MASTER'S THESIS - KU LEUVEN

# Autologous hematopoietic stem-cell transplantation in lymphoma

## A single center experience

**Camille Kockerols**

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Supervised by Prof. Dr. D. Dierickx (first reader) and Prof. Dr. G. Verhoef (second reader).

## Abstract

**High dose therapy (HDT) followed by autologous hematopoietic stem-cell transplantation (ASCT) is an important therapeutic option in the management of hematologic malignancies such as multiple myeloma, Hodgkin lymphoma (HL) and non-Hodgkin lymphoma (NHL). There are still no accepted guidelines regarding indications and recommendations differ between transplant centers. In this retrospective study we describe the applied recommendations and the results in a single transplant center. A total of 178 patients with HL (33) and NHL (145) treated at the transplant center of the University Hospitals of Leuven in 2000-2015 were included. The primary endpoint is overall survival (OS) and secondary endpoints are progression free survival (PFS), transplant-related mortality (TRM) and the incidence of invasive pulmonary aspergillosis (IPA). After a median follow-up of 56 months, 2-year OS and PFS for all lymphoma was 76% and 56%, while 5-year OS and PFS was 54% and 33%, respectively. TRM was 6.7%. In most cases the primary and secondary endpoints are similar as described in other prospective or retrospective cohort studies. Our study demonstrated a significant negative influence of the presence of active disease on fluorodeoxyglucose positron emission tomography (FDG PET) prior to transplantation on both OS and PFS. Other significant prognostic factors include age at transplantation, chemo-sensitivity of the lymphoma and the complication of IPA.**

## Introduction

Autologous hematopoietic stem cell transplantation (ASCT) refers to the intravenous administration of hematopoietic progenitor cells (HPC) after high dose chemotherapy, with the purpose to support the regeneration of the bone marrow. ASCT can be used in the treatment of Hodgkin, non-Hodkgkin lymphoma, myeloma and in some cases autoimmune pathology. We will focus on the use in the management of lymphoma.

The HPC are harvested in the peripheral blood after stimulation of the bone marrow with granulocyte colony-stimulating factor (G-CSF). Peripheral harvesting is preferred over direct harvesting from the bone marrow, because of the quicker engraftment of the HPC after transplantation and a potential for less contamination with tumour cells. The collection preferably takes place when the patient achieved a first metabolic complete remission (CR1) after first line of treatment. The risk of lymphoma cell contamination is the lowest at this point. A second valid option is harvesting when achieving complete remission after salvage chemotherapy in the case of relapsed-refractory (RR) lymphoma. The interest for collection in patients in partial remission or in primary refractory disease needs to be evaluated individually and depends on interfering factors such as patient characteristics, lymphoma characteristics and positive and negative prognostics factors. After collection, the HPC can be cryopreserved until they are required. Today AHSCT is mainly used in RR lymphoma, but in mantle cell lymphoma and in T cell lymphoma the current recommendations propose a transplantation in first complete remission.[1-3] Especially T cell lymphoma with negative prognostic factors have better outcome parameters when transplanted as first line consolidation over RR disease. ASCT allows the administration of myeloablative high-dose chemotherapy, since the infused HPC provide haematopoiesis and immune reconstitution. The recommended conditioning regimen is based on BCNU, etoposide, cytarabine and melphalan (BEAM).[4-6] This high dose chemotherapy will induce an aplasia of the bone

marrow and at this stage the HPC are required to support the reconstitution of the haematopoiesis and the immune system. The engraftment of the HPC can be examined by routine blood analyses. The engraftment of neutrophiles and platelets is defined by more than 500 and more than 20.000 cells per microliter, respectively. During a mean period of three weeks the patient is in pancytopenia and will require supporting treatment such as antibiotics, antimycotics, erythrocyt or platelet transfusions and in some cases growth factors to stimulate a quicker engraftment.

In ASCT the infused stem cells originate from the patient's own peripheral blood, which is an essential difference with allogeneic hematopoietic stem cell transplantation. This brings both advantages as disadvantages (table 1). Firstly in ASCT there is no need to search for a matched donor, resulting in an increased number of patients who can undergo the procedure. Secondly the infused cells do not cause Graft versus Host Disease (GVHD), which results in less morbidity and mortality than in allogeneic stem cell transplantation. Therefore there is no need for long term immunosuppressive medication, diminishing the risk for infectious complications.

