Clinical factors and outcome in T-cell lymphoma: a population-based perspective

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LUND UNIVERSITY

DOCTORAL DISSERTATION

by due permission of the Faculty of Medicine, Lund University, Sweden. To be defended in the Lecture Hall, Radiotherapy building, floor 3, Department of Oncology, Skåne University Hospital, Lund, on Friday 18th March, at 01.00 pm.

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Organization LUND UNIVERSITY, Department of Clinical sciences, Lund, Oncology and Pathology, Sweden	Document name: Doctoral Dissertation	
	Date of issue: 2016-03-18	
Author(s): Fredrik Ellin	Sponsoring organization	
Title and subtitle: Clinical factors and outcome in T-cell lymphomas: a population-based perspective		

Abstract: The heterogeneous group of T-cell lymphomas consist mostly of aggressive diseasess, with generally unfavourable outcome compared to aggressive B-cell lymphomas following similar therapy. This thesis focus on outcome and risk factors for inferior survival, in an unselected population-based cohort of T-cell lymphoma patients.

In the first study, outcome of the precursor malignancy T-cell Lymphoblastic Lymphoma was investigated. This lymphoma has many similarities to T-cell Acute Lymphoblastic Leukemia, and intensive chemotherpay developed for leukemia is known to result in better outcome, than standard lymphoma therapies. The study confirms the superior survival after intensive therapy also in a population-based setting. Intensive as opposed to non-intensive treatment was the main prognostic factor for survival, while age was not associated with an inferior outcome among intensively treated patients.

The other three studies focus on outcome in peripheral T-cell lymphomas (PTCL). The second study investigates outcome according to treatment and standard clinical factors at diagnosis. Male gender was found to be associated with inferior survival. Intensification of first-line treatment with up-front autologous stem cell transplantation (auto SCT) consolidation was found to be associated with a favourable outcome in patients younger than 70 years. Relapsing patients had a dismal outcome, with a median post relapse survival of 6 months.

Study number three focused on the occurance of central nervous system (CNS) relapse in PTCL. In all, 28 patients (4.5%) experienced CNS relapse, most commonly with leptomeningeal involvement. Extensive extranodal involvement, skin or gastrointestinal involvement was associated with a higher risk for secondary CNS spread. At relapse patients had a very poor survival, irrespective of CNS involvement or not, with no survival difference between the groups.

The last study investigates the impact of comorbidity in PTCL. Using the Charlson Comorbidity Index (CCI), presence of concomittant disease was found to be independently associated with inferior survival. CCI was the only factor at diagnosis that showed an association with survival after first-line auto SCT. The association with favourable outcome in patients treated with auto SCT found in the second study, was still significant when adjusting for CCI. In patients ≥75 years, a similar survival in patients treated with curative and low-intensity chemotherapy was found. This was not changed when adjusting for the CCI.

In summary, the studies included in this thesis provides information on risk factors and population-based outcomes in T-cell lymphomas. Associations between treatment intensification and better outcome suggests a beneficial effect of these strategies in younger patients. The thesis also provides information on previously poorly documented disease, and patient-related, factors in PTCL, and will possibly serve as comparative data for future population-based studies.

Key words: T-cell Lymphoblastic Lymphoma, peripheral T-cell lymphoma, prognostic factors, autologous stem cell transplantation, central nervous system relapse, comorbidity		
Classification system and/or index terms (if any)		
Supplementary bibliographical information		Language: English
ISSN and key title: 1652-8220		ISBN 978-91-7619-254-2
Recipient's notes	Number of pages: 95	Price
	Security classification	

Signature _____ Date _____

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Cover photo: The Baltic sea at Kalmarsund by the author

Back cover photo: Bugun Liocichla, Liochichla bugunorum by James Eaton, with permission

Lund University, Faculty of Medicine
ISBN 978-91-7619-254-2
ISSN 1652-8220

Lund University, Faculty of Medicine
Doctoral Dissertation Series 2016:28

Printed in Sweden by Media-Tryck, Lund University
Lund 2016

It gets late early out there.

Yogi Berra

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List of papers

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I. Treatment outcome in T-cell lymphoblastic lymphoma in adults – a population-based study from the Swedish Lymphoma Registry

Ellin F, Jerkeman M, Hagberg H, Relander T

Acta Oncologica, 2014; 53: 927–934

II. Real-world data on prognostic factors and treatment in peripheral T-cell lymphomas: a study from the Swedish Lymphoma Registry

Ellin F, Landström J, Jerkeman M, Relander T

Blood. 2014;124(10):1570-1577

III. Central nervous system relapse in peripheral T-cell lymphomas: A Swedish Lymphoma Registry study

Ellin F, Landström J, Jerkeman M, Relander T

Blood. 2015;8: 2014-2022

IV. Impact of comorbidity on survival in peripheral T-cell lymphomas: a Swedish Lymphoma Registry study

Ellin F, Jerkeman M, Landstrom J, Brudin L, Relander T

Manuscript

My contribution to the papers

Paper I

I was responsible for collection and analysis of the data and for writing the paper.

Paper II

I participated in the design of the study and the collection of data. I was responsible for analysis of the data and the writing of the paper.

Paper III

I was responsible for the design of the study, collection and analysis of the data and writing of the paper.

Paper IV

I was responsible for the design of the study, participated in the collection of data and was responsible for analysis of the data and writing of the paper.

Selected abbreviations

ALCL	Anaplastic Large Cell Lymphoma
ALL	Acute Lymphoblastic Leukemia
ALK	Anaplastic Lymphoma Kinase
AITL	Angioimmunoblastic T-cell Lymphoma
allo SCT	allogeneic Stem Cell Transplantation
auto SCT	autologous Stem Cell Transplantation
ATLL	Adult T-cell Leukemia/Lymphoma
CD	Cluster of Differentiation
CHOP	Cyclophosphamide, doxorubicin, vincristine and prednisone
CHOEP	Cyclophosphamide, doxorubicin, vincristine, etoposide and prednisone
CCI	Charlson Comorbidity Index
CNS	Central Nervous System
CR	Complete Remission
DLBCL	Diffuse Large B-cell Lymphoma
EATL	Enteropathy-associated T-cell Lymphoma
EBV	Epstein-Barr Virus
EFS	Event-Free Survival
HR	Hazard Ratio
HSTCL	Hepatosplenic T-cell Lymphoma
HTLV-1	Human T-cell leukemia virus type 1
IPI	International Prognostic Index
NHL	Non-Hodgkin Lymphoma

NK	Natural Killer
ORR	Overall Response Rate
OS	Overall Survival
PFS	Progression-free Survival
PR	Partial Remission
PTCL(s)	Peripheral T-cell Lymphoma(s)
PTCL NOS	Peripheral T-cell Lymphoma Not Otherwise Specified
SPTCL	Subcutaneous Panniculitis-like T-cell Lymphoma
T-LBL	T-cell Lymphoblastic Lymphoma

Introduction

The very first description of a malignancy with a lymphoid origin was published by Thomas Hodgkin in 1832.[1] Honoring his historic work, lymphomas are still, after more than 150 years, grouped into Hodgkin or non-Hodgkin lymphomas (NHLs). Diagnostic methods of lymphomas in clinical practice have evolved from anatomic and histological patterns, to today's integration of clinical, morphologic and multiple molecular parameters. With an increasing insight in disease biology and its diversity, the classification of lymphomas has been the subject of several thorough revisions over the years. Improvement and international harmonization in the classification of lymphomas have been instrumental in the evolution of lymphoma therapeutics.

In 1973, the first study demonstrating a malignancy to have the characteristics of T-cell lymphocytic origin, the Sézary syndrome, was published.[2] Evidence subsequently accumulated that other lymphomas displayed properties consistent with T-cell phenotype, but these seemed substantially more uncommon than B-cell lymphomas.[3] Although advocated at an early stage as being of significance,[4] the importance of T- or B-cell origin was initially not obvious. The first broadly used classification system for lymphomas to incorporate T-cell phenotype as an important characteristic of the tumor, was the updated version of the Kiel classification published in 1988.[5]

The currently used lymphoma classification is the 4th edition of the World Health Organization (WHO) Classification of Haematopoietic and Lymphoid Tissues published in 2008.[6] Based on combinations of clinical characteristics, immunohistological differences and recurrent genetic alterations, it identifies more than 50 different lymphoproliferative diseases with additional provisional entities. This classification aims at identifying clinical distinct entities, and relate the tumor cells to its underlying non-malignant cell counterpart.

The classification of T-cell lymphomas

From the progenitor cells residing in the bone marrow, T- and NK-cells undergo different steps of maturation, schematically illustrated in Figure 1. As a consequence of the complicated pattern of maturation of functional T-cells, through different paths, the malignancies arising among T- and NK-cells, have a very heterogeneous cellular origin. Reflecting cell-of-origin and several other characteristics, the current WHO classification separates the T- and NK-cell malignancies more than 15 entities with mature T-or NK-cell origin as well as the precursor T lymphoblastic leukaemia/lymphoma, as listed in Table 1.

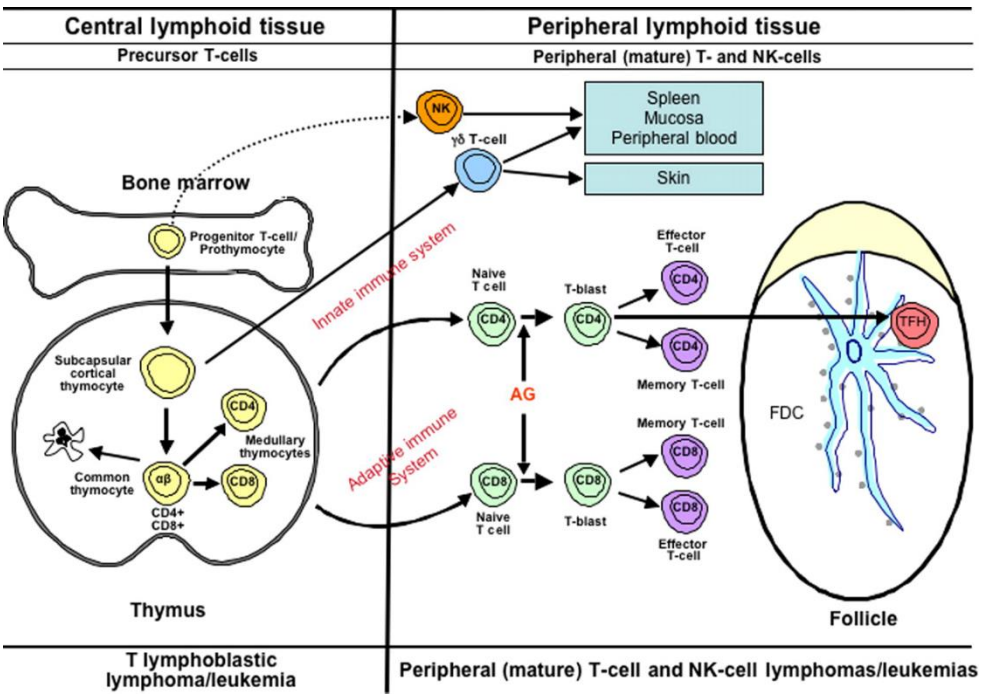

Figure 1. Schematic illustration of T-lymphocyte maturation. Precursor T-cells enter the thymus and develop into different naïve T-cells. NK- and γδ T-cells, parts of the innate immune system, mature along separate paths compared to αβ T-cells that undergo antigen exposure and develop into effector T-cells of different types. T-cell neoplasms correspond to different developmental stages along the differentiation. *From [7] with permission from the American Society of Hematology.*

Not only cell-of-origin will influence tumor behavior, but different oncogenic molecular events can be assumed to influence tumor biology differently in lymphomas with a similar cell-of-origin. The genetic and epigenetic background behind tumorigenesis in T-cell malignancies are to large extents unknown, but the knowledge of recurrent genetic alterations in T-cell neoplasia is steadily growing.

This expanded insight into the differences in the molecular background of T- and NK-cell lymphoproliferative disorders, is expected in part to be reflected in the awaited revised 4th WHO classification, due to be published in 2016.

Table 1.
Classification of T-cell malignanices in the WHO 2008 classification

T-cell lymphoid neoplasms			
Precursor lymphoid neoplasms			
T lymphoblastic leukemia/lymphoma			
Peripheral T-cell lymphomas			
Nodal	*Extranodal*	*Primary cutaneous*	*Primary leukemic*
Anaplastic large cell lymphoma, ALK+	Enteropathy-associated T-cell lymphoma	Mycosis fungoides	T-cell prolymphocytic leukemia
Anaplastic large cell lymphoma, ALK-*	Hepatosplenic T-cell lymphoma	Sézary syndrome	T-cell large granular lymphocytic leukemia
Angioimmunoblastic T-cell lymphoma	NK/T-cell lymphoma, nasal type	Primary cutaneous CD30 positive T-cell lymphoproliferative disorders	Chronic lymphoproliferative disorders of NK cells*
Peripheral T-cell lymphoma NOS	Subcutaneous panniculitis-like T-cell lymphoma	Primary cutaneous gamma-delta T-cell lymphomas	Aggressive NK cell leukemia
		Primary cutaneous peripheral T-cell lymphomas*	
		Hydroa vacciniforme-like lymphoma*	
Multiple organ involvement			
Systemic EBV-positive T-cell lymphoproliferative disease of childhood*			
Adult T-cell leukemia/lymphoma			

* provisional entity

Geographic patterns and epidemiologic aspects

The relative frequency of different lymphomas varies geographically, in part related to known etiologic factors, but in many instances the reasons are unknown. In all populations, PTCLs constitute a minority of NHLs, with frequencies around 10% reported in many studies.[8-12] In some regions PTCLs are more frequent, most notably in East Asia, where T-cell lymphomas constitute almost 20% of all NHLs.[12]

There are also some known differences in the distribution of particular PTCL entities. The mostly leukemic variant, adult T-cell leukemia/lymphoma, ATLL, is a disease associated with the retrovirus human T-cell leukemia virus type 1 (HTLV-

1). Endemic HTLV-1 infection is present in Japan and the Caribbean Basin,[13] and thus ATLL has a much higher prevalence in these regions, than in other areas. The disease can present as one of several clinically distinct subtypes, with a difference between Japanese and Caribbean populations in their relative distribution.[14]

The International T-Cell Lymphoma Project [15] performed a study on samples from a large number of PTCL cases retrieved from 22 institutions in three continents (North America, Europe and Asia). In this study, ATLL was the most common PTCL in Asia, although restricted to the Japanese contribution of the study. The second most common PTCL subtype among Asian cases was NK/T-cell lymphoma, and when excluding Japan, this lymphoma accounted for almost 50% of the PTCLs. ALCL, AITL and EATL were uncommon in Asia, while these were much more prevalent in Europe and North America. AITL and EATL were more common in Europe than in North America. The latter finding was mainly due to a north European contribution by a Norwegian center. Since EATL type I has an association to coeliac disease, which is more common in people with Northern European ancestry, this was an expected finding. For AITL, there is no similar explanation for the finding that this lymphoma was more common in Europe than North America. [15] A recent French analysis of national network data, found AITL to be the most common subtype of PTCL, representing 36% of all cases, confirming that there seems to be a geographical variation in the prevalence of this lymphoma.[16]

Etiology of T-cell lymphomas

Although not much is known about etiology in PTCL, a few factors with an established, or possible, oncogenic role have been identified. The strongest etiologic relation known for any PTCL, is the HTLV-1 infection seen in ATLL patients.[6] All ATLL patients carry the infection, but only a minority of all HTLV-1 infected individuals develop lymphoma. Transmission of the HTLV-1 virus early in life, usually through breast-feeding, is a risk factor for ATLL development. [17] The latency period between the infection and lymphoma development is very long, and other factors in addition to the viral infection itself certainly play a role in the development of this lymphoma.[18]

NK/T-cell lymphomas of the nasal type are almost always positive for Epstein Barr virus (EBV) infection, which is suggestive of an etiologic role of the virus, but this has not been fully established.[6] EBV infection is very common in most parts of the world, but NK/T-cell lymphomas are much more common in East Asia and Central America than in other areas, suggesting that host genetic factors are very important for the development of NK/T-cell lymphomas.[10, 12]

EBV infection is almost universally present also in AITL. In this lymphoma, it is the by-stander B-cells, and not the actual lymphoma cells that harbor the viral infection. The possible mechanistic role of EBV in this lymphoma is however still unclear.[6]

In EATL type I, most patients express the Human Leucocyte Antigen DQ2 or DQ8, [6] variants known to be associated with coeliac disease. [19, 20] Most patients also have some clinical signs of coeliac disease, but the lymphoma is not restricted to patients with severe enteropathy, since many patients have not been diagnosed with coeliac disease prior to the lymphoma.[21]

Immunosuppression seem to impact the risk of developing the very rare HSTCL, and an increased risk has been reported in young patients with inflammatory bowel disease, treated with immunosuppressive medication such as azathioprine and anti-Tumor Necrosis Factor-antibodies.[22] The exact mechanisms involved are not known.

