Late toxicities in lymphoma: Real-world data on cardiotoxicity, diabetes mellitus, and second malignancies

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DOI (link to publication from Publisher):
10.54337/aau679683661

Publication date:
2023

Document Version
Publisher's PDF, also known as Version of record

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BY
JOACHIM BAECH

DISSERTATION SUBMITTED 2023

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Dissertation submitted 2023

Dissertation submitted: 10-11-2023

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PhD Series: Faculty of Medicine, Aalborg University

Department: Department of Clinical Medicine

ISSN (online): 2246-1302
ISBN (online): 978-87-7573-602-7

Published by:
Aalborg University Press
Kroghstræde 3
DK – 9220 Aalborg Ø
Phone: +45 99407140
aauf@forlag.aau.dk
forlag.aau.dk

Printed in Denmark by Stibo Complete, 2023

PREFACE

This PhD thesis presents some of the research that I have conducted during my time as a PhD student at the Department of Hematology at Aalborg University Hospital and the Department of Clinical Medicine, Aalborg University. It also involves some of the research that I have conducted prior to my PhD, as I have been lucky to have been affiliated with the Department of Hematology since 2011.

I started my affiliation with the Department of Hematology when I was approached by our family friend, the late Hans E. Johnsen, who asked if I wanted to spend my sabbatical year after high school by working in the hematological biobank. I enjoyed my time there and came back to work at the biobank during the following summers, while enrolled as a medical student. Hans suggested that I should pursue my interest in research and introduced me to Tarec C. El-Galaly in 2016. During the rest of my time in medical school, I did research in my spare time and was employed on and off at the Department of Hematology and the Department of Epidemiology. I continued to conduct research during my first clinical rotation as a medical doctor and pursued this PhD right after that initial rotation.

I want to express my deepest gratitude to Hans for always believing in me and giving me the many great opportunities that have led me here today, the greatest among them being the introduction to Tarec. I could not have asked for a better supervisor, mentor, and colleague, someone who has guided me in both my research and my career choices. Tarec, you have always pushed me to excel and given me the opportunities needed to do so. This mentoring has spurred many collaborations as well as having led to many presentations in both national and international forums.

Marianne Tang Severinsen deserves great gratitude for stepping in as my main supervisor while Tarec was working in Switzerland. I have enjoyed your open-door policy and consistently good mood, and the many clinical discussions and input.

Acknowledgments extend to Karolinska Institutet for the exchange opportunity, where many colleagues and friends were met. Special appreciation goes to Karin, Caroline, Sandra, Tove, and Joshua for creating a welcoming and fortunate environment during the stay, as well as before and after.

Great thanks to my colleagues at the Department of Hematology. I have known some of you for 12 years, and a lot has happened in that period. I always feel at home when I am at work and for that I am very grateful. A special thanks to my friends from my office, with whom I have shared many great memories. Eva, Andreas, Lasse, Rasmus, Mikkel, Rasmus, Daniel, Paw, Ahmed, and Jonas, I hope that we will be working together again.

Thank you to my beautiful family, Anna, Philip, and Alexander, to whom I look forward to coming home every day.

Lastly, I want to say that while I have often heard from fellow PhD students about the inevitable highs and lows of the doctoral journey, I can genuinely say that I have never experienced a low period throughout my PhD. For that, I thank all of my colleagues and especially Tarec.

Joachim Bæch, November 2023

LIST OF STUDIES

1. **Baech J**, Hansen SM, Lund PE, et al. Cumulative anthracycline exposure and risk of cardiotoxicity; a Danish nationwide cohort study of 2440 lymphoma patients treated with or without anthracyclines. Br J Haematol. 2018;183(5):717-726. doi:10.1111/bjh.15603
2. **Baech J**, Severinsen MT, Øvlisen AK, et al. Risk of diabetes and the impact on preexisting diabetes in patients with lymphoma treated with steroid-containing immunochemotherapy. Blood Adv. 2022;6(15):4427-4435. doi:10.1182/bloodadvances.2021006859
3. Trab T*, **Baech J***, Jakobsen LH, Husby S, Severinsen MT, Eloranta S, et al. Second primary malignancies in patients with lymphoma in Denmark after high-dose chemotherapy and autologous haematopoietic stem-cell transplantation: a population-based, retrospective cohort study. Lancet Haematol. 2023;3026:1–11.
4. **Baech J***, Husby S*, Trab T. Cardiovascular diseases after high dose chemotherapy and autologous stem cell transplant for lymphoma: a Danish population-based study (under review: British Journal of Haematology).

The following studies were published during my time at the Department of Hematology at Aalborg University Hospital, but they were not included as part of this PhD thesis.

1. Juul MB, Jensen PH, Engberg H, et al. Treatment strategies and outcomes in diffuse large B-cell lymphoma among 1011 patients aged 75 years or older: A Danish population-based cohort study. Eur J Cancer. 2018;99:86-96. doi:10.1016/j.ejca.2018.05.006
2. El-Galaly TC, Villa D, Gormsen LC, **Baech J**, Lo A, Cheah CY. FDG-PET/CT in the management of lymphomas: current status and future directions. J Intern Med. 2018;284(4):358-376.
3. **Baech J**, Hansen SM, Jakobsen LH, et al. Increased risk of osteoporosis following commonly used first-line treatments for lymphoma: a Danish

Nationwide Cohort Study. Leuk Lymphoma. 2020;61(6):1345-1354. doi:10.1080/10428194.2020.1723015

4. Jensen P, Jakobsen LH, Bøgsted M, et al. A randomized trial of alendronate as prophylaxis against loss in bone mineral density following lymphoma treatment. Blood Adv. 2022;6(8):2549-2556.
5. Jakobsen LH, Øvlisen AK, Severinsen MT, et al. Patients in complete remission after R-CHOP (-like) therapy for diffuse large B-cell lymphoma have limited excess use of health care services in Denmark. Blood Cancer J. 2022;12(1):16.
6. Juul MB, Jelicic J, Anru PL, et al. Cardiovascular diseases in elderly survivors of diffuse large B-cell lymphoma: a Danish population-based cohort study. Leuk Lymphoma. 2022;63(9):2074-2083.
7. Maksten EF, Jakobsen LH, Kragholm KH, et al. Work disability and return to work after lymphoma: a Danish nationwide cohort study. Clin Epidemiol. Published online 2023:337-348.
8. Villa D, Jiang A, Visco C, et al. Time to progression of disease and outcomes with second-line BTK inhibitors in relapsed/refractory mantle cell lymphoma. Blood Adv. Published online 2023.
9. Pedersen, MA, Gormsen, LC, Jakobsen, LH, et al. The impact of CHOP versus bendamustine on bone mineral density in patients with indolent lymphoma enrolled in the GALLIUM study. Accepted in British Journal of Haematology.

In review:

1. **Baech, J**, Jakobsen, LH, Simonsen, MR, et al. No disparities in survival outcomes between immigrants and Danish-born patients with hematological malignancies: A nationwide, population-based register study. In review: European Journal of Epidemiology.
2. Vandtved, JH, Øvlisen, AK, **Baech, J**, et al. Pulmonary diseases in classical Hodgkin lymphoma survivors relative to a matched background population:

A Danish national cohort study. Under submission: British Journal of Haematology

Citations: 231

ENGLISH SUMMARY

The overall survival for patients with lymphoma has increased in recent decades due to advances in treatment. An increasing number of patients with lymphoma thus are becoming long-term survivors, which entails a risk of late toxicities associated with the chemotherapy regimens used to treat their lymphoma. The aim of this PhD research was to investigate these late toxicities in a real-world setting by establishing associations, risks, and risk factors.

This PhD thesis includes four population-based epidemiological cohort studies:

Study I showed an increased risk of congestive heart failure and cardiovascular diseases in general, respectively, for patients with follicular lymphoma or diffuse large B-cell lymphoma treated with anthracycline-containing immunochemotherapy compared to patients treated without. Furthermore, a dose-response relationship was established.

Study II was focused on the risk of new-onset steroid-induced diabetes mellitus for patients with non-Hodgkin lymphoma treated with steroid-containing immunochemotherapy compared to a matched background population and identified no significantly increased risk. However, patients with pre-existing diabetes mellitus treated with steroid-containing immunochemotherapy had an increased risk of first insulin prescriptions compared to matched comparators with pre-existing diabetes mellitus.

Study III showed an increased risk of second primary malignancies for patients with aggressive lymphoma treated with high-dose therapy with autologous stem cell transplant (HDT-ASCT) compared to a matched background population and patients treated without HDT-ASCT, respectively. The increased risk was driven by an increased risk of non-melanoma skin cancer and myelodysplastic syndrome/acute myeloid leukemia, but not solid tumors.

Study IV identified an increased risk of congestive heart failure and other cardiovascular diseases, respectively, for patients with aggressive lymphoma treated with HDT-ASCT compared to a matched background population and patients treated without HDT-ASCT, respectively. The increased risk was persistent for more than 10 years following treatment initiation.

The included studies add important knowledge to the existing literature regarding late toxicities, which may help clinicians in selecting optimal treatment, screening for adverse effects, and helping patients make informed decisions.

DANSK RESUME

Overlevelsen blandt patienter med lymfekræft er steget i de seneste årtier grundet bedre behandlingsmuligheder. Derfor bliver flere og flere patienter med lymfekræft langtidsoverlevere, hvilket introducerer en risiko for sentoksicitet som følge af den kemoterapi, der bruges til behandlingen af deres lymfekræft. Formålet med denne ph.d. var at undersøge disse sene toksiciteter i den virkelige verden ved at undersøge sammenhænge, risici og risikofaktorer.

Denne ph.d. omfatter fire nationale epidemiologiske kohortestudier:

Studie I fandt en øget risiko for henholdsvis hjertesvigt og kardiovaskulære sygdomme for patienter med follikulært lymfom eller diffust storcellet B-cellelymfom behandlet med antracyklinholdig immunkemoterapi sammenlignet med patienter, der blev behandlet uden. Derudover fandt studiet et dosis-responsforhold.

Studie II undersøgte risikoen for nyopstået steroid-induceret diabetes mellitus hos patienter med non-Hodgkin lymfom behandlet med steroidholdig immunkemoterapi sammenlignet med en matchet baggrundspopulation og fandt ingen signifikant øget risiko. Patienter med eksisterende diabetes mellitus, som blev behandlet med steroidholdig immunkemoterapi, havde dog en øget risiko for at få ordineret insulin for første gang sammenlignet med matchede individer med diabetes mellitus.

Studie III fandt en øget risiko for anden primær malignitet hos patienter med aggressivt lymfom behandlet med højdosisterapi med autolog stamcelletransplantation (HDT-ASCT) sammenlignet med henholdsvis en matchet baggrundspopulation og patienter behandlet uden HDT-ASCT. Den øgede risiko var drevet af en øget risiko for ikke-melanom hudkræft og myelodysplastisk syndrom/akut myeloid leukæmi, men ikke af solide tumorer.

Studie IV fandt en øget risiko for henholdsvis hjertesvigt og andre kardiovaskulære sygdomme hos patienter med aggressivt lymfom behandlet med HDT-ASCT sammenlignet med henholdsvis en matchet baggrundspopulation og patienter

behandlet uden HDT-ASCT. Risikoen var vedvarende i mere end 10 år efter behandlingsstart.

De inkluderede studier bidrager med vigtig viden til den eksisterende litteratur om sene toksiciteter, som kan hjælpe klinikere med optimale behandlingsvalg, screening for bivirkninger samt hjælpe patienterne med at træffe informerede beslutninger.

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Table 1. Incidence rates of SPMs per 1000 person years and IRRs.

ABBREVIATIONS

ABVD	Adriamycin, bleomycin, vinblastine, dacarbazine
AML	Acute myeloid leukemia
ASCT	Autologous stem cell transplantation
ATC	Anatomical Therapeutic Chemical Classification System
Axi-cel	Axicabtagene ciloleucel
(E)-BEACOPP	(Escalated) Bleomycin, etoposide, adriamycin, cyclophosphamide, vincristine, procarbazine, prednisone
BEAM	Carmustine, etoposide, cytarabine, melphalan
BV	Brentuximab vedotin
CAR-T	Chimeric antigen receptor T cell
CD	Cluster of differentiation
CHF	Congestive heart failure
CHOEP	Cyclophosphamide, doxorubicin, vincristine, etoposide, prednisone
CHOP	Cyclophosphamide, doxorubicin, vincristine, prednisone
CI	Confidence interval
CNS	Central nervous system
CoxPH	Cox proportional hazards
CPR	Civil personal register
CVD	Cardiovascular disease
CVP	Cyclophosphamide, vincristine, prednisone
DA-EPOCH-R	Dose-adjusted etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin, and rituximab
DAG	Directed acyclic graph
DLBCL	Diffuse large B-cell lymphoma
DM	Diabetes mellitus
DNPR	The Danish National Patient Register
DST	Statistics Denmark
FIG	Figure
FL	Follicular lymphoma

G-CSF	Granulocyte colony-stimulating factor
GHSG	German Hodgkin Study Group
HDT	High-dose therapy
HF	Heart failure
HL	Hodgkin's lymphoma
HR	Hazard ratio
ICD	International Classification of Diseases
ICD-O	International Classification of Diseases for Oncology
INRT	Involved-node radiotherapy
IPI	International prognostic index
IR	Incidence rate
IRR	Incidence rate ratio
LVEF	Left ventricular ejection fraction
LYFO	The Danish Lymphoma Registry
MCL	Mantle cell lymphoma
MDS	Myelodysplastic syndrome
MOPP	Mechlorethamine, vincristine, procarbazine, and prednisone
NHL	Non-Hodgkin lymphoma
OS	Overall survival
PET	Positron emission tomography
PFS	Progression-free survival
PTCL	Peripheral T-cell lymphoma
R	Rituximab
RCT	Randomized controlled trial
R-DHAP	Rituximab, dexamethasone, cytarabine, and cisplatin
R-ICE	Rituximab, ifosfamide, etoposide, and carboplatin
RWD	Real-world data
SEER	Surveillance, Epidemiology, and End Results
SI-DM	Steroid-induced diabetes mellitus
SPM	Second primary malignancy

CHAPTER 1. INTRODUCTION

1.1 LYMPHOMAS

Lymphomas are a heterogenous group of cancers originating in the lymphatic system. Like other cancers, lymphomas involve uncontrolled and abnormal growth and division of cells, which in the case of lymphomas involve white blood cells known as lymphocytes. Lymphomas can present in any part of the lymphatic system, including lymph nodes in all areas of the body, as well as at extranodal sites, such as the spleen or bone marrow. The location of the lymphoma and the extent vary depending on the type and stage. Staging is similar across lymphoma subtypes and is generally based on tumor location and disseminated disease. Ann Arbor staging is the international staging system for lymphomas and is used in prognostic scores and treatment selection along with other variables (1). Common symptoms of lymphomas include enlarged lymph nodes, excessive night sweats, fever, fatigue, weight loss, and itching (2). Although the lymphoma subtypes share many characteristics, they differ in several ways, including age distribution, biology, risk factors, treatment options, and prognosis. In the last decades, treatment of lymphomas has evolved rapidly, enabling most patients with lymphoma to live longer. Although advancements in lymphoma treatment have focused on a better prognosis in terms of progression-free survival (PFS) and overall survival (OS), late effects, which may occur years to decades following initial treatment, have received less attention. In the first section of this dissertation, lymphomas relevant for this work are briefly described, with a focus on treatment and the development of treatment regimens over time, to explain the improved survival for patients with lymphomas. After an overview of the treatment regimens, a short section describes the prognosis and survival for patients with lymphoma in cohort studies. Finally, a section describes late toxicities that patients treated for lymphoma and with expected long-term survival may be at increased risk for experiencing.

Overall, lymphomas can be divided into two categories: Hodgkin lymphoma (HL) and non-Hodgkin lymphoma (NHL) (3,4).

1.1.1 HODGKIN LYMPHOMA

Hodgkin lymphomas constitute about 10% of lymphoma cases and are defined by the presence of Reed–Sternberg cells in the lymph nodes. In Denmark, about 160 individuals are diagnosed with HL each year (5). The age distribution of HL is bimodal, with an early peak in young adulthood (age 15–35) and a second peak at age >55 years (6). Today, OS is generally excellent, with a 5-year OS above 80% (7–9), but the prognosis can be more specific when stratifying patients into limited-stage disease (favorable and unfavorable) or advanced-stage disease (10).

