’ baseline characteristics, it cannot be definitively stated which treatment approach leads to the highest risk of cardiotoxicity.

As a result of the detailed documentation of numerous parameters, we were able to analyze their association with CV events. As expected, the presence of CV comorbidities and the intake of its respective CV co-medication were significantly associated with CV events. Moreover, most of the detected risk factors were associated with reduced CV-EFS and OS (Table 2).

The incidence of CV events increased with rising age, reaching up to 35.2% in octogenarians, and can certainly be an explanation for the simultaneously rising prevalence of CV comorbidities.

To determine whether the incidence of CV events is increased in NSCLC patients compared to an age- and sex-matched normal population, we calculated the patient-specific general CV risk profile using a recently published risk model based on the well-known Framingham heart study as a surrogate. This model includes patient age, body mass index, antihypertensive treatment, systolic blood pressure, diabetes, and smoking status and provides an estimation of the 2-year risk for the development of CV disease (CHD, stroke, peripheral vascular disease, heart failure). This model was only applicable in patients without preexisting CHD; therefore, 127 patients were included into this estimation. Utilizing this model, the median 2-year CV disease risk in our study was estimated to be 1.5%. The applicability of the Framingham calculation model is obvious: the 2-year event rate was 1% in our cohort.

The difference is well explained by the fact that events like stroke, peripheral vascular disease, or CHD without invasive interventions were not documented in our study. Thus, the absolute CV risk rate might be somewhat higher in our cohort.

In NSCLC patients with a CV event, OS is not significantly shorter than in those without a CV event (Figure 2C). This observation indicates that NSCLC rather than CV events is the cause of most deaths in NSCLC patients.

Considering the substantial number of CV events in NSCLC patients, accompanied by a high prevalence of CV comorbidities, the question arises whether patients should be screened for CV disease before NSCLC treatment. To our knowledge, no established workup has been described for NSCLC patients so far. Therefore, it is uncertain if a pretreatment evaluation including electrocardiography, echocardiography, and determination of specific laboratory parameters might be some kind of overdiagnosis. Moreover, it is questionable if the treatment approach should be altered in case of newly detected CV diseases because in our analysis, mortality due to NSCLC distinctly exceeds CV mortality. To elucidate the most feasible and convincing pretreatment CV workup, prospective trials are warranted. Such a trial was started in Austria recently, with CV events of patients receiving curative treatment being documented prospectively. The aim of this study is to define risk factors and to provide data on the feasibility and utility of an extended CV workup in patients treated in daily routine.

Conclusion

Here we show for the first time that patients with NSCLC have a high burden of CV comorbidities and develop a considerable number of CV events. The detailed analysis of comorbidities and CV events in a large consecutive cohort of NSCLC patients may serve as a benchmark for physicians as they estimate the diseases in their NSCLC patients. We propose that in future trials, especially if CV adverse effects are a relevant parameter, a focus should be set on patients treated in clinical routine, without exclusion of patients with CV disease.

Clinical Practice Points

- Patients with NSCLC and CV disease often share a similar demographic profile. Data on CV comorbidities and CV events in NSCLC patients is lacking.
- The aim of our analysis was to assess the prevalence and significance of preexisting CV comorbidity and events occurring after diagnosis of NSCLC.
- Both CV disease and CV events were frequently observed in NSCLC patients and showed a direct correlation with increasing age.
- Preexisting CV comorbidities like atrial fibrillation, myocardial infarction, and cardiomyopathy were significantly associated with the development of CV events.
- OS was not reduced in patients who experienced a CV event compared to patients without a CV event.
- The presented data might serve as a benchmark in the risk assessment of CV events in NSCLC patients.
- For further recommendations on the feasibility and relevance of screening for CV disease in NSCLC, prospective trials are warranted.
Acknowledgments
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Disclosure
The authors have stated that they have no conflicts of interest.

References
Non-pegylated liposomal doxorubicin in lymphoma: patterns of toxicity and outcome in a large observational trial

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Abstract The anthracycline doxorubicin plays a major role in the treatment of lymphoproliferative disorders. However, its use is often limited due to cardiac toxicity, which seems to be much less in the liposomal non-pegylated formulation (Myocet®). The aim of this study was the evaluation of efficacy and toxicity of Myocet®-containing treatment regimens, with a focus on cardiotoxicity during treatment in lymphoma patients. A total of 326 consecutive patients, treated between March 2008 and December 2013 in 11 Austrian and 1 Italian cancer centers, were retrospectively assessed. Patients’ baseline and treatment-related parameters were obtained by reviewing hospital records. Median age was 74 years (range 26–93). The most common histology was DLBCL (60 %), followed by FL (13 %) and MCL (8 %). At least one cardiovascular comorbidity was present in 72 % of patients. Most common grade 3/4 toxicities were hematologic, namely, leukopenia, neutropenia, thrombocytopenia, and febrile neutropenia in 44, 40, 17, and 16 %. Overall, 43 patients suffered a cardiac event (any grade) with most patients developing congestive heart failure. Parameters significantly associated with severe cardiac events (grades 3–5) were the presence of cardiovascular comorbidities, chronic obstructive pulmonary disease, and elevated baseline NT-proBNP. Treatment response after first line Myocet®-containing therapy was ≥58 % among all entities (range 58–86 %) and therefore comparable to those of conventional therapeutic regimens. Herein, we provide a detailed toxicity profile of Myocet®-containing chemotherapy regimens. Despite the high rate of patients with preexisting comorbidities, the number of adverse events was encouraging. However, these results need to be confirmed in a prospective randomized trial.