Specific T-cell lymphoma entities

T cell lymphoblastic leukaemia/lymphoma

This is the only precursor lymphoid malignancy of T-cell origin. Cases are denoted leukemia (T-ALL) or lymphoma (T-LBL) based upon the extent of bone marrow involvement. Lymphoma cases commonly present with a mediastinal mass, but this can also be present in leukemia patients, and the arbitrary limit of less than 20% blast cells in the bone marrow defines cases that should be classified as T-LBL.[6] T-ALL/LBL most typically occurs in adolescents or young adults, with a male predominance. The disease has a high risk of central nervous system (CNS) involvement, either at diagnosis or during the course of disease.[23]

Most of the work on the underlying genetic alterations in T-ALL/LBL has been performed in T-ALL, and several studies describe findings in pediatric patients. Mutations in the *NOTCH1* and *FBXW7* genes belong to the most frequently encountered genetic events, and these mutations have been associated with a superior outcome in adult T-ALL[24], with even better outcome in absence of mutations in *K-RAS*, *N-RAS* or *PTEN*.[25]

The genetic landscape in T-LBL has been investigated far less extensively, but the high prevalence and favorable outcome associated with the presence of *NOTCH1/FBXW7* mutations was confirmed in a study on pediatric and adolescent patients.[26] In this study, loss of heterozygosity at chromosome 6q was associated

with an inferior outcome. There are some evidence for a distinct mutational pattern in T-LBL compared to T-ALL in pediatric patients.[27] Different cellular properties, with a higher expression of BCL-2, ICAM1 and S1P1 expression in T-LBL compared to T-ALL cells, have also been described.[28] There are results indicating that molecular prognostic subgroups might not have the same prognostic value, when tested in different age groups or in lymphoma cohorts compared to leukemia cohorts.[29]

Anaplastic large cell lymphoma

Anaplastic large cell lymphoma (ALCL) belongs to the peripheral T-cell lymphomas. The initial attention to ALCL as a separate lymphoma entity was brought by the recognition of anaplastic NHL cases with expression of CD30 (Ki-1).[30] Most typically the tumor cells are large and pleomorphic, with horseshoe- or kidney-shaped nuclei, referred to as hallmark cells, illustrated in Figure 2. Usually one or several T-cell markers are expressed, but a minority of cases lack T-cell antigens completely, and are known as null-cell phenotype lymphomas.[6] In ALCL the recurrent chromosomal translocation t(2;5) is present in a substantial proportion of cases, coding for a *NPM-ALK* fusion transcript.[31] This correlates to the expression of the NPM-ALK fusion protein, detectable by immunohistochemistry for ALK, and this staining is applied in routine care to separate ALCL into ALK+ ALCL or ALK- ALCL. ALK- ALCL was included in the WHO 2008 classification as a provisional entity, but evidence for a unique genetic background in ALK- compared to ALK+ ALCL has been established.[32, 33] ALK- ALCL is expected to be recognized as a separate entity in the upcoming WHO classification.[34]

There are several morphologic patterns recognized in ALCL, and since CD30 is also expressed in non-ALCL T-cell lymphomas, the diagnosis of ALK- ALCL can be challenging. Although ALK- ALCL often express cytotoxic markers such as TIA1, granzyme B and/or perforin, this is not universal. These proteins can also be found in other lymphomas, and there is no single immunohistochemical staining that distinguishes ALK- ALCL from other CD30+ PTCLs.[6]

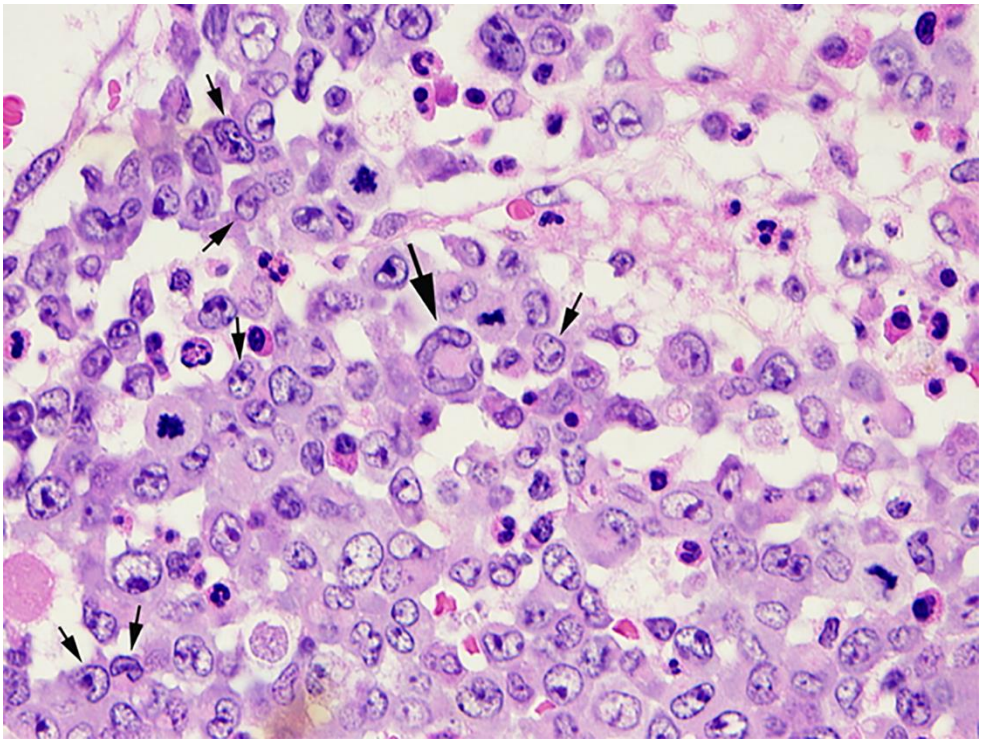

Figure 2. Histology of Anaplastic large cell lymphoma. Anaplastic large cell lymphoma represented by a pleomorphic bone marrow infiltration. The large arrow indicates an anaplastic cell with a horseshoe nucleus (hallmark cell). The small arrows indicate several smaller atypical cells with more round vesiculated nuclei dispersed throughout the infiltrate. *From ASH Image Bank 2011-3315, John Lazarchick, Gregor Krings, with permission from the American Society of Hematology.*

ALCL frequently involves extranodal tissues, including the skin. Cases that only involves the skin are regarded a separate disease entity, primary cutaneous ALCL (c-ALCL). On rare occasions regional lymph node involvement can be present in c-ALCL.[6] c-ALCL has a distinct clinical behavior with an indolent course and favorable long term outcome. Almost all c-ALCL are ALK-, but very rare cases of ALK+ c-ALCL have been described.[35, 36]

Another distinct presentation of ALCL is in the setting of breast implant prostheses, first described in 1997.[37] Most cases present with an effusion lymphoma contained in the fibrous capsule around the implant, but some patients present with a mass lesion. These patients may have a more aggressive course, than the usually favorable long term outcome of capsule contained lymphoma cases.[38]

On the genetic level several studies have shown that ALK- ALCL displays a distinct genetic profile compared to CD30+ PTCL not otherwise specified (NOS), but that there seem to be a degree of similarity between ALK+ and ALK- ALCL.[39-41] In

ALK+ ALCL, the defining ALK expression is in approximately 85% of the cases related to a t(2;5) chromosomal translocation, but there are several other variant translocation partners to the *ALK* gene on chromosome 2 described.[6] In ALK- ALCL there seems to be a considerable heterogeneity in the molecular mechanism involved. There is no recurrent genetic event currently known to occur in a majority of cases, but lately several alterations has been described, including the translocation t(6;7) involving the *DUSP22* gene, rearrangement of the *TP63* gene, [42, 43] and *JAK1/STAT3* mutations.[44] A very recent publication found an additional subset of patients characterized by *ERBB4* and *COL29A1* gene overexpression, not found in other PTCL entities.[45]

Angioimmunoblastic T-cell lymphoma

The morphologic architecture in AITL is characterized by a polymorphic cell infiltrate with a marked arborizing proliferation of high endothelial venules within the lymph nodes. Eosinophils, plasma cells and an expanded follicular dendritic cell meshwork is present to a variable degree. In the great majority of cases there are EBV-positive B-cells present, usually in part as an expansion of B-cell immunoblasts. The actual neoplastic cells are less abundant and stain positive for many common T-cell antigens, and tend to congregate around follicles and endothelia. The tumor cells also express CD10, CXCL13 and PD-1, which are markers associated with normal follicular T-helper cells (TFH).

In concordance with the histologic pattern suggesting a complex immunologic milieu, patients frequently present with a polyclonal hypergammaglobulinemia and sometimes hemolytic anemia. Splenomegaly and advanced stage disease, with a propensity for skin involvement, are other common features.[6]

When initially identified, this disease was thought to represent a non-malignant process with a risk of developing secondary cancers and the term angio-immunoblastic lymphadenopathy with dysproteinaemia, was the most commonly used name.[46] At the time the revised Kiel classification was published, there were sufficient evidence for the process being neoplastic, and AITL was included among the low-grade T-cell lymphomas.[5]

Following the characterization of normal TFH cells, several studies demonstrated expression of proteins suggesting the malignant cells in AITL to have a TFH origin,[47-50] and this has later been confirmed by gene-expression profiling,[51] establishing TFH as the normal cell counterpart of AITL.

Recent work has demonstrated a number of recurrent genetic events in AITL. The first mutation to be described was inactivating mutations of the *TET2* gene, [52] followed by the demonstration of *DNM3A* mutations,[53] and *IDH2* mutation, [54]

all of them involved in DNA methylation processes. In 2014 several groups reported in parallel, a mutation in the *RHOA* gene resulting in a Gly17Val substitution and subsequent loss of RHOA GTPase activity, a protein which is postulated to link T-cell receptor signaling and extracellular matrix signaling pathways. [55-57]

Enteropathy-associated T-cell lymphoma

This aggressive T-cell lymphoma arises in the gastrointestinal tract, and is divided into two types in the current WHO classification. The classic form of EATL (type I), has an association with coeliac disease. At least some evidence for coeliac disease is mostly present, although not strictly required for the diagnosis. The tumor cells are CD3+ and often CD30+, sometimes CD8+, but CD4- and CD56- and mostly T-cell receptor (TCR) β+. [6]

The disease commonly presents with intestinal perforation and malnutrition, sometimes in individuals with refractory coeliac disease, in whom the nutritional status can be severely affected .[58] There are evidence for a prodromal state or precursor lesions in EATL type I, since it has been demonstrated that monoclonal T-cells with properties of neoplastic EATL cells, exist in the intestinal mucosa of patients with refractory coeliac disease and in the mucosa surrounding the actual tumor in EATL cases.[59]

The monomorphic, or EATL type II, has no association to coeliac disease, although it sometimes arises in the context of enteropathy. EATL type II has a distinct immunophenotype with malignant cells being CD56+ and TCR β+.[6] It has been suggested that the type II EATL is sufficiently different from type I, to be recognized as a separate entity, with the proposed name monomorphic intestinal T-cell lymphoma.[60]

There are a number of chromosomal aberrations that have been described in EATL. Gains of 9q31.3-qtr and 16q12.1 are shared by both type I and II. Gains in 1q and 5q are frequently seen in type I, and gains in the *MYC* gene are present in type II.[61] A very recent genetic study in 78 EATL type I and II cases, demonstrated a large number of genetic aberrations. In contrast to what was expected, more similarities than differences between type I and type II EATL was found.[62]

The spectrum of T-cell lymphoproliferative disorders in the intestine also includes a monoclonal T-cell proliferation with TCR-γ chain rearrangements, that merits awareness, since this disease has an indolent course.[63]

Extranodal NK/T-cell lymphoma, nasal type

This lymphoma has a very strong association with EBV-infection. Most cases have a NK-cell phenotype, but a minority displays characteristics consistent with a cytotoxic T-cell origin. The lymphoma often has an angiocentric growth pattern and necrosis is frequently present. Lymphoma cells are CD56+ and EBV+, although rare cases can lack one of these antigens, but not both. The lymphoma involves primarily extranodal tissue, with the nasal cavity and paranasal sinuses most commonly involved. Skin and the gastrointestinal tract are other frequent sites of involvement.[6]

There are multiple genetic abnormalities reported in NK/T-cell lymphomas. Out of the more frequently detected, deletion of a 6q region has been characterized in more detail, which has provided evidence for the *PRDM1* and *FOXOP3* genes as candidates for tumor suppressor function in NK/T-cell lymphomas.[64-66]

Subcutaneous panniculitis-like T-cell lymphoma

This lymphoma infiltrates subcutaneous tissue, often in a multifocal pattern. Tumor cells usually express CD8 and cytotoxic molecules and are TCRαβ positive. Lymphomas that express TCRγδ were previously included in this entity, but are now regarded a separate disease, cutaneous γδ T-cell lymphoma.[6] Hemophagocytic lymphohistiocytosis is relatively frequently seen in this disease, with 11 out of 63 patients suffering from this complication in one study.[67] The genetic background of the disease has not been described.

Hepatosplenic T-cell lymphoma

An extranodal lymphoma usually with γδ cytotoxic T-cell phenotype. Hepatosplenomegaly is present, and the lymphoma often involves bone marrow.

Isochromosome 7 or other chromosome 7 abnormalities have been reported repeatedly.[68, 69]

Peripheral T-cell Lymphoma, not otherwise specified

PTCL NOS, as defined in the WHO 2008 classification, is a diagnosis harboring a spectrum of aggressive systemic T-cell lymphomas. Cases are assigned to this entity when criteria for any of the other specified PTCL entities are not met. The diagnosis is widely accepted as a lumping of biologically different diseases, with currently

insufficient knowledge on how to separate into meaningful distinct entities. Forming a minority of cases, morphologically distinct groups of PTCL NOS includes the lymphoepitheloid (Lennert's), T-zone and follicular variants.

The disease often presents with nodal involvement, but can also be limited to extranodal sites. CD4 positive cases are more common than CD8 positive, but any combination of these markers has been described. [6] CD30 expression is present in approximately 30% of cases, [70] and the overall immunohistochemical pattern together with morphology discriminates these cases from ALK- ALCL. Cases with a disease restricted to the skin are contained in a number of provisional entities, primary cutaneous peripheral TCL, with a variable disease course depending further subclassification.[6]

Considering the fact that PTCL NOS, in some ways consists of the "left overs" in diagnostics, it is not surprising that there is a wide spectrum of molecular and genetic disruptions found. Gene expression profiling in a study including a large number of PTCL NOS cases, demonstrated that the cohort could be divided into two major groups. The differences in gene expression provided a rationale for different biologic backgrounds, one characterized by high GATA3 expression and one by increased TBX21 signaling.[41] There is also a small subset of PTCL NOS cases which seems to have a follicular T-helper cell signature, reminiscent of AITL cases, but lacking some key diagnostic features for this disease.[51, 71] Other known recurrent molecular events include dysregulation in T-cell receptor signaling [72, 73]

Treatment of aggressive lymphomas

In the early 1970's, evidence that doxorubicin was an efficient drug for treatment of lymphomas was at hand. It was also established, that it was feasible to combine this drug with other cytotoxic compounds. [74] In 1976, McKelvey and colleagues,[75] reported a high rate of complete remission (CR) and overall response rate (ORR), in a study on 204 patients with advanced stage NHL treated with a combination chemotherapy. The combination used was cyclophosphamide 750 mg/m^2 day 1, doxorubicin 50 mg/m^2 day 1, vincristine 1.4 mg/m^2 (maximum 2 mg) day 1 and prednisone 100 mg day 1-5, and became known by its acronym CHOP. The longevity of this regimen in the treatment of NHL, can hardly have been foreseen by the investigators, but has proved to be nothing less than remarkable.

CHOP-treatment resulted in a substantial fraction of cured patients, but a proportion of patients did not respond or subsequently relapsed. Thus efforts were made to develop combinations even more efficient than CHOP, and during the 1980's

several intensive combinations were reported to yield, what seemed to be better response rates and survival, compared to previous results. In 1993 Fisher et al,[76] reported a randomized phase III trial performed by the South Western Oncology Group (SWOG), comparing CHOP to methotrexate with leucovorin rescue, bleomycin, doxorubicin, cyclophosphamide, vincristine and dexamethasone (m-BACOD) and prednisone, doxorubicin, cyclophosphamide and etoposide followed by cytarabine, bleomycin, vincristine and methotrexate with leucovorin rescue (ProMACE-CytaBOM) and methotrexate with leucovorin rescue, doxorubicin, cyclophosphamide, vincristine, prednisone and bleomycin (MACOP-B). None of the more intensive combinations showed a superior survival, and due to the combination of low cost and favorable toxicity profile, CHOP was established as the standard treatment for advanced intermediate- or high-grade NHL.

With the incorporation of granulocyte-colony stimulating factor in the supportive care of patients treated for aggressive NHL, it became feasible to shorten the interval between chemotherapy cycles from three to two weeks. This approach and the addition of etoposide, delivered on day 1-3, to CHOP (CHOEP) was evaluated in two randomized trials conducted by the Deutsche Studiengruppe Hochmaligne Non-Hodgkin Lymphome (DSHNHL) group. In patients up to 60 years with normal lactate dehydrogenase (LDH) levels, bi-weekly CHOEP (CHOEP 14) was suggested as new standard therapy due to superior event-free survival (EFS) and marginally improved overall survival (OS) compared to the other schedules evaluated.[77] In patients aged over 60 years, the addition of etoposide was less well tolerated, but CHOP 14 resulted in a better survival than three-weekly CHOP (CHOP 21). CHOP 14 was therefore suggested as standard therapy for patients above 60 years of age.[78]

Studies applying identical primary treatment in aggressive NHL of both B- and T-cell phenotype, came to an end with the appearance of rituximab, an IgG1 anti-CD20-antibody. In 2002 Coiffier et al, [79] showed that patients with diffuse large B-cell lymphoma (DLBCL), aged between 60 and 80 years, had superior OS if rituximab was added to CHOP (R-CHOP). The improvement in survival with R-CHOP has subsequently been confirmed in several studies in different types of B-cell lymphoma, and is now considered a part of standard treatment for all B-cell malignancies. With the addition of rituximab to chemotherapy, the results from the DSHNHL intensification studies has been challenged, since no difference in outcome has been demonstrated comparing R-CHOP 14 to R-CHOP 21 in DLBCL.[80, 81]

Treatment of T-LBL

The treatment of lymphoblastic lymphoma has followed a slightly different evolution compared to treatment of PTCL and DLBCL. Lymphoblastic lymphoma was initially viewed upon as an aggressive NHL, although its distinct biology and cellular similarity to lymphoblastic leukemia was recognized at an early stage.[23] Using various treatment regimens for NHL, initial studies reported rapid responses, but with short durations and frequent relapses in the CNS. These treatments very rarely translated into long term survival. [23, 82, 83] Chemotherapy protocols designed for ALL treatment were increasingly used in pediatric patients during the 1970's [84, 85] and influenced treatment in adult patients. Treatment modifications included intensified CNS prophylaxis, and favorable outcome compared to previous results was reported. [86] However, local and CNS relapses continued to be major areas of concern also with ALL treatment, and these problems have been the focus of further treatment modifications, in order to optimize outcome.