Treatment for patients with HL is considered curative, except for the oldest and most frail patients, and treatment selection is based on disease stage and clinical judgment, incorporating risk factors for toxicities and the patient's fitness. In the two decades preceding 1992, MOPP (mechlorethamine, vincristine, procarbazine, and prednisone) was the standard multiagent chemotherapy regimen for HL. Its primacy was challenged by a new four-drug combination, ABVD (doxorubicin, bleomycin, vinblastine, and dacarbazine), developed by the Milan Cancer Institute for second-line therapy in 1975 (11). In 1992, a study in the *New England Journal of Medicine* compared ABVD to MOPP and MOPP alternating with ABVD among 361 patients with advanced-stage HL. The results established a superiority of ABVD in terms of 5-year failure-free survival (MOPP 50%, ABVD 61%) and 5-year OS (MOPP 66%, ABVD 73%), with a better safety profile (12). ABVD became the standard of care for first-line treatment of HL, but around the same time, 1991, BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone) was proposed by the German Hodgkin's Lymphoma Study Group (GHSG) as an intensified treatment alternative (13). An escalated version of BEACOPP (eBEACOPP) was also introduced, with increased doses of cyclophosphamide, etoposide, and doxorubicin. In the HD9 trial by the GHSG, ABVD/COPP was compared to BEACOPP and eBEACOPP for patients with advanced-stage HL. In a 10-year follow-up with a median follow-up of 111 months, the 10-year OS was 75% for ABVD/COPP, 80% for BEACOPP, and 85% for eBEACOPP (9). The favorable outcome in terms of survival and disease control

gained by treatment with eBEACOPP was, however, accompanied by severe acute and long-term toxicities. To mitigate toxicities, a positron emission tomography (PET)-guided treatment regimen was proposed to minimize the number of chemotherapy cycles needed to maintain disease control. The HD18 trial by the GHSG included 1964 patients with advanced-stage HL from 301 European sites. Patients were randomized according to their PET-2 result after two cycles of eBEACOPP. Those with a positive PET scan were randomized to either standard of care with an additional 6 X eBEACOPP or 6 X eBEACOPP combined with rituximab (R), a chimeric monoclonal antibody. Patients with a negative PET scan were randomized to either an additional 6 X eBEACOPP or 2 X BEACOPP. During the study period, the standard of care was reduced to six cycles and an amendment to the study was needed. All patients with a positive PET then received an additional 4 X eBEACOPP, and patients with negative PET were randomized to an additional 4 or 2 X eBEACOPP (14). The trial results showed that among patients with a positive PET, the 5-year PFS was 89.7% for eBEACOPP and 88.1% for R-eBEACOPP, suggesting no improvement with the addition of R. For patients with a negative PET, there was no inferiority between 4 X eBEACOPP vs 6/8 X eBEACOPP, with PFS values of 90.8% vs 92.2%, respectively. Furthermore, 4 X eBEACOPP was associated with fewer severe infections and organ toxicities (14). These findings influenced the Danish treatment guidelines for advanced-stage HL to include PET-guided eBEACOPP (15). In the ECHELON-1 randomized trial, efficacy was compared between ABVD and A+AVD (brentuximab vedotin, doxorubicin, vinblastine, and dacarbazine) in 1334 patients with advanced-stage HL, with a median follow-up of 60.9 months. For all patients, the 5-year PFS was superior with A+AVD (82.2% vs 75.3%) (16), leading to the inclusion of A+AVD as a treatment option for patients with advanced-stage (IV) HL in Denmark (15). At the American Society of Hematology Annual Meeting in 2022, researchers reported results for the randomized HD21 study that compared eBEACOPP to a remodeled eBEACOPP that also included brentuximab vedotin (BV), i.e., BrECADD (BV, etoposide, cyclophosphamide, doxorubicin, dacarbazine, dexamethasone) as first-line treatment, describing a significantly lower risk of treatment-related morbidities for BrECADD (17). The

BrECADD treatment regimen has not yet been implemented in Danish national guidelines but may be once the peer-reviewed study has been published.

For limited-stage disease, the Danish guidelines were based on an approach investigated in the H10 trial from 2017 by the European Organisation of Research and Treatment of Cancer. This randomized controlled trial (RCT) on limited-stage HL involved early PET after two cycles of ABVD followed by randomization either to ABVD with involved-node radiotherapy (INRT) regardless of the PET result or to the experimental arm where PET-negative patients received ABVD only and those who were PET positive received 2 X eBEACOPP and INRT (8). Among the 1925 patients with stages I and II HL who received PET, 18.8% had a positive PET. For these patients, early treatment adaption to eBEACOPP + INRT resulted in an increased 5-year PFS of 89.6% compared to 77.4% for standard ABVD + INRT (8). The experimental PET-negative arm with ABVD only was closed prematurely because interim futility analysis results showed that omission of radiotherapy led to an increased risk of early relapse (18).

The standard treatment regimen for younger and fit patients with relapsed or refractory HL in Denmark is high-dose therapy (HDT) with autologous stem cell transplant (ASCT), which is explained in further detail later. A novel treatment approach was suggested in the AETHERA trial, which randomized patients with relapsed or refractory HL to consolidation therapy with BV following HDT-ASCT or to placebo. Among 329 patients and with a median follow-up of 30 months, the median PFS was 42.9 months in the BV arm compared with 24.1 months in the placebo arm (19).

1.1.2 NON-HODGKIN LYMPHOMA

NHL constitutes around 90% of all lymphomas and consists of many different lymphoma subtypes. Subtypes can be divided into categories based on the type of lymphocyte giving rise to the lymphoma: B-cell NHL, T-cell NHL, and natural killer–cell NHL. The most common subtype is diffuse large B-cell lymphoma (DLBCL), which accounts for around 30% of all adult NHL cases (20). The NHL subtypes

included in this PhD thesis are briefly described below with an emphasis on DLBCL, as this subtype was included in all studies in this PhD work.

1.1.3 TREATMENT AND SURVIVAL FOR PATIENTS WITH DLBCL

The mean age at diagnosis for DLBCL is 65 years, and the 6-year OS with modern treatment is about 90% for a young patient with good prognosis, whereas the 3-year OS for elderly patients is around 55%–67% (21–23). The International Prognostic Index (IPI) is a clinical index score intended to risk-stratify patients according to risk factors. The risk factors are dichotomized for easy use in the clinic. Risk factors included in the IPI are age >60 years, stage III or IV disease, elevated serum lactate dehydrogenase, Eastern Cooperative Oncology Group performance status of 2, 3, or 4, and >1 extranodal site (24). It was developed in 1993 for NHL, and later a revised IPI was proposed as well as a relapsed/refractory IPI (25,26). The prognostic index scores are easy for clinicians to apply, as they can calculate the scores by hand using readily available dichotomized variables, but the dichotomization of variables comes at the cost of loss of information and less accurate estimates (27).

The most frequently used first-line immunochemotherapy regimen for DLBCL in the last two decades has been the combination of R, cyclophosphamide, hydroxydaunorubicin, oncovin, and prednisolone (R-CHOP). CHOP has been considered standard therapy for DLBCL since 1993, when a study compared CHOP with three other intensive chemotherapy regimens — m-BACOD, ProMACE-CytaBOM, and MACOP-B — for advanced-stage disease. The study, which was published in the *New England Journal of Medicine*, showed a similar efficacy among the treatments in terms of OS, but a lower risk of toxicity with CHOP (28). In 2002, a study by Coiffier et al. compared CHOP to R-CHOP for elderly patients with DLBCL and found an increase in complete response and OS without a clinically significant increase in toxicity (22). Since then, R-CHOP has been the standard first-line treatment regimen for patients with DLBCL, although this status has been challenged in recent years by (R)-CHOP combinations with obinutuzumab, lenalidomide, and ibrutinib (29–31). A modified CHOP regimen was developed by the National Cancer Institute that included etoposide as well as a prolonged infusion

time in an attempt to maximize dose intensity and lessen cardiac toxicity. In a phase III trial of DA-EPOCH-R (dose-adjusted etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin, and R) compared with R-CHOP, the former was found to be more toxic without improving tumor control or OS in general. However, for high-risk patients, there was a trend towards better outcomes for those treated with DA-EPOCH-R (32). Patients with high-risk DLBCL are at an increased risk of central nervous system (CNS) progression. In a Nordic phase II trial of high-risk DLBCL, treatment with dose-dense immunochemotherapy combined with systemic CNS prophylaxis was investigated to improve outcomes and minimize the risk of CNS events. A total of 139 patients were treated with two cycles of high-dose methotrexate combined with R-CHOP-14 followed by four cycles of R-CHOEP and one cycle of high-dose cytarabine combined with R. Additionally, liposomal cytarabine was given intrathecally at cycles 1, 3, and 5. Median follow-up was 5 years, and failure-free survival, OS, and CNS progression were 74%, 83%, and 2.3%, respectively (33). The CNS progression incidence was lower than expected based on historical data (34).

Patients who experience relapse are treated with salvage chemotherapy regimens followed by HDT-ASCT. The CORAL trial compared salvage regimens prior to HDT-ASCT for patients with relapsed DLBCL (35). The 396 included patients were randomized to R-ICE (R, ifosfamide, etoposide, and carboplatin) or R-DHAP (R, dexamethasone, cytarabine, and cisplatin) followed by HDT-ASCT. The researchers found no difference in response rate after salvage chemotherapy before transplantation (R-ICE 63.5%, R-DHAP 62.8%). Similarly, in Denmark, the salvage chemotherapies predominantly used are R-ICE or R-DHAP, and BEAM is used for conditioning prior to HDT-ASCT (36). As of October 2023, chimeric antigen receptor T-cell (CAR-T) treatment was approved for use in patients with DLBCL in second-line treatment who experience relapse within 12 months of first-line treatment or whose disease is refractory (37). This approval was based on the ZUMA-7 phase 3 trial comparing CAR-T to HDT-ASCT in second line for early high-risk DLBCL, showing a 2-year complete response of 65% after CAR-T compared to 32% for HDT-ASCT (38). Novel therapies, such as the bispecific CD3xCD20 antibodies

epcoritamab and glofitamab (39,40) and the CD79b antibody-drug conjugate polatuzumab (41), also have shown promising results in relapsed/refractory DLBCL in the third-line setting, with complete response rates of 38.9%, 39%, and 38.7%, respectively.

With a mean age at diagnosis of around 65 years for patients with DLBCL and OS being generally high, patients can expect a long life after treatment for DLBCL. This was further established in 2017, where Jakobsen et al. showed that patients with DLBCL had a minimal loss of lifetime after experiencing 2 years of PFS (42), as later confirmed by Maurer et al. (43).

1.1.4 FOLLICULAR LYMPHOMA

Follicular lymphoma (FL) is an indolent lymphoma and the second most frequent NHL subtype, accounting for 25% of all newly diagnosed NHL (44). Similar to the IPI, a specific prognostic score for FL has been proposed, called FLIPI (45). The mean age at diagnosis is 65 years, and 4-year OS is very high (around 80%) (46), although the disease is associated with a high relapse rate, especially within the first 2 years after first-line treatment (47). For patients with limited-stage disease, radiotherapy is the preferred treatment, but for selected patients with an optimistic prognosis, R monotherapy is an option with fewer side-effects. Furthermore, a “watch and wait” approach can be chosen, as treatment is not necessarily needed for a long period of time for this patient group (48). Standard first-line treatment regimens for advanced-stage FL are R-CVP, R-CHOP, or R-bendamustine (48). Relapses are considered inevitable, but remission can be prolonged by maintenance therapy with R, as shown in the PRIMA trial (44,49). A novel anti-CD20 antibody, obinutuzumab, has shown promising results in comparison to R-based immunochemotherapy and maintenance therapy. In the GALLIUM trial, 1202 patients were randomized to induction treatment with obinutuzumab-based or R-based chemotherapy followed by 2 years of maintenance therapy for those with a response. The estimated 3-year PFS was 80.0% with immunochemotherapy based on obinutuzumab vs 73.3% for R (50). However, there was no OS benefit with obinutuzumab.

1.1.5 PERIPHERAL T-CELL LYMPHOMA

Peripheral T-cell lymphoma (PTCL) accounts for around 15% of all cases of NHL. The standard first-line treatment regimens include treatment with CHOP or CHOEP, followed by consolidation with HDT-ASCT for transplant-eligible patients. The 5-year OS is around 50%–70% (51). A 2012 Danish single-arm trial of 166 patients with PTCL investigated the response from biweekly CHOEP treatment (for patients age >60 years, etoposide was omitted) followed by HDT-ASCT for those experiencing complete or partial remission. The median age of included patients was 57 years, and the 5-year OS and PFS were 51% and 44%, respectively (52).

1.1.6 MANTLE CELL LYMPHOMA

Mantle cell lymphoma (MCL) accounts for around 5%–7% of all lymphomas, and the median age at diagnosis is 60–70 years (53). As with the IPI and FLIPI, a MCL IPI has been proposed as a prognostic index score (54). Selected patients with no symptoms can be handled without treatment (watch and wait), but most patients receive alternating courses of maxi-CHOP and high-dose ara-C followed by HDT-ASCT, also known as the Nordic regimen (55). The Nordic regimen was established in the MCL2 trial involving 160 patients with MCL and conducted by the Nordic Lymphoma Group. In a 15-year follow-up of the MCL2 trial, with a median follow-up of 11.4 years, the median OS was 12.7 years and PFS was 8.5 years (56). Novel treatment combinations also are emerging for patients with MCL. A trial by the SHINE investigators published in the *New England Journal of Medicine* in 2022 randomly assigned elderly patients with untreated MCL to ibrutinib, a Bruton's tyrosine kinase inhibitor, or placebo in addition to six cycles of bendamustine and R. Maintenance with R was given to patients with a response. The study included 523 patients with a median follow-up of 84.7 months. Median PFS was 80.6 months for the ibrutinib arm and 52.9 months for the placebo arm, but OS was similar between the two arms (57). Results for another ibrutinib combination were presented at the American Society of Hematology's annual meeting in 2022, from the randomized TRIANGLE trial. In that trial, patients were randomized to first-line treatment with three cycles of R-CHOP/R-DHAP followed by HDT-ASCT without ibrutinib (arm

A), ibrutinib-R-CHOP/R-DHAP followed by ASCT and ibrutinib maintenance (A+I), or ibrutinib-R-CHOP/R-DHAP followed by ibrutinib maintenance (I). Failure-free survival rates were 72% in arm A compared to 85% in the I arm and 88% in the combined A+I/I arm, suggesting non-inferiority, but more follow-up is needed (58).

1.2 TREATMENT-RELATED TOXICITIES

As seen in the selected trials described above, treatment regimens have evolved in the last decades and even in the last years. As treatment evolves, the life expectancy of patients with lymphoma increases, and patients can expect to live long after treatment for most lymphomas. This longevity is also reflected by cohort studies based on real-world data (RWD) for patients who are not necessarily included in clinical trials. Patients with DLBCL can expect a minimal loss of lifetime compared to the background population when in remission and event free at 24 months after treatment. In the 8 years following this landmark, the average loss of lifetime was 0.31 months per year, with increased mortality largely explained by relapses (42). This pattern was further established in a study of 5853 patients with DLBCL, enrolled in clinical trials and treated with R and anthracycline-containing immunochemotherapy. Patients were followed from the time they were without progression for 24 months and compared with a sex- and age-matched population. The 7-year OS after this landmark was 80% for patients, compared with the expected 83.7% for the general population (43). Patients with FL treated in the R era have increased survival compared to previous years. In a Swedish cohort study of 2641 patients with FL, 5-year OS values were 68%, 74%, and 77% for the calendar years 2000–2002, 2003–2007, and 2008–2010, respectively. A Nordic cohort study of 2582 young patients with HL investigated OS during 2000–2013. The 5-year OS was 95%, and the 5-year loss of lifetime was 45 days compared with the background population and 13 days if patients survived for 2 years without relapse (7). OS for patients with MCL was investigated in a retrospective cohort study of 1029 younger (<65 years) patients from 25 US medical centers. Median OS was 11.5 years in the entire cohort (59). In a Danish cohort study based on RWD from registers and medical records, 239 patients with limited-stage nodal PTCL during 2000–2014 were identified in Denmark and Sweden to investigate survival outcomes. Patients were treated with CHOP(-like) therapy in 89% of cases, and of these, 16% received HDT-ASCT. Median age was 62 years, 5-year OS was 58%, and PFS was 53% (60). As the life expectancy for lymphomas is high and to varying degrees is near that of the background population, it is imperative to shift the

research focus from OS alone to an investigation and understanding of treatment-related late toxicities.

1.2.1 ANTHRACYCLINE-RELATED CARDIOTOXICITY

Anthracyclines, a class of drugs that includes hydroxydaunorubicin from the CHOP regimen, have been suspected since 1971 of being associated with cardiac toxicities (61). In 1973, Lefrak et al. found a dose-response relationship between cumulative doses of doxorubicin and congestive heart failure (CHF). A cumulative dose of anthracycline >550 mg/m^2 was associated with a 30% risk of CHF compared to treatment with a lower cumulative dose, which led to only a 0.3% risk (62). In the modern age of treatment with R-CHOP, a standard treatment regimen consists of six cycles, but previously up to eight cycles were frequently used. As the full dose of anthracycline is 50 mg/m^2 doxorubicin per cycle, the cumulative dose is 400 mg/m^2 (3,63). In 1998, a review, "Doxorubicin-induced Cardiomyopathy," was published in the *New England Journal of Medicine*, citing as risk factors older age, mediastinal radiotherapy, and previous cardiac disease (64). That report, along with other studies, may have led to cautions against using anthracyclines in the treatment of elderly patients, especially for older patients and those with previous CHF. Subsequently, in 2006, Grann et al. reported that older age, CHF, and other comorbidities were strongly associated with receiving treatment without the inclusion of doxorubicin (65). Similarly, Hershman et al. reported that patients with DLBCL and pre-existing cardiovascular disease (CVD) were less likely than patients with DLBCL and no CVD to be treated with anthracyclines (66). In a Danish cohort study from 2018 investigating treatment strategies in elderly patients with DLBCL, only 46% of patients ages 80–84 years, scheduled for full dosing, completed treatment without dose reductions (67). The study by Grann et al. suggested that mitigating the risk of cardiotoxicity in older patients by excluding anthracyclines may come at the cost of lower OS, as patients treated with anthracyclines had more than twice the OS compared to patients treated without anthracyclines. Some of these findings may, of course, have been influenced by confounding by indication, as patients selected for treatment with anthracyclines could have been more fit and had fewer comorbidities

compared with patients selected for anthracycline-free treatment (65). The study from Hershman et al., which was based on register data from the Surveillance, Epidemiology, and End Results (SEER) and Medicare databases, found only a 5% lower CHF-free survival rate at 8 years for patients treated with anthracyclines compared to patients who did not receive any chemotherapy. Again, this comparison may have been biased, as it is not normal practice for patients with DLBCL not to be treated for their lymphoma, and the choice of no treatment may arise from factors related to fitness, comorbidities, and pre-existing CVD. Besides the difficulty in finding the right reference population, other drugs in the R-CHOP regimen may be associated with cardiotoxicity to some degree. R, cyclophosphamide, and vincristine have all been linked to cardiotoxicity, although only in case reports (68–73).