Keywords Anthracycline · Cardiac toxicity · Lymphoma · Myocet · R-CHOP

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Introduction

Non-Hodgkin’s lymphoma (NHL) is the most common lymphoproliferative disorder. Since anthracyclines became available in 1969 with doxorubicin, the prognosis of many lymphomas has dramatically improved, especially when added to polychemotherapy regimens such as cyclophosphamide, vincristine and prednisolone (CHOP), and its variants (CHOP-like) [1]. However, especially in elderly patients, the use of doxorubicin is often limited due to anthracycline-induced cardiac toxicity [2–4]. These side effects often require dose reductions, treatment delays, or even omission of the anthracycline, leading to a dismal outcome [5]. Consequently, less toxic and equally potent options are needed.

Alternative formulations of doxorubicin, such as non-pegylated liposomal doxorubicin (Myocet®), with less cardiac side effects but preserved efficacy could represent an interesting alternative. Indeed, there is evidence that the ejection fraction, as a surrogate parameter for cardiac performance, is not affected by the administration of Myocet® [6–11]. A randomized controlled trial in patients affected by metastatic breast cancer showed comparable efficacy with less cardiac events when comparing Myocet® with doxorubicin (13 vs 29 %) [8]. Hence, Myocet® has also been administered off-label to many lymphoma and myeloma patients as a less toxic alternative to doxorubicin. Also, according to the guidelines of the European Society for Medical Oncology, substitution of doxorubicin by liposomal doxorubicin is recommended for patients with cardiac dysfunction or who are otherwise unfit [12]. Preliminary data regarding efficacy and toxicity in elderly patients with poor risk DLBCL showed a high response rate after the combination of rituximab, cyclophosphamide, Myocet®, and prednisone (R-COMP) with only a few treatment-related cardiac events [10, 11]. Even in patients with preexisting cardiac disorders, favorable results were observed [13]. However, real-live data of large patient cohorts assessing the efficacy and tolerability of Myocet®-containing treatment regimens is lacking. Therefore, we performed the so far largest multicenter observational study evaluating the spectrum and frequency of side effects and the efficacy of Myocet®-based chemotherapy in a real-life setting.

Patients and methods

Patients

Eleven Austrian and one Italian cancer center retrospectively assessed all patients affected by a lymphoproliferative disease, who underwent a Myocet®-based treatment between March 2008 and December 2013. This resulted in a cohort of 326 consecutive, unselected patients. Patients’ characteristics at diagnosis (Table 1), chemotherapy details, toxicities (Tables 2 and 3, Supplementary Table 1), and outcome (Table 4, Figs. 1 and 2) were registered. Follow-up data was obtained from hospital files and primary physicians. The final data update was performed in January 2014. This study was approved by the Ethics Committee of the Medical University of Innsbruck.

Treatment

All patients who received at least one Myocet®-containing therapy and met the above-mentioned criteria were included into this analysis. Most patients underwent R-COMP (cyclophosphamide 750 mg/m², vincristine 2 mg, Myocet® 50 mg/m², prednisone 40 mg/m², and rituximab 375 mg/m²; n = 287). 19 T-NHL patients received COMP without rituximab. While a curative approach was intended in all cases, dose modifications, treatment delays, switches to another treatment regimen, and premature treatment termination were often necessary. Other treatment regimens containing Myocet® were the following: alemtuzumab plus COMP (three patients); bortezomib plus COMP (one patient); cyclophosphamide, vincristin, procarbazine, prednisone alternating with Myocet®, bleomycin, vinblastine, and dacarbazine (COPP-MBVD, one patient); ofatumumab plus COMP (one patient); bortezomib, Myocet®, and dexamethasone (ten patients); and cyclophosphamide, navelbine, Myocet®, prednisone (four patients). In accordance with the European Organisation for Research and Treatment of Cancer guidelines [14], granulocyte colony-stimulating factor (G-CSF) support was given in most cases.

Evaluation of toxicity

Toxicities, documented within the time interval between administration of first Myocet® dose and 2 months after the last dose of the respective therapy line, were graded according to the NCI Common Terminology Criteria for Adverse Events (CTCAE, version 4.0). Cardiotoxicity was documented during Myocet®-based therapy and at any time point thereafter. In order to better distinguish early from late onset cardiotoxicity, we categorized whether cardiotoxicity was experienced “during Myocet®-based therapy” (including the time interval of 2 months after last dose) or in the subsequent period (Table 3, Supplementary Table 1). To identify possible risk factors, the association of baseline characteristics and laboratory parameters with all cardiac events and cardiac events of grades 3–5 was analyzed. The following parameters were evaluated: sex, age (<60 vs ≥60 years), histology, stage of disease, performance status (ECOG ≤1 vs ≥2), presence or absence of B symptoms, international prognostic index (IPI), and co-morbidities at times of diagnosis such as cardiovascular diseases, diabetes, chronic obstructive pulmonary disease (COPD), gastrointestinal disorders, rheumatic diseases,
renal impairment, impaired cardiac function (ejection fraction [LVEF] <55%), and prior cancers with or without prior antitumor therapies. Moreover, the following laboratory parameters were evaluated: hemoglobin level, count of leukocytes, neutrophils and thrombocytes, troponin T, NT-proBNP, C-reactive protein.
Evaluation of response and survival

Complete remission (CR) and partial remission (PR) were assessed according to the disease-specific response criteria [15–18]. In all cases, response had to persist for at least 2 months. Progression-free survival (PFS) was measured from first day of the Myocet®-based therapy to disease progression or death, whatever occurred first, and overall survival (OS) was measured from initiation of Myocet® therapy to last follow-up or death of any cause.