An important disadvantage of ASCT is the possibility of tumour cell contamination within the graft, which can cause relapse. This limits the ability to use ASCT to treat patients who are not in remission. Furthermore there is an absence of the therapeutic graft-versus-lymphoma effect, well known in allogeneic stem cell transplantation. Due to previous exposure of the collected stem cells to chemotherapy or radiotherapy, there is also an increased risk of secondary dysplasia or malignancies. In summary, advantages and disadvantages of ASCT are listed in the table below

| Advantages | Disadvantages |
|---|---|
| No need for a matched donor | Not possible when bone marrow invasion |
| No risk for GVHD | No Graft versus Lymphoma effect |
| No need for chronic immunosuppressive therapy | Risk for secondary malignancies |
| Faster engraftment, faster reconstitution of the haematopoiesis and the immune system | Risk for residual lymphoma in the graft |
| Large patient population | Insufficient collection of stem cells |

**Table 1: the advantages and disadvantages of ASCT compared with allogeneic hematopoietic stem-cell transplantation.**

# Methodology

## Study design

We conducted a single center retrospective analysis of all patients with lymphoma who underwent a first AHCT at the transplant center of the University Hospitals of Leuven between 2000 and 2015. Data were collected from an institutional database of AHCT recipients and from review of patient records. The local institutional review boards approved this retrospective study.

## Patients

The study included a population of 178 patients diagnosed with Hodgkin lymphoma (HL) (n=33) and non-Hodgkin lymphoma (NHL) (n=145) among which diffuse large B-cell lymphoma (DLBCL),

mantel cell lymphoma (MCL), Burkitt lymphoma (BL), other B-cell lymphoma (OBCL), follicular lymphoma (FL) and peripheral T-cell lymphoma (PTCL). The PTCL were analyzed as one group but includes peripheral T-cell lymphoma not otherwise specified (PTCL-NOS), T-lymphoblastic lymphoma (TLBL), anaplastic large T-cell lymphoma (ALTCL), intestinal T-cell lymphoma (ITCL), extranodal NK/T-cell lymphoma (ETCL) and angio-immunoblastic T-cell lymphoma (AILD). The BL and OBCL were included when analysis of primary and secondary endpoints in all lymphoma, but they were excluded when the analysis was performed on smaller well-defined subdivisions. The disease stage at diagnosis was defined by the Ann Arbor classifications and the Cotswold modifications.[6] The international prognostic index (IPI), the follicular lymphoma IPI (FLIPI) and the mantle cell lymphoma IPI (MIPI) were used to evaluate prognostic scoring at diagnosis. The data were interpreted as one group and divided in subclasses of low, intermediate and high scoring.

All patients had a good performance status with an Eastern Cooperative Oncology Group (ECOG) scale scoring 0 or 1 prior to transplantation. All patients were transplanted with cryopreserved HPC collected from peripheral blood. The high intensity conditioning chemotherapy was BEAM (BCNU, etoposide, cytarabine, melphalan) or a BEAM-related regimen.

The response to initial chemotherapy, the response to salvage chemotherapy and the status pre-transplantation were evaluated by the results of fluorodeoxyglucose (FDG) positron emission tomography–computed tomography (PET-CT). Positive FDG PET was defined as any focal or diffuse area of increased activity in a location incompatible with normal anatomy/physiology and suspect for residual disease on visual assessment. Mediastinal blood pool structure activity was used as a reference for normal. The FDG PET-CT were reviewed by experienced nuclear medicine experts and CT experts.

A total of 44 patients were excluded for: insufficient post-transplant follow-up information, insufficient pre-transplant information, primary central nervous system invasion and composite lymphoma.

### Study endpoints

The primary endpoint of this analysis was overall survival (OS). Secondary endpoints included progression-free survival (PFS), transplant-related mortality (TRM), and the complication of invasive pulmonary aspergillosis (IPA). OS was defined as the time of ASCT to death from any cause. PFS was defined as survival without an event of death, relapse or progression reported at the date of last contact. The date of first event was used in calculating the PFS. Relapse or progression was defined by evidence of disease recurrence on FDG PET-CT or on biopsy of lymphoma suspected lesions. TRM was defined by any death in 100 days after transplantation and by any transplant-related death. The complication of IPA was defined as a positive aspergillosis antigen on blood analyses in combination with clinical suspicion and start up of antimycotic treatment; or a positive aspergillosis antigen on bronchoalveolar lavage (BAL).

### Statistical analysis

The prognostic value of various characteristics was analyzed by comparison of OS and PFS in different subgroups using survival curves calculated according to the Kaplan-Meier method. Differences between subgroups were analyzed by the two-sided log-rank test and by the Cox proportional hazards model. The programmes used for descriptive and analytic statistics were Microsoft Excell and GraphPad Prism.

# Results

## Patient-, lymphoma- and transplant-related characteristics

A total of 178 patients were enrolled. Patient-related characteristics are shown in table 2. There was a male predominance. Median age at diagnosis and at transplantation was 50 and 51 years, respectively. 75 patients (42%) were younger than 50 years old, 103 (58%) were older. The forced expiratory volume in one second (FEV1) was reduced in 9 patients (5%), the Tiffeneau index (FEV1/Forced Vital Capacity) was reduced in 19 patients (11%) and the diffusion capacity (DLCO) corrected for haemoglobin was reduced in 6 patients (4%). The data were collected of 103 aggressive NHL (57%) of which 55 DLBCL and 47 MCL, 33 HL (19%), 21 PTCL (12%) and 16 indolent NHL (9%) who were all FL. There were 6 OBCL including 2 BL and 4 composite lymphoma. The PTCL were a heterogeneous group of 1 ITCL, 9 PTCL-NOS, 5 AILD, 1 TLBL, 1 ETCL and 4 ALTCL.