The mechanism of anthracycline-induced cardiotoxicity is thought to involve formation of free radicals that cause oxidative stress, damaging cardiomyocytes and resulting in their death through apoptosis or necrosis. This form of cardiotoxicity is characterized as a type 1 toxicity because of the cardiomyocyte death rather than dysfunction, and thus is believed to be irreversible (74). However, in a 2015 study by Cardinale et al., patients treated with anthracyclines who developed a decline in left ventricular ejection fraction (LVEF) based on echocardiography, were treated with enalapril (40 patients) or enalapril + beta-blockers (186 patients). A total of 82% of treated patients recovered to some extent. A full recovery was noted in 11% of all patients who had experienced a decline in LVEF, while 71% partially recovered (75). In that study, cardiotoxicity was defined as a <50% decline in LVEF and a reduction in LVEF of >10 percentage points. Recovery was defined as an increase in LVEF of >5 percentage points and a LVEF of >50% without any symptoms of CHF or, as a single requirement, full recovery to baseline LVEF. A recently published randomized study compared prophylactic treatment with atorvastatin vs placebo to reduce risk for LVEF decline with treatment using anthracycline-containing chemotherapy regimens. Prophylactic treatment with atorvastatin reduced the risk of LVEF decline, but there was no statistically significant reduced risk of CHF (76).

As these studies suggest, treatment/prophylaxis may be possible, making early detection of CHF imperative so that treatment can be initiated. Additionally, it is important to know the risk factors associated with the development of anthracycline-induced CHF, both to select alternative treatments for patients at very high risk and to better identify patients who may need cardiac surveillance. A Danish cohort study from 2017 showed that previous CVD was a risk factor for the development of CVD after treatment with anthracycline-containing chemotherapy for NHL along with older age and male sex (77). Other risk factors include hypertension and mediastinal radiotherapy (78).

In this PhD work, an investigation of the association between treatment with anthracycline-containing immunochemotherapy and the risk of cardiotoxicity was conducted in a group of patients with lymphoma receiving R-CHOP, an anthracycline-containing immunochemotherapy, compared with patients treated with R-CVP, an immunochemotherapy regimen without anthracyclines. The hypothesis was that it would be possible to tease out the contribution of anthracyclines to the risk of cardiotoxicity, separate from the combination of having lymphoma and being treated with chemotherapy in general. Furthermore, a dose-response relationship was investigated (79).

1.2.2 STEROID-INDUCED DIABETES MELLITUS

A well-known complication of treatment with high-dose steroids is steroid-induced diabetes mellitus (SI-DM), as steroids can lead to an increased resistance to insulin in muscle, liver, and fat tissue and to a lesser extent, to increased gluconeogenesis by the liver (80–82). Prednisolone is a steroid that is included in commonly used standard first-line treatments for lymphoma such as R-CVP and R-CHOP because of its positive effect on chemotherapy-related nausea and fatigue and because of a limited cytotoxic effect against lymphocytes (83–87). Each treatment cycle contains 100 mg of prednisolone a day for 5 consecutive days, and treatment cycles are usually given 6–8 times every 14–21 days (3). SI-DM can be a temporary and a chronic disease. The insulin resistance caused by steroids is usually temporary and leads to hyperglycemia after 4–6 hours that lasts for more than 16 hours (88). For some

patients, hyperglycemia does not normalize after the end of treatment and is then referred to as SI-DM. It is, however, difficult to disentangle these situations, and the nomenclature is used interchangeably. Some have hypothesized that SI-DM is just an unmasking of an already pre-existing diabetes mellitus (DM). However, a study from 2012 compared clinical variables among patients with new-onset SI-DM, patients with type 2 DM receiving treatment with steroids, and patients with type 2 DM not receiving steroids. Patients were matched on gender, age, ethnicity, HbA1c, and duration of DM, and patients with new-onset SI-DM were significantly less likely to have a family history of DM and were less overweight. Furthermore, these patients had less retinopathy, suggesting that they had been less exposed to longer periods of hyperglycemia. Overall, the study suggested that the risk of SI-DM is not simply an unmasking of a pre-existing DM (89).

Although the association between steroid treatment and hyperglycemia is well-known (90–92), information about the risk of new-onset DM following treatment with steroid-containing immunochemotherapy has been sparsely studied. Knowledge of the risk of SI-DM has primarily been obtained from patients treated for longer consecutive periods of time rather than the very high-dose treatment that is given in pulse during lymphoma treatment. To our knowledge, no larger studies have investigated the risk of SI-DM. In 2014, Lee et al. published a retrospective study on 80 patients treated with CHOP, with the endpoint being DM (93). The definition of DM in that study was a random plasma-glucose level of 200 mg/dL or more. The researchers found that 32.5% of the patients developed DM following the treatment. Lamar et al. published a retrospective study in 2018 of 160 patients treated with R-CHOP(-like) treatment, with the outcome being a hyperglycemic episode during treatment. Among the included patients, 27% had pre-existing DM. The results showed that 47% of the treated patients had a hyperglycemic episode and that pre-existing DM was a major risk factor (hazard ratio [HR] 12.7) (94). Substantial evidence indicates that treatment with steroids exacerbates hyperglycemia for patients with pre-existing DM, and further evidence is needed regarding their treatment (80,92,95). The Joint British Diabetes Societies recommends treatment of steroid-

induced hyperglycemia for patients with pre-existing type 2 DM, with an increase in the dosage of gliclazide or metformin (if the patient is already receiving one of these drugs) or a temporary addition of treatment with insulin (80). Patients with both pre-existing DM and lymphoma may be at an increased risk of CVD because of the combined or even synergistic effect of the known associations between 1) DM and CVD (96), 2) treatment with anthracyclines and CVD (79), and 3) the effect of steroids on hyperglycemia, which is also associated with CVD (97).

For this PhD work, we investigated the risk of new-onset SI-DM for patients with NHL treated with steroid-containing immunochemotherapy compared with a matched background population. Furthermore, we assessed the risk of a first insulin prescription among patients with NHL and pre-existing type 2 DM treated with steroid-containing immunochemotherapy compared with a matched background population with pre-existing type 2 DM. Lastly, we investigated the risk of CVD for NHL patients with pre-existing type 2 DM treated with immunochemotherapy containing both anthracyclines and steroids compared with matched comparators who had pre-existing type 2 DM (98).

1.2.3 SECOND PRIMARY MALIGNANCIES FOLLOWING HIGH-DOSE TREATMENT AND AUTOLOGOUS STEM CELL TRANSPLANT

HDT is an intensive treatment regimen that, while effective against the lymphoma, is very toxic for the bone marrow (99). Therefore, HDT is followed by treatment with ASCT to regenerate the bone marrow from the patient's own stem cells. Patients undergo an induction treatment with chemotherapy along with a stem cell mobilization with granulocyte colony-stimulating factor (G-CSF) to prepare the stem cells for leukapheresis (100). The stem cells are then collected by leukapheresis and cryopreserved. As bone marrow cells are now stored externally, conditioning with HDT is given to eliminate lymphoma cells, which also results in severe bone marrow toxicity. For lymphoma patients in Denmark, the conditioning regimen used, according to national guidelines, is BEAM (carmustine, etoposide, cytarabine, and melphalan) (101). Finally, the cryopreserved bone marrow cells are transferred back via stem cell infusion to help restore bone marrow function (**Fig. 1**).

In 1995, a prospective randomized study compared HDT-ASCT to salvage chemotherapy in patients with relapsed chemotherapy-sensitive NHL. The study included 109 chemotherapy-sensitive patients treated between 1987 and 1994, who were randomized to treatment with 4 X chemotherapy + radiotherapy or radiotherapy + HDT-ASCT. Event-free survival was 46% in the HDT-ASCT group and 12% for conventional chemotherapy, and OS was 53% vs 32%, respectively (102). For HL, a randomized trial compared conventional chemotherapy, in the form of dexamethasone-BEAM, to HDT-ASCT. The study included 161 younger (<60 years) patients with HL. The 3-year freedom from treatment failure was higher with HDT-ASCT (55%) compared with conventional chemotherapy (34%), but no difference in OS was found (103).

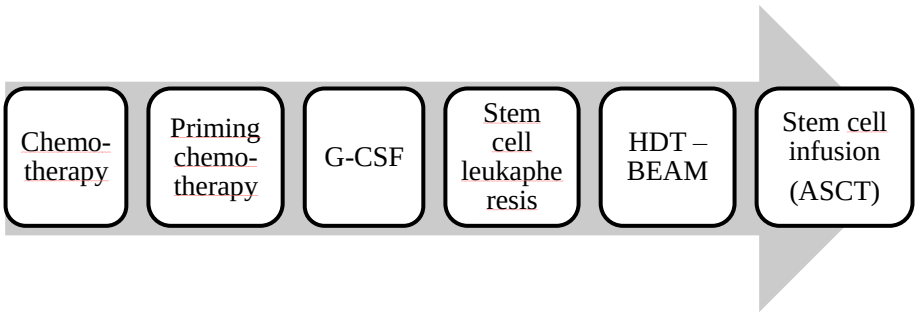

Figure 1. The stepwise order of treatments and leukapheresis for HDT-ASCT in patients with lymphoma.

Treatment with HDT-ASCT is used as first-line consolidation for patients with PTCL and MCL, and it is the standard of care for patients with DLBCL or HL with refractory or relapsed disease (3,52,103,104). In DLBCL, this approach has been replaced in selected patients by CAR-T in many countries. Direct comparisons between HDT-ASCT and CAR-T have been made, and treatment with CAR-T in second line seems to improve PFS and OS (38,105). In the Zuma-7 study, axicabtagene ciloleucel (axi-cel) was investigated as second-line therapy in 359 patients with early (<12 months) relapsed/refractory DLBCL. Patients were randomized to standard of care (2-3 cycles

of investigator-selected chemotherapy followed by HDT-ASCT) or axi-cel (38). In the latest update, median follow-up was 47.2 months and median PFS was 14.7 months in the axi-cel arm vs 3.7 months in the standard-of-care arm (106). Although the response to CAR-T is superior compared with HDT-ASCT, CAR-T is more expensive, and the logistics involved in developing the T cells are complex and time-consuming. The administration of CAR-T therapy introduces novel challenges, including the emergence of adverse events such as cytokine release syndrome and neurologic toxicities, necessitating a learning curve to refine their effective management. HDT-ASCT is still relevant for late relapses (>12 months), and the long-term complications of CAR-T are unknown and have yet to be compared to those of HDT-ASCT.

Many patients with lymphoma become long-term survivors following treatment with HDT-ASCT and CAR-T, and thus live long enough to experience late toxicities associated with the treatment. It is therefore imperative that the late toxicities of these treatment regimens are investigated to provide knowledge for selecting the right treatment on an individual basis.

Previous studies have shown an increased risk of second primary malignancies (SPMs) following treatment with HDT-ASCT for patients with lymphoma compared to expected rates in the background population (107–109). However, first-line treatments received before HDT-ASCT also are associated with SPMs, and the isolated contribution of HDT-ASCT to the risk of SPM has not been established. Furthermore, current studies lack long follow-up and complete registers and often have been based on expected risks from lifetime tables, which does not allow for adjustment of confounders such as education level or comorbidities associated with both the treatment decision and the risk of SPM. The importance of investigating SPMs has been established from previous studies reporting SPMs to be major causes of non-relapse mortality (110,111).

In this PhD research, we compared the rates of SPMs for patients with lymphoma treated with HDT-ASCT to the risk in a matched background population while

accounting for confounders. Furthermore, we investigated cause-specific cumulative incidences of SPM in patients and comparators in a real-world setting with death before SPM as a competing event to determine the size of the impact. For patients with lymphoma treated with HDT-ASCT, risk factors for SPM were determined from clinical and lifestyle-associated variables. Lastly, we aimed to estimate the isolated added effect of HDT-ASCT on the risk of SPM among patients with lymphoma treated with HDT-ASCT compared to patients treated without HDT (112).

1.2.4 CARDIOVASCULAR DISEASES FOLLOWING HIGH-DOSE TREATMENT AND AUTOLOGOUS STEM CELL TRANSPLANT

As noted above, accruing more information regarding late toxicities of treatment with HDT-ASCT is imperative, as new treatment regimens are emerging and comparisons of toxicities are important in the optimal treatment selection for patients.

Patients with lymphoma treated with anthracyclines have an increased risk of CVD, particularly so for CHF, compared to patients treated without anthracyclines, as shown by Study I (79), and the background population (113–116), respectively. Although the association between anthracyclines and CVD has been intensively investigated, the association between HDT-ASCT and CVD is less explored. Clinical trials establishing the use of HDT-ASCT have not investigated the risk of CVD, and because of the limited follow-up of 2.3–4.4 years in these studies, the true risk of CVD would likely not be possible to establish in this setting (103,117–119). Only a few studies have investigated the association between HDT-ASCT and CVD. In Norway, 274 patients treated with HDT-ASCT were screened using echocardiography at a median of 12 years after treatment. That cross-sectional study found a 16% prevalence of left ventricular dysfunction (115). Armenian et al. performed a nested case-control study to investigate risk factors for CHF among patients treated with HDT-ASCT and found that treatment with anthracyclines prior to HDT-ASCT was a risk factor (120). Studies investigating causes of death among patients with lymphoma treated with HDT-ASCT have found CVD to be a major cause of death (110,111).

In this PhD research, patients with lymphoma treated with HDT-ASCT were compared with matched comparators to assess the rates of CVD following HDT-ASCT while controlling for confounders. The extent of the association was investigated in a real-world setting with death before CVD as a competing event. Because conventional chemotherapy, especially with anthracyclines, is associated with CVD, we also investigated the added effect of HDT-ASCT vs conventional chemotherapy on the risk of CVD (121).

1.3 REAL-WORLD DATA

RWD is defined by the US Food and Drug Administration as "*data relating to patient health status and/or the delivery of health care routinely collected from a variety of sources*" (122). Examples of RWD are data from electronic health records, nationwide registers, disease-specific registers, and collected by new technology such as wearable health devices. RWD sources can be defined as either opportunistically collected data or purposefully collected data (123). An example of a widely used opportunistically collected dataset is the SEER-Medicare–linked database that combines two pre-existing administrative data sources (124). An example of purposefully collected data is the Danish Lymphoma Registry, which contains continuously collected clinical information on all patients with lymphoma in Denmark (125). The quality of RWD depends on the completeness and accuracy of the primary data sources, which may be either unknown or estimated from validation studies comparing administratively collected data (such as billing information) to electronic health records. Furthermore, a thorough data cleaning is needed to check for logical inconsistencies in the data that could be corrected or used to evaluate data quality.

RWD is a complementary source of data to findings from clinical trials. Among the main strengths of RWD is the ability to investigate rare diseases and events. Such events can include data on rare lymphoma subtypes treated with certain regimens and late toxicities that may occur decades after initial treatment, which are not investigated in the short follow-up in clinical trials. The use of RWD also allows for a wider generalizability, as it is often possible to include larger cohorts and longer follow-up. Clinical trials might be biased by inclusion of fit patients compared to how patients present in the real world. Using detailed and complete RWD allows for inclusion of all patients within specific criteria, not just those who are most fit, and makes it possible to compare to the background population. RCTs are still the gold standard for medical research because the randomization removes any confounding between the investigated groups (126); however, RCTs often are limited by shorter follow-up, which makes it difficult to investigate any late effects associated with a given exposure. As an example, the phase 2 trial investigating the efficacy and safety of

glofitamab for relapse/refractory DLBCL, which led to the approval for its use in Denmark, had a median follow-up of only 12.6 months (39). The phase 3 trial comparing obinutuzumab to rituximab in a first-line setting for DLBCL reported 29 months of median follow-up (29). In comparison, our cohort study on the risk of diabetes had a median follow-up of 8.5 years (98), our study investigating second primary malignancies had a median 7.8 years of follow-up (112), and our investigation of CVD after HDT-ASCT had a median follow-up of 7.6 years (121). In the last case, the risk of CVD was increased through the whole follow-up period, suggesting that a study with limited follow-up would fail to report the true incidence of CVD. For second primary malignancies, a biological lag of time between exposure and outcome prevents studies with short follow-up from detecting any differences in outcomes, even though the true difference could be significant later. Furthermore, rare events are, of course, more likely to be identified during a longer follow-up period and in a larger cohort. The GOYA trial, a large phase 3 trial, included around 1500 patients, while large cohort studies can include many times more (29,98).

1.4 RATIONALE FOR RESEARCH

Survivors of lymphoma have a long life expectancy following both first- and second-line treatments, which entails increased risk of treatment-related late toxicities. These toxicities may affect both quality of life and morbidity and mortality of the patients, who are otherwise often considered cured. More information regarding the risks and risk factors are needed to enable better individualized treatment decisions, better and faster identification of developed toxicities, and ultimately better treatment outcomes for patients with lymphoma.