Statistical analyses

Chi-square test was performed to assess the significance of differences between categorical variables. The significance of distribution differences between subgroups was assessed with the Mann–Whitney U test. PFS and OS were plotted as a curve using the Kaplan–Meier method. Log-rank test was employed to assess the impact of categorical variables on survival. A P value of <0.05 was considered as statistically significant. All statistical analyses were performed with the Statistical Package for the Social Sciences (SPSS) software v.17.0.1 (SPSS, Chicago, IL, USA).

Results

Patient characteristics at start of Myocet®-based therapy

Patient characteristics at start of Myocet®-based therapy are summarized in Table 1. Overall, most patients were of advanced age (median 74 years, range 26–93 years) and of male gender (58 %). Only the minority had a poor performance status (90/314 informative cases, 29 %). The most common lymphoproliferative disorder was DLBCL (n=194; 60 %), followed by FL grade 3 (25; 8 %), MCL (24; 7 %), peripheral T-NHL (19; 6 %), and other lymphoma entities. Most patients presented with advanced stage of disease and adverse prognosticators (Table 1).

<table>
<thead>
<tr>
<th>Cardiac event</th>
<th>During treatment N</th>
<th>Valid</th>
<th>%</th>
<th>After treatment N (%)</th>
<th>Valid*</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arrhythmia</td>
<td>15**</td>
<td>326</td>
<td>5</td>
<td>5***</td>
<td>274</td>
<td>2</td>
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<tr>
<td>Instable angina pectoris</td>
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<td>2</td>
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<tr>
<td>ACS/MCI</td>
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<td>4</td>
<td>3</td>
<td>1</td>
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<td></td>
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<tr>
<td>CHF</td>
<td>27</td>
<td>8</td>
<td>13</td>
<td>5</td>
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<tr>
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<td>0.6</td>
<td>2</td>
<td>0.7</td>
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<tr>
<td>Blood pressure dysregulation***</td>
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<td>0.9</td>
<td>0</td>
<td>0</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Cave one patient may have suffered from >1 cardiac event, ACS acute coronary syndrome, MCI myocardial infarction, CHF congestive heart failure, SCD sudden cardiac death

**During treatment: atrial fibrillation (n=11), arrhythmia not otherwise specified (3); atrioventricular block (1); after treatment: atrial fibrillation (5)

***Orthostatic dysregulation (n=2); hypertensive emergency (1)
Overall, the median cumulative Myocet® dose was 225 mg/m² (20–400 mg/m²), and the median number of chemotherapy cycles containing Myocet® was 5 (range 1–8 cycles). In detail, in first line therapy, a median of 6 cycles of Myocet®-containing chemotherapy was administered (range 1–8) with an overall median cumulative dose of 240 mg/m² (range 20–400 mg/m²). Seventy patients (21 %) received previous chemotherapy while 22 (7 %) were pretreated with radiotherapy (RT). In patients treated in higher lines, number of cycles (median 4, range 1–6) and cumulative Myocet® doses (150 mg/m², 37.5–300 mg/m²) were significantly lower compared to the first line therapy (P<0.001 for each comparison). There was no difference in numbers of cycles and cumulative dose in the different tumor entities, both in the first and higher line setting, respectively. In 21/326 patients (6 %), a switch from doxorubicin to Myocet® within a treatment line (after a median of 3 cycles, range 1–5 cycles) was performed. Of 1581 anthracycline-containing chemotherapies, 1494 contained Myocet® (95 %). RT within the same therapy line (mostly with intent of consolidation) was delivered to 31 patients (11 %).

**Toxicity of Myocet®-based treatment**

Hematologic and extrahematologic toxicities during Myocet®-based therapy and within 2 months after last dose, according to the CTC grades, are detailed in Table 2. As expected, the most common grade 3/4 toxicities were hematologic consisting mainly of leukopenia, neutropenia, thrombocytopenia, as well as febrile neutropenia in 142/326 (44 %), 131/326 (40 %), 55/326 (17 %), and 51/326 cases (16 %), respectively. Severe hematologic toxicities, including febrile neutropenia, were significantly more often observed in patients who had undergone a previous treatment line (neutropenia, 58 vs 36 %, P=0.001; thrombocytopenia, 39 vs 12 %, P<0.001; febrile neutropenia, 25 vs 13 %, P=0.022). Non-hematologic toxicities were less frequent, but more often led to fatal events (n=20).