| **Patient-related characteristics** | |
|---|---|
| Gender | *N = 178* |
| • Men | *114 (64%)* |
| • Women | *64 (36%)* |
| Age at diagnosis | *N = 178* |
| • Median (range), y | *50 (5 - 68)* |
| • < 50 year | *83 (47%)* |
| • ≥ 50 year | *95 (53%)* |
| Age at ASCT | *N = 178* |
| • Median (range), y | *51 (7 - 69)* |
| • < 50 year | *75 (42%)* |
| • ≥ 50 year | *103 (58%)* |
| Pulmonary function pre-transplantation | *N = 163* |
| • FEV1 < 70% | *9 (5%)* |
| • Tiffeneau index < 70% | *19 (11%)* |
| • DLCO (cHb) < 50% | *6 (4%)* |
| Lymphoma type | *N = 178* |
| • Aggressive B NHL | *102 (57%)* |
| ○ *DLBCL* | *55* |
| ○ *MCL* | *47* |
| • Indolent B NHL | *16 (9%)* |
| • Other B NHL | *6 (3%)* |
| • T NHL | *21 (12%)* |
| • HL | *33 (19%)* |

**Table 2: y = years; ASCT = autologous hematopoietic stem-cell transplantation; FEV1 = forced expiratory volume in one second; Tiffeneau index = FEV1/FVC (forced vital capacity); DLCO = diffusion capacity; cHb = corrected for haemoglobin; B NHL = B cell non-Hodgkin lymphoma; DLBCL = diffuse large B-cell lymphoma; MCL = mantel cell lymphoma; T NHL= T-cell NHL; HL = Hodgkin lymphoma.**

Lymphoma-related characteristics are shown in table 3. The majority of the patients had stage III-IV lymphoma counting for 81% and reported B-symptoms in 61% of the cases. The prognostic scoring was grouped based on IPI, MIPI and FLIPI scores. There was a majority of patients with a intermediate prognostic scoring in 56% of the cases, 42 patients (33%) with a low scoring and 13 (10%) with a high scoring. For 121 patients (68%) complete remission (CR) was achieved after first chemotherapy, for 46 (26%) partial remission (PR) and for 11 (6%) there was no response, indicating primary refractory disease (PRD). Mean duration of first complete remission (if relapse before transplantation) was 26 months with a range between 1 and 262 months. A total of 126 patients received salvage chemotherapy due to RR disease or PRD. 78 patients (62%) achieved CR, 45 (36%) PR and only 3 patients (2%) had no response at all. Of these patients a total of 33 had chemotherapy-resistant lymphoma and never achieved a CR. 144 patients had chemotherapy-sensitive lymphoma, in this study defined by achieving CR after at least one line of treatment.

| **Lymphoma-related characteristics** | |
|---|---|
| Stage | *N = 178* |
| • Stage I - II | *34 (19%)* |
| • Stage III - IV | *144 (81%)* |
| Presence of B-symptoms | *N = 169* |
| • Yes | *103 (61%)* |
| • No | *66 (39%)* |
| Prognostic scoring if B-NHL * | *N = 126* |
| • Low | *42 (33%)* |
| • Intermediate | *71 (56%)* |
| • High | *13 (10%)* |
| Best response to first line of treatment | *N = 178* |
| • CR | *121 (68%)* |
| • PR | *46 (26%)* |
| • NR | *11 (6%)* |
| Duration CR1 if relapse before ASCT | *N = 84* |
| • Mean (range), m | *26 (1 - 262)* |
| Best response to salvage chemotherapy | *N = 126* |
| • CR | *78 (62%)* |
| • PR | *45 (36%)* |
| • NR | *3 (2%)* |

**Table 3: B-NHL = B-cell non-Hodgkin lymphoma; CR = complete remission; PR = partial remission; NR = no response; ASCT = autologous hematopoietic stem-cell transplantation; m = months. * Prognostic scoring was based on the international prognostic index (IPI), the follicular lymphoma IPI (FLIPI) or the mantel cell lymphoma IPI (MIPI).**

The preferred time of transplantation differs depending type of lymphoma, but varies also between transplant centers. The data about the time of transplantation in this cohort are listed in table 5. Most patients with DLBCL were transplanted in RR disease status. A total of 6 patients were already transplanted after first line of chemotherapy. It is remarkable that these transplantations were performed between 2000 and 2006, except one in 2014 (Richter

transformation of a marginal zone lymphoma). This is indicating that the tendency to transplant in first remission has disappeared over the years, as today more concrete recommendations are merging. Most patients with MCL were transplanted after initial chemotherapy, however a total of 14 patients were transplanted after salvage chemotherapy. Six out of 14 did not achieve CR after first line of treatment, thus indicating PRD. Patients with TCL were mostly transplanted when RR, but the last couple of years there is a tendency for transplantation already after first line of treatment. The 6 patients in this last group were transplanted between 2010 and 2015. Patients with FL or HL were only transplanted in case of RR disease, which is a known recommendation for these lymphoma.