In the pediatric setting, the retrospective analysis of 105 pediatric patients enrolled in the prospective NHL-Berlin-Frankfurt-Münster 90 (NHL-BFM 90) study, found an encouraging 90% progression-free survival (PFS) at 5 years. In this study, patients were treated with an ALL protocol including prophylactic cranial irradiation, but without local radiotherapy for extra-CNS manifestations. Maintenance therapy with oral 6-mercaptopurine and methotrexate was administered until 2 years from start of treatment. [87] The results from this study proved that a very high cure rate was possible to achieve in T-LBL, raising hope also for adult patients.

Background of current studies

Current treatment in T cell lymphoblastic lymphoma

In adult T-LBL several retrospective series have been reported, but few prospective studies have been published. Patients prospectively enrolled in the German Multicenter Study Group for ALL (GMALL) studies 04/89 and 05/93 were treated with a similar induction and re-induction chemotherapy treatment as in the pediatric NHL-BFM 90 study. In the GMALL studies, both cranial and mediastinal radiotherapy (24 Gy) was however recommended. Consolidation treatment was administered in up to 12 months. The estimated OS and probability of continuous disease remission in CR patients at 7 years was 51% and 65% respectively. Only one patient suffered a CNS relapse, but 6 patients (13%) experienced mediastinal relapse despite irradiation. There were no statistically significant risk factors for outcome, and relapsed patients responded very poorly to salvage treatment.[88]

Recognizing the frequent, and mostly deleterious event, of relapsing disease, different strategies of consolidation treatment in responding patients have been explored.

Maintenance chemotherapy for 2-3 years was used in a prospective single institution study by Thomas et al, reporting an estimated 3 year OS of 67% in 33 adult LBL patients. Patients received induction treatment with a combination of fractionated cyclophosphamide, vincristine, Adriamycin and dexamethasone (hyper-CVAD) alternated with high-dose methotrexate and cytarabine. All patients with mediastinal disease were recommended to receive local radiotherapy (30-39 Gy), but no prophylactic CNS irradiation was applied.[89] Two out of 17 patients (12%) receiving mediastinal radiotherapy relapsed in the mediastinum.

As an alternative to maintenance chemotherapy, consolidative treatment with stem cell transplantation (SCT) has been explored. Outcome after a hybrid NHL/ALL induction followed by cyclophosphamide and total body irradiation as conditioning before autologous SCT (auto SCT), was evaluated in a population-based retrospective study. The reported 4 year EFS of 68% in 34 T-LBL was concluded to be favorable compared to previously published studies.[90] In a prospective trial, patients responding to ALL-type induction treatment, were randomized to receive either maintenance treatment for at least one year, or high-dose treatment with

carmustine, etoposide, cytarabine and melphalan (BEAM) or cyclophosphamide and total body irradiation followed by auto SCT. One-hundred nineteen patients were enrolled, but only 68 were randomized and the study was closed because of poor accrual. Failure of randomization was mostly due to patients' preferences. The study did not demonstrate any difference in 3-year OS between the randomized groups (56% versus 45% in auto SCT and maintenance group respectively), although there was a non-significant trend for a superior relapse-free survival in the auto SCT group (55% versus 24%, p=0.065).[91]

Consolidation with allogeneic SCT (allo SCT) has been compared to auto SCT through retrospective analysis of transplant registry data. In a study with 76 allo and 128 auto SCT patients, allo SCT was associated with a higher treatment related mortality (TRM) but lower relapse rate, resulting in a similar long term outcome for both strategies.[92] A similar outcome between allo and auto SCT was also reported in a smaller French patient series.[93]

Although risk factors are not well established in T-LBL patients entered in the prospective T-LBL/ALL GOELAL02-study were stratified using known parameters of prognostic importance in T-ALL. Patients were assigned to a high-risk group if any of the following risk factors were present: bone marrow involvement in combination with age > 35 years, white blood cell total count > $30x10^9$/L or failure of CR in bone marrow after the first induction treatment. These patients received consolidation with an intensified conditioning and auto SCT. Non-high risk patients were randomized between auto SCT after standard conditioning, or maintenance treatment, as consolidation. The 7 year OS was 64% and there were no significant differences between the treatment groups. Mediastinal recurrence rate (4/40) was similar to what was reported from the GMALL study (7/42), despite the omission of mediastinal radiotherapy from the treatment.[94]

Table 2.
Summary of studies reporting treatment and outcome in T-cell lymphoblastic lymphoma.

Reference	Study design	N	Median age (range)	Induction/ consolidation/ radiotherapy	Outcome
Hoelzer [88]	Prosp. multic	45	25 (15-61)	ALL-induction,cranial and mediastinal irradiation	7-y OS 51% 7-y DFS 62%
Sweetenham [91]	Prosp. randomized	119	26 (15-65)	ALL-induction, auto SCT vs maint.1y	3-y OS auto 56% maint. 45%
Hunault [94]	Prosp. randomized	45	27 (NR)	ALL- induction, TBI-conditioning auto SCT, low risk randomized to maint	7-y OS 64% 7-y RFS 65%

Lepertre [95]	Prosp. multic	131	33 (18-59)	ALL-induction, cranial RT, maint 2 y, allo SCT in some	3-y OS 69% 3-y EFS 63%
Thomas [89]	Prosp. single c	33	28 (17-59)	ALL-induction, mediastinal RT, maint. 2-3y	3-y OS 70% 3-y PFS 66%
Jabbour [96]	NR	27	31 (15-57)	ALL-induction, cranial RT, maint.1y	3-y OS 63%
Xie [97]	Retrosp, single c	57	26 (14-54)	ALL-induction, no RT, maint 1y, 17 auto SCT + maint	3-y OS 64% 3-y PFS 60%
Wang [98]	Retrosp, single c	36	20 (15-55)	ALL-induction, no RT, maint 2.5 y	3-y OS 67% 3-y PFS 65%
Fortune [99]	Retrosp, single c	31	23 (16-55)	ALL-induction, no RT, allo SCT in 21 patients	5-y OS allo 57%
Bersvendsen [100]	Retrosp, single c	25	33 (15-65)	mediastinal RT, auto SCT	8-y OS 84% 8-y PFS 76%
Song [90]	Retrosp. pop-based	34	26 (18-56)	Hybrid NHL/ALL-induction, auto SCT, TBI conditioning	4-y OS 72% 4-y EFS 68%
Milpied [93]	multic	25	22 (16-43)	Variable induction, allo SCT or auto SCT	4-y DFS allo 67% auto 70%
Bouabadallah [101]	Retrosp, single c	62	35* (14-70)	Variable induction, allo or auto SCT in CR1 in 27 pt	5-y OS 49%
Dabaja [102]	Retrosp, single c	43	NR	Variable induction, +/- mediastinal RT, maint. NR	5-y OS 66% 5-y FFP 64%
Levine [92]	Retrosp, registry	204 ¶	† 27 (5-53) ‡ 31 (2-67)	Variable induction,, allo SCT vs auto SCT	5-y OS allo 39% auto 44%
Le Gouille [103]	Prosp. multic	92	31 (18-61)	Lymphoma induction, 23 auto SCT 69 chemo	5-y OS 32% 5-y PFS 22%

§ (26 T-LBL); §§ (19 T-LBL); * mean age; ¶ 76 allo SCT,128 auto SCT; † allo SCT; ‡ auto SCT. allo, allogeneic stem cell transplantation; auto, autologous stem cell transplantation; DFS, disease-free survival; FFP, freedom from progression; maint, maintenance; multic, multicenter; Prosp, prospective; RFS, relapse-free survival; Retrosp, retrospective; RT, radiotherpay; single c, single center.

The possible association between mediastinal radiotherapy and a favorable outcome has been analyzed in a retrospective study on 43 patients with mediastinal disease at presentation. The patients had a CR to various chemotherapy regimens and patients treated with mediastinal radiation had a superior freedom from progression in the mediastinum (100% compared to 67% in the non-radiation group). There was no significant difference in overall freedom from progression or OS between the groups. The most common chemotherapy administered was hyper-CVAD (n=22),

and almost all patients receiving mediastinal radiotherapy belonged to this group (n=19). In the hyper-CVAD treated patients 2/16 patients receiving radiotherapy relapsed outside the mediastinum, while 2/6 not receiving radiotherapy relapsed within the mediastinum. The authors suggested that mediastinal irradiation was more beneficial in the context of better overall disease control after intensive chemotherapy.[102]

Without doubt, ALL type induction treatment leads to better outcome, than treatment with standard NHL regimens, in patients able to tolerate this intensive therapy. Except for this, there is however no evidence for one treatment regimen being superior to another in adult patients. Some of the details in a number of the published studies are summarized in Table 2. The small patient numbers and the mostly retrospective studies, are major obstacles to what conclusions can be drawn from the published literature. The scarce prospective studies are very difficult to compare, since there are multiple differences in the applied treatments. A major difficulty is also the lack of factors proven to be associated with outcome. Factors identified in some studies have not been prognostic in other cohorts, and many studies have failed to find any factors associated to outcome. Whether these disparities depend on differences in the applied treatment, or in non-measured patient- or disease-related characteristics, remains unclear.

It is notable that the reported outcomes following ALL type treatment, are based on more or less heavily selected patient populations. The population-based study by Song et al, [90] analyzing outcome in T-LBL patients from British Columbia, also applied a degree of selection by only including patients up till the age of 65 years. In the unselected cohort reported by Lamvik et al, [104] there was no detailed description of T-LBL patients. Clinical trials are designed to avoid confounding factors, and thereby introduces selection bias, with patients not fulfilling pre-specified inclusion criteria not reported. Single center studies also have a degree of selection bias in a rare diseases like T-LBL. For case series derived from tertiary centers, the oldest and most rapidly progressing cases are less likely to be included. The outcome in a population-based setting with current treatment strategies is thus not known.

Treatment in peripheral T-cell lymphomas

Initial studies on aggressive NHLs were by natural reasons dominated by B-cell NHLs, but included small numbers of PTCL patients. Although formally not demonstrated for PTCL specifically, the lack of evidence for a treatment superior to CHOP in aggressive NHL, led to CHOP being adopted also for the treatment of PTCLs.

The impact of T- versus B-cell phenotype NHL on outcome was not evident at first, and initial studies reported conflicting results.[105, 106] An analysis of the Groupe d'Etude des Lymphomes de l'Adulte (GELA) trial LNH84 convincingly demonstrated that T-cell lymphomas had a worse outcome than B-cell lymphomas when treated uniformly,[107] and this was confirmed in a retrospective analysis of B- versus T-cell phenotype of the LNH87 protocol, performed by the same study group.[108]

First-line treatment in PTCL

In studies with larger numbers of PTCL patients, a long term survival of 20-40%, have been reported for most subtypes.[15, 109] The exception from this poor survival is the outcome in ALK+ ALCL and SPTCL. ALK+ ALCL has repeatedly been found to have a favorable outcome with CHOP-like treatment.[15, 110, 111] For SPTCL, excellent outcome has been reported in cases without hemophagocytic syndrome.[67] Both these entities tend to occur in relatively young patients, and for ALK+ ALCL it has been a matter of debate, if age and other factors known to be associated with favorable outcome, may contribute more to the good prognosis, than the biologic features of the lymphoma itself.

The need for better treatments in other subtypes of PTCLs has long been evident, and efforts to find a treatment with a better outcome than CHOP has been made. Since PTCLs are rare lymphomas, much of the data on treatment derives from retrospective analyses, including relatively few patients, unfortunately resulting in rather low level of evidence. The inclusion of several distinct PTCL entities, results in even smaller subgroups, leading to further limitations of many studies.

At present there is only one randomized prospective trial published, focusing on first-line treatment in PTCL. In this trial, 88 patients were treated with either 8 cycles of three-weekly CHOP or etoposide, ifosfamide, cisplatin alternating with doxorubicin, bleomycin, vinblastine and dacarbazine, with 3 cycles of each delivered (VIP-rABVD). A similar 2-year EFS was achieved with both treatments, 45% for VIP-rABVD and 41% for CHOP 21. There was no difference in OS either, and the authors concluded that CHOP 21 remained the standard reference treatment.[112]

A recurrent finding in PTCL studies is that approximately 15-30% of the patients are refractory to first-line CHOP-treatment.[113-115] Hypothesizing that this could be attributed to an expression of multidrug resistance gene 1/P-glycoprotein, a phase 2 trial combining cisplatin, etoposide, gemcitabine and methylprednisolone (PEGS) was performed by the SWOG. These drugs are not influenced by the postulated

chemotherapy resistance mechanism. Twenty-seven out of 33 patients enrolled in the study were previously untreated, and among these, a disappointing 2-year PFS and OS of 14% and 36% respectively was achieved.[116]

In a Japanese multicenter phase II trial, 84 PTCL patients were treated up-front with cyclophosphamide, vincristine, bleomycin, etoposide, doxorubicin and prednisone (CyclOBEAP). The study included 14 patients with ALK+ ALCL, but in the remaining 70 patients with PTCL NOS or AITL, a 5-year PFS and OS of 58% and 67% respectively, was reported. In contrast to other studies, there were very few events during the first 2 years of the trial.[117]

A retrospective analysis of PTCL patients recruited in German DSHNHL prospective trials, has addressed the possible benefit of the addition of etoposide to CHOP. In 144 patients with age $\leq$ 60 years and normal LDH, CHOEP or variants of CHOEP were associated with a better EFS without a difference in OS. Forty-six out of the 144 patients, were diagnosed with ALK+ ALCL, and in this group CHOEP was associated with a better EFS (p=0.012), while it did not reach statistical significance among non-ALK+ ALCL PTCL patients (p=0.065). In patients > 60 years there was no association between a better outcome and the addition of etoposide or a bi-weekly compared to three-weekly therapy.[118] Whether further dose escalation in young ($\leq$ 60) high risk patients could have a beneficial effect was analyzed in 38 patients treated with 8 cycles of CHOEP 14 or 4 cycles of Mega-CHOEP 21. The outcome was inferior in the Mega-CHOEP group, and results did not suggest that further intensification would be of benefit, although the number of patients was small.[118]

Recently, encouraging results have been achieved in treatment of relapsed ALCL and other CD30+ PTCL by brentuximab vedotin (BV), an anti-CD30 antibody conjugated to a chemotoxin. These results have prompted studies of BV in front-line treatment. Results from a phase I trial with the sequential addition of BV to CHOP and BV maintenance after chemotherapy in CD30+ PTCLs has demonstrated this to be a feasible combination. Although not being the primary objective of the trial, it was noted that all 27 patients had responded at the end of treatment, and the estimated 1-year PFS was 71%.[119] This approach is currently being evaluated in an ongoing randomized phase III trial.