<table>
<thead>
<tr>
<th>Histological entity</th>
<th>ORR</th>
<th>CR</th>
<th>PR</th>
<th>SD</th>
<th>PD</th>
<th>Treatment not completed</th>
<th>Death during therapy</th>
<th>Relapse</th>
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<tr>
<td>DLBCL first line</td>
<td>124</td>
<td>75</td>
<td>100</td>
<td>60</td>
<td>24</td>
<td>14</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>FL G III first line</td>
<td>17</td>
<td>81</td>
<td>15</td>
<td>71</td>
<td>2</td>
<td>10</td>
<td>1</td>
<td>5</td>
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<tr>
<td>FL G I/II first line</td>
<td>12</td>
<td>86</td>
<td>10</td>
<td>71</td>
<td>2</td>
<td>14</td>
<td>0</td>
<td>0</td>
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<tr>
<td>MCL first line</td>
<td>14</td>
<td>78</td>
<td>12</td>
<td>67</td>
<td>2</td>
<td>11</td>
<td>1</td>
<td>6</td>
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<tr>
<td>T-NHL first line</td>
<td>11</td>
<td>58</td>
<td>6</td>
<td>32</td>
<td>5</td>
<td>26</td>
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<td>0</td>
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</tbody>
</table>

**Response and relapse according to the histological subgroup**

<table>
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<th>ORR</th>
<th>CR</th>
<th>PR</th>
<th>SD</th>
<th>PD</th>
<th>Treatment not completed</th>
<th>Death during therapy</th>
<th>Relapse</th>
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</thead>
<tbody>
<tr>
<td>Histological entity</td>
<td>N</td>
<td>%</td>
<td>N</td>
<td>%</td>
<td>N</td>
<td>%</td>
<td>N</td>
</tr>
<tr>
<td>DLBCL first line</td>
<td>124</td>
<td>75</td>
<td>100</td>
<td>60</td>
<td>24</td>
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<td>3</td>
</tr>
<tr>
<td>FL G III first line</td>
<td>17</td>
<td>81</td>
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<td>71</td>
<td>2</td>
<td>10</td>
<td>1</td>
</tr>
<tr>
<td>FL G I/II first line</td>
<td>12</td>
<td>86</td>
<td>10</td>
<td>71</td>
<td>2</td>
<td>14</td>
<td>0</td>
</tr>
<tr>
<td>MCL first line</td>
<td>14</td>
<td>78</td>
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<td>67</td>
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<td>11</td>
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**Fig. 1** This Kaplan–Meier plots illustrates progression-free survival (PFS) in five different lymphoma entities treated in first line with R-COMP (or COMP regimen in T-NHL). The median PFS and 3-year PFS were 44.3 months and 50 % in DLBCL (n=166), respectively; 57.7 months and 62 % in follicular lymphoma grade 3 (FL G3, n=21), respectively; not reached and 92 % in follicular lymphoma grades 1 and 2 respectively; 42.8 months and 68 % in mantle cell lymphoma (MCL, n=18), respectively; and 6.9 months and 11 % in peripheral T cell lymphoma (T-NHL, n=19).

**Fig. 2** This Kaplan–Meier plots illustrates overall survival (OS) in five different lymphoma entities treated in first line with R-COMP (or COMP regimen in T-NHL). The median OS and 3-year OS were not reached and 66 % in DLBCL (n=166), respectively; 68.5 months and 75 % in follicular lymphoma grade 3 (FL G3, n=21), respectively; not reached and 83 % in follicular lymphoma grades 1 and 2, respectively; not reached and 68 % in mantle cell lymphoma (MCL, n=18), respectively; and 11.3 months and 23 % in peripheral T cell lymphoma (T-NHL, n=19).
A major focus was set on the detailed analysis of cardiac events occurring during the treatment period (after the first dose of Myocet® until 2 months after the last dose). In Supplementary Table 1, the most important characteristics of patients who suffered cardiac events during a Myocet®-based therapy are described, including long-term follow-up information. Briefly, in 43/326 patients (13 %) a cardiac event was documented within the above-mentioned time period. Four patients experienced grade 3 toxicities, namely, clinically manifest congestive heart failure, accompanied with acute coronary syndrome in two cases, and 12 patients suffered from grade 4 toxicities consisting of severe congestive heart failure in 10 cases, myocardial infarction in one, and arrhythmia accompanied with an atrioventricular block of grade 3 in one patient. Therapy-associated cardiac deaths were documented in seven cases, myocardial infarction in one, and arrhythmia accompanied with an atrioventricular block of grade 3 in one patient. Therapy-associated cardiac deaths were documented in seven patients of whom four experienced a myocardial infarction leading to fatal congestive heart failure, two a sudden cardiac arrest, and one a fatal congestive heart failure during first cycle of a Myocet®-based therapy. All therapy-associated events of any grade are summarized in Table 3.

Parameters associated with elevated incidence of cardiac adverse events irrespective of grade were the presence of COPD (in 33 vs 10 % in patients without COPD, P<0.001) and elevated NT-proBNP (20 vs 4 %, P=0.05). Parameters associated with severe cardiac toxicity (grades 3–5) were the presence of cardiovascular comorbidity (9 vs 2 %, P=0.035), COPD (19 vs 5 %, P=0.002), and elevated NT-proBNP (15 vs 0 %, P=0.04). The most homogeneous cohort in our observational trial was the group of DLBCL patients treated with R-COMP in first line (n=149). A comparison of this cohort to historical cohorts who received conventional doxorubicin has recently been published [19]. Of note, the proportion of cardiotoxicity and severe cardiotoxicity in this group (including cardiac deaths) was not different when compared to the rest of patients (n=177), who were characterized by varying patients’ characteristics, were partly pretreated, and often received different Myocet-based regimens.