| Transplantation after | First line of chemotherapy | Salvage chemotherapy |
|---|---|---|
| **DLBCL** | *6 (11%)* | *49 (89%)* |
| **MCL** | *33 (70%)* | *14 (30%)* |
| **PTCL** | *6 (29%)* | *15 (71%)* |
| **FL** | *0* | *16 (100%)* |
| **HL** | *0* | *33 (100%)* |

**Table 4: the time of transplantation differs between type of lymphoma. DLBCL = diffuse large B-cell lymphoma; MCL = mantelcell lymphoma; PTCL = T-cell lymphoma; FL = follicular lymphoma; HL = Hodgkin lymphoma.**

Transplant-related characteristics are shown in table 4. Disease status pre-transplantation was evaluated by mean of FDG PET-CT. 33% of the patients were in metabolic complete remission on PET-CT before transplantation and 66% of the patients had residual lymphoma indicating relapsed-refractory of primary refractory disease. Mean engraftment for neutrophils and for platelets was 10 days and 14 days respectively, with failing of engraftment in 2% and 5%, respectively.

| Transplant-related characteristics | |
|---|---|
| Status at transplantation: | *N = 177* |
| • FDG PET-CT negative (CR) | *59 (33%)* |
| • FDG PET-CT positive (RR, PRD) | *118 (66%)* |
| Engraftment: | *N = 178* |
| • Neutrophils (> 500/µl) | *174 (98%)* |
| • Neutrophils, median duration (range) | *10 (8 - 36)* |
| • Thrombocytes (>20.000/µl) | *169 (95%)* |
| • Thrombocytes, median duration (range) | *14 (4 - 175)* |

**Table 5: FDG PET-CT = fluorodeoxyglucose positron emission tomography-computed tomography; CR = complete remission; RR = relapsed refractory disease; PRD = primary refractory disease.**

## Primary and secondary endpoints

In table 6 the primary and secondary endpoints are shown for all lymphoma and for separate lymphoma. At a median follow-up time of 56 months the median OS was 65 months and the median PFS was 28 months for all lymphoma. A total of 76 (42%) events of death were reported in all lymphoma, of which 24 (44%) in DLBCL, 20 (43%) in MCL, 12 (57%) in PTCL, 9 (56%) in FL and 9 (27%). A total of 102 (58%) events of death or progression were

reported in all lymphoma, of which 32 (58%) in DLBCL, 30 (64%) in MCL, 15 (71%) in PTCL, 13 (81%) in FL and 11 (33%) in HL.

| | All (n=178) | DLBCL (n=55) | MCL (n=47) | PTCL (n=21) | FL (n=16) | HL (n=33) |
|---|---|---|---|---|---|---|
| **Median FU (m)** | *56* | *54* | *53* | *29* | *69* | *75* |
| **Median OS (m)** | *65 (0-206)* | *60 (0-205)* | *64 (0-151)* | *40 (0-154)* | *94 (11-185)* | *92 (1-205)* |
| **OS** | | | | | | |
| • **2-year** | *135 (76%)* | *38 (69%)* | *39 (83%)* | *13 (62%)* | *13 (81%)* | *27 (82%)* |
| • **5-year** | *97 (54%)* | *28 (50%)* | *24 (51%)* | *5 (24%)* | *13 (81%)* | *24 (72%)* |
| **Death** | *76 (42%)* | *24 (44%)* | *20 (43%)* | *12 (57%)* | *9 (56%)* | *9 (27%)* |
| • **TRM** | *14 (7%)* | *5 (9%)* | *2 (4%)* | *4 (19%)* | *0* | *2 (6%)* |
| • **DRM** | *33 (19%)* | *13 (24%)* | *10 (21%)* | *3 (14%)* | *4 (25%)* | *2 (6%)* |
| • **Other** | *19 (10%)* | *3 (5%)* | *3 (6%)* | *3 (14%)* | *5 (31%)* | *5 (15%)* |
| • **Unknown** | *10* | *2* | *6* | *2* | *0* | *0* |
| **Median PFS (m)** | *28 (0-198)* | *29 (0-198)* | *28 (0-143)* | *9 (0-147)* | *26 (1-142)* | *69 (0-194)* |
| **PFS** | | | | | | |
| • **2-year** | *99 (56%)* | *30 (55%)* | *28 (60%)* | *6 (29%)* | *7 (44%)* | *23 (70%)* |
| • **5-year** | *58 (33%)* | *19 (35%)* | *10 (21%)* | *3 (14%)* | *5 (31%)* | *17 (52%)* |
| **Progression or death** | *102 (58%)* | *32 (58%)* | *30 (64%)* | *15 (71%)* | *13 (81%)* | *11 (33%)* |
| **IPA** | *8 (4%)* | *3 (5%)* | *1 (2%)* | *2 (9%)* | *0* | *1 (3%)* |