Combined modality chemo-radiotherapy

In patients with localized disease, a shorter course of chemotherapy consolidated with local radiotherapy can be an alternative strategy to consider, and has been shown to translate into excellent outcome in limited stage aggressive NHL.[120, 121] This strategy has been very poorly studied in the setting of PTCL specifically. In a study in ALCL, 46 patients with limited stage disease treated with

chemotherapy followed by local radiotherapy were found to have a favorable outcome with a 5-year median OS of 84%. The median age was only 38 years and the delivery of preceding chemotherapy was very heterogeneous in terms of number of cycles (range 1-14), making conclusions from the study difficult.[122] In another analysis of 75 patients with nodal PTCL entities with limited stage disease, no significant improvement was seen in patients who received consolidating radiotherapy after chemotherapy, compared to patients treated with chemotherapy only. Also in this study, the chemotherapy delivered was heterogeneous.[123]

Treatment considerations in specific PTCL subtypes

The best established exception from CHOP-like treatment as a reasonable choice in first-line therapy involve the NK/T-cell lymphomas of nasal type. In patients with stage I/II disease localized to the upper respiratory tract, early radiotherapy is associated with an improved survival compared to chemotherapy treatment.[124, 125] It has been an area of controversy, whether combined radio-chemotherapy results in improved outcome in these patients. Recently there has been two large studies published in favor of combined modality treatment, [126, 127] with one of the studies identifying a low-risk group that seems to do well without the addition of chemotherapy. [127] For patients with disseminated disease CHOP treatment is largely inefficient, as these lymphoma cells express the multidrug resistance gene 1/P-glycoprotein conferring resistance to doxorubicin and vinca alkaloids.[128] Based on efficacy in relapsed NK/T-cell lymphomas, a regimen consisting of dexamethasone, methotrexate, ifosfamide, L-asparaginase and etoposide (SMILE) was developed for the treatment of advanced stage NK/T-lymphomas. [129] Although associated with substantial hematological toxicity and frequent infectious complications, this treatment resulted in high ORR and Complete Remission (CR) rates in a phase II trial. [130] In 34 patients treated outside the phase II trial, an estimated 5 year OS of 50% was achieved, with the majority of patients receiving auto or allo SCT consolidation.[131]

Another disease where CHOP treatment seem largely inefficient, is the very uncommon hepatosplenic γδ T-cell lymphoma. Very poor outcome has been reported following CHOP-treatment, [132, 133] but there are no true informative studies on which induction chemotherapy would be preferred. For HSTCL patients achieving CR, there is a registry based study, supporting allo SCT instead of auto SCT as first-line consolidation. [134]

It is of note that the extranodal PTCL entities with very limited response to CHOP-like treatment, the NK/T-cell lymphomas and gamma-delta lymphomas, mainly derives from the innate immune systems (illustrated in Figure 1). This points to a

markedly different biology in these lymphomas, compared to PTCLs with an origin in the adaptive immune system.[6]

Stem cell transplantation as consolidation

Apart from a substantial part of PTCL patients being refractory to front-line chemotherapy, relapses occur frequently. In the early GELA study by Coiffier et al, [107] this was in fact the main reason for the inferior outcome in PTCL patients compared to the B-cell NHL patients. Treatment of relapsed aggressive NHL has typically included a second-line multiagent chemotherapy consolidated with high-dose treatment and auto SCT in responding patients. Evaluation in relapsed PTCL patients established that long term remissions were achievable with this approach.[135, 136] Due to the frequent relapses in PTCL, this strategy has been moved into up-front treatment, with the intention of lowering the rate of treatment failure. Several studies have reported outcome with up-front auto SCT, [114, 115, 137, 138] but the strategy has never been tested in a randomized study. The largest prospective study so far, was performed by the Nordic Lymphoma Group (NLG), and enrolled 160 PTCL patients. The outcome at 5 years were 44% and 51% for PFS and OS respectively, and was considered encouraging compared to historical results.[139]

In an analysis of EATL patients specifically, the adoption of a new treatment strategy containing ifosfamide, vincristine and etoposide (IVE) alternating with intermediate dose methotrexate, followed by up-front auto SCT, was compared to a historical CHOP-based approach. Compared to the old CHOP-like treatment, the OS was significantly better in the IVE plus auto SCT group, with several long term survivors. However, the CHOP-treated group was identified from a population-based source, while there was some selection of the IVE group.[140] The feasibility of long term remission in EATL patients after auto SCT has been further established in a transplant registry data set,[141] and the prospective NLG T-01 study.[139]

Recently, a prospective randomized trial comparing auto SCT to allo SCT in first CR, was stopped at interim analysis, since the hypothesized EFS advantage in the allo SCT group was deemed unlikely to be met. [142]

Treatment in relapsed PTCL

In relapsed and refractory PTCL patients, a multitude of different treatment regimens have been explored, many with few patients included in the studies. In fit patients, second-line combination therapy, typically cisplatin, cytarabine and

dexamethasone (DHAP) or ifosfamide, carboplatine and etoposide (ICE) have been used to bring the patient into a second remission. Depending on the primary treatment, consolidation with either auto SCT if not performed up-front, or allo SCT has often been recommended. A retrospective registry based study with 241 patients undergoing auto or allo SCT, concluded that there is a substantial higher treatment related mortality (TRM) with allo SCT, but found a 30% long term survival in patients receiving allo SCT in second or later remission.[143]

Most PTCL patients will not be eligible for allo SCT at relapse due to high age and comorbidities. Prognosis after relapse in the general population of PTCL patients is dismal. In a series from British Columbia including only patients not treated with SCT at relapse, median OS from time of relapse was 5.5 months. Relapse or progression occurred at a median of 6.7 months from initial diagnosis. Patients treated with a multiagent chemotherapy at relapse had a better outcome compared to patients treated with single agent therapy, although the study was retrospective, and results must be interpreted cautiously in this respect.[144] A population-based series, including 53 relapsed or refractory patients, reported a median survival after relapse of 2.5 months, and a 3-year OS post relapse of 19%.[145] In both these studies approximately 60% of the relapsed patients received chemotherapy.

Chemotherapy alone without consolidation has a very modest effect on long-term outcome in relapsed PTCL, and care must be taken not to cause unnecessary toxicity to old and frail patients with a treatment providing slim chances of a lasting remission. Although several low-intensity chemotherapy regimens have been used over the years and empirically proved to offer some relief, there are few studies reporting outcome in single agent chemotherapy regimens in relapsed PTCL. The effect of single agent gemcitabine has been reported in a series of 19 mycosis fungoides (MF) and 20 PTCLU (according to the Revised European-American Classification of Lymphoid Neoplasms) patients with relapsed/refractory disease. The ORR in PTCLU patients was 55%, with 30% CR.[146]

Bendamustine has been studied in relapsed/refractory PTCL in the "BENTLY" trial. Out of 60 patients enrolled 91% were diagnosed with PTCL NOS or AITL. The ORR was 50% with 30% CR. Only 25% of patients received the planned 6 cycles, with the low rate mostly due to progressive disease. The median duration of response was a disappointingly 3.5 months.[147]

Since cytostatic drugs provide limited benefit at relapse, a number of targeted treatment options have been explored in relapsed PTCL. Studies reporting outcome after single agent treatment are listed in Table 3. Many trials report an ORR around 30%, and the number of substances found to have an efficacy in PTCL is steadily increasing.[148-155]

Table 3.
Summary of studies on single agent treatment in relapsed/refractory PTCL.

Substance (Reference)	Diseases included	N	ORR/CR (%)	DOR (mo)	PFS (mo)	Mechanism of action
Alisertib [148]	PTCL/MF	37	30/5	NR	3	Aurora kinase inhibitor
Romidepsin [149]	PTCL	130	25/15	28	4	class 1 HDAC inhibitor
Belinostat [156]	PTCL	129	26/11	13.6	1.6	pan HDAC inhibitor
Everolimus [150]	PTCL/MF	16	44/	8.5	4.1	mTORC1 inhibitor
Lenalidomide [155]	PTCL	54	22/11	3.6	2.5	Immuno-modulatory
Pralatrexate [151]	PTCL/tMF	115	29/11	10.1	3.5	chemotherapy
Gemcitbine [146]	PTCL/MF	39	51/23	NR	NR	chemotherapy
Bendamustine [147]	PTCL	60	50/28	3.5	3.6	chemotherapy
Mogamulizumab [152]	PTCL/CTCL	24	35/14	NR	3.0	Anti CCR4 mab
Alemtuzumab [154]	PTCL	14	36/21	NR	NR	Anti CD52 mab
Zanolimumab [153]	PTCL	21	24/10	NR	NR	Anti CD4 mab
Brentuximab Vedotin[157]	ALCL	58	86/57	12.6	13.3	Anti CD30 mab cytotoxic conjugate

ALCL, anaplastic large cell lymphoma; DOR, duration of response; HDAC, histone deacetylase; MF, mycosis fungoides; mab, monoclonal antibody; mo, months; mTOR, mammalian target of rapamune; PTCL, peripheral T-cell lymphoma; t, transformed.

The most promising results hitherto, have been reported from the treatment of ALCL patients with brentuximab vedotin. Treatment of relapsed ALCL patients resulted in an ORR approaching 90% with comparatively long duration of responses.[157]

Central nervous system relapse in lymphoma

CNS involvement of the lymphoma can occur at diagnosis, or appear during the course of the disease. For most lymphomas this is a very uncommon localization, but in T-LBL and Burkitt lymphoma, it is a more regular feature.[6] Since many cytotoxic drugs routinely used for the treatment of lymphomas do not cross the blood-brain barrier, CNS involvement conveys a particular challenge in the management of the patient.

Relapse or progression, with secondary involvement of the CNS, is associated with very poor survival in aggressive NHL.[158] When more efficient therapies for advanced NHL became available, the need for preventing CNS involvement increased, and efforts to identify patients at risk for this complication began.[159]

The frequency of secondary CNS involvement varies depending on the lymphoma population under study, but for aggressive NHL, not including lymphoblastic lymphoma or Burkitt lymphoma, frequencies between 2-7% have been reported.[160-163]

Different studies have identified slightly different factors associated with an increased risk for CNS relapse, but elevated LDH and involvement of ≥ 2 extranodal localizations belong to the factors most frequently associated with this risk.[158, 160, 163] A high International Prognostic Index, a score based on, among other factors, LDH and number of extranodal manifestations, has also repeatedly been found to be associated with an increased risk. [161, 162, 164] The involvement of a number of specific anatomical localizations has also been identified as high-risk features, with engagement of testis, [162, 165, 166] breast,[167] and kidney [168, 169] as notable examples.

The role of prophylactic treatment to prevent CNS relapse has been extensively debated. The administration of intrathecal injections of methotrexate or in combination with cytarabine and/or prednisone has commonly been used, but with limited evidence for an effect.[170-172] Etoposide crosses the blood-brain barrier to some extent, and addition of this drug to CHOP has also been associated to a lower risk of later CNS spread.[163] Addition of rituximab to the treatment of DLBCL has resulted in more patients achieving a CR, and several studies have found a decrease in the overall incidence of CNS relapse, [168, 173] suggesting that the risk of CNS relapse is correlated to the general disease control. Analyses of the effect of intrathecal treatment and addition of etoposide within the R-CHOP era, have failed to establish an association to a lower incidence of CNS relapse.[173, 174]

High-dose methotrexate is a very important component in the treatment of primary CNS lymphoma, and has been explored as a prophylactic treatment in DLBCL. Comparing results with historical outcome in patients with a similar risk of CNS relapse, there are a few studies that have indicated a possible prophylactic effect of this treatment, [161, 175, 176] but randomized trials are lacking.

The incidence and risk factors for CNS relapse in PTCL has been very little studied. In a study by Yi et al, [177] an incidence of 8% was demonstrated, with elevated LDH and paranasal sinus involvement identified as risk factors. Outcome in patients with CNS relapse was dismal. The study by Yi and colleagues excluded patients with NK/T-cell lymphomas, but patients with this specific lymphoma were

characterized in a separate study, where a CNS relapse incidence of 5.6% was found. Advanced stage disease was the main risk factor for later CNS relapse.[178]

In a single center evaluation Pro et al, [179] found CNS relapse to occur in 2.6% of 250 PTCL patients. The majority of these events were seen late in the disease course, and were described as a rare and terminal complication.

Evaluating 153 PTCL patients with relapse, Mak et al, [144] found 8% of the relapses to involve the CNS, the majority as part of a systemic relapse, but further details was not reported.

Prognostic models in PTCL

In 1993, the work by an international collaboration on prognostic factors for survival in aggressive NHL was published. The study included over 3000 patients from clinical phase II and III trials, and resulted in five factors incorporated into a prognostic score. These five factors were age ($\leq$ 60 versus > 60 years), Ann Arbor stage (I-II versus III-IV), WHO PS (0 or 1 versus $\geq$ 2), extranodal site involvement (0-1 versus $\geq$ 2) and LDH ($\leq$ upper limit of normal (ULN) versus > ULN). This score has become known as the International Prognostic Index (IPI).[180] The validity of the IPI score was soon established in a population-based cohort,[181] and it has become a standard assessment tool for prognosis in aggressive NHLs.

The diagnostic classification of cases included in the 1993 publication, was made according to the Kiel or Rappaport diagnostic criteria, and details on B- or T-cell phenotype was not reported. The majority of patients in the initial studies were certainly B-cell NHL, but the validity of the IPI was subsequently tested in a small series of PTCL cases, and demonstrated to have a similar prognostic capacity.[182]

With increasing focus on biologic and clinical distinctions between different PTCL entities, the prognostic performance of the IPI and other factors have been evaluated for a number of the specific T-cell lymphomas. Focusing on PTCL NOS, a score was developed based on age, WHO PS and LDH, applying the same cut-offs as in the IPI, together with information on bone marrow infiltration. This so called PIT-score, was found to have a superior prognostic capacity, compared to the IPI, in the original study.[183] In the large series of mixed PTCL entities studied by the International T-Cell Lymphoma Project, IPI had a prognostic association in the entire cohort.[15] They also reported a separate analysis on PTCL NOS, where the IPI and PIT-scores were found to have a similar prognostic capacity.[70]

In ALCL, the IPI has been found to be prognostic in several studies. Apart from the IPI, the ALK+ ALCL has consistently been found to be associated with a better prognosis.[110, 118, 184] There is however a strong association between age and

ALK-expression (and thereby IPI score), and it has been a matter of debate about what factor contributes most to the good prognosis. In a retrospective analysis of ALCL patients enrolled in a number of clinical trials, performed by Sibon et al,[111] age < 40 years and low β2-microglobulin were the only independent prognostic factors for a superior outcome. ALK-positivity was not independently associated with outcome in this series of ALCL patients.[111] Another study demonstrated CD56-expression to be associated with an inferior outcome in both ALK+ and ALK- ALCL, and found ALK-expression to be very tightly associated with age, resulting in a lack of independent association with survival.[185]

Even though young ALK- ALCL patients with a low IPI might have a prognosis similar to young ALK+ ALCL, [184] this is not the case for patients with high IPI or age. Still, some patients with high-risk IPI are cured with CHOP-like treatment. A recent finding of recurrent genetic aberrations in the *DUSP22* and *TP63* genes, with prognostic associations, might offer an explanation to this fact. The cases carrying the *DUSP22* rearrangement had an outcome similar to ALK+ ALCL cases included in the study, while the few cases with rearranged *TP63* had a dismal outcome. Triple negative cases had an outcome intermediate between these two groups and there was no age related pattern in the distribution of the genetic groups.[186]

AITL is a disease that often presents at an advanced stage and patients tend to be older than the average PTCL patient,[15] and thus the IPI can be expected to discriminate groups with different survival less well in this disease. The poor performance of IPI as a prognostic tool was demonstrated in a cohort of 157 AITL patients included in GELA studies, where instead male gender, anemia (hemoglobin <120 g/dL) and mediastinal lymphadenopathy were significant risk factors.[187] In another cohort, only some of the IPI factors had a prognostic association, and both IPI and PIT-scores performed poorly in separating groups with different survival. Instead a score built on age > 60 years, WHO PS ≥ 2 and ≥ 2 extranodal sites involved, together with platelet count < 150 x 10^9/L and presence of B-symptoms revealed a low-risk group (0-1 points) and a high-risk group (2-5 points).[188] This score was demonstrated to have a similar performance when applied in the independent cohort of the 157 patients in the GELA study.[188]

For patients with EATL included in the large study by the International T-Cell Lymphoma Project, the PIT score had a better prognostic capacity for survival than the IPI. Apart from the PIT score, a patient history of coeliac sprue was the only factor of independent prognostic association, as it was associated with a shorter failure-free survival, but not OS. [21] This cohort was not population-based and the majority of patients had been treated with chemotherapy.

In a recent analysis of 92 EATL patients, the presence of B-symptoms had a very marked impact on outcome and identified a high-risk group. In patients without B-

symptoms, an IPI of 0-1 identified a low-risk group, while IPI 2-5 translated into an intermediate-risk group in a proposed EATL-specific prognostic index (EPI). Intestinal perforation at diagnosis did not associate to an inferior survival.[189]

The impact of different factors on outcome is related to the treatment applied. In NK/T-cell lymphoma nasal type, treatment strategy is very different in localized compared to advanced stage disease. Unprecedented in size, a cohort of 1273 patients with limited stage (Ann Arbor I-II) NK/T-cell lymphoma, was described in a recent publication. Results demonstrated presence of any of the risk factors age > 60 years, WHO PS ≥ 2, stage II disease, LDH > ULN or primary tumor invasion (into neighboring structures or organs) to be associated to inferior survival if patients were treated with radiotherapy only, as compared to radiotherapy followed by chemotherapy. Treatment with chemotherapy only resulted in an inferior survival regardless of any risk factors.[127]

In patients with advanced NK/T-cell lymphoma treated with the SMILE regimen, IPI before treatment has been shown to be associated to OS and disease-free survival in a cohort including both newly diagnosed and relapsed patients.[131] In this series, EBV levels in peripheral blood after SMILE treatment was a strong prognostic factor. Patients having undetectable levels of EBV at start, or reaching this during or after SMILE treatment, had a superior outcome compared to patients with detectable EBV.[190] This factor has also been evaluated in patients treated with SMILE consolidated with auto SCT, where a pre-transplant level of < 60 copies/ µL was the only factor associated with a better OS.[191]

Comorbidity and survival in lymphoma

In the efforts to improve treatment and outcome in lymphoma patients, focusing on the malignant disease itself is natural, but many of the patients are elderly and have a complicated medical history. In clinical trials, individuals with significant concomitant disease are frequently excluded. In contrast, in the every-day clinical setting, comorbidities are common and important challenges in the care of the individual patient.