Finally, cardiac events occurring >2 months after the last dose of Myocet® were documented in 18 cases (6 %), as detailed in Supplementary Table 1 and Table 3. In three of these patients, cardiotoxicity was also observed during Myocet®-based therapy. However, it is likely that in a relevant number of patients, cardiac events in the time after Myocet®-based therapy were not documented due to less frequent hospital visits after completion of chemotherapeutic treatment. Thus, no further analyses were performed in this cohort.

Response upon Myocet®-based therapy

Treatment response upon a Myocet®-based first line therapy according to the different histologic subtypes is summarized in Table 4. High overall response rates (ORR) were observed among all entities and were comparable to those of conventional therapies (e.g. of (R)-CHOP).

Overall, a response was achieved in 226/326 patients (ORR 69 %). Response in first line and higher line of therapy was achieved in 76 and 47 %, respectively (P<0.001). Non-responders had significantly more often an elevated LDH (P<0.001), poor performance status (P<0.001), LVEF<50 % (P=0.001), elevated NT-proBNP (P=0.014), and thrombocytopenia <150 G/L (P=0.028) at time of treatment initiation.

Survival analysis was performed in patients with Myocet®-based treatment in first line setting (n=262). PFS was calculated only for the major histologic entities, namely, DLBCL (n=166, 3 year PFS 50 %), FL grade 3 (n=21, 3-year PFS 62 %), peripheral T-NHL (n=19, 3-year PFS 11 %), MCL (n=18, 3-year PFS 68 %), and FL grades 1–2 (n=14, 3-year PFS 92 %) (Fig. 1). Apart from the type of lymphoproliferative disease, PFS was also negatively influenced by an elevated C-reactive protein (P<0.001), unfavorable IPI in the case of aggressive B cell NHL (P<0.001), low hemoglobin (P<0.001), presence of B symptoms (P=0.005), elevated β2-microglobuline (P=0.023), NT-proBNP (P=0.029) above the upper normal value, and LVEF<55 % (P=0.047).

OS, again calculated in patients with Myocet® in first line, varied according to the different entities, and 3-year OS was 66 % for DLBCL (n=166), 75 % for FL grade 3 (n=21), 23 % for peripheral T-NHL (n=19), 68 % for MCL (n=18), and 83 % for FL grades 1–2 (n=14) (Fig. 2). Survival was significantly influenced by an elevated C-reactive protein (P<0.001), low hemoglobin (P<0.001), unfavorable IPI in the case of aggressive B cell NHL (P<0.001), LVEF<55 % (P=0.003), elevated NT-proBNP (P=0.011), and the presence of B symptoms (P=0.002).

Discussion

In our previous work, we retrospectively showed that R-COMP as first line chemo-immune therapy in DLBCL is efficacious and well tolerated when compared with R-CHOP, together with the Austrian prospective phase II data by Fridrik et al. [19, 20], it is convincingly demonstrated that R-COMP is able to cure patients with DLBCL, and its potential is comparable with the standard R-CHOP regimen. The reason for substituting classic doxorubicin by Myocet® is mainly to protect the heart from doxorubicin-associated acute and long-term cardiotoxicity. Nevertheless, Myocet® is licensed in combination with cyclophosphamide in metastatic breast cancer, and two large phase III studies as well as one
meta-analysis evidenced that liposomal doxorubicin is less cardiotoxic than classic doxorubicin [7, 8]. Nevertheless, the authors of the meta-analysis concluded that the definitive recommendation in favor of liposomal formulations cannot be given so far [21]. On the other hand, the ESMO guidelines [12] suggest the substitution of doxorubicin with liposomal doxorubicin as option for patients with DLBCL and cardiac dysfunction. Apart from biological issues, several clinical questions still have to be answered: Can the favorable tolerability of Myocet® also be taken for granted in lymphoma? Should Myocet®-based therapy be reserved for the elderly and/or patients with preexisting cardiac comorbidities [22, 23]? Should it also be administered to the young patients facing a long lifetime after cure? Should Myocet® be given to all patients requiring a Doxorubicin-containing (immuno-) chemotherapy?

In this observational study, we put the focus on detailed analyses of toxicity and efficacy of Myocet®-based therapies in the so far largest cohort of patients affected by a hematologic neoplasia (n=326). This enabled us to provide detailed subgroup analyses. However, due to the retrospective nature and the lack of a direct comparison to analogous therapies using classic doxorubicin, it cannot definitely be stated whether a Myocet®-based therapy is less cardiotoxic or not.

The pattern of acute, non-severe, and severe cardiac events in the present analysis reflected the expected spectrum of adverse events of an anthracycline-based therapy, such as congestive heart failure, arrhythmia, acute coronary syndrome, and even sudden cardiac death. Indeed, the quantity of cardiac events appears significant in our study. Nevertheless, it must be considered that the present study population is highly selected for preexisting cardiac comorbidities, representing patients in whom administration of conventional doxorubicin would have been contraindicated. Indeed, this might be an explanation for the high percentage of cardiovascular events occurring during Myocet® treatment. Long-term cardiovascular events in our study probably are underreported due to the retrospective study design with a considerable proportion of patients lost to follow-up. Anyhow, such an analysis certainly should be performed prospectively and demands a long, closely monitored observational period [24].