**Table 4: All = all lymphoma; DLBCL = diffuse large B-cell lymphoma; MCL = mantelcell lymphoma; TCL = T-cell lymphoma; FL = follicular lymphoma; HL = Hodgkin lymphoma; FU = follow-up; OS = overall survival; TRM = transplant-related mortality; DRM = disease-related mortality; PFS = progression free survival; IPA = invasive pulmonary aspergillosis.**

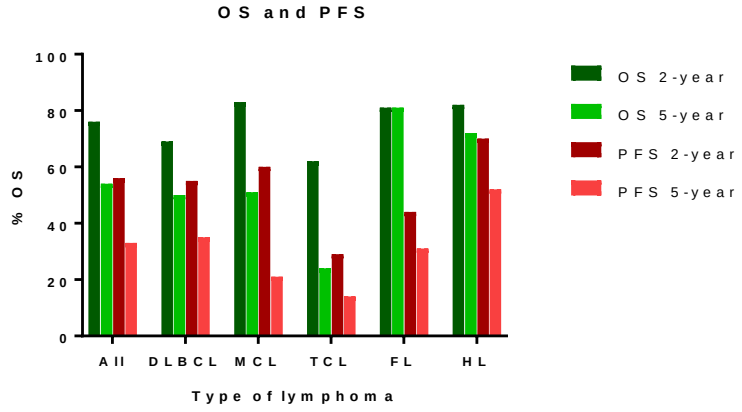


**Figure 1: shown are the primary and secondary endpoints in all lymphoma and in separate lymphoma. OS = overall survival; PFS = progression free survival; All = all lymphoma; DLBCL = diffuse large B-cell lymphoma; MCL = mantle cell lymphoma; PTCL = peripheral T-cell lymphoma; FL = follicular lymphoma; HL = Hodgkin lymphoma.**

The estimated 2-year and 5-year OS for all lymphoma was 76% and 54% and the estimated 2-year and 5-year PFS 56% and 33%, respectively. These data, as well as the data for the individual lymphoma types are shown in table 4 and figure 1.

The causes of mortality were divided in transplant-related mortality (TRM) (n=14), disease-related mortality (DRM) (n=33), other (n=19) and unknown (n=10) (Table 6; Fig. 2). When

TRM was defined as mortality within 100 days after transplantation, only 12 patients were included (instead of 14) counting for 15.7% of total mortality and 6.7% of the total transplanted population. This value is mentioned separately because TRM is mostly defined this way in literature, making it more efficient to compare different studies. In all patients with TRM (14), 4 did never achieve neutrophil engraftment and 8 did never achieve platelet engraftment. DRM was the main cause of death in all lymphoma, in DLBCL and in MCL, while other mortality was the main cause of death in FL and HL. Other mortality was subdivided in mortality due to secondary malignancy, mortality due to allogeneic SCT and other causes.

The incidence of IPA as post-transplantation complication in this cohort study was 4% (n=8). 50% of these patients (n=4) died shortly after transplantation, thus contributing to 29% of the total TRM.

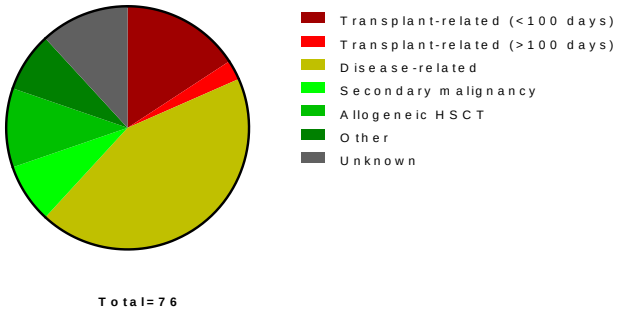


**Figure 2: shown are the different causes of mortality.**

In table 7 data about death and progression are furthermore examined. After a median follow-up of 65 months an OS of 102 patients and 76 events of death are reported. The group of survivors can be divided in 76 (75%) patients without and 26 (25%) patients with disease progression. The group of deceased patients can be divided in 31 (41%) patients death without progression and 45 (59%) patients death with progression.

| | Alive (n=102) | Death (n=76) |
|---|---|---|
| **Without progression** | *76 (75%)* | *31 (41%)* |
| **With progression** | *26 (25%)* | *45 (59%)* |
| • **Because of progression** | | *33 (73%)* |
| • **Other** | | *12 (27%)* |

**Table 5: characteristics of survival and death**

## Prognostic factors

The following curves (Fig. 3 – Fig. 7) show the results of the Kaplan-Meier analysis of PFS or OS in well-defined groups. The hazard ratio and p values are based on a stratified log-rank test. Following parameters were assessed: age of the patient at transplantation, chemotherapy-sensitivity of the lymphoma, active disease on FDG PET-CT prior to ASCT, the influence of IPA, the correlation of TRM and engraftment, the gender, the disease stage, the IPI scoring and the presence of B-symptoms.