CHAPTER 2. AIMS

The aims of the studies included in this PhD thesis were to investigate the risks of treatment-related toxicities among patients with lymphoma and to establish risk factors for these individual toxicities. Four studies, all investigating late toxicities in different treatment settings and patient populations, were included in this thesis. The studies had the following primary aims:

Study I: To investigate the risk of cardiotoxicity following anthracycline-containing immunochemotherapy regimens for patients with diffuse large B-cell lymphoma and follicular lymphoma

Study II: To investigate the risk of steroid-induced diabetes mellitus and worsening of pre-existing diabetes mellitus for patients with non-Hodgkin lymphoma treated with R-CHOP(-like) treatment regimens

Study III: To investigate the risk of second primary malignancies for patients with lymphoma treated with high-dose therapy and autologous stem cell transplant

Study IV: To investigate the risk of cardiotoxicity for patients with lymphoma treated with high-dose therapy and autologous stem cell transplant

CHAPTER 3. METHODS

3.1 THE DANISH CIVIL REGISTRATION NUMBER

In Denmark, all Danish citizens are given a unique 10-digit civil personal register (CPR) number at birth or immigration, which enables identification in the Danish Civil Registration System, which has been used since 1968 (127). The CPR number is used for all official identifications, such as in hospitals, at general practitioners, for vehicle registration, and to obtain passports. It also is used to collect data for the Danish registers, and because all Danish registers use the same CPR number for each individual, the nationwide registers can be combined at an individual level (127,128) (**Fig. 2)**. Individuals can be followed until death or emigration from Denmark, and registers are continuously updated. This practice allows for cohort studies with very little to no missing data and without unnecessary loss to follow-up. The registers used in this PhD thesis are described below.

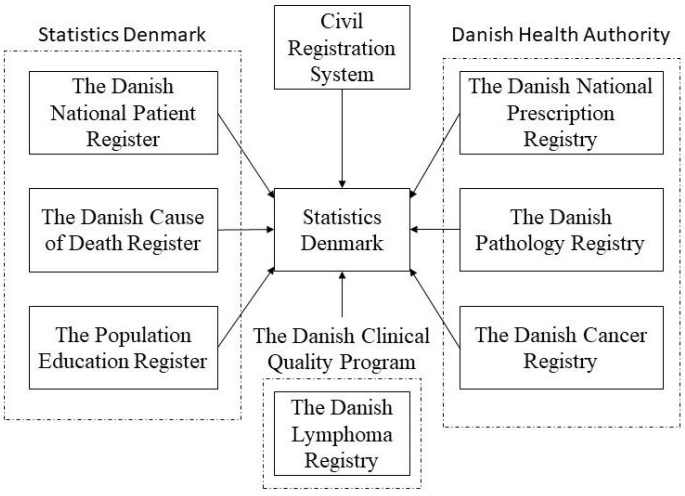

Figure 2. The combination of registers from different sources.

3.2 RESEARCH ENVIRONMENT AT STATISTICS DENMARK

The data management and analysis were performed on a server at Statistics Denmark (DST). During this PhD research, the Department of Hematology, Aalborg University Hospital, led the work of setting up a research environment with all the data needed for epidemiological research and making it available for all cancer researchers in the North Denmark Region. The work involved in setting up the DST server was part of this PhD work.

DST is a government institution responsible for creating informational statistical reports on Danish demographics. Besides doing statistical reports, DST collects data for and hosts several Danish nationwide registers and provides a safe electronic environment for conducting research (129). Data is uploaded to the server at DST, where the 10-digit personal identification number is pseudonymized from a CPR number to a PNR number to ensure that identification of single individuals is not directly possible. Data can be extracted only from the server in an aggregated form (such as tables and figures) by a user with administrative rights. Because of the strict rules at DST, only data cells containing ≥3 individuals can be extracted, as otherwise it would be possible to identify individuals. DST hosts more than 350 different national registers with data on the entire Danish population, living and dead. Registers from DST relevant for this PhD work are described in detail below.

3.3 REGISTERS

3.3.1 REGISTERS FROM STATISTICS DENMARK

The Danish National Patient Register (DNPR) is a nationwide register containing data relating to all hospital contacts. When it was established in 1977, the register included information only on somatic inpatients, but from 1995, data from outpatients, emergency rooms, and psychiatric wards also were collected. Notably, information on contacts with the primary sector is not obtained. The data collected in the DNPR includes both administrative and clinical data. The administrative data relates to the CPR number, the in and out dates from the hospital, hospital and hospital ward identification, and municipality. The clinical data consist of diagnosis codes and procedure codes. The diagnosis codes used to identify the main diagnosis of the hospital contact are the International Classification of Diseases (ICD) ^{10}th Revision (ICD-10) codes. Before 1995, ICD 8th (ICD-8) revision codes were used. For each hospital contact, one main diagnosis and one optional secondary diagnosis are registered. Procedure codes in the register are classified with Health Care Classification (SKS) codes and include information on procedures such as surgical procedures, treatments (including chemotherapy), and radiotherapy. The DNPR is considered to be the most comprehensive register of this kind (130,131).

The Danish Cause of Death Register has collected data on all causes of death since 1970, but registration of death certificates has been mandatory by law since 1871 (132). The causes of death were not used in this PhD work, but the dates of death were used throughout the included studies. The dates of death are also integrated into the Danish civil registration system, so the Danish Cause of Death Register was not cited in the methods sections of the individual papers.

The Population Education Register contains data on the highest completed education for 96.4% of individuals in Denmark ages 15–69. Education is identified with International Standard Classification of Education codes (133). In the included studies, the highest completed education level was identified at the time of inclusion

for all individuals and stratified into low or high, or low, medium, or high according to the length of the education.

3.3.2 REGISTERS FROM THE DANISH HEALTH DATA AUTHORITY

The Danish Health Data Authority is governed by the Ministry of Health and is responsible for collecting data for several registers on the health of the Danish population (134).

The Danish National Prescription Registry contains information on all dispensed prescription drugs since 1994. The information on the dispensed drugs is available on an individual level and is classified according to Anatomical Therapeutic Chemical Classification System (ATC) codes. For every drug, a dispensing date is available. Over-the-counter drugs sold without a prescription and in-hospital drugs are not recorded (135).

The Danish Pathology Registry contains data on pathology diagnoses from all departments of pathology in Denmark since 1990. In 1997, it became mandatory by law to report pathology data, the reporting of pathology was streamlined to be similar, and the Danish Pathology Registry was established. The pathology diagnoses are classified using a Danish version of the Systematized Nomenclature of Medicine (136).

The Danish Cancer Registry is a research register collecting data on all new cancers in Denmark. It was established in 1942, and reporting to the register has been mandatory by law since 1987. Data includes diagnoses from ICD-10 codes, date of diagnosis, stage (tumor, node, metastasis classification), topography, morphology, and more. Morphology and topography codes are classified with the ICD for Oncology (ICD-O) 3rd edition. The register is linked to the Danish Pathology Registry to automatically allow acquisition of information on histology (137).

3.3.3 REGISTERS FROM THE DANISH CLINICAL QUALITY PROGRAM

The Danish Clinical Quality Program is responsible for the infrastructure of the Danish clinical quality registers and administers 85 clinical quality registers. Information in the registers is a mix of re-used available data and data collected prospectively by clinicians (138).

The Danish Lymphoma Registry (LYFO) is a clinical quality register containing clinical variables for all newly diagnosed lymphoma patients in Denmark since 2000. Information is collected prospectively by clinicians at all departments of hematology in Denmark at the time of diagnosis and at the time of an eventual relapse. The clinical variables include information on lymphoma diagnosis, treatment regimens, date of treatments, number of treatment cycles, immunochemotherapy, radiotherapy, relapse, performance status, stage, blood sample values, and outcomes. The coverage of LYFO for all lymphoma patients diagnosed during 2000–2011 was tested against the DNPR and the Danish Cancer Register using a capture–recapture method in 2016, and LYFO was found to cover 94.9% of all newly diagnosed patients with lymphoma. Random samples of 3% of LYFO data were selected to validate the quality of the variables by comparing them to medical records, the DNPR, and laboratory data. The completeness of variables was 92%–100%, and the positive predictive value was 87% to 100% for all variables (125). The study populations for all studies included in this PhD work were identified in LYFO.

3.3.4 COMBINATION OF REGISTERS TO IDENTIFY EVENTS

The events investigated in the four studies included in this PhD work were identified in the described registers by either one or more registers. A combination of registers is sometimes needed, as the individual registers may not capture all events. One such example, taken from Study II, is in the definition of DM as an event. Type 2 DM is often diagnosed and treated by general practitioners and may not necessarily need diagnostic workup or treatment in a hospital setting. Subsequently, the diagnosis of DM in the DNPR is not complete. The positive predictive value may be high, but the negative predictive value would be low. To rectify this situation, the events of DM in

the DNPR were combined with information from the Danish National Prescription Registry. This combination enabled identification of DM events from ICD-10 codes registered with hospital visits and from any redeemed prescriptions of antidiabetic medications, thus catching events of DM treated outside a hospital setting (98). In the National Diabetes Register, which was not accessible for this study, similar methods were used, but even more extensively. In the register, DM was identified as in our study, but with the addition of specific services from the National Health Service Register, i.e., chiropody for patients with DM, five blood glucose measurements a year, or two blood glucose measurements per year in 5 consecutive years (139). In a validation of the data using data samples from general practitioners, the register found 96% of true DM cases when including data from blood glucose measurements and 91% when not including them. Similarly, in Study IV, the identification of events of non-CHF CVD were defined by a combination of ICD-10 codes and SKS codes (121). The event definitions will be described for each study in their respective methods sections.

3.4 GENERAL METHODS

The four papers included in this PhD thesis relied on some similar methods. The methods shared among papers are described generally in this section and expanded upon, when necessary, in a section for each paper.

3.4.1 RETROSPECTIVE COHORT STUDIES

The studies included in this PhD work were all retrospective cohort studies. A cohort study is observational, and study populations are defined by their exposure status at inclusion (exposed/not exposed), and the pre-defined outcomes are unknown at the time of inclusion but should be able to develop in the time frame from inclusion to time of analyses (**Fig. 3**) (140). The included studies were retrospective but were based on prospectively collected data.

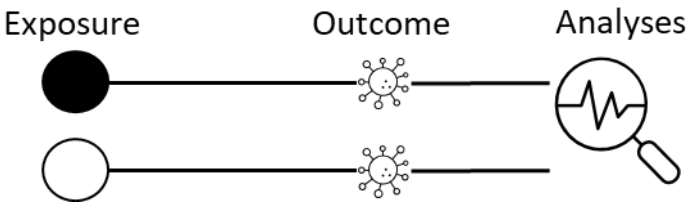

Figure 3. Timeline of retrospective cohort studies.

3.4.2 MATCHING

Matching is used to create a comparison cohort that is equally distributed across selected parameters compared with the patient cohort. The selected matching criteria are chosen by their status as confounders in the association between exposure and outcome. It is possible to adjust for confounders at a later stage, but matching is a more efficient method to adjust for confounders, as explained later in the methods section.

In our studies, comparators were matched on exact birth year and sex of the index patient, but additional criteria were applied in some of the studies. Three of the four included studies were matched cohort studies. Patients were included based on

different inclusion criteria in the studies, but all patients had newly diagnosed lymphoma. Patients (index patients) were then matched to comparators from the Danish background population (matched comparators) in a ratio of one to five (141). Matched comparators had to be alive and living in Denmark, and similar exclusion criteria were applied for matched comparators as for index patients at the time of inclusion.

The choice of a sampling ratio of 5 was based on the observation of Heide-Jørgensen et al. that statistical power gain is questionable when exceeding a sampling ratio of 4. More may be needed if several subgroup analyses are performed or if the event of interest is very rare (141). Sampling matched comparators was done without replacement, as the cohort of possible comparators was very large (everyone in Denmark), and we estimated that doing so would not introduce immortal time bias from too few possible comparators (141). Another approach to comparing patients with lymphoma to a general population would be to implement relative survival analyses based on population-based tables (142), such as population mortality files (143). However, matching from the general population provides the option of controlling for additional confounders that are not available in population-based tables; for example, the Charlson comorbidity index score. Matching also allows for finer stratification (population files are often stratified in 5-year intervals), and very few countries have complete population tables on events other that mortality.

3.5 THOUGHTS ON THE CHOICE OF METHODS

Many options are available when conducting epidemiological research. The several study designs have different strengths and limitations, and statistical methods offer even more options. Choices must be made according to the data available and the assumptions that are needed for an analysis to be valid. In this section, I describe some of the thoughts that went into choosing the statistical methods for the included studies.

The main research question in the included studies was whether a specific treatment was related to the toxicity under evaluation. Of many options available, two of the main ways to address this question are associated with how competing events are handled. The first method is to consider the question in a hypothetical world, where it is not possible to experience competing events, i.e., addressing whether there is an association between the treatment and the toxicity where differences in competing events are censored. In the included studies, this question was answered using a Cox proportional hazards (CoxPH) model adjusted for relevant confounding. The CoxPH model yields HR values that are representative of the instantaneous risk of experiencing the outcome at a given time, given that the event has not yet occurred (144). The CoxPH model does not incorporate information about competing events but rather includes them as a censoring, and the HR resulting from this approach can be thought of as an estimate of the hazard of an event in a hypothetical world, where there are no competing events. The CoxPH model estimates this value on an individual level, rather than at a population level, by adjusting for chosen variables between the compared groups. With adjustment for age and sex, for example, the HR can be interpreted as the HR of an event between an exposed and unexposed individual of the same sex and age, thus removing differences in sex and gender from the association. This process yields a conditional estimate. Several assumptions are needed for a CoxPH model to be valid, the most fundamental of which is the proportional hazards assumption which assumes that the HR between the two compared groups remains constant over time. This assumption can be assessed visually by plotting Schoenfeld residuals or tested formally, but these are rarely reported (145). The proportional hazards assumption is often violated in studies where

an exposure–outcome is investigated, as the exposure most likely influences the HR at the time right after exposure more than during later follow-up. In the included studies, the proportional hazards assumption of the CoxPH models was tested visually using Schoenfeld residuals, and if the assumption was violated, another approach was taken or supplementary analyses were added (146). The alternative approach used in Study II was to estimate time-varying incidence rates and ratios using a spline-based Poisson regression as described by Carstensen (147). A spline is a piecewise-defined function that consists of polynomial segments joined together smoothly at specific points called knots. As the risk over time is essentially estimated for the interval between each pair of knots, this approach allows for flexibility of the baseline hazard and enables the detection of complex patterns and non-linear effects in the data. In Study IV, a flexible parametric model approach, which incorporates splines in the modeling, was chosen to show the time-varying HR along with the hazard from the Cox regression model (148).

The second method is to ask as a main research question whether there is an association in a real-life setting, where competing events may prevent the occurrence of the outcome. The latter is also a question of the extent of the association (if any) in a real-life setting. This question is best answered using a competing risk model such as the Aalen-Johansen estimator (149). This model incorporates the knowledge that competing events (such as death before an event) preclude occurrence of the event of interest. These analyses yield cause-specific cumulative incidences, a measurement of the crude probability of an event. Whereas the CoxPH model yields a relative estimate of the risk on a hazard scale, the Aalen-Johansen estimator yields an absolute risk in percentage. It is important to be aware that competing risk models do not account for (and thus do not remove) the impact of competing events, but rather incorporate the information into the estimate to provide an estimate of the risk in the real world, where competing events may happen. An example of a misinterpretation of this method was debated in 2014 when Grytli et al. reported that beta-blockers were associated with a 20% reduction in prostate-specific mortality and stated that the competing risk analysis had addressed the potential bias that patients had a higher risk of dying from competing causes compared to comparators (150). This claim was not accurate, as

was pointed out to them by colleagues from the London School of Hygiene and Tropical Medicine in a letter to the editor (151). Competing events (or absorbing events) are, as previously stated, events that preclude occurrence of events of interest. In an analysis of the risk of cancer, death before cancer would be a competing event. In all included studies, death before the event of interest was treated as a competing event. However, in Study I and Study II, relapse before the event of interest also was used as a competing event. Although the event of interest may happen after a relapse, the study questions were related to first-line treatments, and as a relapse often requires second-line treatment, the event of interest would be prevented from occurring from the first-line treatment alone. This choice was made for the first two papers, but I have since shifted away from considering relapse as a competing event, as the interpretation of the analyses could be considered as: “What is the risk of the event of interest given that you do not experience a relapse?” In the end, it all comes down to the research question and whether the assessed event is of limited interest after a relapse or is important in the patient trajectory, relapse or not.

3.6 CAUSALITY

In observational studies, correlation does not imply causation (152). An easy-to-understand example is represented in the following: “An increase in the number of ice creams sold correlates with the number of swimming accidents.” In this example, the two events are correlated, but a causal association is lacking because the number of ice creams sold does not directly influence the number of swimming accidents. It is more likely that good weather causes an increase in ice creams sold as well as an increase in people swimming, which then increases the risk of accidents. In this association, a confounder — a factor influencing both the exposure and the outcome in an association — leads to incorrect interpretations, as is the case in analyses when confounders are not considered (example, **Fig. 4**).

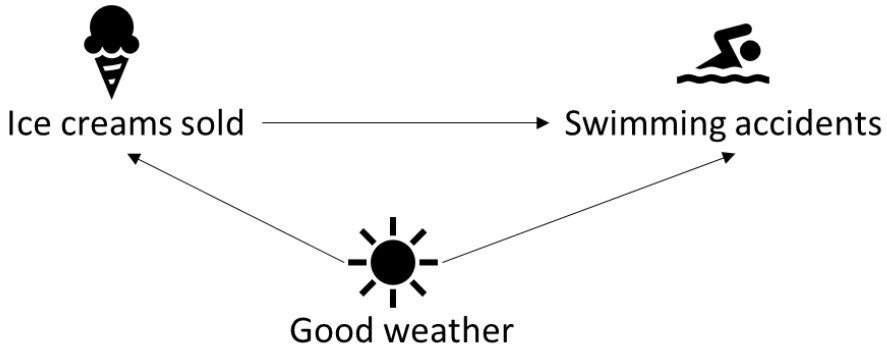

Figure 4. An example of confounding. Good weather influences both the number of ice creams sold and the number of swimming accidents, thus confounding the association between ice creams sold and swimming accidents.