Maybe the most important finding in this study is the identification of factors predicting the occurrence of cardiac events. Herein, for the first time, baseline clinical parameters associated with Myocet®-associated cardiotoxicity were identified. Of all evaluated factors, cardiac comorbidities of any kind, elevated NT-proBNP and preexisting COPD, appeared to represent a state of elevated risk for cardiotoxicity under Myocet®-based therapy. Unexpectedly, impaired LVEF at treatment start did not unambiguously predict cardiotoxicity, in line with the observation by Jurzak et al. [25]. Nevertheless, early decline in LVEF was reported to predict cardiotoxicity in lymphoma patients [26]. The remaining parameters suggestive for a poor outcome, namely, increased age, poor performance status, anemia, and parameters indicative of advanced disease, such as high stage of disease or elevated LDH, did not favor the occurrence of cardiac events. Finally, cardiotoxicity was not increased in patients who were treated with a Myocet®-containing therapy in a higher line, i.e., after relapse in salvage therapy. Therefore, we recommend a complete cardiac workup including electrocardiography, echocardiography, spirometry, and determination of NT-proBNP before starting any kind of anthracycline-based therapy. Despite the herein reported favorable toxicity profile in patients with preexisting cardiac comorbidities, studies with a long-term follow-up to investigate whether this drug should be reserved to similar patients or if also others without such disorders might profit from Myocet® are urgently warranted. Indeed, data from breast cancer studies proved that liposomal doxorubicin is less cardiotoxic when compared prospectively to classic doxorubicin. Therefore, the use of Myocet®-based therapy would be of major importance in younger patients who have the chance of cure and an estimated rather long survival.

Other severe toxicities such as cytopenia, severe infections, and febrile neutropenia were frequent, but manageable in most cases. The number of adverse events was within the expected range, when compared to a phase II trial evaluating R-COMP in elderly DLBCL patients [27]. This observation certainly reflects the quality of our retrospective toxicity assessment.

Considering the accumulation of comorbidities in the presented cohort, response and cure rates are encouraging, suggesting that this treatment is a valid option for doxorubicin-unfit patients (Table 4; Figs. 1 and 2). Although this analysis was not powered to evaluate the response rate, the ORR of DLBCL patients after first line therapy was similar to the one reported by Luminari et al. [27] (ORR 71 % as compared to 75 % in our study) and others [19, 22]. However, PFS and OS seem slightly inferior in our cohort, certainly explained due to the inferior basic characteristics. Nevertheless, patients who received ≥300 mg/m² Myocet® had a 3-year OS close to 80 % (not shown in detail).

In conclusion, in this real-life patient setting, we characterized in detail the spectrum of cardiotoxicities which can occur during a Myocet®-based therapy in lymphoma, identified prognosticators for such events, and showed that these treatments offer a reasonable chance of cure. However, a definite superiority of Myocet® in terms of toxicity and/or efficacy can only be demonstrated in prospective trials comparing Myocet®-containing regimens to the actual standard of care for each entity.

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(St. Johann) and Stephan Schreieck (Reutte), for providing patient data and advice.

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References


Is gender a risk factor for secondary cardiovascular events in R-CHOP treated DLBCL patients?

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INTRODUCTION
Cardiotoxicity is a well known side effect of anthracycline treatment. Some studies indicate, that women are at increased risk of cardiac side effects following anthracycline treatment. These results were deduced from studies investigating survivors of childhood cancers. Prompted by these findings we investigated the role of gender on the devlopment of cardiovascular events in a large consecutive cohort of diffuse large B-cell lymphoma patients [DLBCL] patients treated with the combination rituximab, cyclophosphamide, doxorubicin, vincristine and prednisolone [R-CHOP].

PATIENTS AND METHODS
184 patients diagnosed with DLBCL between 2000 and 2012 at Medical University of Innsbruck were included into this analysis. Parameters of most interest were cardiovascular comorbidities present at diagnosis (all grades) and cardiovascular events (heart failure, conduction disorders, acute coronary syndrome, valvular replacement) appearing during course of disease. Comparison of the respective parameters was performed according to patients gender.

RESULTS
Clinical Characteristics
85 (46.2%) of the 184 patients were female. Mean age at diagnosis was 60.2 in women and 55.9 years in men (p=0.076). Both genders were characterized by a comparable burden of cardiovascular comorbidities (women 40.0%, men 30.3%, p=0.170) (Table 1). The mean administered cumulative dose of anthracyclines was similar (women 284 mg/m², men 296 mg/m²; p=0.383).

Cardiovascular Events
Mean follow-up was comparable in women and men (55.7 vs. 65.0 month; p=0.151). Overall, 14 women (16.5%) and 9 men (9.1%) developed a cardiac event (p=0.179) (Table 2). Distribution of different cardiovascular events (p=0.141) and time to cardiovascular event (5-year EFS, women 82.5%, men 95.6%; p=0.124) was comparable between the groups (Figure 1).

Parameters associated with Cardiovascular Events
In women the presence of atrial fibrillation (p=0.030) or a previous myocardial infarction (p=0.023) were associated with an increased occurence of cardiac events. In men conduction disorders (p=0.042) and heart failure (p=0.042) were associated with cardiovascular events.