A younger age at transplantation was associated with a better OS (Fig. 3) with a hazard ratio (HR) for death in the group <50 years versus the group ≥ 50 years was 0.59 (95% confidence interval (CI), 0.37-0.92; p = 0.1677). Patients diagnosed with HL were excluded because of the younger disease population than other lymphoma.

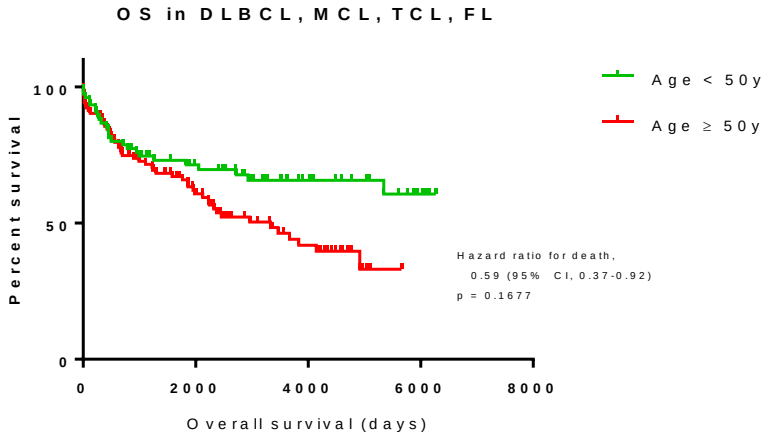


**Figure 3: OS = overall survival; DLBCL = diffuse large B-cell lymphoma; MCL = mantelcell lymphoma; PTCL = peripheral T-cell lymphoma; FL = follicular lymphoma;**

Patients who achieved at least one CR, thus indicating chemotherapy-sensitivity of the lymphoma, had a better PFS than patients who only achieved a PR or did not response (NR) at all (Fig. 4). Patients were grouped in "Best response: CR" when achieving CR after at least one line of chemotherapy. Other patients were grouped in "Best response: PR of NR". The HR for progression or death in the CR-group versus de PR or NR-group was 0.552 (95% CI, 0.318-0.0.957; p = 0.0095).

Disease status pre-transplantation evaluated by FDG PET-CT had an important and significant influence on primary outcome parameters. Patients were divided in the PET-CT negative group when they achieved metabolic CR on the last FDG PET-CT after last line of treatment but before transplantation. When there was still active disease on FDG PET-CT, patients were divided in the PET-CT positive group. OS was analyzed in aggressive NHL and PTCL (Fig. 5), HR for death was 0.479 (95% CI, 0.264-0.867; p = 0.0052). Analysis of OS in all lymphoma was also significant (Fig. 6), with a HR for death of 0.510 (95% CI, 0.312-0.832; p = 0.003). PFS was markedly reduced in MCL and FL when there was residual lymphoma on PET-CT before transplantation (Fig. 7). The HR for progression or death was 0.264 (95% CI, 0.108-0.646; p < 0.0001).

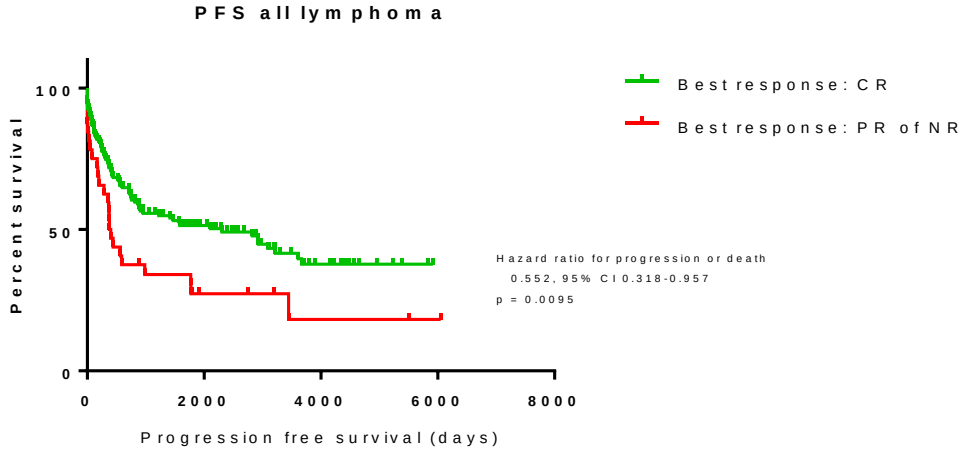


**Figure 4: PFS = progression free survival; CR = complete remission; PR = partial remission; NR = no reponse. Patients were grouped in "Best response: CR" when achieving CR after at least one line of chemotherapy.**