Confounders are present in all observational studies and are identified before analysis of an association. Such identification is done by using subject-matter knowledge, reviewing current literature, and drawing a directed acyclic graph (DAG) that connects all relevant (observed and unobserved) variables to visualize where confounding may happen (153). An example of a simplistic DAG involving a

confounder is shown in **Figure 4**. Although a confounder is often described as a factor that influences the association between two other variables (as above), it is described as a backdoor path in the part of the causal inference framework known as graph theory. In graph theory, a DAG is drawn, and backdoor paths are noncausal paths between exposure and outcome, which do not involve variables causally affected by the exposure. To avoid bias introduced by confounding, all backdoor paths must be blocked by adjusting/controlling for them in an analysis. This is known as the backdoor criterion as defined by Pearl (154). When defining the DAG, it is also important to decide whether any of the variables are mediators of the effect from exposure to outcome, as controlling for a mediator would remove some of the true effect in the exposure–outcome association (155).

It is possible to completely avoid confounding by introducing randomization, as in RCTs. As all included individuals in RCTs are randomized between treatment arms, no factors influence the exposure (treatment), and therefore no confounding is possible. Statistical methods try to emulate this setting to attain causality. Examples are inverse probability of treatment weighting (156), propensity scoring (157), or standardization (158). The CoxPH model also estimates a causal association when a correct model is specified, and all confounders are controlled for using, as an example, inverse probability of treatment weighting. However, a multivariable CoxPH model does not yield a causally interpretable HR with adjustment only for confounders. Instead, the HR can be interpreted as a conditional estimate, as mentioned previously, which is a useful estimate in a clinical setting and recognized by most researchers and clinicians because of its popularity in medical research. Even if the model is specified correctly, the interpretation of the HR may still not be causal when reporting a single HR, as the true HR often changes during follow-up (which is a violation of the proportional hazards assumption). Therefore, the single HR depends on the duration of the follow-up (159). An example can be seen in **Figure 14** from Study IV (not yet presented), where the time-varying HR is plotted. In that study, the HR was highest right after treatment and declined during follow-up. Had the follow-up time in the study been shorter, the single HR would have been higher (121). The combination of

a cause-specific HR and cause-specific cumulative incidence is often used in medical research, as colleagues are familiar with these measurements and often expect them. As mentioned in the matching section of the methods, matching is also a way of controlling for confounding. It is possible to adjust for some confounding variables in the matching setup while leaving others to be adjusted for in the statistical analyses. This step may be feasible from a practical perspective, as the number of possible comparators becomes increasingly limited as the number of matching variables increases. When combining matching and adjusting additional variables, it is important also to adjust for the matching variables again in the statistical analyses, as shown by Sjölander et al. (160).

3.7 SOFTWARE

Data management was performed using SAS Software 9.4 (161), and all statistical analyses were conducted using R version 3.4.1 (162).

3.8 ETHICS

All studies were registered in the North Denmark Region where they were designed and conducted (Study I ID: 2008-58-0028, Study II ID: 3-3013- 2536/1, Study III ID: 2021-047, Study IV ID: 2021-150). Danish laws state that no ethical approval or written consent is needed for retrospective studies based on register data. Data was pseudonymized and analyzed on a closed server hosted by DST.

CHAPTER 4. METHODS, RESULTS, AND DISCUSSION OF INCLUDED STUDIES

4.1 STUDY I

Cumulative anthracycline exposure and risk of cardiotoxicity; a Danish nationwide cohort study of 2,440 lymphoma patients treated with or without anthracyclines (79)

4.1.1 METHODS

4.1.1.1 PATIENT INCLUSION

Patients included in this study were identified in LYFO according to the following inclusion criteria: 1) newly diagnosed DLBCL or FL in the period 2000–2012; 2) age ≥16 years at diagnosis; and 3) treatment with anthracycline-containing regimens for ≥3 cycles or with regimens not containing anthracyclines. Patients were not included if they had received <3 cycles of anthracycline-containing immunochemotherapy because cessation may have been the result of early treatment termination associated with severe adverse effects, which could confound the relationship between number of treatment lines and cardiotoxicity. Patients treated with regimens not containing anthracyclines were treated with regimens such as R-CVP and R-CEOP (cyclophosphamide, etoposide, vincristine, and prednisolone). The only exclusion criterion applied was any diagnosis of previous CVD before inclusion, as the aim of study was to investigate the risk of new-onset CVD.

4.1.1.2 EVENTS AND COMORBIDITIES

Events were identified in the DNPR using ICD-10 codes. The following ICD-10 codes for CVD were grouped to capture CVD events as one common entity: I48 (atrial fibrillation and flutter), I490 (ventricular fibrillation and flutter), I20-I25 (ischemic heart disease), and I50 (congestive heart failure). CHF also was a separate event and was identified using I50 (congestive heart failure).

Comorbidities that were considered confounders a priori were identified in the DNPR and registered only if they occurred within 5 years before the inclusion date. The following comorbidities were identified as confounders: K70-K77 (diseases of liver), F20-F39 (mental disorders), N00-N19 (diseases of kidney), I10-I82 (diseases of the circulatory system), J43-J44 (chronic obstructive pulmonary disease), I60-I69 (cerebrovascular disease), and E03-E05 (disorders of thyroid gland).

4.1.1.3 STATISTICS

Patient follow-up started at 30 days following the end of chemotherapy treatment to allow completion of the intended number of cycles while excluding patients developing CVD during or right after treatment. As the study aim was to explore a dose-response relationship between number of treatment cycles and risk of CVD, it was important to start follow-up after the end of treatment, to avoid conditioning on the future when using number of treatment cycles as a baseline variable. This measure also eliminated immortal time bias, which would have otherwise been introduced by starting follow-up at diagnosis or treatment initiation. Patients were followed until an event (CVD or CHF), censoring due to emigration from Denmark or end of study on 31 December 2014, or a competing event (relapse or death), whichever came first. The number of anthracycline-containing treatment cycles was stratified into 0, 3–6, 6, and >6 cycles to investigate a dose-response relationship. To investigate the association between treatment with anthracycline-containing regimens and cardiotoxicity, Cox regression analyses were performed. Univariable and multivariable Cox regressions were performed to investigate the crude HR for the associations between treatment and CVD and CHF, respectively. Risk factors for CVD and CHF were investigated using univariable Cox regression with the following variables of interest: sex, age, number of R-CHOP/CHOEP treatment cycles, World Health Organization performance status, radiotherapy, comorbidities, histology (FL or DLBCL), and cycle length (14 vs 21 days). In the multivariable Cox regression of CVD and CHF, the same variables, except for cycle length, were adjusted for. Cause-specific cumulative incidences were computed using the Aalen-Johansen estimator with death before CVD/CHF as a competing event. A sensitivity analysis, where

follow-up started at 90 days after the end of treatment, was conducted to test that the results were robust.

4.1.2 RESULTS

A total of 2440 patients with FL or DLBCL were included (1994 treated with anthracycline-containing immunochemotherapy and 446 treated without). In the anthracycline-treated cohort, 371 (18.6%) received 3–5 cycles of R-CHOP/CHOEP, 1032 patients (51.8%) received 6 cycles, and 591 (29.6%) received >6 cycles. There were 446 patients treated without anthracyclines. Median follow-up (time to event, death, or censoring) was 3.8 years for anthracycline-treated patients and 3.9 years for patients treated without anthracyclines (79).

Congestive heart failure

A total of 108 (5.4%) anthracycline-treated patients developed CHF during follow-up as compared to 3 (0.7%) patients treated without. There was a direct dose-response relationship between the number of anthracycline-containing treatment lines and the risk of CHF. Relative to patients treated without anthracyclines, the adjusted HRs for CHF were 5.0 (95% confidence interval [CI] 1.4;18.5) for patients treated with 3–5 cycles, 6.8 (2.0;23.3) for 6 cycles of treatment, and 13.4 (4.0;45.0) for >6 cycles. In a competing risk setting, patients treated with 3–5 cycles had an 8-year CHF risk of 5.2%, those treated with 6 cycles had a risk of 8.1%, and those treated with >6 cycles had a risk of 9.4%. Patients treated without anthracyclines had a risk of 1.6% (**Fig. 5**). Results were consistent in the sensitivity analysis starting at 90 days after the end of treatment (79).

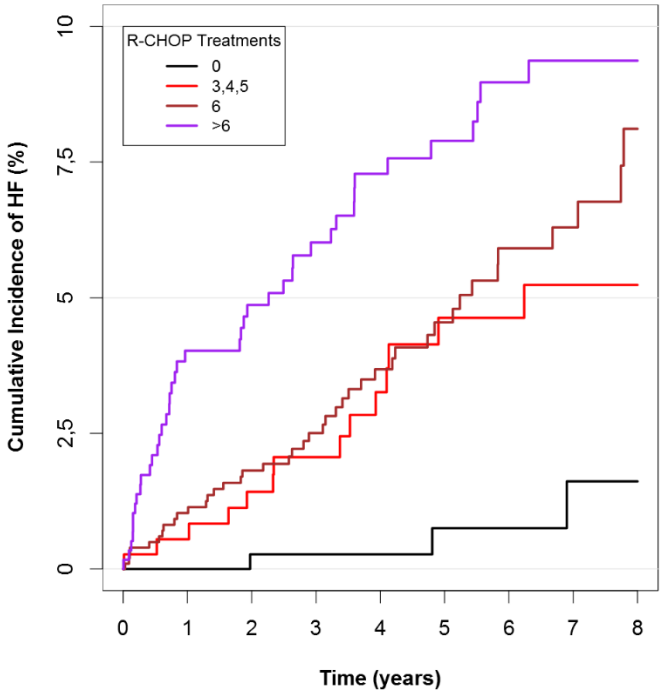

Figure 5. Cumulative incidence of congestive heart failure (HF) according to number of R-CHOP/CHOEP treatment cycles, with death before HF as the competing event (79).

Cardiovascular disease

A total of 243 (12.2%) anthracycline-treated patients developed CVD during follow-up as compared to 23 (5.2%) patients treated without. There was a direct dose-response relationship between the number of anthracycline-containing treatment lines and the risk of CVD. Compared to patients treated without anthracyclines, the adjusted HR for CVD was 2.0 (1.1;3.6) for patients treated with 3–5 cycles, 2.1 (1.2;3.5) for 6 cycles of treatment, and 3.2 (1.9;5.3) for >6 cycles. In a competing risk setting, patients treated with 3–5 cycles had an 8-year CVD risk of 17.2%, those treated with 6 cycles had a risk of 21.2%, and risk was 21.7% for patients treated with >6 cycles. Patients treated without anthracyclines had a risk of 7.8% (**Fig. 6**). Results

were consistent in the sensitivity analysis starting at 90 days after the end of treatment (79).

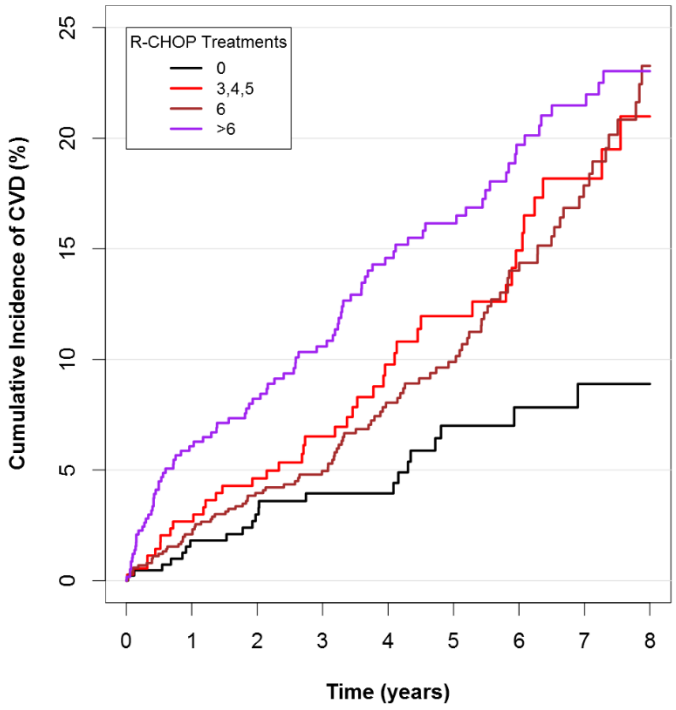

Figure 6. Cumulative incidence of cardiovascular disease (CVD) according to number of R-CHOP/CHOEP treatment cycles, with death before CVD as the competing event (79).

4.1.3 DISCUSSION

This is the first nationwide cohort study comparing patients treated with anthracycline-containing immunochemotherapy to patients treated without anthracyclines. The study established an increased risk of both CHF and CVD related to the inclusion of anthracyclines in treatment regimens for lymphoma. The increased risk was independent of immunotherapy, which all patients received during treatment. Furthermore, the study confirmed a dose-response relationship with increasing risk

for each increment in treatment cycles. Treatment with >6 cycles of anthracycline-containing therapy led to a 13.4 times higher risk of CHF and 3.2 times higher risk of CVD, respectively, compared to treatment without anthracyclines. The 8-year cumulative risks of CHF and CVD were respectively 9.4% and 17.2% for patients treated with anthracyclines compared to respectively 1.6% and 7.8% for patients treated without them (79).

The incidence of CVD and CHF may have been underestimated in this study, as only events registered at hospitals were identified, i.e., only symptomatic events requiring diagnostic work up, hospitalization, or treatment at a hospital. CVD treated only by general practitioners is not captured by the DNPR, but this would have affected patients equally and should not have led to any bias in relative estimates. The ICD-10 codes for CVDs were validated in a Danish study comparing admission ICD-10 codes to medical journals by random sampling (163). Generally, the positive predictive values were high (mean positive predictive value, 88%), but the positive predictive value of CHF was only 76% in the validation study. This difference may be explained by the greater inclusion of ICD-10 codes used in the validation study (I500, I501, I502, I503, I508, I509, I110, I130, I132, I420, I426, I427, I428, I429) rather than the specific code (I50) used in the present study. A low positive predictive value for CVD would have led to an underestimation of the cumulative incidence of CVD in the study, but the effect would have been equally large in both patient populations.

The cumulative incidence of events in the present study increased throughout follow-up, which is in contrast to a study by Cardinale et al. in Italy. They screened 2625 patients receiving anthracycline-containing chemotherapy for a variety of oncological diseases (28% NHL), using echocardiography to identify changes in LVEF. Cardiotoxicity was defined as a reduction in LVEF >10 percentage points from baseline and LVEF <50%. The study showed that in the 9% of patients who developed cardiotoxicity, 98% of the events occurred within the first year following treatment (75). This pattern suggests that changes in LVEF may arise within the first year, but according to the present study, they could become symptomatic after a much longer period. This latency is further indicated by the fact that the CHF in 81% of patients in

the Cardinale et al. study was New York Heart Association class I to II (75). The present study investigated only the risks of CVD/CHF for patients with no history of CVD. Inclusion of patients with prior CVD in our study could have led to an increased incidence of CVD, as seen in Salz et al. Using Danish registers, they found that comorbidities such as hypertension, dyslipidemia, and DM were associated with an increased risk of CHF for patients with NHL (77). Lastly, the true incidence and relative risk of CVD/CHF following anthracycline-containing therapy may have been underestimated because of dose-reductions in anthracyclines (164). LYFO does not contain information about doses or dose reductions, and thus full doses were assumed in the calculation of the cumulative doses from number of cycles.

Overall, the present study found that treatment with anthracyclines in an immunochemotherapy regimen led to an increased risk of both CVD and CHF, with a dose-response relationship. The RICOVER-60 trial found no superiority of treatment with eight cycles of R-CHOP compared to six cycles for elderly patients with aggressive CD20+ B-cell lymphomas, as also shown in observational data by Wästerlid et al. (165,166). In the present study, treatment with >6 cycles of R-CHOP led to an increase in CVD/CHF risks. Careful consideration and risk assessment for CVD/CHF should be applied when treating patients with anthracycline-containing immunochemotherapy, especially for more than the standard number of cycles.

4.2 STUDY II

Risk of diabetes and the impact on preexisting diabetes in patients with lymphoma treated with steroid-containing immunochemotherapy (98)

4.2.1 METHODS

4.2.1.1 PATIENT INCLUSION

Patients were identified in LYFO and included if they 1) had newly diagnosed NHL, 2) were treated with steroid-containing immunochemotherapy in first line in the period 2002–2015 for ≥3 cycles, and 3) were age ≥18 years. Three populations were included: 1) patients without pre-existing DM, 2) patients with pre-existing DM who never received any insulin treatment, and 3) patients with pre-existing DM treated with R-CHOP/CHOEP and with no history of CVD. Patients were matched on birth year, sex, Charlson comorbidity index score, and duration of DM.

4.2.1.2 EVENTS AND COMORBIDITIES

Three types of events were of interest in this study. The primary event was incident DM for patients without pre-existing DM, defined using ICD-10 codes for DM in the DNPR (insulin-dependent DM, non-insulin-dependent DM, and other DM; ICD-10 codes E10, E11, and E12-E14, respectively) or any antidiabetic treatment registered in the National Prescription Register (insulin or oral antidiabetic medicine; ATC codes A10A and A10B, respectively). For patients with pre-existing DM, incident insulin prescriptions were of interest and identified using ATC code A10A in the National Prescription Register. For patients with pre-existing DM treated with R-CHOP/CHOEP, CVD events were identified using the following ICD-10 codes in DNPR: I20-I25 (ischemic heart disease), I70 (atherosclerosis), I46 (cardiac arrest), I71 (aortic aneurysm and dissection), and I50 (congestive heart failure).