The impact of comorbidity in cancer has been investigated in many different settings. It has been demonstrated that the aggressiveness of the tumor, and the available treatment, both influence to what degree comorbid conditions affects survival.[192, 193]

Comorbidity is common in lymphoma patients, from an age that approximately corresponds to the median age of many NHL diagnoses. In a Dutch population-based series, only 13% of the patients < 60 years suffered from any comorbidity,

while 82% of patients aged ≥ 60 years suffered from at least one concomitant disease.[194]

Comorbidity has been found to impact treatment of lymphoma patients. In a retrospective study in DLBCL patients, the Cumulative Illness Rating Scale (CIRS) comorbidity score was associated to a dose reduction of chemotherapy, independent of age.[195] Using the Charlson Comorbidity Index (CCI), a retrospective analysis in DLBCL patients aged over 70 years, could not detect any association between the CCI score, and delivery of treatment less intense than standard treatment (R-CHOP).[196] In contrast, a study in DLBCL patients ≥ 65 years found an association between CCI ≥ 2 and a lower received dose intensity (RDI) in CHOP-treated patients.[197] In aggressive NHL patients aged over 60 years, a population-based study found that a CCI score of ≥ 2 was associated to less frequent administration of chemotherapy compared to radiotherapy or no therapy. However, no further age-stratification was performed in this study.[198] An unselected prospective trial in DLBCL patients aged ≥ 18 years established an association between CCI score ≥ 2 and a lower RDI and increased incidence of grade III/IV toxicity events.[199] Most of these studies indicate that comorbidity impacts choice of therapy, and tolerance to treatment outside clinical trials.

Several studies have established increased comorbidity as an independent risk factor for inferior survival in lymphoma.[197-200] This has also been investigated in two studies in younger NHL patients treated with high-dose chemotherapy and auto SCT at relapse. In a retrospective analysis of 151 patients, a correlation between CCI score and treatment related mortality was found.[201] In another study, comorbidity was assessed using the hematopoietic SCT comorbidity index in 156 NHL patients, with an association between increase in comorbidity and lower likelihood of receipt of auto SCT. In both studies, comorbidity was independently associated with OS after performed auto SCT.[202]

There are no studies published, investigating comorbidity in PTCL specifically.

Aims of this work

The aim of the work presented in this thesis was to investigate how treatment and clinical factors may influence survival in a population-based cohort of T-cell lymphomas. The identification of groups with inferior outcome would aid in the design of future clinical trials and identify patients most likely to benefit from novel therapies. The analysis of a population-based cohort could make a valuable contribution by including patient groups poorly covered by clinical trials, and validate the general applicability of current treatment strategies. The studies included had the focus as follows:

- The aim of the first study (paper I) was to investigate the association between clinical factors, treatment and outcome in T-cell lymphoblastic lymphoma, in an unselected patient cohort
- In the second study (paper II), the aim was to investigate population-based survival in PTCLs, with regards to treatment and clinical characteristics at diagnosis. The study also had the more specific aim of analyzing the effect of up-front autologous stem cell transplantation and the addition of etoposide in primary treatment
- The third study (paper III), aimed at investigating the occurrence of, risk factors associated with, and outcome of secondary central nervous system involvement in PTCL
- The aim of the last study (paper IV), was to investigate the impact of comorbidity on outcome in an unselected cohort of PTCL patients

Patients

The patients in all studies in this thesis were identified through the Swedish Lymphoma Registry (SLR). Since 1958, it is mandatory to report all malignancies diagnosed in Sweden to the Swedish Cancer Registry (SCR). Reports to the SCR are primarily performed by the pathology departments. The information on lymphomas registered in the SCR does not reflect modern classification, and does not include clinical parameters in any detail.

The SLR was initiated by the Swedish Lymphoma Group in 2000, in order to improve the low resolution of data contained in the SCR. The SLR is one of several registries for quality control in Swedish healthcare, and administered through the Regional Cancer Centers (RCC). The RCC gets notified by the SCR at the registration of a lymphoma diagnosis. The RCC then initiates a case file and contacts the local healthcare unit responsible for the patient, to complete the SLR file. During the first years of the SLR, cases were reported through paper forms sent to the RCC, but from 2008 and onwards, this is managed by a web-based report system. Between 2000 and 2007, the registry contained basic clinical characteristics, e.g. stage and WHO performance status. From 2008 additional information such as treatment and response was included. The coverage of the SLR has been validated to include 92 – 95 % of all lymphoma cases registered in the SCR.[203]

For the purpose of the studies in this thesis, all patients with a first time diagnosis of T-cell lymphoma between 1st of January 2000 and 31st of December 2009 were selected from the SLR. This 10-year cohort, or parts of the cohort, formed the population investigated in all of the studies.

Methods

Data collection and validation

Three different lymphoma classifications were used during the selected 10-year study time period. To validate the diagnosis entered in the registry, all pathology reports, except for cases classified as mycosis fungoides, were checked and classified according to the WHO 2008 classification. There was no pathology review included in the studies, except in a few selected cases. All cases not fulfilling the diagnoses intended to be studied were excluded. The group of excluded cases mainly consisted of primary cutaneous TCL including primary cALCL.

After obtaining written informed consent from living patients, medical records from the treating institution were reviewed, and relevant data was collected.

Response and relapse

The generally accepted standard criteria for response, relapse and survival measures used in clinical lymphoma trials until very recently, were published by the International Harmonization Project in 2007.[204] The response criteria in these guidelines were defined to meet the increasing use of positron-emission tomography/computed tomography (PET/CT) in clinical trials. Detailed definitions are provided in the publication, but in short the previously used complete remission/unconfirmed (CRu) for small residual masses when using CT evaluation was omitted. PET/CT negative masses in PET-avid lymphomas should be considered CR, while residual nodal masses > 1.5 cm in longest axis were defined as PR when PET/CT is not used. PR was defined as a regression of perpendicularly measured nodal diameters of ≥50% with no new lesions, and if PET is used, at least one previously present lesion still PET-positive. We recorded responses according to these criteria, but detailed measurements were not included in all radiology reports, and typically only measurements of the most prominent lesions were mentioned together with a summarizing conclusion of partial or complete remission. In a few cases, no radiology report could be retrieved, and journal entries were used

as classification of response. There were also a variation with regard to the timing of treatment evaluation between cases.

The term relapse was defined by the International Harmonization Project, as new nodal lesions > 1.5 cm in the long axis, and for patients in PR, progression was defined as ≥50% increase of previously involved lesions. Measurements to establish the latter case were not always documented explicitly in patients' records and radiology reports. Management of lymphoma patients outside clinical trials in Sweden, has not included regular radiologic examinations in the absence of symptoms. Thus, follow-up radiologic exams were performed in the case of disease symptoms, and radiologic relapse/progression as documented in this "real-life" setting, was almost invariably followed by a treatment decision.

Comorbidity

Data on comorbidity was collected from the records kept at the department responsible for the treatment of the patient's lymphoma. Only comorbid conditions documented to be present before the onset of lymphoma were included. Comorbidity was recorded using the CCI, which includes the blood chemistry defined conditions, liver failure and renal failure. These laboratory abnormalities could be caused by the lymphoma itself, and if a relevant diseases was not documented to have been present before the onset of the lymphoma, the sole presence of laboratory abnormalities was not included among the patients' concomitant diseases. All previous malignancies except for non-melanoma skin cancers were recorded, regardless of the time lapse between the other malignancy and the lymphoma. In the original CCI, diabetes mellitus was divided into cases with or without complications. The presence of complications to diabetes mellitus was not reliably established from the available records, and therefore diabetes mellitus was recorded as present or absent, with a score of one point awarded in the present study.

Statistics

General

In all studies OS was defined as the time from the diagnostic procedure to the time of death from any cause or latest follow-up, measured in days. PFS was defined similarly, as the time from diagnostic procedure to the time of investigation

establishing either a recurrence or progression of disease, death from any cause or latest follow-up. All tests were 2-sided, and a p-value <0.05 was considered statistically significant. All statistics were performed with IBM SPSS version 22.0 (version 19.0 in paper I) (SPSS Inc., Chicago, IL).

Paper I

Distribution differences of clinical characteristics at the categorical level were analyzed using χ^2-test, and age distributions were analyzed using Mann-Whitney U-test. Time to progression was defined as the time from the diagnosis to time of procedure proving relapse or death from lymphoma. Survival curves were calculated using the Kaplan-Meier method and compared by log-rank test. Risk factors for OS and PFS were analyzed using the Cox proportional hazard ratios method, with hazard ratios given as the mean values for the entire time interval. Individual factors were analyzed in univariable analysis and factors with $p \leq 0.1$ were tested in a multivariable model.

Paper II

Distribution differences of clinical characteristics at the categorical level were analyzed using χ^2-test, and age distributions were analyzed using Mann-Whitney U-test. Survival curves were calculated using the Kaplan-Meier method. Risk factors for OS and PFS were analyzed using the Cox proportional hazard ratios method, with hazard ratios given as the mean values for the entire time interval. Individual factors were analyzed in univariable analysis and factors with $p \leq 0.1$ were tested in a multivariable model, and final models were constructed using stepwise backward elimination of factors.

Paper III

Distribution differences of clinical characteristics at the categorical level were analyzed using χ^2-test or Fisher's exact test. OS from relapse was defined as time from diagnostic procedure establishing relapse to time of death from any cause or latest follow-up. Survival curves were calculated using the Kaplan-Meier method and groups were compared by log-rank test. Cumulative risk for CNS events was calculated using the Kaplan-Meier method, censoring for death from any cause. Risk factors for CNS relapse, and for OS after first relapse or progression, were analyzed with Cox proportional hazard ratios, with hazard ratios given as the mean values for the entire time interval. Individual factors were analyzed in univariable

analysis and factors with $p \leq 0.1$ were tested in a multivariable model, and a final model was constructed using stepwise forward selection of factors.

Paper IV

Distribution differences of clinical characteristics at the categorical level were analyzed using χ^2-test or Fisher's exact test. Survival curves were estimated using the Kaplan-Meier method and groups were compared using log-rank test. Odds ratios for receiving different intensities of treatment or treatment reduction were calculated by logistic regression in univariable analysis, and factors with $p \leq 0.1$ were included in multivariable logistic regressions and modeled through backward elimination of factors. Risk factors for OS and PFS were analyzed with Cox proportional hazard ratios, with hazard ratios given as the mean values for the entire time interval. Individual factors were analyzed in univariable analysis and factors with $p \leq 0.1$ were tested in a multivariable model. Final Cox models were constructed using stepwise backward elimination of factors.

Methodological considerations

All papers: The documentation of progression was in many aspects more consistent with the definition of an event, but progression-free survival was chosen instead of event-free survival, since the SLR is built upon the terms progression and relapse, and does not include other events.

Paper I: In the time to progression analysis in hyper-CVAD treated patients, the non-irradiated group could have included patients with early relapse before radiotherapy theoretically could have started. This would have created an unfair comparison. However, all patients treated with hyper-CVAD started their planned consolidation therapy, leaving all patients eligible for radiotherapy, something that is not evident from the description of the analysis included in the paper.

Paper III: Death is to be considered a competing event to the CNS event end point. Censoring for competing events influence the results relatively little if the competing event is uncommon, which was not the case in this study. Censoring of the competing event has influenced the Kaplan-Meier estimates of cumulative risk of CNS events, with curves illustrating an overestimation of the risk.

Paper IV: The choice of CCI as the score to document comorbidity, was based on its previous frequent use in a wide variety of diseases, including studies in aggressive NHL and DLBCL. Parameters included in this score were assumed to be relatively well documented in patients' records and reliably measured in retrospect.

The CCI does not cover all aspects of coexisting disease, and for some particular patient groups, like SCT patients, other scores have been shown to be more suitable. The use of other scores may have resulted in different findings, but a more extensive data collection was not feasible.

Paper IV: Absolut survival is perhaps not the most appropriate measure in an elderly population. Relative survival might be considered in the survival analysis of patients $\geq$ 75years old and could possibly reveal different results.

Paper IV: The risk associated with one particular exposition is not necessarily constant, but can depend on other expositions, and thus vary between groups. This phenomenon is known as statistical interaction, and can be explored in multivariable models. The risk of increase in CCI, might not be equal in different age groups, and this should be considered to be included in the analysis in paper IV.

Results

Outcome in T-cell lymphoblastic lymphoma – Paper I

The first study aimed at investigating the outcome of current treatment strategies in an unselected cohort of T-LBL patients.

In all, 39 patients were confirmed to be diagnosed with T-LBL during the selected 10-year period. An additional 7 patients were registered with T-LBL in the SLR, but were found to have bone marrow infiltration exceeding 25%, and were re-classified as T-ALL and excluded from the analyses.

The median age in the cohort was 40 years, with a male predominance (62% of patients). The great majority of patients had a mediastinal tumor and 2/3 had bulky disease. Two patients presented with CNS involvement at diagnosis and pleural effusion was common. Female patients were found to be significantly older than male patients (median age 66 years compared to 37 years, p=0.027).

A large number of regimens had been used in the cohort. Seven different intensive ALL-type regimens were used, as well as 3 different non-intensive lymphoma regimens. Analysis of data was performed for the entire cohort and for the intensive treatment group separately. The group receiving non-intensive treatment consisted of 7 patients and a separate analysis was not meaningful, due to the small number of patients. Data on treatment were missing in two patients.

In the entire cohort, the 5-year OS was 42%, with only one patient surviving after non-intensive treatment. In the group receiving various ALL-oriented treatments the 5-year PFS was 49%, as illustrated in Figure 3, with no relapses later than 33 months after initial diagnosis.

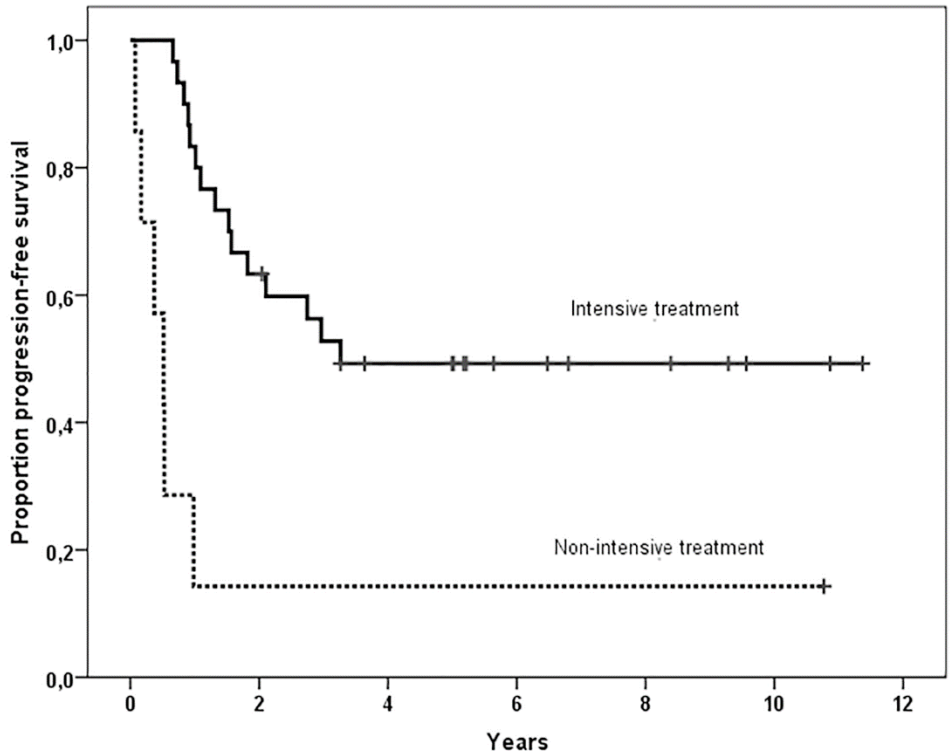

Figure 3. PFS in T-LBL patients by treatment intensity. Intensive treatment (solid line) and non-intensive treatment (dashed line).

Factors associated with inferior survival are listed in Table 4. Age, female gender and non-intensive treatment were associated with each other. In patients treated with intensive regimens CNS-involvement at diagnosis was the only factor associated with inferior survival, while age and gender showed no association with outcome.

Relapse was the main reason for treatment failure. PET/CT was used in a non-uniform manner for treatment evaluation in 13 of the patients receiving intensive treatment. All PET-scans were interpreted as negative, but 7 of these patients relapsed.

The most common intensive treatment was hyper-CVAD. Among the 19 patients treated with hyper-CVAD, four received mediastinal irradiation. There were no relapses among the irradiated patients, resulting in a significantly longer time to progression (p=0.047) compared to the non-irradiated group.

Table 4.

Risk factors associated to outcome in T-LBL (paper I). Univariable and mutivariable analysis of overall and progression-free survival.

Factor	OS			PFS		
	N	Univariable, HR (95 % CI); p	Multivariable, HR (95 % CI);p	N	Univariable, HR (95 % CI);p	Multivariable, HR (95 % CI);p
Total cohort						
age	39	1.04 (1.01-1.06) ; p=0.007	1.01 (0.98-1.05); p=0.432	37	1.03 (1.01-1.06); p=0.021	1.01 (0.97-1.04); p=0.773
female gender	39	4.67 (1.96-11.1); p=0.001	4.29 (1.68-11.0); p=0.002	37	4.18 (1.74-10.0); p=0.001	3.71 (1.47-9.37); p=0.006
non-intensive treament	37	5.63 (2.11-15.0); p=0.001	4.09 (1.04-16.1); p=0.002	37	5.18 (1.96-13.7); p=0.001	3.90 (0.97-15.7); p=0.056
Intensive treatment group						
female gender	30	2.55 (0.90-7.24); p=0.078	1.94 (0.59-6.31); p=0.273	30	2.37 (0.84-6.68); p=0.103	1.71 (0.52-5.55); p=0.375
CNS involvement	30	7.44 (1.42-39.0); p=0.017	4.59 (0.74-28.6); p=0.103	30	13.3 (2.18-81.4); p=0.005	8.96 (1.23-65.1); p=0.030

Treatment and prognostic factors in peripheral T-cell lymphomas – Paper II

This study aimed at investigating how clinical factors and treatment strategies associated with outcome in PTCL patients from a population-based series.