Cardiovascular Events and Survival
Survival was not reduced in patients experiencing a cardiovascular event compared to patients without an event. In pairwise comparison with regard to gender, survival was similar with 5-year OS of 64.3% vs. 70.9% in women (p=0.474) and 88.9% vs. 77.4% in men (p=0.229) (Figure 2).

CONCLUSION
Our data indicate that cardiovascular events are considerable complications in DLBCL patients. In our series gender did not prove to be a risk factor with respect to cardiotoxicity. Nevertheless, adequately powered prospective studies are needed to validate our results.
CURRICULUM VITAE AND PUBLICATION LIST

PERSONAL DETAILS

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EDUCATION

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expected graduation 09/16
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  Oncology (C. Zielinski, Wien), 04/2012-05/2012
  Family Medicine (B. Fürthauer, Maishofen), 06/2012

2008-2011  Clinical electives
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  Trauma surgery (H. Thöni, Zell am See)
  Ophthalmology (M. Landegger Zell am See)
  Pathology (G. Mikuz, Innsbruck)
  Dermatology (M. Schmuth, Innsbruck)

10/2006-07/2012  Medical studies at the Medical University of Innsbruck


09/1997-07/2005  Secondary school, Bundesrealgymnasium Zell am See
  Final exams: June 2005

09/1993-07/1997  Primary school, VS Schüttdorf, Zell am See
QUALIFICATIONS IN CLINICAL TRIAL MANAGEMENT

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10/2013-01/2014  Postgraduate course “Durchführung Klinischer Prüfungen”,
H. Baumgartner/ÖÄK, Innsbruck,

Practical experiences

CACOCA Trial

• Protocol development
• Development of case report form
• Development of study contract
• Submission to ethics committee and regulatory board
• Development of a clinical trial registry
• Database management and data acquisition
• Initiation of study centers
• Monitoring of study centers
• Patient recruitment
• Organisation of study meetings

TAX-AT 1.203 Trial

• Data acquisition and development of database
• Data analysis
• Preparation of manuscript
TYROL Study (Twenty Years Retrospective of Lung Cancer)

• Database management and development
• Data acquisition and data analysis
• Preparation of manuscripts

INN 06 Study

• Data acquisition and data analysis
• Assistance in preparation of manuscript

BIOLUME 1

• Assistance in protocol development
• Development of case report form

ADDITIONAL TRAINING

03/2014 Workshop “Kommunikation in der Onkologie/ Onkotalking”, P. Hofmann, Graz/Wien
02/2013 Workshop “Durchflusszytometrie”, S. Sopper, Innsbruck
11/2012-01/2013 Lecture “Statistics for Doctoral students”, G. Obermair, Innsbruck
Additional training within the CCR PhD studies

05/2013  Cell culture, B. Kircher

06/2013  Immunological techniques, M. Reindl

03/2013-05/2013  Advanced statistics, H. Ulmer

11/2012-06/2013  Clinical trial development and legal aspects, S. Embacher-Aichhorn
MEMBERSHIP

12/2012  Member of ÖGHO (Österreichische Gesellschaft für Hämatologie und Onkologie)

03/2013  Member of “Verein für Tumorforschung”

10/2013  Member of ICOS (International Cardio-Oncology Society)

09/2014  Member of ESMO (European Society for Medical Oncology)
## LECTURES/PRESENTATIONS

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<tr>
<td>20.11.2012</td>
<td>Presentation/ Discussion of Cardiologic Endpoints and Case report Form of CACOCA Trial, Study meeting, Innsbruck</td>
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<td>24.11.2012</td>
<td>Presentation CACOCA Trial, Laboratory Meeting, Meran</td>
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<td>25.01.2013</td>
<td>Presentation of Study Protocol, Informed Consent, Case Report Form. Study meeting, Vienna</td>
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<td>31.01.2013</td>
<td>Presentation CACOCA Trial, Staff Meeting, Innsbruck</td>
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<td>01.02.2013</td>
<td>Presentation of PHD-Thesis, Rationale, Cardiotoxicity, Trial design, Timeline, Thesis Day, Innsbruck</td>
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<td>CACOCA Trial Launch meeting, Update on progress, CACOCA Launch meeting, Linz</td>
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<td>Cardiotoxicity of Cancer treatment, Update on CACOCA Trial, Laboratory meeting, Meran</td>
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<td>14.01.2014</td>
<td>Gender specific aspects of Cardiotoxicity, Gender lecture, Innsbruck</td>
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<td>01.02.2014</td>
<td>Update on CACOCA Trial, Thesis day, Innsbruck</td>
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<td>06.03.2014</td>
<td>Presentation of CACOCA Trial and Update, Morning lecture, Innsbruck</td>
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<td>03.04.2014</td>
<td>CRF Presentation of BIOLUME-1, Start-up meeting, Innsbruck</td>
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<td>CACOCA Trial study meeting, Innsbruck</td>
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<td>Update on CACOCA Trial, Thesis day, Innsbruck</td>
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14.05.2014  CACOCA Trial Progress Report, Thesis Committee Meeting, Innsbruck
27.05.2014  Liver transplantation Associated Lung Cancer, Pneumoupdate, Igls
28.05.2014  Cardiotoxicity in cancer treatment, Pneumoupdate, Igls
05.07.2014  Progress Report CACOCA Trial, Thesis day, Innsbruck
28.08.2014  Cardiotoxicity and cardiovascular events in NSCLC, lecture, Wilhelminenspital Wien
23.11.2014  Progress Report CACOCA Trial, Laboratory meeting, Meran
25.11.2014  Cardiotoxicity and cardiovascular events in NSCLC, lecture, LKH Bregenz
29.10.2015  Incidental diagnosis of NSCLC, Morning lecture, Innsbruck
18.05.2016  A case of metastasized parachordoma treated with immunotherapy, Onko-Stammtisch, Innsbruck
**ABSTRACTS/POSTER** (first authorship only)