The following comorbidities were included if they were present >6 months prior to inclusion: cardiovascular diseases (I20 to I25, I46, I47, I48, I49.0, I50), liver disease (K70 to K77), renal disease (N00 to N19, N28.9, N08.3, I12), cerebrovascular

diseases (I60 to I69), circulatory diseases (I10 to I82), and chronic obstructive pulmonary disease (J43 to J44, J84).

4.2.1.3 STATISTICS

Patients were followed from initiation of first-line treatment until an event of interest (DM, insulin prescription, or CVD), death, relapse, NHL diagnosis (for matched comparators), or censoring (administrative censoring on 31 December 2018 or emigration from Denmark), whichever came first.

Cox regression models were used to compute crude and adjusted HRs. Adjustments were made for the comorbidities listed above, all deemed to be confounders. When the Cox proportional hazards assumption was violated, a spline-based Poisson regression approach was used, which yielded time-varying incidence rates (IRs) per 1000 person years and incidence rate ratios (IRRs) with 95% CIs. Follow-up time was split into 2-month intervals, and the time-varying rates were smoothed using natural cubic splines with five knots. The Aalen-Johansen estimator was used to compute cause-specific cumulative incidence of events with death, relapse, and NHL diagnosis (for comparators) as competing events. Risk differences were calculated using pseudo-observations (167), and Gray's test was applied to test for differences between groups.

Two sensitivity analyses were performed. To examine the cumulative incidence of insulin prescriptions after the first year, a landmark analysis was conducted on patients still alive one year after treatment. This analysis allowed insulin prescriptions from the original index date up to the one-year landmark analysis. To investigate the effect of surveillance bias on the risk of DM, another sensitivity analysis was conducted to compare NHL patients managed by watch-and-wait with NHL patients treated with steroid-containing immunochemotherapy.

4.2.2 RESULTS

A total of 5672 NHL patients and 28,360 comparators were included across all main analyses. Median age at baseline was 66 years, and median follow-up was 8.5 years

(reverse Kaplan–Meier method) (98). The CONSORT diagram of patients included in each main analysis is shown in **Fig. 7** (98).

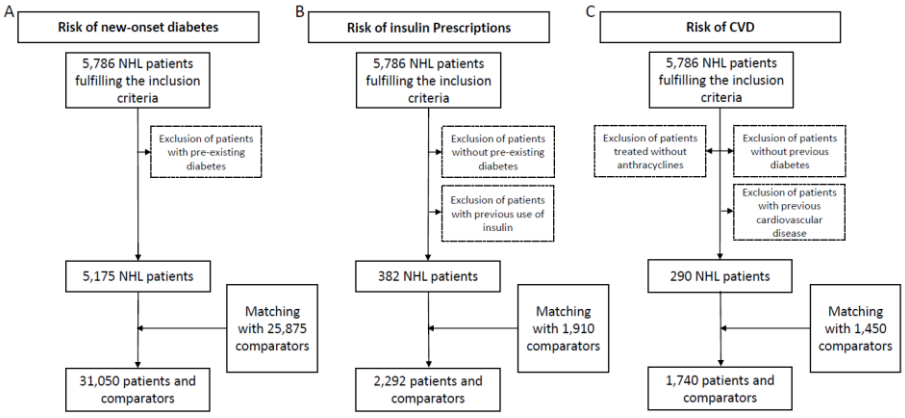

Figure 7. CONSORT diagram of included patients for each main analysis (98).

Diabetes mellitus

Patients had a higher IRR for DM compared with comparators in the first year following treatment (maximum IRR between 0 and 1 years: 2.68 [95% CI 1.91;3.77]), but a lower IRR from 1 to 4 years (minimum IRR, 0.58 [0.43;0.79]). There was no significant difference from 4 to 10 years (**Fig. 8**).

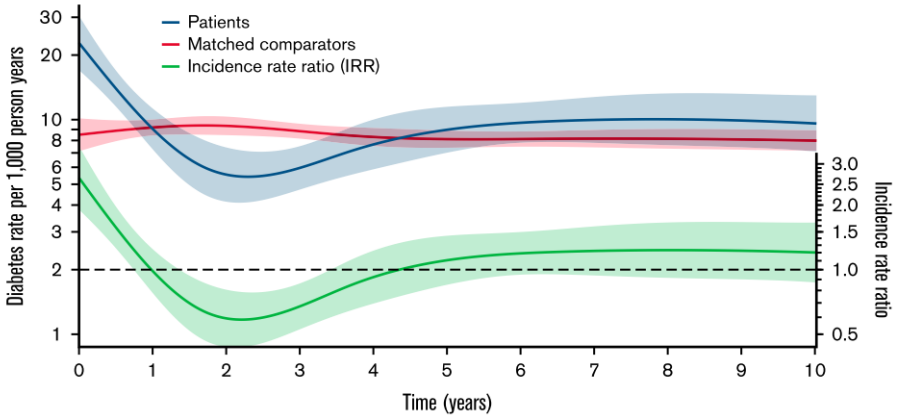

Figure 8. Time-varying incidence rates of new-onset diabetes mellitus per 1000 person-years for patients (blue) and matched comparators (red). Incidence rate ratio between patients and matched comparators (green) (98).

After 2.5 years, patients with NHL treated with steroid-containing immunochemotherapy had a higher risk of new-onset DM compared with matched comparators. The 10-year cumulative risk of developing DM for patients was 5.7% (5.0;6.4), and the cumulative incidence of DM was 1.6 percentage points higher for matched comparators ($p < 0.001$) (**Fig. 9**) (98).

In the sensitivity analysis comparing NHL patients treated with steroid-containing immunochemotherapy to those managed by watch-and-wait, the adjusted HR was 1.14 [0.86;1.51] (98).

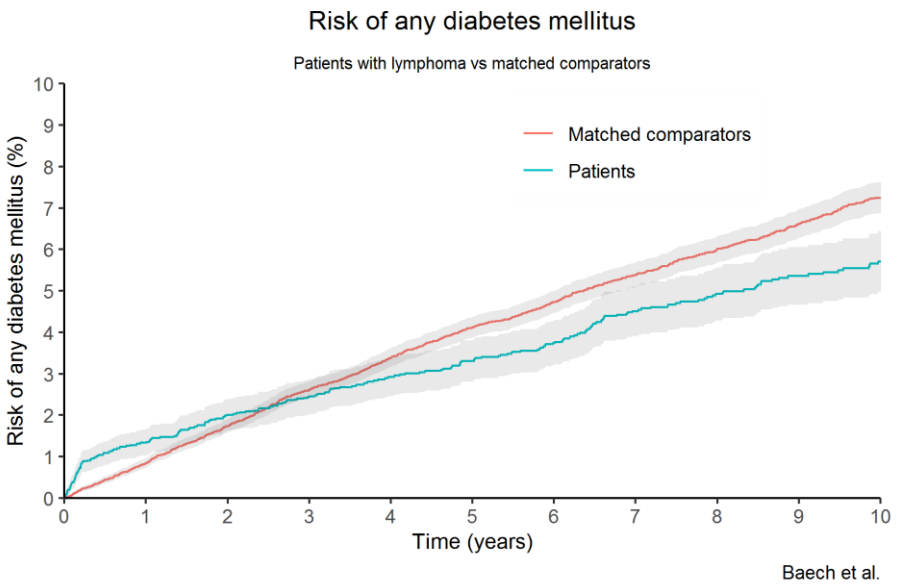

Figure 9. Cumulative incidence of diabetes mellitus for patients (blue) and matched comparators (red) with death, relapse, and NHL diagnosis (for matched compactors) before diabetes mellitus as the competing event (98).

Insulin prescriptions

NHL patients treated with steroid-containing immunochemotherapy had a 10-year cumulative risk of any insulin prescription of 36.1% (30.4;41.9). The cumulative incidence difference was 6.0 percentage points higher for patients than for comparators at 10 years (**Fig. 10**) (98).

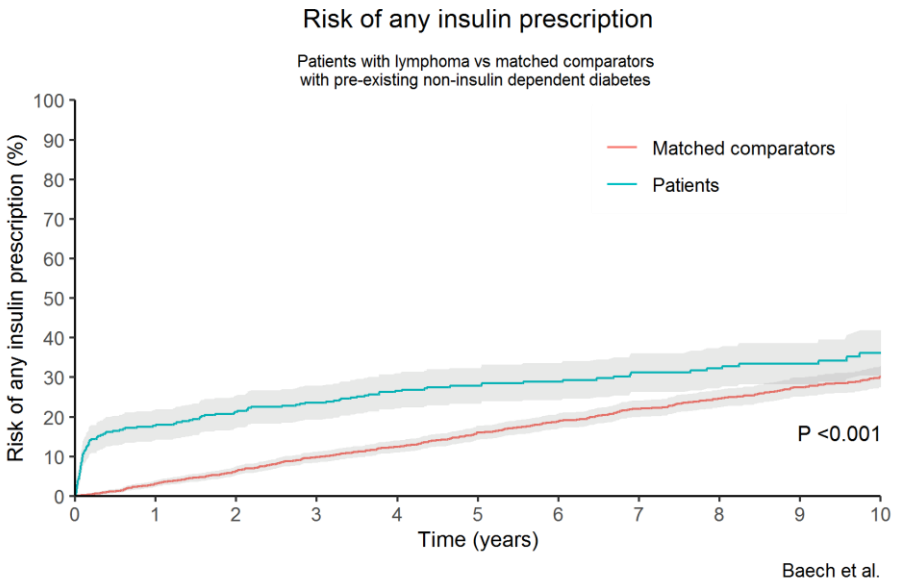

Figure 10. Cumulative incidence of a first insulin prescription for patients with pre-existing diabetes mellitus (blue) and matched comparators (red) with death, relapse, and NHL diagnosis (for matched compactors) before insulin prescription as the competing event (98).

Anthracycline-related cardiovascular complications

Patients had a higher IRR for CVD relative to comparators in the first year following treatment (maximum IRR between 0-1 years, 8.44 [4.77;14.93]), but lower IRR from 1 to 3 years (minimum IRR, 0.53 [0.29;0.97]). There was no significant difference from 3 to 10 years (**Fig. 11**) (98). NHL patients had 10-year cumulative risks of CVD of 29.4% (23.4;35.4), which was not statistically significant different from comparators (**Fig. 12**).

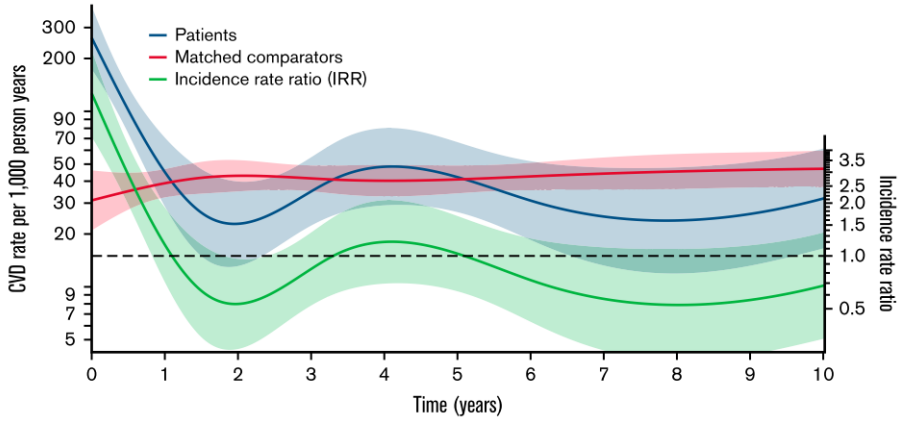

Figure 11. Time-varying incidence rates of new-onset cardiovascular diseases (CVD) per 1000 person-years for patients (blue) and matched comparators (red). Incidence rate ratio between patients and matched comparators (green) (98).

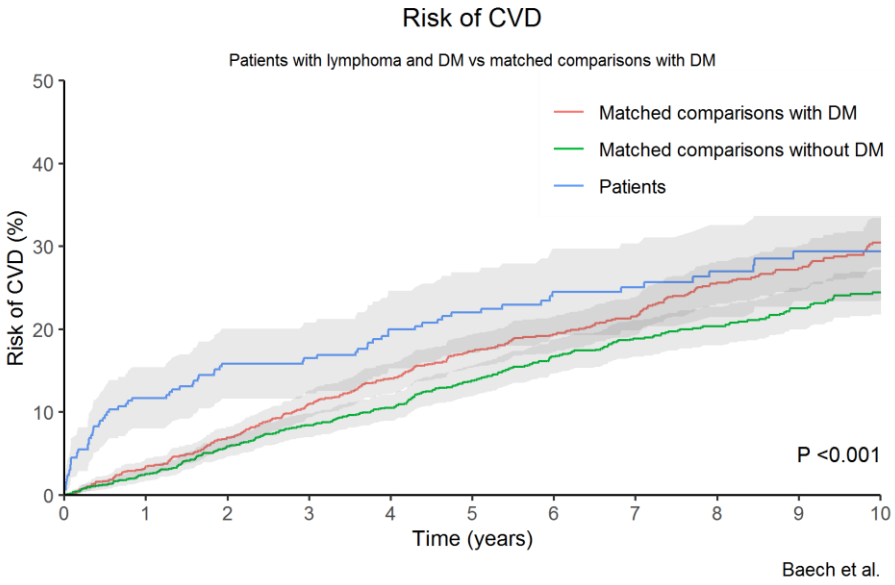

Figure 12. Cumulative incidence of new-onset cardiovascular diseases (CVD) for patients with pre-existing diabetes mellitus treated with anthracycline-containing immunochemotherapy (blue) and matched comparators (red) with death, relapse, and NHL diagnosis (for matched compactors) before CVD as the competing event (98).

4.2.3 DISCUSSION

In this study, there was no clinically relevant increased risk of DM for patients treated with steroid-containing immunochemotherapy when compared to matched comparators, although there was a small increased cumulative incidence in the first year. This lack of difference was further established by a comparison of steroid-treated patients to patients managed with watch-and-wait, which also showed no significant difference in DM risk between the groups, thus eliminating surveillance bias from the association. The results may underestimate the relative risk of DM because patients selected for R-CHOP–like treatment were most likely more fit and could have been living a healthier lifestyle compared with matched comparators, as the treatment is known to be cardiotoxic. The risk of this selection bias was reduced by including the Charlson comorbidity index score in the matching algorithm. Furthermore, it is possible that patients who had a perceived increased risk of DM (because of unhealthy lifestyle, obesity, etc.) may have been treated with reduced doses of prednisolone, which also would have led to underestimated relative risk associated with the treatment. In a competing risk setting, patients had a lower risk of DM after 3 years relative to comparators, but this difference most likely was driven by an increased risk of competing events for patients (i.e., patients dying before developing DM).

For the patients with NHL and pre-existing DM, treatment with steroid-containing immunochemotherapy led to an increased risk of redeeming an insulin prescription compared to matched comparators with DM. However, the increased risk was restricted to the first year following treatment, as shown in the one-year landmark analysis (98). An overestimation of the perceived risk of insulin use is possible, as patients with NHL also are at an increased risk of infections that may force use of insulin to control infection-related hyperglycemia rather than steroid-induced hyperglycemia. However, this is most likely an in-hospital scenario, and the prescriptions used to identify events of insulin use were redeemed only at pharmacies.

Patients with NHL and DM who were treated with R-CHOP–like treatment had an increased risk of CVD in the first year following treatment. DM is a risk factor with anthracycline-related CVD, as shown by Salz et al. (77), and as previously shown,

treatment with anthracyclines is associated with an increased risk of CVD (79). Steroid-induced hyperglycemia may worsen the effect of diabetes on the risk of CVD, and the increased risk of CVD in the first year corresponds with the increased need for insulin in the first year following treatment. The one-year cumulative incidence of CVD in this study was 11.7%, which was much higher than the cumulative risks of CVD in patients with DLBCL and FL treated with anthracyclines in Study I, whose DM status was not assessed (79).

To the best of our knowledge, this is the largest cohort study of SI-DM in a lymphoma setting and adds important, clinically relevant, knowledge to treatment with steroid-containing immunochemotherapy for different patient cohorts. Based on this study, there is not a high risk of SI-DM for patients treated with steroid-containing immunochemotherapy, but for patients with pre-existing diabetes, great care should be taken in monitoring and preventing hyperglycemia, that may result in increased risks of insulin use and CVD (98).

4.3 STUDY III

Second primary malignancies after high dose chemotherapy with autologous stem cell transplant for lymphoma: A Danish retrospective population-based cohort study (112)

Study III is a published paper that was a continuation of the work of a supervised student's master thesis. We shared first authorship of the paper and worked equally on it. There have been major revisions since the submission of the master's thesis.

4.3.1 METHODS

4.3.1.1 PATIENT INCLUSION

Patients in this study were identified in LYFO according to the following inclusion criteria: age ≥18 years on the date of lymphoma diagnosis; diagnosis of DLBCL, MCL, classical HL, or nodal PTCL (PTCL, not otherwise specified; angioimmunoblastic T-cell lymphoma; anaplastic large cell lymphoma); and treatment with HDT-ASCT consolidation therapy in first line or at first relapse/refractory setting between 1 January 2001 and 31 December 2017. Patients were matched in a ratio of one to five by birth year and sex with comparators from the background population. Exclusion criteria for patients and comparators were malignancies prior to inclusion, organ transplant, or human immunodeficiency virus infection.