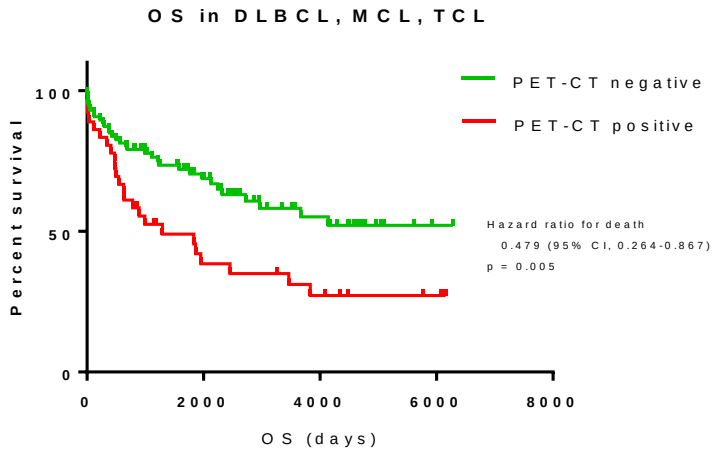


**Figure 5: OS = overall survival; DLBCL = diffuse large B-cell lymphoma; MCL = mantelcell lymphoma; PTCL = peripheral T-cell lymphoma; PET-CT = positron emission tomography-computed tomography; the PET-CT negative group was defined as the presence of a complete metabolic remission on FDG PET-CT after last line of treatment and before transplantation.**

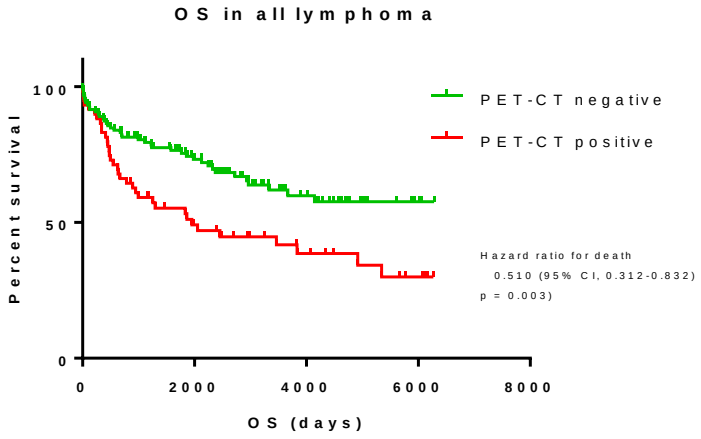


**Figure 6: OS = overall survival; PET-CT = positron emission tomography-computed tomography; the PET-CT negative group was defined as the presence of a complete metabolic remission on FDG PET-CT after last line of treatment and before transplantation.**

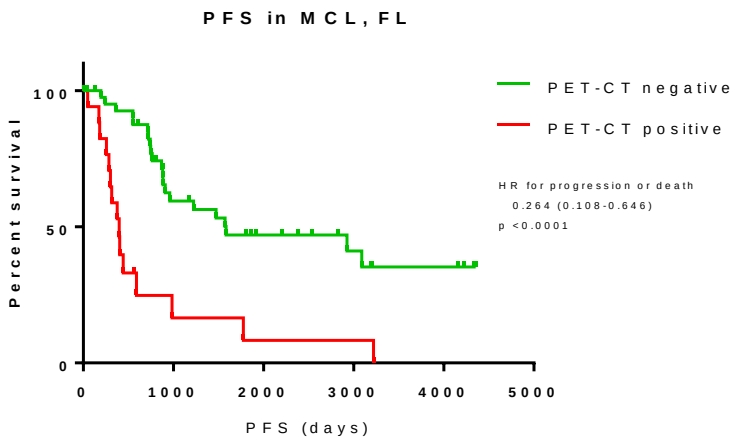


**Figure 7: PFS = progression free survival; MCL = mantelcell lymphoma; FL = follicular lymphoma; PET-CT = positron emission tomography-computed tomography; the PET-CT negative group was defined as the presence of a complete metabolic remission on FDG PET-CT after last line of treatment and before transplantation.**

The incidence of IPA as complication after transplantation was associated with a significantly reduced overall survival. The HR for death was 0.107 (95% CI, 0.025-0.455; p =0.002; graph not shown). A total of 4 (50%) patients with IPA died shortly after transplantation, thus contributing for 25% of the total TRM in this population.

Failing of engraftment was strongly associated with a higher rate of mortality with a HR for death of 0.094 (95% CI, 0.011-0.817; p < 0.0001; graph not shown).

The OS or PFS in all lymphoma was not influenced significantly by the gender (HR 1.017 95% CI, 0.634-1.632; p = 0.94), nor by the period of transplantation (2000-2009 vs 2010-2015), by the Ann Arbor stage (II vs. III vs. IV), nor by the presence of B-symptoms. The OS of PFS in DLBCL was not influenced significantly by the IPI score (p = 0.205, data not shown).

## Discussion

High-dose chemotherapy with ASCT is now extensively used in patients diagnosed with Hodgkin or non-Hodgkin lymphoma. It can offer long-term PFS and OS, depending on risk factors. In this retrospective cohort study the efficacy of ASCT at the transplant center of University Hospitals of Leuven in different types of lymphoma was evaluated and described as primary and secondary end points. Furthermore the prognostic value of patient-, lymphoma- or transplant-related characteristics was analyzed. Considering the heterogeneity of the different lymphoma, the population was frequently subdivided based on lymphoma type or lymphoma character (aggressive or indolent).