A total of 1230 patients with any type of T-cell lymphoma were identified through the SLR, constituting 7.4% of all Swedish lymphoma cases during this 10-year period (B-cell Chronic Lymphocytic Leukemia excluded). 755 patients were confirmed to have a non-leukemic, non-cutaneous type PTCL after review of pathology reports and patient's files.

The most common nodal PTCL was PTCL NOS followed by ALCL and AITL. Extranodal PTCL entities were less frequent than nodal subtypes, with EATL being the most common extranodal PTCL. In 57 out of 755 (7.5%) cases, a specific subtype diagnosis was not established, in many instances because limited diagnostic material was available. For the purpose of analyses, these patients were denoted T-cell lymphoma unspecified (TCL U), not representing any specified lymphoma entity in the WHO classification.

The median age in the entire cohort was 67 years, with median age in the various subtypes ranging from 41 years in ALK+ ALCL to 72 years in TCL U. There was a male predominance and a majority of the patients presented with an advanced stage disease (65%) and an elevated LDH (54%).

Long term survival was superior in ALK+ ALCL (5-year OS 79%) compared to the other nodal PTCL entities ALK- ALCL, AITL and PTCL NOS (5-year OS: 38%, 32% and 28% respectively). NK/T-cell lymphoma showed an inferior survival compared to PTCL NOS with a 5-year OS of 20.5% (p=0.001).

Risk factors associated with survival in the entire cohort are displayed in Figure 4. Notably, male gender was independently associated with inferior survival.

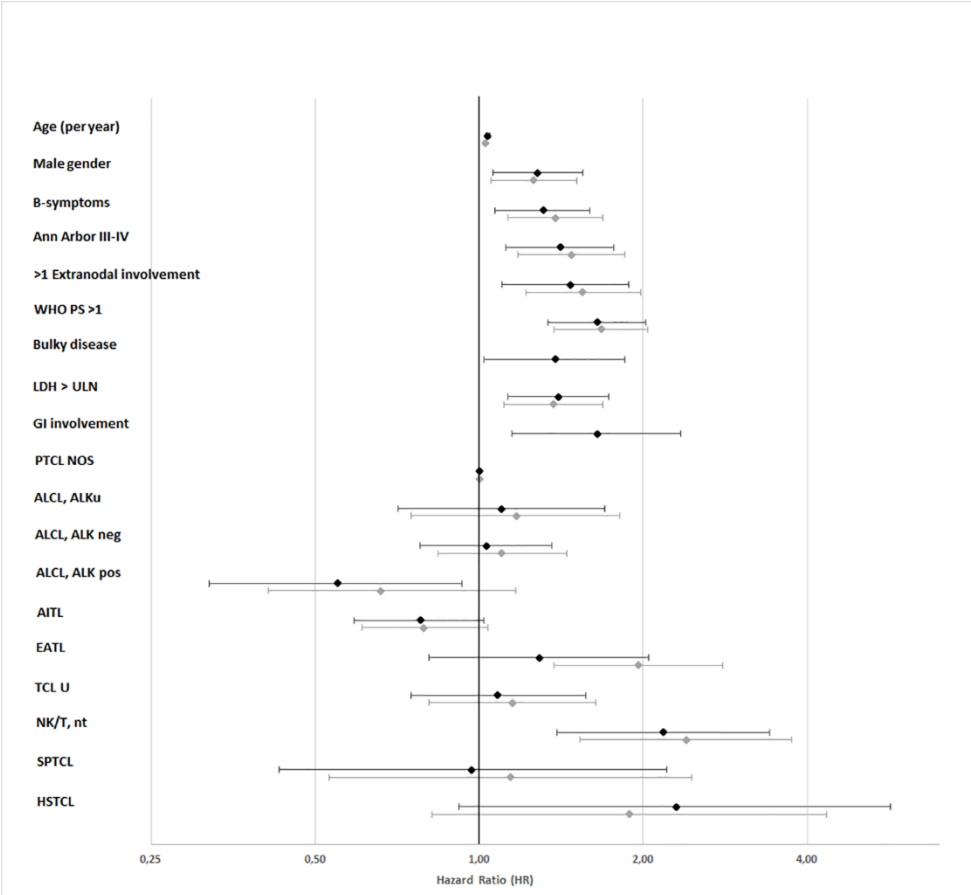

Figure 4. Graphic illustration of risk factors associated with survival in PTCL. HR values above 1 indicate an increased risk, while HR values below 1 indicate a decreased risk. Numeric values are published in Table 2, paper II. Black diamonds and bars represent OS, grey diamonds and bars represent PFS.

The treatment in the cohort was heterogeneous, but the most common primary treatment was CHOP (n=326) or CHOEP (n=157). One-hundred four patients received up-front auto SCT, and 5 patients received up-front allo SCT. Patients were divided into two groups by the intention of treatment with up-front auto SCT or not, based on documentation in patients' files. Patients fulfilling criteria for the current recommendations in national treatment guidelines to receive auto SCT consolidation in first-line treatment were selected for analysis. In this subset of 252 patients, 128 patients were planned for auto SCT. Auto SCT was associated with superior OS (HR 0.58 95% CI 0.40-0.84, p=0.004) and PFS (HR 0.56 95% CI 0.39-0.81, p=0.002) in multivariable analysis. In the same subset of patients, the association between CHOEP compared to CHOP and outcome was analyzed. In

patients up to 60 years, CHOEP treatment was associated to a better PFS (HR 0.49 95% CI 0.29-0.83, p=0.008).

Outcome in limited stage (Ann Arbor I-II), nodal PTCL was compared between patients treated with 3 or 4 courses of CHOP or CHOEP treatment consolidated with local radiotherapy and patients treated with at least 6 courses of CHOP or CHOEP without any consolidation therapy. No significant difference in survival was found.

The prognostic capacity of IPI and PIT-scores were compared in PTCL NOS. Both scores separated the cohort into categories with different subsequent survival, as illustrated in Figure 5.

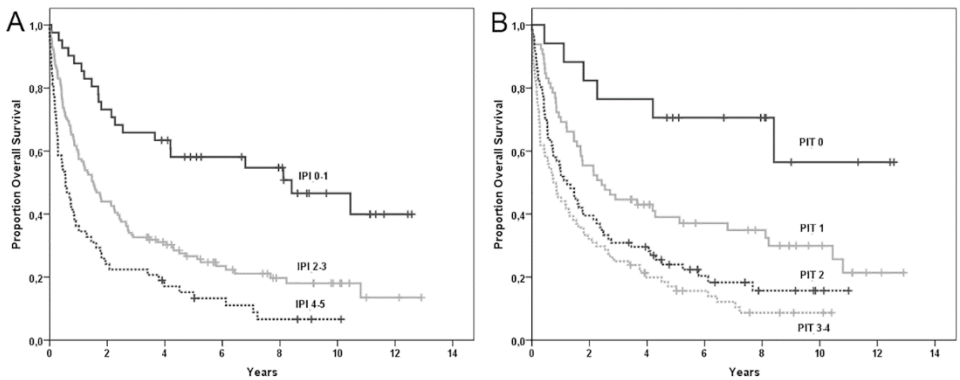

Figure 5. Survival according to IPI and PIT in patients with PTCL NOS. Overall survival according to (A) IPI-score and (B) PIT-score.

CNS relapse in PTCL – Paper III

This study aimed at investigating the occurrence of, and risk factors associated with CNS relapse in PTCL.

Out of 635 patients, 10 cases with CNS involvement at diagnosis were excluded from further analysis. Among the remaining 625 patients with complete data, 369 experienced relapse or progression. In 28 of the 625 patients (4.5%) disease recurrence involved the CNS. CNS involvement occurred at a median of 4.3 months after initial diagnosis, with the latest CNS relapse recorded after 30 months. Leptomeningeal involvement was more common than parenchymal involvement. Twenty-one out of 28 CNS events occurred at first relapse or progression.

Risk factors for CNS involvement identified in multivariable analysis were > 1 extranodal involvement, GI involvement and skin involvement. Cumulative risk of CNS relapse in patients with or without risk factors are illustrated in Figure 6.

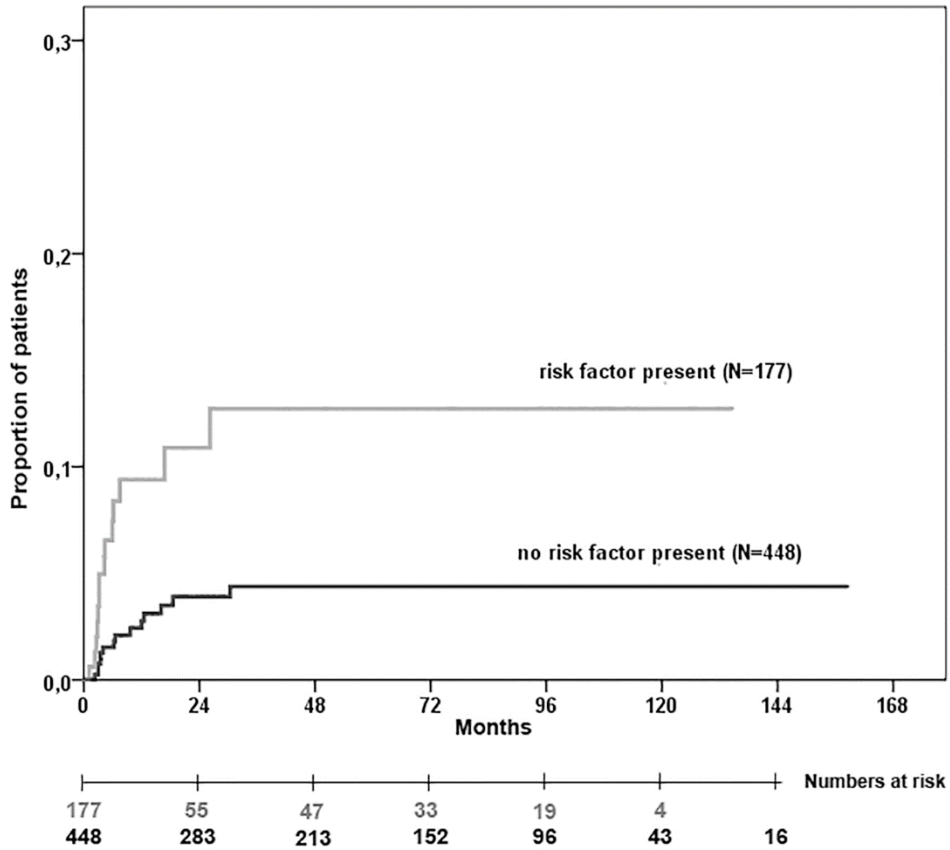

Figure 6. Cumulative incidence of CNS relapse/progression. Separation by risk factors, any risk factor present (grey line and grey numbers) or no risk factor present (black line and black numbers).

Treatment modifications with intrathecal administration of chemotherapy, addition of etoposide to CHOP and auto SCT and the association with CNS relapse was analyzed, but no associations to the risk of CNS relapse could be established.

Patients suffering from CNS relapse had a dismal prognosis, but this was true also for relapsing patients without CNS involvement. There was no significant difference in OS from time of relapse or progression in patients with CNS (median OS 1.1 months) compared to without CNS involvement (median OS 3.8 months) (log rank p=0.082).

Impact of comorbidity in PTCL – Paper IV

The fourth study aimed at investigating the possible impact of comorbidity on outcome in PTCL.

Comorbidity was recorded according to the CCI, and at least one concomitant disease was present in 263 in the 694 patients (38%) for whom data on comorbidity was available. Presence of comorbidity correlated to an increase in age.

An increase in CCI score was associated with inferior survival. Survival in patients with CCI score of 2 was not significantly different compared to patients with a higher score, and CCI was thus grouped into three categories (0, 1, ≥ 2), for further analyses.

The association between inferior survival and increase in CCI was found to be independent from other prognostic factors in multivariable analysis in the entire cohort.

To explore the relationship between comorbidity and treatment intensity, chemotherapy regimens were classified into curative treatments, consisting of CHOP or more intensive treatments, low intensity treatments and a group not receiving treatment.

Increase in CCI was not independently associated with low intensity or no treatment in multivariable logistic regression. Age was the factor with the strongest association with low intensity treatment (per year increase OR 1.17, CI 95% 1.12-1.21, $p < 0.001$).

In CHOP and CHOEP treated patients, the association between dose reduction and increase in CCI was analyzed. The presence of comorbidity was independently associated with dose reduction in this subset of patients (CCI 1 OR 1.45, 95% CI 1.07-1.97 and CCI ≥ 2 OR 2.10 95% CI 1.14-3.88, p=0.016).

The impact of comorbidity was analyzed in the oldest patients (≥ 75 years), among which the treatment was most variable and comorbidity was most prevalent. Patients treated with curative and low intensity treatment showed a similar survival as illustrated in Figure 7A, and this was not changed by adjusting for CCI and age in multivariable analysis.

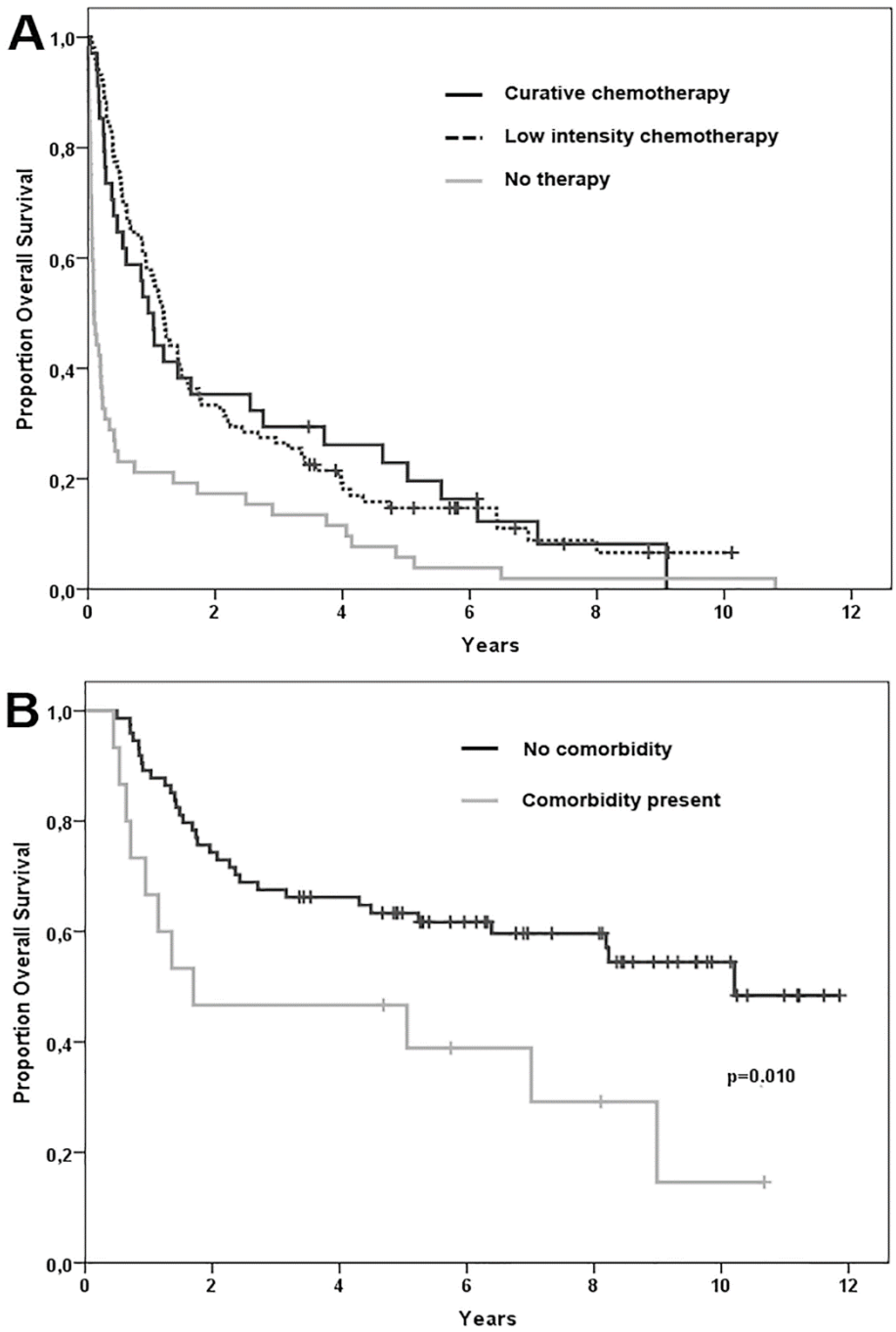

Figure 7. Overall Survival in PTCL patients. (A) OS in patients ≥ 75 years according to first-line treatment strategy (B) OS in patients after auto SCT according to presence of comorbidity.

The impact of comorbidity was also investigated in the subset of patients in which the association of up-front auto SCT and CHOEP treatment was analyzed in paper III. In this subset of patients a CCI ≥2 was more common in patients not planned for auto SCT. CCI was independently associated with survival in this cohort, but auto SCT was still independently associated with a better OS (HR 0.65 95% CI 0.44-0.96, p=0.030) and PFS (HR 0.63 95% CI 0.43-0.92, p=0.017) when adjusting for this factor. CCI score was the only factor at diagnosis with a prognostic impact after performed auto SCT, illustrated in Figure 7B.