**04/2013**

**ÖGHO-Frühjahrstagung 2013, Linz**

1. Long term cardiotoxicity in patients treated with chemotherapy and/or targeted drugs, a prospective non interventional trial.  

**06/2013**

**Pneumo-Update 2013, Innsbruck/Igls**

2. CACOCA-Trial-Long term cardiotoxicity in patients treated with chemotherapy and/or targeted drugs, a prospective non interventional trial.  
Pneumologie 2013; 67 - P27

**04/2014**

**ÖGHO Frühjahrstagung 2014, Innsbruck**

3. Multicenter Phase II Study evaluating Dxl/Cis as Induction Regimen prior to Surgery or Radiochemotherapy in Stage II-IIIB NSCLC Patients (TAX-AT 1.203).  
Memo Volume 7, Issue 1 Supplement p 34. Abstract P53

4. Relevanz von PET Untersuchungen im Staging und prognostische Bedeutung des metabolischen Ansprechens beim neoadjuvant therapierten NSCLC im Stadium IB-IIIA.  
Memo Volume 7, Issue 1 Supplement p 31, Abstract P51

5. Update CACOCA Trial (Cardiovascular Complications of Cancer Treatment). A prospective non-interventional trial.  
Memo Volume 7, Issue 1 Supplement p 8. Abstract K09
   J Clin Oncol 32, 2014 (suppl; abstr e12531)

7. Update CACOCA Trial (Cardiovascular Complications of Cancer Treatment). A prospective non-interventional trial.

8. Multicenter Phase II Study evaluating Dxl/Cis as Induction Regimen prior to Surgery or Radiochemotherapy in Stage II-IIIB NSCLC Patients (TAX-AT 1.203).

9. Cardiovascular Complications of Cancer Treatment: Update CACOCA Trial

10. Is gender a risk factor for secondary cardiovascular events in R-CHOP treated DLBCL patients?
    **Kocher F**, Volgger A, Willenbacher W, Fiegl M, Hilbe W.

11. Octogenarians Perform Equally to Younger Patients in Lung Cancer Surgery
    J thoracic oncology - Accepted
1. A Success Story: How a Single Targeted Therapy Molecule Impacted Treatment and Outcome of Diffuse Large B-Cell Lymphoma.

Anticancer Res. 2014 May;34(5):2559-64.

2. Small steps of improvement in small-cell lung cancer (SCLC) within two decades: A comprehensive analysis of 484 patients.


3. Multicenter Phase II Study evaluating Dxl/Cis as Induction Regimen prior to Surgery or Radiochemotherapy in Stage II-IIIB NSCLC Patients (TAX-AT 1.203).


5. Longitudinal analysis of 2293 NSCLC patients: a comprehensive study from the TYROL registry.


6. Cardiovascular comorbidities and cardiovascular events in NSCLC: often underestimated but worth being considered

Kocher F, Fiegl M, Mian M, Hilbe W.
   Clin Lung Cancer. 2015 Sep;16(5):e75-81.

8. Multicenter phase II study evaluating two cycles with docetaxel, cisplatin and cetuximab as induction regimen prior to surgery in chemotherapy-naive patients with NSCLC stage IB-IIIA (INN06-study).

9. Routine use of bendamustine in consecutive patients with B-cell chronic lymphocytic leukemia (CLL): an observational study
   Anticancer Res. 2015 Sep;35(9):5129-39.

10. NSCLC without Antineoplastic Treatment: Incidence, Characteristics, and Outcome as Outlined in the TYROL Study
    **Kocher F**, Lunger F, Pircher A, Hilbe W, Fiegl M.

11. Incidental Diagnosis of Asymptomatic Non-Small-Cell Lung Cancer: A Registry-Based Analysis.
    **Kocher F**, Lunger F, Seeber A, Amann A, Pircher A, Hilbe W, Fiegl M.


13. Predominant expression of truncated EpCAM is associated with a more aggressive phenotype and predicts poor overall survival in colorectal cancer.
REVIEWS/ COMMENTS

1. ASCO 2013: new developments in lung cancer
   Pircher A, Fiegl M, Kocher F, Hilbe W.
   memo (2013) 6:236-239

2. Chemo- und Immuntherapie-induzierte Kardiotoxizität bei Tumorpatienten.
   Kocher F, Fridrik M, Keil F, Pölzl G, Samonigg H, Hilbe W.
   Spectrum Onkologie (2013) 4: 22-27

3. 20 Jahre Lungenkrebsfassung: TYROL-Studie
   Kocher F, Fiegl M, Hilbe W.

   Kocher F, Lunger F, Seeber A, Amann A, Pircher A, Hilbe W, Fiegl M.