A second cohort was identified specifically to investigate the effect of HDT-ASCT on SPM risk relative to conventional chemotherapy. This cohort consisted of patients with newly diagnosed HL and DLBCL between 1 January 2001 and 31 December 2017, ages 18–63 years and with a performance status of 0-1 at the time of diagnosis. This cohort was not exposed to HDT-ASCT at inclusion, and HDT-ASCT was analyzed as a time-dependent exposure.

4.3.1.2 EVENTS AND COMORBIDITIES

SPM was the main outcome of interest and identified in the DNPR and the Danish Cancer Register using ICD-10 codes listed in **Appendix A**. SPM was defined as any malignancy following treatment with HDT-ASCT for patients and after inclusion for

comparators. Lymphoma or lymphoma-related malignancies (lymphoid leukemia [C91], malignant immunoproliferative diseases [C88], and other unspecified malignancies of lymphoid, hematopoietic, or related tissues [C96]) did not count as events of SPM as these diagnoses could have been misclassifications of the initial lymphoma diagnosis.

Comorbidities identified as confounders and registered more than 6 months prior to inclusion included the following: DM, chronic pulmonary disease, CVD (congestive heart failure, ischemic heart disease, and atrial or ventricular fibrillation), and alcohol-related disease (chronic or harmful use, Wernicke encephalopathy, withdrawal syndrome, or alcohol-related diseases of the nervous system, cardiovascular system, liver, or pancreas). Comorbidities were identified by a combination of ICD-10 codes in the DNPR and ATC codes in the National Prescription Registry (**Appendix B)**.

4.3.1.3 STATISTICS

Patients were followed from the day of ASCT and matched comparators from the date of inclusion. Patients and comparators were followed until a first event of SPM, death, or censoring (administrative censoring on 31 December 2018 or emigration from Denmark), whichever came first. Cause-specific HRs for events between patients and comparators were computed using univariable and multivariable Cox regression models. The multivariable Cox regression was adjusted for age, sex, education level, DM, chronic pulmonary disease, CVD, and alcohol-related diseases.

Cause-specific cumulative incidence of first SPM was computed using the Aalen-Johansen estimator with death before SPM as a competing event. Differences between groups were tested using Gray's test. A 2-year landmark analysis was performed as a sensitivity analysis.

The contribution of HDT-ASCT to the risk of SPM compared to chemotherapy alone was assessed in a second patient cohort followed from the date of the first lymphoma diagnosis. HDT-ASCT was treated as a time-dependent exposure in a Cox regression model adjusted for sex, age, and lymphoma subtype.

Lastly, absolute IRs and IRRs between patients and comparators were calculated for each SPM type using a Poisson regression and presented per 1000 person-years.

4.3.2 RESULTS

The main study population consisted of 803 patients with lymphoma and 4015 matched comparators. Median follow-up was 7.76 years (interquartile range 4.77;11.73) (reverse Kaplan–Meier method). Patients had a higher relative rate of SPM with an adjusted HR of 2.35 (1.93;2.87) (112). In a competing risk setting with death before SPM as a competing event, the 10-year cumulative risk of first SPM was 20% (17;23) for patients compared to 14% (13;15) for comparators (**Fig. 13**a). The adjusted HR was 2.94 (2.10;4.11) for non-melanoma skin cancer, 1.21 (0.89;1.60) for solid tumors, and 41.13 (15.77;107.30) for myelodysplastic syndrome (MDS)/acute myeloid leukemia (AML) (112).

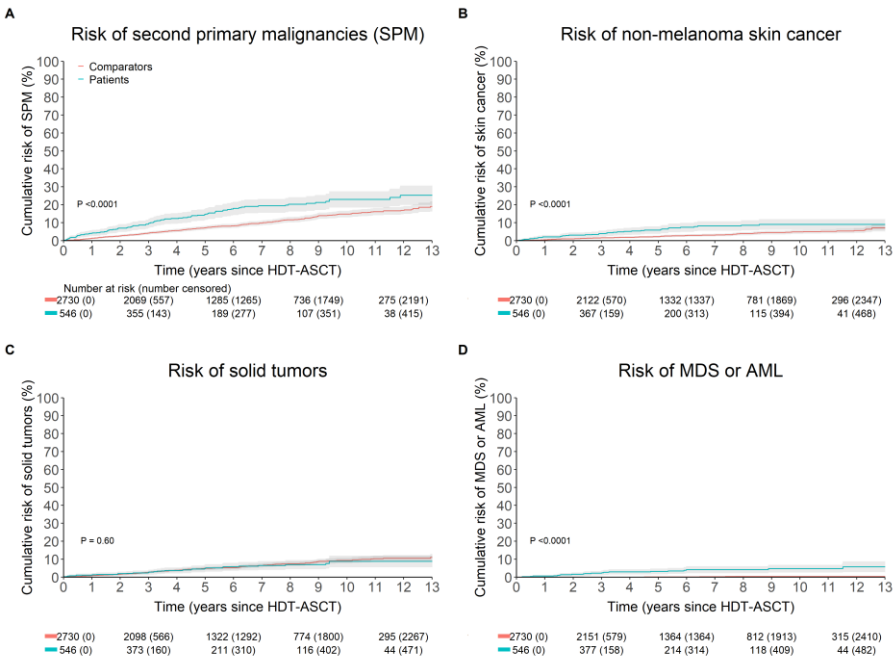

Figure 13. Cumulative incidence for patients (blue) and comparators (red) for risk of A) second primary malignancies, B) non-melanoma skin cancer, C) solid tumors, and D) myelodysplastic syndrome (MDS) or acute myeloid leukemia (AML) (112).

In the landmark analysis starting at 24 months of follow-up, patients still had a higher adjusted HR for SPM of 2.23 (1.75;2.85), driven by differences in rates of non-melanoma skin cancer and MDS/AML but not solid tumors (112).

The IR of SPM per 1000 person-years for HDT-ASCT–treated patients was 30.71, versus 15.77 for comparators. Most SPM rates were similar between patients and comparators, but the IRR was 2.38 (1.71;3.26) for non-melanoma skin cancer, 12.84 (7.56;22.48) for all hematological (non-lymphoid) malignancies combined, and 33.78 (15.09;89.99) for MDS/AML (**Table 1**) (112).

	Matched control individuals	Patients with lymphoma	IRR (95% CI)*	p value
Overall	15·77	30·71	1·95 (1·62–2·33)	<0·0001
Lip, oral cavity, and pharynx	0·40	0·63	1·56 (0·36–4·84)	0·49
Gastrointestinal tract	2·47	1·88	0·76 (0·36–1·43)	0·44
Respiratory organs	1·89	3·34	1·77 (0·99–2·99)	0·042
Non-melanoma skin cancer	4·39	10·45	2·38 (1·71–3·26)	<0·0001
Melanoma	0·68	0·84	1·23 (0·36–3·21)	0·70
Mesothelial	0·03	0·21	6·76 (0·27–170·87)	0·18
Soft tissue	0·19	0·42	2·25 (0·33–9·78)	0·32
Breast	1·27	0·21	0·16 (0·01–0·76)	0·075
Female genital organs	..	..	..	..
Vulva or vagina	0·03	0·21	6·76 (0·27–170·87)	0·18
Cervix uteri	0·09	0·42	4·50 (0·59–27·19)	0·10
Corpus uteri	0·09	0·21	2·25 (0·11–17·59)	0·48
Ovaries	0·15	0·21	1·35 (0·07–8·38)	0·78
Male genital organs	2·38	1·88	0·79 (0·37–1·49)	0·50
Urinary tract	0·74	0·84	1·13 (0·33–2·91)	0·83
CNS	0·28	0·42	1·50 (0·23–5·83)	0·60
Endocrine organs	0·12	0·21	1·69 (0·09–11·42)	0·64
Ill-defined, secondary, unspecified sites	0·09	0·21	2·25 (0·11–17·59)	0·48
Haematological	0·62	7·94	12·84 (7·56–22·48)	<0·0001
Myelodysplastic syndrome or acute myeloid leukaemia	0·19	6·27	33·78 (15·09–89·99)	<0·0001
Myelodysplastic syndrome	0·06	3·76	60·81 (17·56–382·61)	<0·0001
Acute myeloid leukaemia	0·12	2·51	20·27 (7·06–72·51)	<0·0001

IRR=incidence rate ratio. SPMs=second primary malignancies. *IRRs between SPM rates in patients with lymphoma and matched comparison individuals.

Table 1. Incidence rates of SPMs per 1000 person years and IRRs (112).

In the analysis of the second cohort with HDT-ASCT as a time-dependent exposure, 3146 patients were included. HDT-ASCT was associated with a higher rate of SPM (HR 1.58 [1.14;2.17]), adjusted for sex, age, and lymphoma subtype. This difference was driven by higher rates of MDS/AML (HR 10.61 [4.65;24.23]) and non-melanoma skin cancer (HR 1.95 [1.12;3.39]). There was no difference for solid tumors (HR 0.81 [0.48;1.37]) (112).

4.3.3 DISCUSSION

In this study, patients treated with HDT-ASCT for lymphoma had about double the risk of SPM compared to match comparators. The increased risk was driven by increased risks of non-melanoma skin cancer and MDS/AML and persisted after 2 years, suggesting surveillance bias of the lymphoma patients was not the only explanation. The 10-year cumulative incidence of SPM was 20% for patients treated with HDT-ASCT, which was high compared with previously published literature. A retrospective Norwegian cohort study from 2016 investigated the risk of SPM in patients with NHL (111). The authors reported a 10-year cumulative incidence of 7.9% for SPMs consisting of lymphoid/hematopoietic malignancies and solid malignancies, but this incidence may not have included non-melanoma skin cancer, which is often reported separately. In the present study, the 10-year cumulative risk of non-melanoma skin cancer was 8% for patients, which would have doubled their estimate of SPMs, making it comparable to the estimate found in the present study. Although their cumulative incidence was lower, the relative risk compared to the background population was 2, similar to the present study. A study from British Columbia reported an 8% 10-year cumulative risk of SPM following HDT-ASCT, not including non-melanoma skin cancer, but in comparison to patients treated with conventional chemotherapy, no significant increased risk was identified. This finding is in contrast to our study, where we noted a 60% increased risk with HDT-ASCT treatment compared to conventional therapy, which may be explained by differences in first-line treatments and the different use of radiotherapy during 1976–2001 (109). A study of 154 patients at Stanford University Medical Center also showed a 10-year cumulative risk for SPM of 8% following treatment with HDT-ASCT for HL, which again did not include non-melanoma skin cancer. In a comparison with patients from SEER treated without HDT-ASCT, the relative risk was 3.0 (168).

The study from British Columbia also identified older age as a risk factor, as shown in the present study. Compared with the median age of 57 years in the current study, patients included in earlier investigations were generally younger. The median age was 51 years in Smeland et al. (111), 27 years in Forrest et al. (109), 26 years in Minn

et al. (168), and 65 years in Bilmon et al. (107), and median age was not reported in Seshadri et al. (169). Further reasons for the higher incidence of SPM in the present study include a very complete register and minimal loss to follow-up.

In conclusion, patients treated with HDT-ASCT for lymphoma have an increased risk of non-melanoma skin cancer and AML/MDS, but no increased risk of solid cancers. Patients should be informed about these risks and be made aware of the importance of limiting sun exposure to the skin. Furthermore, this study suggests that the implementation of screening programs for solid cancers is not needed, as the risks are like that of the general population (112).

4.4 STUDY IV

Cardiovascular diseases after high dose chemotherapy and autologous stem cell transplant for lymphoma: A Danish population-based study (121)

This study had a shared first authorship.

4.4.1 METHODS

4.4.1.1 PATIENT INCLUSION

Patients in this study had similar inclusion criteria and were matched to comparators from the background population, as in Study III. Exclusion criteria for patients and comparators were previous CVD.

A second cohort was identified specifically for investigating the effect of HDT-ASCT on SPM risk relative to conventional chemotherapy. This cohort consisted of patients with newly diagnosed HL and DLBCL between 1 January 2001 and 31 December 2017, 18–65 years of age, and with a performance status of 0–2 at the time of diagnosis. This cohort had not been exposed to HDT-ASCT at inclusion, and HDT-ASCT was analyzed as a time-dependent exposure.

4.4.1.2 EVENTS AND COMORBIDITIES

The main outcome of interest was CHF, and the secondary outcome was CVD not defined as CHF (non-CHF CVD). Events were identified in the DNPR by the ICD-10 codes listed in **Appendix C**. Comorbidities that were confounding the relationship between HDT-ASCT and CHF/CVD were identified in DNPR and the Danish prescription register using ICD-10 codes and ATC codes, respectively (**Appendix D)**.

4.4.1.3 STATISTICS

Patients were followed from the date of ASCT, and matched comparators were followed from the date of inclusion. Follow-up ended at the occurrence of an event of interest (CHF or non-CHF CVD), death, emigration, or the end of study on 31 December 2018, whichever came first.

Crude and adjusted HRs for CHF and non-CHF CVD, respectively, were computed using univariable and multivariable Cox regression models. Adjustments were made for sex, age, education level, and the comorbidities listed in **Appendix D**. As the proportional hazards assumption was violated for these analyses, an additional time-varying HR was plotted using a flexible parametric model with 2 degrees of freedom for the main effect and 2 degrees of freedom for the time-interaction.

In a competing risk setting, cause-specific cumulative incidence was computed using the Aalen-Johansen estimator with death before an event as a competing event. P values for differences between the groups were calculated using Gray's test.

A multivariable Cox regression was performed with HDT-ASCT as a time-dependent exposure, which was adjusted for age and sex and stratified on lymphoma subtype to allow for different baseline hazards.

4.4.2 RESULTS

A total of 787 patients with lymphoma treated with HDT-ASCT and 3935 matched comparators were included and followed for a median of 7.6 years (reverse Kaplan–Meier method) (121).

Congestive heart failure

Patients with lymphoma treated with HDT-ASCT had a higher risk of CHF relative to matched comparators with an adjusted HR of 5.3 (3.7;7.7). The HR remained above 3.6 for 10 years of follow-up and was highest right after treatment with HDT-ASCT (**Fig. 14a**). The 10-year cumulative risk of CHF was 8.0% (5.7;10.3), as compared to 2.0% (1.5;2.5) for comparators (**Fig. 15**).

In the time-dependent analysis of the second lymphoma cohort, the adjusted HR for CHF associated with HDT-ASCT treatment was 2.6 (1.8;3.8) relative to conventional chemotherapy (121).

Non-CHF CVD

Patients with lymphoma treated with HDT-ASCT had a higher risk of non-CHF CVD relative to matched comparators with an adjusted HR of 2.3 (1.8;2.9). The HR remained above 1.2 for 10 years of follow-up and was highest right after treatment with HDT-ASCT (**Fig. 14b**). The 10-year cumulative risk of non-CHF CVD was 15.2% (12.2;18.3) for patients and 9.6% (8.5;10.8) for matched comparators (**Fig. 16**).

In the time-dependent analysis of the second lymphoma cohort, the adjusted HR for non-CHF CVD associated with HDT-ASCT treatment was 1.9 (1.4;2.6) relative to conventional chemotherapy (121).

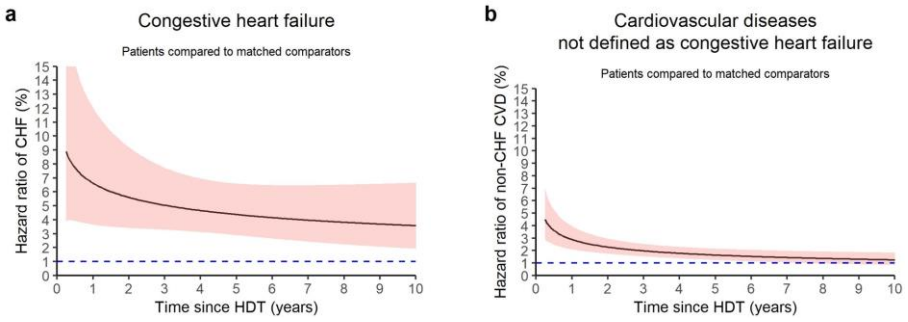

Figure 14. Time-varying hazard ratio over the follow-up time computed with a flexible parametric model. a) Congestive heart failure (CHF) and b) cardiovascular diseases not defined as congestive heart failure (non-CHF CVD) (121).

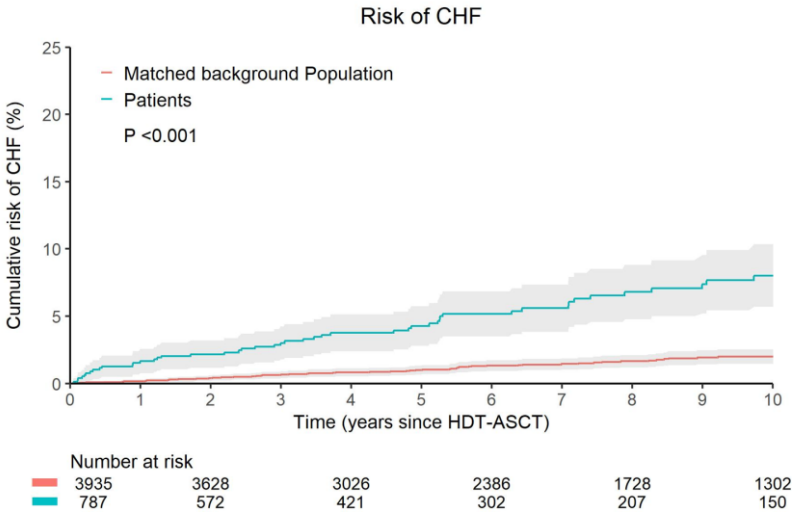

Figure 15. Cumulative incidence of congestive heart failure (CHF) for patients (blue) and matched comparators (red), with death before CHF as the competing event (121).