Discussion and future perspectives

Population-based data

The basis of all four studies in this thesis is a cohort of patients identified through a population-based registry. The advantage of population-based studies are the inclusion of certain groups of patients that are possibly under-represented in clinical trials and case series from large centers. In clinical trials, there is often a strict selection of patients. Age, performance status and comorbidities are common selection criteria, excluding the oldest and most frail patients from studies.

Case series from large centers often include consecutive patients and do not apply any exclusion criteria. These studies will most likely include a proportion of patients that are excluded from clinical trials, but for rare diseases like T-cell lymphomas, academic centers rely to a high degree on referral cases. This dependence on patients being referred will create a referral-bias of mostly unknown degree, again probably excluding the oldest and most frail patients.

Population-based studies complement other types of studies in a valuable way. For the description of the disease, population-based cohorts are likely to provide the most complete overall picture. By providing the most complete spectrum of patients, they will also offer the best opportunity to identify groups of patients with the worst outcome, and possibly in the greatest need of better treatment. Population-based series will also, by their non-selection, have the benefit of including relatively large number of patients, an advantage when looking for rare events.

There are several disadvantages of population-based cohorts as well. When including all patients, there will be a great heterogeneity in the patient population. This heterogeneity will introduce a large number of confounding factors, making possible causal relations behind associations difficult to untangle.

As in many other population-based cohorts, the data in the present studies, was collected retrospectively. Retrospectively collected data will introduce further limitations to the study. Missing data will be one such problem. In individual cases, standard parameters may not have been documented and novel or exploratory prognostic factors are difficult to investigate, since these data are often missing or measured in a non-standardized manner.

Treatment decisions are made taking into account multiple parameters which are, in standard practice, not always documented explicitly. The assignment to a particular treatment will be based on partly undocumented factors, which when viewed in retrospect will introduce a degree of selection bias in different treatment groups.

The outcome of patients is often difficult to compare between studies. In general however, the outcome in population-based series can be expected to be inferior to outcomes in clinical trials, due to a more frail patient population in an unselected cohort.

Outcome in T-LBL

Although there are no randomized trials comparing standard lymphoma chemotherapy to ALL-type chemotherapy, long-term survival after introduction of ALL-type treatment have consistently been far better than in the studies applying lymphoma oriented treatment. There is however no single ALL-regimen that can be regarded as standard treatment of T-LBL in adults. Studies are relatively few, low number of patients are mostly included and the treatment regimens are almost as many as the published series. The lack of an established first-line treatment is reflected by the great diversity of ALL-regimens delivered in the present cohort. During parts of the studied time period, hyper-CVAD was recommended for the treatment of T-ALL in Swedish national guidelines, and this regimen was the most commonly used also for T-LBL in the present series.

All the different ALL-regimens have in common a higher intensity and more prolonged delivery of chemotherapy, than standard lymphoma regimens. This will limit the tolerability in older and frail patients, and raises the question of what outcome can be expected in an unselected patient cohort, something that has been poorly documented in the literature.

At the time of our study, there was only one publication [90] with a more population-based character, although an upper age limit of 65 years was applied in that study, since the aim was to investigate outcome after auto SCT consolidation. Patients older than 60 years are very few in the published series, but some of the intensive regimens can be tolerated in fit patients above this age.

The median age was 40 years in our series, one of the highest ever reported. The high median age was influenced by including patients not eligible for intensive chemotherapy, typically excluded in other studies, and illustrates the fact that T-LBL occur, though very rarely, also in elderly. The finding that median age was higher among female patients, has not been reported previously to our knowledge.

With the limited patient number this may be due to chance, although a true difference cannot be excluded, but needs to be validated in independent cohorts.

There was one male patient who was, by far, the youngest individual treated with low intensity treatment, and became a long term survivor. This individual could be regarded as an outlier in statistical terms, and influenced the results of the multivariable analysis. The rather unusual history of this case, in concert with the lack of pathology review in the study makes the inclusion of this individual open to discussion. If this individual was excluded, gender was no longer associated to outcome, and only non-intensive treatment was associated to inferior survival (HR 39; 95% CI 4.2-365, p=0.001).

Among patients treated with intensive regimens, an increase in age was not associated with an inferior outcome in our series, and three out of four patients aged above 60 years treated with intensive treatment became long-term survivors. In contrast, all but one patient, treated with lymphoma-type treatment succumbed to the disease. Our finding that age was not associated to outcome in patients treated with intensive therapy, has been reported previously in studies with ALL-type therapy.[88, 89, 94] This age independence is in contrast to most other lymphomas, in which higher age is almost invariably associated to inferior outcome and might be related to a very different biology in T-LBL, compared to e g PTCLs. Interestingly, there are indications that age as a risk factor is influenced by treatment, since studies with less intensive treatment have reported age to be associated with inferior survival also in T-LBL.[103, 205]

The 5-year OS of 49% among intensively treated patients in our series, is among the lowest reported. In part this may be explained by the population-based cohort including also some frail patients, but in the unselected series from British Columbia published by Song et al,[90] a 4-year OS of 72% was achieved. The ORR of 97% in the present study is comparable to other series, even though the CR rate of 57% the series is rather low.

The major reason for treatment failure in our cohort was, as in previous studies, relapse. Four hyper-CVAD treated patients received mediastinal radiotherapy, and none of them relapsed, resulting in a superior time to progression compared to hyper-CVAD treated patients not receiving radiotherapy. Numbers are small, and results should be interpreted with caution. It is difficult to tell if the inferior outcome in our study could possibly be relate to treatment modifications, like mostly omitting radiotherapy after hyper-CVAD, or just reflect chance variation. It is however of note, that the only risk factor for inferior survival in the hyper-CVAD series reported by Thomas et al, [89] was CNS involvement at diagnosis. This was associated to an inferior PFS also in our series, and both patients with CNS disease at diagnosis in our cohort, were treated with hyper-CVAD. Again, results should be interpreted

cautiously, since numbers were very low, but might indicate that a different treatment is preferable in this subset of patients.

The role of PET in the evaluation and prognostication of patients in T-LBL had not been investigated at the time of our study. PET/CT evaluation after induction treatment was performed in 13 patients, but did not obviously provide any valuable information, since 7 of these patients relapsed despite a normal PET-scan. The PET/CT evaluation was by no means performed in an uniform manner in our series, but a very recent publication from a prospective French trial, similarly could not find any prognostic value from PET-evaluation.[95] A German prospective trial reported as a meeting abstract, found a positive PET-scan to be correlated to PR, but not to OS or EFS.[206] At present PET/CT does not seem to be very promising for prediction of relapse in T-LBL, but further evaluation of its role is warranted before firm conclusions can be made.

The recent publication of Lepertre and colleagues,[95] seem to offer a step forward in the search for prognostic markers in T-LBL. In this study, the mutational status of the *NOTCH1/FBXW7/PTEN/RAS* genes previously reported to have a prognostic impact in T-ALL, was found to have independent prognostic impact in T-LBL patients. A robust prognostic model seems necessary to optimize consolidation strategies in T-LBL, and efforts should be made to further evaluate this genetic classifier in prospective interventional studies.

In many aspects the results from our study are in line with what has been published before, but point to the unmet need of more efficient therapy for elderly T-LBL patients. At present, all fit patients should be offered intensive therapy if they are judged to tolerate this. Whether different combinations of induction and consolidation treatment, than used in the present study, result in better outcome in a population-based cohort is unclear. This might be possible to evaluate in a future SLR-based study, since the Swedish treatment guidelines for adult T-LBL have changed since 2009.

Treatment and prognostic factors in peripheral T-cell lymphomas

The incidence of different lymphoma entities are known to vary between populations, and in the literature PTCLs are often stated to constitute around 10% of all NHL. This frequency is probably an over-estimation in a Swedish context, since the 755 patients identified in the second study (paper II) constitutes 4.6% of all NHL during this period. Counting all T-cell lymphomas, primary cutaneous and leukemic entities included, a total of 7.4% of all lymphomas displayed a T-cell

phenotype. This relatively low proportion might be representative in the wider Nordic area, since a bi-national study on ALCL demonstrated this lymphoma to constitute 1.3% of all lymphomas in both Sweden and Denmark separately.[207]

PTCL NOS was found to be the most frequent entity in our cohort, an expected result, since the work by the International T-Cell Lymphoma Project demonstrated this lymphoma to be the most common entity in both North America and Europe.[15] ALCL was found to be more frequent than AITL in our series, which was similar to the North American cohort described by the International T-Cell Lymphoma Project, with the difference of ALK- ALCL being more common than ALK+ ALCL in the present cohort.

EATL is over-all a very rare lymphoma, but an unusually high frequency has been reported from northern Europe, where coeliac disease is most prevalent. In our cohort, EATL represented 9% of all PTCLs, which in a global perspective is a high frequency, and EATL represented 61% of all PTCLs with gastrointestinal involvement. As expected, other primary extranodal PTCLs were exceedingly rare. It must however be underscored that there was no pathology review performed in the study, and the exact frequency of different subtypes must be considered somewhat preliminary.

The overall outcome of PTCL patients in the present study was rather poor, with 5-year OS ranging from approximately 20-40% between the different subtypes. Only ALK+ ALCL showed a clearly superior survival. This fits well into what has been published before, and a relatively low OS compared to other series can possibly be explained by the population-based nature of the series, an assumption supported by the similar outcome in the previously largest population-based study published by the British Columbia group. [109] The British Columbia study included patients diagnosed during the two decades preceding our study, and the similar outcome between the studies illustrate the general lack of progress in the treatment of PTCL.

In limited stage (Ann Arbor I-II) disease, a short chemotherapy treatment with radiotherapy consolidation may be an attractive alternative. The results from our study with a similar outcome in patients treated with 3-4 cycles of CHOP/CHOEP plus radiotherapy and $\geq$ 6 cycles of CHOP/CHOEP without radiotherapy are in agreement with a previous study,[123] but our study is the first to analyze the outcome of a shorter chemotherapy course in combination with radiotherapy in PTCL specifically.

The most pursued strategy to improve outcome has, until recently, been intensification of up-front treatment. The Nordic Lymphoma Group conducted a single-arm prospective trial (the NLG T-01 trial) during 2001-2007, treating newly diagnosed PTCL patients with CHOEP 14 x 6 (CHOP 14 in patients > 60 years) and auto SCT.[139] During the time period covered by the present study, the treatment

applied in the NLG T-01 study gradually became a standard approach for younger PTCL patients in Sweden. However, all Swedish centers did not participate in the NLG T-01 study, and some centers adopted this strategy slower than others. Due to this gradual adoption of up-front auto SCT, all patients meeting the selection criteria but not treated with up-front SCT, could automatically be assumed to be more frail or in other ways ineligible for this treatment.

The outcome in the NLG T-01 trial compared favorably to historic results, but there are no randomized trials comparing up-front auto SCT consolidation to no consolidation, and the evidence for the benefit of this strategy is limited. In an attempt to analyze the impact of up-front auto SCT we sorted patients into two groups, according to intention to treat (ITT) with up-front auto SCT or not. This retrospective classification most likely introduced some grouping bias. Auto SCT was generally planned very early, but this intention was not always documented in the patient's record at the start of the treatment. The bias most likely to have been introduced, derives from some cases with a very short survival, where auto SCT was never mentioned given the rapid and fatal course of the disease. With a longer survival these patients might have had a planned SCT documented.

A subset of patients matching those that currently are recommended up-front auto SCT in the Swedish national guidelines were selected for analysis. In these patients an association with superior OS and PFS in the auto SCT ITT group was found. An alternative analysis would have been to select patients in PR/CR after completion of first-line therapy, and compare outcome between transplanted and non-transplanted. In reality, this turned out to be difficult due to a substantial number of patients where a pre-transplant evaluation was missing.

In our series, an association between improved PFS and CHOEP treatment was present only if patients $\leq$ 60 years were included. This is similar to results from German studies demonstrating that CHOEP is poorly tolerated in patients above 60 years.[78] In contrast to the German study in PTCL, [118] the association with superior PFS in the present study also included patients with an elevated LDH.

The median age in the study cohort was 67 years, clearly illustrating that from a general perspective, intensification of chemotherapy will have a limited role to improve survival in PTCL. Approximately half of the patients will not be eligible for this type of treatment, and even for those able to tolerate the treatment, outcome is not overwhelmingly good. New treatment options are much needed, and for the elderly patients, targeted treatment without adding severe toxicity will be necessary to improve outcome. This need for completely novel treatment options are especially evident in relapsed disease. Survival from relapse in our series was 6 months in patients responding to first-line treatment, while it was only 2.5 months in patients with primary refractory disease. The survival in relapsed patients in our

series confirm the results published by the British Columbia group, who found a similarly dismal outcome in relapsed/refractory PTCL patients.[144]

We confirmed that several clinical factors are prognostic for outcome in a cohort of mixed PTCLs. We could not find evidence for a superior prognostic capacity by the PIT-score compared to the IPI-score in PTCL NOS, and it is likely that the better performance of PIT compared to IPI in the original publication by Gallamini et al, [183] was a result of over-fitting. As in previous studies, clinical factors are not sufficient to identify a true low-risk group among PTCLs (except young ALK+ ALCL). Additional unmeasured tumor or host factors seem to be important determinants for whom will be cured or not with today's treatment.

To bring the field forward, further molecular and genetic work has to be performed, and the collection of biologic material from the cohort described in this study is currently ongoing. In order to gather enough number of patients for meaningful statistical analyses, large international collaborations seem necessary, and will be crucial for the ultimate goal of prospective trials exploring treatment modifications in biologically homogeneous groups.

Central nervous system relapse in PTCL

Limited information exists about the risk of CNS involvement following relapse or progression in PTCL, and since biology differs markedly between PTCL and aggressive B-cell lymphomas, extrapolation between diseases might not be relevant.

In our study we found 28 cases with a secondary involvement of the CNS, representing 4.5% of all patients. Two previous studies in PTCL reported an incidence of 8.8% and 2.6% respectively.[177, 179] Our series is the largest of the published series, and since the frequency of CNS involvement falls in between the previously reported series, it probably reflects the average risk rather well.

The definition of CNS involvement by neurologic symptoms combined with confirmatory investigation by either cytological findings in cerebrospinal fluid or radiologic findings, may have resulted in an under-estimation of the incidence. In patients receiving palliative or no treatment, establishing a CNS involvement by extensive work-up may not have altered the treatment, and thus not been performed. This hypothesis was to some extent supported by known cases where emerging neurological symptoms in patients with palliative treatment, never were investigated in detail. All cases with an established CNS involvement had received treatment with curative intent.

CNS relapses in our series occurred early, with a median of 4.5 months after initial diagnosis. Most CNS involvements were part of the first relapse/progression, and isolated CNS involvement was equally common as involvement as part of a disseminated relapse in these patients. Leptomeningeal involvement were more frequent than parenchymal lymphoma. This pattern of CNS involvement largely agree with previous descriptions, since both Yi et al,[177] and Pro et al,[179] found leptomeningeal disease to be commonest. In the study on relapsed patients by Mak et al, [144] CNS involvement most frequently occurred in first relapse/progression. In the study by Yi et al, the majority of CNS involvements were part of a systemic relapse, but occurrence in first or later relapse was not reported explicitly.[177]

Risk factors for CNS involvement in our study related to extranodal involvement of the lymphoma at diagnosis. This pattern is reminiscent but not identical to risk factors in aggressive B-cell lymphomas, and further studies are needed to establish possible differences or similarities.

Some anatomic localizations of lymphoma, known to increase the risk for CNS involvement in aggressive NHL, were absent or present in very low numbers in our series. One example was testicular involvement, which was present in only 5 cases. One of these patients developed CNS involvement, and one patient with CNS relapse later developed a testicular involvement not present at initial diagnosis. It is likely that testicular involvement would have been found to have a significant risk for CNS spread, if numbers would have been higher.

The occurrence of CNS spread could be influenced by the treatment. Intrathecal treatment was applied in a minority of cases, likely to represent the patients estimated to have been at highest risk for CNS relapse. Etoposide and auto SCT have also been suggested to influence CNS relapse incidence, and given the great heterogeneity of our series, no meaningful conclusion could be made regarding treatment and risk. The possible benefit of treatment modifications should be analyzed in prospective trials, although large trials in PTCL have been few, and this question might be very difficult to answer.

The outcome of patients with CNS relapse/progression was very poor in our cohort. In the publication by Yi et al,[177] the outcome was found to be significantly worse among patients with CNS involvement, but the comparative group in that study included patients without relapse. In our series, the survival among patients with CNS involvement at first relapse/progression was not statistically inferior to other relapsed patients. Since the number of CNS relapses were low, it is possible that a larger cohort would reveal a survival difference, but our results further illustrate the dismal outcome in relapsed PTCL in general.

CNS relapse has a very poor outcome in PTCL, but it is not a major reason for the dismal outcome in relapsed PTCL patients at present, and efforts should focus on

treatment of relapsed PTCL in general. Our study provide a description of this poorly investigated complication, and provide baseline data for future comparisons.

Impact of comorbidity in PTCL

Since the impact of comorbidity is known to depend on the aggressiveness and treatment outcome of the tumor under study, it is not evident that results in aggressive B-cell lymphomas are relevant to PTCL. The treatment outcome is less favorable in PTCL compared to DLBCL, and comorbidity could be hypothesized to have less impact in PTCL.

In our study we demonstrate an association between comorbidity, measured by the CCI score, and outcome. This association was independent of other risk factors, and is in agreement with most previous studies in NHL. The majority of the patients in our series died from lymphoma progression, and the CCI was still associated with outcome when censoring for death unrelated to the lymphoma. We could demonstrate an association between elevated CCI and dose reduction in patients treated with CHOP or CHOEP, suggesting that poorer tolerance to treatment may be one of the factors leading to the inferior outcome associated with comorbidity. This has been suggested by some of the previous studies in lymphoma patients.[197, 199]

The CCI score was the only factor at diagnosis that was associated with survival in patients receiving up-front auto SCT. This finding is in concordance with results from patients, mostly non-PTCL, undergoing auto SCT at relapse.[201, 202] Our results suggested that presence of comorbidity was not only associated with all-cause mortality, but also lymphoma-related mortality specifically, also in this group of patients. The mechanisms behind this association is unclear, but might relate to treatment modifications not measured.

In the subset of patients selected for ITT auto SCT analysis in paper II, we found an imbalance in CCI score ≥ 2 between the groups, which was not unexpected, since patients with advanced comorbidity are not eligible for auto SCT. Comorbidity was independently prognostic in this group, but the risk reduction associated with auto SCT was still statistically significant when adjusting for CCI. Other methods to record comorbidity might however be better suited in this patient population, and may have yielded different results.

The oldest group of patients received the most variable first-line treatment, and outcome was analyzed in patients ≥ 75 years, according to treatment intensity. As CHOP is used for treatment with curative intent in younger patients, this term was adopted also for the elderly patient group. Less intensive treatments were denoted

low intensity treatment and were used with more outright palliative intention. Treatment with corticosteroids only, was not regarded as a disease modifying treatment equivalent to chemotherapy, and was grouped with patients not receiving any treatment at all.

The no treatment group had an inferior survival, but the finding that there were some long term survivors in this group was unexpected. It could possibly, to some extent, be explained by some heterogeneity of PTCL as a group. Two of the long term survivors were subject to surgery for small intestinal tumors, which turned out to be PTCLs, and these patients might actually have been cured from their lymphoma by the surgical procedure. In some cases corticosteroids might also have had a disease modifying effect, greater than assumed.

We could not detect any difference in survival between patients receiving curative treatment or low intensity treatment, despite adjusting for age, CCI and IPI. The retrospective nature of our data limit the conclusions on causality to be drawn, but the seeming lack of benefit of CHOP in elderly PTCL patients would be interesting to explore in a prospective study.

This study provides evidence that, despite unsatisfactory outcome from current treatment, comorbidity is an important factor for survival in PTCL. This should preferably be taken into account when analyzing population-based data in the future.

Conclusions

Paper I

Outcome with intensive ALL-type treatment is superior to standard lymphoma-type treatment in a population-based series of T-LBL, including patients ≥ 60 years of age. CNS-involvement at diagnosis, but not age, was associated with inferior survival in intensively treated patients.

Paper II

Male gender was associated with inferior outcome in a large population-based cohort of PTCL patients. Up-front auto SCT was associated with superior OS and PFS in patients ≤ 70 years with nodal PTCL (ALK+ ALCL excluded) or EATL in multivariable analysis. Addition of etoposide to CHOP was associated with superior PFS in nodal PTCL (ALK+ ALCL excluded) or EATL patients ≤ 60 years. PIT was not superior to IPI for prognostication in PTCL NOS.

Paper III

In PTCL, CNS involvement at relapse or progression occurred in a similar frequency as in aggressive B-cell NHL. Extensive (> 1 site) extranodal involvement, GI or skin involvement were associated with an increased risk for secondary CNS spread. Patients with CNS involvement at first relapse/progression had a similar dismal subsequent survival, as patients without CNS involvement at relapse.

Paper IV

Comorbidity measured by CCI showed an independent association with survival in PTCL. Elevated CCI was the only factor at diagnosis with an association with survival in patients undergoing auto SCT. Age, but not CCI, was associated with low intensity or withholding treatment in PTCL. Among patients ≥ 75 years there was no apparent difference in survival between patients treated with curative or low-intensity chemotherapy.

Concluding remarks

To achieve the ultimate goal of a personalized treatment in lymphoma patients, maximizing the benefit for every individual, multiple parameters have to be taken into consideration. This thesis illustrates some of the different factors, not only tumor-related, that need to be accounted for.

Young patients suffering from T-cell lymphoma can probably benefit to some extent from intensification of treatment already available. This benefit is most evident in T-LBL, a disease with a unique biology compared to PTCLs. In the larger patient group of PTCL, studies included in this thesis suggest a beneficial effect from treatment intensification in first-line, by addition of etoposide and up-front auto SCT.

The treatment intensification in PTCL most likely leads to a modest improvement, and the population-based data this thesis is built upon, depicts a reality where many of the PTCL patients are old and frail. These individuals will never benefit from intensification of treatment, and the results from paper IV demonstrate how abundant comorbidity is among elderly. Even standard chemotherapy can be difficult to tolerate, and the finding suggesting that "sub-standard" treatment does not translate into inferior survival, calls for Hippokrates words "primum non nocere", to be remembered. But foremost, these result serve as an illustration of how far from adequate PTCL-treatments we still are.

Prognostic factors are several and can guide in directing the efforts of developing new treatment strategies, but there is still much work to be done in order to find properties that predict response to therapy. As illustrated by the prognostic gene signature recently described in T-LBL, it is likely that molecular factors will play an important role in defining treatment strategies in the future. Apart from the gene signature in T-LBL, the alterations in the *DUSP22* and *TP63* genes in ALK- ALCL, are at present the molecular tests that probably have the greatest potential to be incorporated into standard practice in the near future. The favorable genetic group seem to have an excellent outcome to current standard therapy, and if the initial findings can be validated, some ALCL patients might even be available for treatment de-escalation by excluding up-front auto SCT consolidation.

There will probably never be one treatment that fits all PTCL patients, but the recent increase in the number of agents showing activity in PTCL is promising. Among

the novel treatments, brentuximab vedotin at present shows the most promising effect, and has the potential to be incorporated as part of standard treatment for some of the PTCL patients. How to best use this drug is still to be defined, and serving as an example that prediction of response is not always intuitive, there is no linear correlation between CD30 expression levels and effect of this drug.

Many of the other novel drugs show limited ORR, but the histone deacetylase inhibitors romidepsin and perhaps belinostat, have yielded prolonged responses in individual cases. These substances also display moderate toxicity, allowing for combination with chemotherapy, and thus the possibility of incorporation into front-line treatment. Translational research will be crucial to identify predictive markers for treatment response, since these and other novel drugs are probably important additions only in subsets of patients. Based on available data, it is likely that prediction of response will not be dependent on the current PTCL classification, but rather on as yet unidentified properties of the lymphomas. Future diagnostic methods will probably still include classic immunohistochemistry, but for many PTCL entities, molecular profiling will be even more important in the choice of treatment.

An improved molecular stratification will be an important tool in designing future prospective interventional trials. International collaborations will be necessary to perform conclusive studies, but despite ongoing and future efforts to conduct prospective trials, the scarcity of PTCL will continue to be a major challenge for the advancement of knowledge. It is likely that we to some extent will rely on results from non-prospective studies also in the future. One such area is the population-based effects of novel treatments in PTCL, and this thesis will hopefully contribute as a source for future comparison in these diseases.

Populärvetenskaplig sammanfattning

Tumörer med ursprung i lymfceller benämns lymfom och består av en rad olika tumörtyper, innefattande allt från ytterst aggressiva tumörer till stillsamma kroniska sjukdomar. Klassificering av lymfom har i takt med ökande kunskaper förändrats åtskilliga gånger genom åren. För närvarande urskiljs mer än 50 olika lymfom, vilka bedöms ha unika egenskaper och sannolikt ha uppstått genom olika mekanismer. Att identifiera specifika sjukdomsgrupper har varit avgörande för att utveckla nya, mer effektiva behandlingsmetoder för denna grupp av sjukdomar.

Lymfom kan ha sitt ursprung i B- eller T-lymfocyter, där B-cellslymfomen dominerar stort och utgör ca 90 % av alla lymfom. T-cellslymfomen som står för resterande 10 %, delas för närvarande upp i drygt 15 separata lymfomtyper, där flertalet tillhör gruppen aggressiva lymfom. Fördelningen av olika lymfomtyper uppvisar en geografisk variation i ett globalt perspektiv, men T-cellslymfom utgör överallt en liten minoritet. Kunskapen kring T-cellslymfom är sämre än för B-cellslymfom, till stora delar beroende på att sjukdomarna är ovanliga.

Behandling av T-cellslymfom grundar sig till stor del på terapier utvecklade för B-cellslymfom, men det har under lång tid varit känt att resultaten är sämre för patienter med T-cellslymfom än för B-cellslymfom.

Denna avhandling baserar sig på studier av patienter med olika typer av T-cellslymfom, som registrerats i det nationella Svenska lymfomregistret (SLR) under en 10-årsperiod. SLR är ett av Svensk sjukvårds kvalitetsregister och omfattar patienter från 18 års ålder. Registret ger goda förutsättningar att genomföra populationsbaserade studier, dvs studier som inkluderar samtliga patienter i en befolkning. SLR omfattar upp mot 95 % av de lymfompatienter som anmäls till det obligatoriska Svenska cancerregistret. Populationsbaserade studier är ett värdefullt komplement till andra typer av studier, exempelvis kliniska prövningar som i många fall bara omfattar utvalda patientgrupper.

Den första studien beskriver behandling och överlevnad vid T-cells lymfoblastlymfom, en lymfomtyp som har stora likheter med en variant av akut leukemi, och som i relativt hög utsträckning drabbar unga. Sjukdomen är ytterst ovanlig då endast 39 patienter insjuknade under 10-årsperioden. Knappt hälften av de patienter som behandlades med intensiv leukemi-inriktad terapi överlevde, medan de äldre patienter, som behandlades med mindre intensiv terapi klarade sig

ytterst dåligt. Resultaten var förväntade utifrån tidigare kunskap, men behandlingsresultat har inte undersökts i någon större utsträckning i en populationsbaserad patientgrupp. Val av intensiv eller icke-intensiv behandling var den faktor som huvudsakligen förutspådde överlevnad. För de flesta lymfomtyper ger ökande ålder en tydlig risk för sämre chans till bot, men för de personer som bedömdes tåla intensiv terapi i vår studie, var inte högre ålder förknippat med sämre överlevnad. Slutsatsen från studien blev att samtliga patienter som bedöms tåla intensiv behandling bör erbjudas sådan, oavsett ålder.

I avhandlingens övriga arbeten har patienter med vissa typer av perifera T-cellslymfom (PTCL) studerats. Ca 75 personer/år insjuknar i de lymfomvarianter som ingick i studierna. I avhandlingens andra arbete undersöktes överlevnaden i denna patientgrupp, utifrån sjukdoms- och patient-karakteristika samt behandling. Totalt sett avlider majoriteten av patienterna i sin sjukdom, och män klarade sig lite sämre än kvinnor. Vid återfall av sjukdomen är överlevnaden mycket begränsad. Ett samband mellan intensifiering av cellgiftsbehandling och bättre överlevnad kunde ses hos yngre patienter (under 60 år) vilket stöder ett fortsatt användande av denna behandlings-strategi.

I den tredje studien undersöktes förekomsten av sjukdomsspridning till centrala nervsystemet (CNS). Spridning till CNS är en svårbemästrad situation, då cellgifter har en begränsad förmåga att nå denna vävnad. CNS-spridning har tidigare huvudsakligen studerats för B-cellslymfom. Totalt identifierades 28 patienter som drabbades av denna sjukdomsutveckling. Om sjukdomen omfattade flera organ utanför lymfkörtlarna eller fanns i hud eller tarm ökade detta risken för att drabbas av CNS-spridning senare. Patienter med återfall av sjukdomen i CNS hade ytterst begränsad överlevnad, men det gällde även för patienter med återfall utanför CNS.

Den sista studien i avhandlingen fokuserar på samsjuklighet och dess betydelse för överlevnad hos PTCL-patienter. Tidigare studier har visat att samsjuklighet är vanligt hos äldre lymfompatienter och att det vid B-cellslymfom påverkar överlevnaden. Vi kunde i vår studie visa att det fanns ett samband mellan samsjuklighet och sämre överlevnad för PTCL-patienter. Studien visade ett samband mellan samsjuklighet och en ökad risk för att behandlingen genomfördes med cellgifter i lägre doser än standardnivå. Sambandet tyder på att en minskad förmåga att tåla behandling om man har andra sjukdomar än sitt lymfom, kan vara en av de faktorer som leder till sämre överlevnad.

Sammanfattningsvis har arbetena i denna avhandling bidragit till att öka den grundläggande kunskapen kring patient- och tumöregenskapers inverkan på överlevnad hos patienter med T-cellslymfom hämtade ur en patientgrupp representativ för nuvarande svenska förhållanden.

Acknowledgement

My acknowledgments for help and support in completing this thesis goes to people fluent in Swedish, and will therefore be held in this language.

Mats Jerkeman, min huvudhandledare. Med entusiasm och tålamod har du hjälpt mig att genomföra detta. Din positiva energi och oöverträffade förmåga att alltid svara snabbt har gjort min tid som doktorand både lätt och rolig. Jag vet att ditt genuina intresse för lymfomforskning gör det självklart att handleda studenter, men det har varit en stor förmån att ha fått ta din tid i anspråk. Tack för hjälpen!

Thomas Relander, min bihandledare. Att få dela dina kunskaper inom ämnet T-cellslymfom har varit helt centralt för det här arbetet, men minst lika viktigt är att du fått mig att känna mig så välkommen. Du har verkligen tagit hand om mig på bästa sätt! Jag hoppas bara att jag inte prövat ditt tålmod allt för mycket med min usla kommatering.

Till er båda. Det här har varit jätteroligt! Jag hoppas verkligen att vi fortsätter att arbeta tillsammans!

Hans Hagberg, medförfattare i första studien. Det är din förtjänst att detta blev av. Med entusiasm och lätt befallande blick fick du fart på mig där i ett trapphus på Akademiska sjukhuset. Du har efter det varit mig ytterst behjälplig i diverse projekt, och har också varit en stor förebild i det kliniska arbetet. Tack!

Jenny Törnqvist (f Landström). Du reste runt i stora delar av Sverige och hämtade in ovärderliga data. Utan din insats hade de här projekten inte gått att genomföra. Stort tack!

Gunhild Nordesjö Haglund, Klinikchef, Medicinkliniken Kalmar, tillsammans med Forskningskommittén, Landstinget Kalmar. Tack för att ni trott på detta och att ni gett så goda förutsättningar för mig att genomföra detta.

Utan Svenska lymfomregistret hade inte detta arbete kunnat genomföras, och jag vill framföra ett stort tack till Svenska lymfomgruppen som drivit registret och låtit mig ta del av många års bakomliggande arbete. Många personer har i olika sammanhang hjälpt till med datainsamling, men ett extra stort tack vill jag rikta till **Mats Ehinger**, **Christer Sundström**, **Birgitta Sander**, **Karin Ekström Smedby**, **Daniel Molin**, **Karin Pappworth**, **Niklas Theorin**, **Lena Wigren**, **Urban**

Jerlström, **Christina Holm**, **Martin Erlansson**, **Herman Nilsson Ehle** och **Lena Hermansson**.

Lars Brudin, professor och klinisk fysiolog i Kalmar. Tack för din hjälp som bollplank i statistikfrågor.

Tack till Svensk Förening för Hematologi som tilldelade mig 2013 års stipendium för klinisk lymfomforskning, vilket har underlättat arbetet avsevärt.

Johan Häggström, min kliniska handledare. Du har lärt mig det mesta jag kan om klinisk hematologi. Du har en klokskap och erfarenhet som varit ovärderlig, och du har stöttat mig i med- och motgång genom åren. Stort tack!

Hans Tove, **Marie Lindgren** och **Thomas Hybbinette**. Nuvarande och tidigare kollegor på hematologisektionen i Kalmar. Tack för moraliskt stöd och att ni gjort det praktiskt möjligt för mig att ägna mig åt något annat än kliniskt arbete de här åren. Jag hoppas kunna återgälda denna tjänst, bokstavligen åtminstone för din del Marie. Lycka till!

Magnus Adriansson, tidigare kollega. Du inspirerade mig att välja just hematologi, och var en viktig förebild under tiden vi arbetade ihop. Tack också för att du byggt upp den hematologiska verksamheten vid Länssjukhuset i Kalmar.

Många är ni vänner som har bidragit till avhandlingen genom att vi haft roligt ihop, och påmint mig om allt det andra viktiga. Ett särskilt tack till **Daniel B**, **Jonas B**, **Mats R** och **Olle B** som orkat höra på mitt malande under vinprovningarna i ”Il Grotto”. En dåligt ventilerad källare, men en bra ventil för själen.

Erik S. Jag ber uppriktigt om ursäkt, men här har du ännu ett grytunderlägg!

Arnold, **Thomas** & **Maria**. **Anna** (min syster) och **Emil**.

Tack allihop!

Mamma och **Pappa**. Ni sådde fröet till det här på fler en ett sätt. Tack för ert stora stöd i alla år!

Jakob och **Alice**. Ni har bidragit mer än ni anar. Eftersom jag numera hellre är hemma hos er än skådar fågel i främmande länder blev det här av.

Anna, min älskade hustru. Vilket tålamod du har visat! Du har verkligen ställt upp på det här helt och hållet och stöttat mig helhjärtat. TACK!!

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