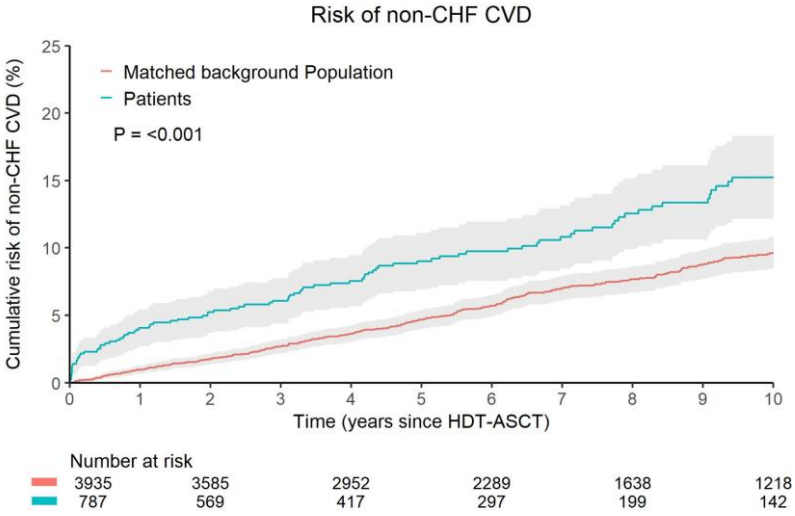

Figure 16. Cumulative incidence of cardiovascular diseases not defined as congestive heart failure (non-CHF CVD) for patients (blue) and matched comparators (red), with death before non-CHF CVD as the competing event (121).

4.4.3 DISCUSSION

In this study, patients treated with HDT-ASCT in a lymphoma setting had an increased risk of CVD and especially CHF relative to matched comparators from the background population. Patients had more than twice the risk of non-CHF CVD and more than five times the risk of CHF compared with matched comparators. Furthermore, the study showed that treatment with HDT-ASCT independently increased the risk relative to conventional chemotherapy, which has otherwise been difficult to establish because of the methodological considerations involved when investigating a risk related to a time-dependent exposure such as HDT-ASCT. As many patients with lymphoma are treated with anthracycline-based chemotherapy regimens prior to HDT-ASCT, it is important to investigate the added effect of HDT-ASCT on the risk of CHF/CVD in patients who also received first-line treatments, rather than only comparing them to a matched population. Further establishing this, a cumulative anthracycline dose ≥300 mg/m^2 prior to HDT-ASCT also was shown to be a risk factor associated with CHF in this study (121). Other risk factors were male sex, treatment with ≥2 lines of therapy prior to HDT-ASCT, and hypertension. The present study found a 10-year cumulative risk for CHF of 8%, which was lower than the value reported for a Norwegian cross-sectional study, in which HDT-ASCT–treated survivors of lymphoma were invited to echocardiography screening (115). The Norwegian study found that 15.7% had left ventricular systolic dysfunction, although only 10.6% were symptomatic. As the present study was performed using ICD-10 codes to identify events, our study could identify only symptomatic events that were diagnosed, followed, or treated in a hospital setting. When comparing symptomatic events between the two studies, results were in a similar range. The cross-sectional study may have overestimated the incidence of cardiotoxicity due to volunteer bias, as patients with cardiac symptoms may have been more likely to respond to and attend the screening. On the other hand, patients had to be healthy enough to travel to the nearest participating hospital to be screened, which may have excluded the worst cases of cardiotoxicity. In the present study, there was an increased HR for CHF during 10 years of follow-up, suggesting that myocardial damage was persistent, and that CHF could potentially develop up to a decade later. The increased time-varying HR also

showed that the perceived increased risk of CHF was not driven only by surveillance bias, which would have led only to an increased HR in the first years following treatment. However, some of the risk may be attributable to the surveillance bias, as patients with lymphoma have more hospital contacts, which could lead to a cardiac diagnostic work-up if symptoms occurred. Other limitations to the study were the lack of information on smoking, alcohol use, body mass index, hypercholesterolemia, and other lifestyle-associated variables that could confound the relationship between HDT-ASCT and CHF/non-CHF CVD. To account for this possibility, education level was included in adjusted analyses, as it correlates with cardiovascular risk factors (170). The main strength of this study was the nationwide setup that made it possible to include all patients with DLBCL, HL, MCL, and PTCL treated with HDT-ASCT. The Danish registers have a very high completeness with very little loss to follow-up, allowing for less biased estimates.

Overall, the study showed a significantly increased risk of CHF and non-CHF CVD for patients treated with HDT-ASCT. Patients should be informed about the increased risk and be made aware of cardiac symptoms, so that they can contact a specialist if any symptoms arise. Furthermore, patients should be advised to lead a healthy lifestyle to minimize the risk of cardiac complications from other factors, such as hypertension. Based on the risk factors pinpointed in this study, it is possible to identify specific patients who may be at increased risk of CHF. Male patients with hypertension who have been treated with anthracycline doses $\geq$300 mg/m^2 and $\geq$2 lines of therapy prior to HDT-ASCT could be screened using echocardiography at one year following treatment to identify any reductions in LVEF (121).

CHAPTER 5. CONCLUSION

As the OS of patients with lymphoma increases, it becomes more and more relevant to shift some of the research focus to investigations of treatment-related toxicities. This PhD work investigated toxicities in the form of CVD, DM, and SPM among patients diagnosed with lymphoma.

Cardiotoxicity after treatment for lymphoma, and even cancer in general, has been extensively studied, with each new investigation exploring different risk factors and treatments associated with cardiotoxicity. Study I of this PhD thesis adds to the existing understanding about anthracycline-related cardiotoxicity by establishing two findings. The first is a clear dose-response relationship between the number of cycles of anthracycline-containing immunochemotherapy for patients with lymphoma and the risk of cardiotoxicity. The second is that the cardiotoxicity is most likely due to the toxicity of anthracycline treatment and is not associated with treatments such as R or related to having a lymphoma diagnosis (79). Study IV adds a completely different aspect of cardiotoxicity following treatment for lymphoma by investigating the risks associated to treatment with HDT-ASCT. The study established an increased risk of cardiotoxicity for patients treated with HDT-ASCT and aimed to disentangle the added risk associated with HDT-ASCT from risks associated with conventional chemotherapy. Previous studies have lacked this aspect, and although HDT-ASCT has been suspected of being cardiotoxic, the current study supplies further supporting evidence (121). Although Study II primarily focused on DM, the study also contributed to knowledge of cardiotoxicity for patients with pre-existing DM treated with anthracycline-containing immunochemotherapy. The results showed an increased risk of cardiotoxicity for these patients only in the first year following treatment, but the extent of the cumulative risk was much higher than identified in Study I, for which patients were not selected based on DM status (98).

SI-DM is a known adverse effect of long-term high-dose treatment with steroids, but no previous large cohort studies have investigated the risk associated with steroid-containing immunochemotherapy. Study II uncovered no clinically relevant increased

risk of DM for patients treated with R-CHOP–like treatment but showed that for patients with pre-existing DM, there was an increased risk of insulin use in the first year following treatment. This result suggests that these patients may experience hyperglycemia due to the steroids in R-CHOP–like treatment regimens. Furthermore, these patients had an increased risk of cardiotoxicity in the first year (98).

Lastly, Study III identified an increased risk of SPM for patients treated with HDT-ASCT. The increase was driven by increased risks of MDS/AML and non-melanoma skin cancer and was prevalent for more than 2 years after treatment initiation. When isolating the effect of HDT-ASCT compared to conventional chemotherapy, a 60% increase in the risk was attributed to the HDT-ASCT treatment (112).

CHAPTER 6. PERSPECTIVES

The findings in this PhD thesis are of clinical importance when selecting optimal treatments for patients. Information about late toxicities is an important factor because it arms patients with the knowledge they need to make informed decisions in collaboration with treating clinicians. New therapies are being approved or are on their way to being approved that will challenge standard treatment regimens, and the choice between current and new treatment regimens will be based on both efficacy and safety, in the long and short terms.

Patients with DLBCL who experience complete remission are followed in the clinic every 3 months for the first year and every 6 months in the second year following remission (36). Based on the results of this PhD work, as well as the current literature, patients are at increased risk of toxicities for a period that exceeds the 2-year clinical follow-up period. It may therefore be beneficial to implement screening programs for specific toxicities that fulfill the requirements of a relevant screening program. A screening should be limited to an important health problem, have the possibility of detection at an early stage, have the possibility of earlier/more effective treatment due to early detection through screening, be cost-effective, and involve a simple, safe, and validated test (171). One example of a treatment-related toxicity that could be screened for is CHF, as described in Study I. The 8-year cumulative risk of anthracycline-induced CHF was 8.1% after six cycles of anthracycline-containing immunochemotherapy, and the risk increased steadily throughout the whole follow-up period (79). In contrast, Cardinale et al., as described earlier, identified 98% of their events of decreased LVEF within the first year following treatment. Their study used echocardiography to screen for events, subsequently identifying events that had not yet fully developed to be of great clinical importance (81% were New York Heart Association class I or II) (75). The combined results of these two studies make a compelling argument for the introduction of a screening program for anthracycline-induced CHF based on the incidence of the disease and the possibility of early detection. The simplicity, safety, and validity of the echocardiography procedure combined with the possibility of early treatment with angiotensin-converting enzyme

inhibitors and beta-blockers, as shown by Cardinale et al. (75), offer additional compelling arguments, fulfilling the criteria for a relevant screening program. As our study also showed an increased risk for treatment with 3–5 cycles (79), screening by echocardiography could be relevant for all patients treated with anthracycline-containing regimens at one year following treatment to identify patients with CHF, regardless of clinical symptoms. In Study IV, the addition of HDT-ASCT following first-line treatment regimens increased the risk of CHF by more than two-fold (HR 2.6), putting these patients at an even higher risk of CHF and thereby making them even more eligible for a screening program (121).

Even though we established an increased risk of non-melanoma skin cancer and MDS/AML following treatment with HDT-ASCT, a specific screening program related to this risk may not be warranted. The risk of non-melanoma skin cancer may be handled by provision of written and oral information on the importance of limiting sun exposure. Patients may be informed about how to check for malignancies of the skin and when to contact a general practitioner for a check-up. Screening for MDS/AML also could be handled in general practice by yearly blood sampling. In the United Kingdom, the ADAPT program, developed by John Radford and colleagues, is monitoring cancer patients for treatment-related toxicities for more than 5 years following treatment. The ADAPT program involves giving patients individualized information on late effects of the treatment that is based on their risk factors and received treatment regimens. A digital platform is in development that can integrate a prompt for interventions and ensure that non-scheduled follow-ups are initiated by the patient (such as a blood sample taken at the general practitioner). This concept was presented at the annual Hodgkin Symposium and has not been published (172). A similar approach would be beneficial in Denmark, as the automatic prompts would help to prevent patients who are at an increased risk of late toxicities from being lost after the end of clinical follow-up.

Although great care was taken when designing and analyzing these epidemiological studies, it is important to remember that the associations found here are not necessarily causal in their interpretation. To fully establish a causal association, RCTs would be

needed to ensure that the associations were not biased by confounding. A study on which I am first author, and that is not included in this PhD thesis, showed an increased risk of osteoporosis for patients treated with steroid-containing immunochemotherapy (173). Following on this result, a RCT of alendronate as preventive treatment against the development of glucocorticoid-induced osteoporosis was performed (174). Similarly, prospective RCTs could be conducted to further investigate the associations studied in this PhD work, but follow-up would need to be long, which is expensive and time-consuming. Furthermore, ethical considerations prevent many trials, as a randomization between a known inferior and superior treatment would not be tolerable. Some endpoints may be better investigated in clinical trials, where the endpoint is specifically registered for an exact purpose, rather than based on registers, where the endpoint may rely on a proxy. One such example is the study (III) of the risk of DM following steroid-containing treatment, where the risk of new insulin prescriptions was investigated for patients with pre-existing DM (98). In that study, insulin prescriptions were used as a proxy for hyperglycemia, as the values for plasma glucose were not available. Even if the data had been available, the results would still be suboptimal, as the plasma glucose value depends on the time since treatment and can change hourly. In this case, a trial with predefined endpoints and time intervals would be a better choice, which could be investigated in the future.

For these reasons, data-driven epidemiological research is still very relevant and needed to answer clinical questions in the real world. In the future, in countries where it is possible, patients enrolled in (randomized) clinical trials could be followed indefinitely using health registers and medical journals, thus combining the randomization of RCTs to remove confounding with the completeness, inexpensive data availability, and possibility of long follow-up associated with RWD.

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APPENDICES

Appendix A. Second primary malignancies in Study III

(112)

Type of second primary malignancy	ICD-10 codes
Lip, oral cavity, and pharynx	C00-C14
Gastrointestinal tract	C15-C26
Respiratory organs	C30-C37, C380, C381, C382, C383, C385, C39
Bone and articular cartilage	C40-C41
Melanoma	C43
Non-melanoma skin cancer	C44
Mesothelioma	C45
Soft tissue – nerves, retroperitoneum, peritoneum, other connective or soft tissue	C46-C49
Breast	C50
Female genital organs – Vulva or vagina – Cervix uteri – Corpus uteri – Ovaries – Other female genital cancer	C51-C52, C53, C54, C56, C57
Male genital organs	C60-C63
Urinary tract	C64-C68
Central nervous system (only counted from the Cancer Register due to risk of misclassification of lymphoma)	C69-C72
Endocrine organs	C73-C75
Unspecified malignancies (only counted if present in the Cancer Register and with no other malignancies present)	C76, C80, C97, C78, C79

Hematological malignancies – Multiple myeloma – Acute myeloid – leukemia (AML) – Myelodysplastic syndrome (MDS)	C90 C92, C93.0, C920, C923, C924, C925, C926, C928, C930, C940, C942, C944, C947 D46

Appendix B. Comorbidities in Study III

(112)

Comorbidity	**ICD-10 Codes**	**ATC codes**
Diabetes mellitus	E10, E11	A10A, A10B
Chronic pulmonary disease	J44	R03AC18, R03AC19, R03AL02, R03AL03, R03AL04, R03AL05, R03AL06, R03BB04, R03BB05, R03BB06, R03BB07, R03DX07
Cardiovascular disease		
- Congestive heart failure	I50	
- Ischemic heart disease	I20-I25	
- Atrial or ventricular fibrillation	I48, I490	
Alcohol-related disease		
- Chronic or harmful alcohol use	F10	
- Wernicke encephalopathy	E512	
- Alcohol withdrawal syndrome	F101-F109	

- Alcohol-related diseases of the nervous system	G312, G621, G721	
- Alcohol-related diseases of the cardiovascular system	I426	
- Alcohol-related diseases of the liver	K70	
- Alcohol-related diseases of the pancreas	K860, K852	

Appendix C. Events in Study IV

(121)

Congestive heart failure (CHF)	ICD-10: I11.0: Hypertensive heart disease with (congestive) heart failure I13.0: Hypertensive heart and renal disease with (congestive) heart failure I13.2: Hypertensive heart and renal disease with both (congestive) heart failure and renal failure I42.0: Dilated cardiomyopathy I42.8: Other cardiomyopathies I42.9: Cardiomyopathy, unspecified I50: Heart failure ICD-8: 427.0, 427.1: Heart failure 425: Cardiomyopathy 428: Other myocardial insufficiency
Cardiovascular disease not defined as congestive heart failure (non-CHF CVD)	ICD-10: I20.0: Unstable angina I21: Acute myocardial infarction I310+I311: Constrictio cordis I34-37: Mitral, aorta, tricuspid, pulmonal valve diseases I42.5: Restrictive cardiomyopathy I46: Cardiac arrest I47.2: Ventricular tachycardia I48: Atrial fibrillation and flutter

	I49.0: Ventricular fibrillation and flutter ICD-8: 394-397: Valve diseases 423.00, 423.02, 423.08, 423.09: Constrictio cordis 411: Unstable angina 410: Acute myocardial infarction 427.27: Cardiac arrest 427.91: Ventricular tachycardia 427.93, 427.94: Atrial fibrillation and flutter 427.97: Ventricular fibrillation and flutter Procedure codes: KFNA, KFNB, KFNC, KFND, KFNE, and KFNF: Coronary artery bypass grafting KFNG: percutaneous coronary intervention

Appendix D. Comorbidities in Study IV

(121)

Renal disease	ICD-10: N00-N19: Diseases of the kidney and urinary system N083: Glomerular disorders in diseases classified elsewhere N289: Other disorders of kidney and ureter, unspecified
Thyroid disease	ICD-10: E03: Other hypothyroidism E04: Other nontoxic goiter E05: Thyrotoxicosis [hyperthyroidism]
Diabetes mellitus	ICD-10: E10: Type 1 diabetes mellitus E11: Type 2 diabetes mellitus E12: Malnutrition-related diabetes mellitus E13: Other specified diabetes mellitus E14: Unspecified diabetes mellitus

	ATC: A10A: Insulins and analogues A10B: Blood glucose–lowering drugs, excluding insulins
Hypertension	ATC: At least two of the following classes of antihypertensive drugs: alpha-adrenergic blockers: C02A, C02B, C02C Non-loop diuretics: C02DA, C02L, C03A, C03B, C03D, C03E, C03X, C07C, C07D, C08G, C09BA, C09DA, C09XA52 Vasodilators: C02DB, C02DD, C02DG, C04, C05 Beta-blockers: C07 Calcium channel blockers: C07F, C08, C09BB, C09DB Renin-angiotensin system inhibitors: C09

ISSN (online): 2246-1302
ISBN (online): 978-87-7573-602-7

AALBORG UNIVERSITY PRESS