### Overall survival and progression free survival

OS as primary end point was 76% at 2-year and 54% at 5-year and PFS as secondary end point was 56% at 2-year and 33% at 5-year in all lymphoma. The study of Gilli *et al.* reported similar OS data (72%) but better PFS (69%).[7] Their study however only included 49 patients. OS was better in indolent NHL and in HL than in aggressive B-cell NHL of T-cell NHL. In

aggressive lymphoma (more specifically DLBCL and PTCL) the PFS diminished similarly as the OS, indicating that disease progression was associated with poorer OS. In indolent lymphoma and in MCL however the PFS was much more affected than OS, indicating that disease progression in these lymphoma was not necessarily associated with poorer OS. ASCT in MCL and FL has a supportive life-lengthening goal more than a curative goal. Therefore it is better to interpret OS more than PFS in the evaluation of efficacy of ASCT in these lymphoma.

HL had the best results for primary and secondary end points, with a 2-year OS of 82% and a 2-year PFS of 70%. The 5-year OS and PFS were 72% and 52%, respectively. The large retrospective study of Yi-bin *et al.* in which the impact of conditioning regimen is evaluated, shows similar results.[5] They reported a 3-year OS and PFS in HL treated with BEAM prior transplantation of 79% and 62%, respectively. The study of Martinez *et al*. had results of a 5-year OS and PFS of 64% and 55% respectively, but included only patients older than 50 years.[8]

PTCL had the poorest results with a 2-year OS and PFS of 62% and 24%, and a 5-year OS and PFS of 29 and 14%. These results were expected, because of the known aggressive character. Although the incidence is rising, PTCL are a rare subset of aggressive lymphoma. This explains why there is a paucity of randomized control trials and why most studies only include a small subset of patients. In the systematic review of Gkotzamanidou *et al*., prospective and retrospective studies were grouped.[3] Studies using a BEAM conditioning regimen and including all PTCL, showed similar results in 2- and 5-year OS, but generally (although not significantly) better results in 2- and 5-year PFS.

DLBCL represented the largest patient group in this study. There was a 2- and 5-year OS of 69% and 50%, and a 2- and 5-year PFS of 55% and 35%, respectively. Based on the PARMA study ASCT has been the standard of care in patients with RR DLBCL who achieved CR of PR after salvage chemotherapy.[9] At 5 years they reported an OS of 53% and a PFS of 46%, but the study already dates from 20 years ago. A more recent study of Sauter *et al.* reported 3-year OS and PFS of 74% (95% CI: 65%-81%) an 67% (95% CI: 58%-75%), respectively.[10] PFS was significantly better, possibly due to the applied criteria. The included patients were all treated with rituximab prior to ASCT and they all had chemotherapy-sensitive lymphoma. In our study these criteria were not applied.

The results for MCL showed a 2- and 5-year OS of 83% and 51%, and a 2- and 5-year PFS of 60% and 21%, respectively. The study of Boltezar *et al*. reported a 5-year OS en PFS of 79% (95% CI 56.1%–91.1%) and 70% (95% CI 45.5%–84.8%), respectively.[11] These results are remarkably better, but could be possibly explained by the post-transplantation treatment with maintenance rituximab. Furthermore the MCL group included only 29 patients. In the randomized control trail of Dreyling *et al.* the 2-year OS was 86% (95% CI 76%-95%) and the 3-year PFS was 54% (95% CI 39%-69%) which is comparable to our results.[1]

In FL the 2- and 5-year OS were both 81% and the 2- and 5-year PFS was 44% and 31%, respectively. In the study of van Besien *et al.* different types of transplantation in FL are compared.[12] They reported in the group of autologous unpurged transplantation (n=597) a 5-

year OS of 55% (95% CI 50%-60%) and a 5-year PFS of 31% (95% CI 27%-36%), respectively. A difference is seen between 5-year OS, but due to their large sample their results are much more reliable.

### Prognostic factors

Our study demonstrates the importance of FDG PET-CT results prior to transplantation, along with other factors, in predicting the outcome of lymphoma. The persistence of residual lymphoma, indicating RR or PRD, after last line of treatment and prior to transplantation had a significant negative influence on OS for all lymphoma, as well as for aggressive lymphoma alone. The influence was also present on PFS in MCL and FL, but this was not necessarily associated with a poorer OS. The significance of FDG PET results prior to transplantation has already been examined in various studies, demonstrating similar results.[10, 13-15]

Secondly chemotherapy-sensitivity has an important influence on the primary outcome. Patients who never achieved CR after one or multiple lines of chemotherapy had poorer outcomes than patients with at least one achievement of CR.

The prognostic value of age was also demonstrated. Patients younger than 50 years at transplantation had significantly better outcome than older patients. This prognostic parameter is well described in multiple studies, such as gender, tumor stage, performance status, B symptoms, sites of lymphomatous involvement, number of extranodal disease sites, size of the largest tumor, and serum concentrations of LDH, albumin, and beta$_2$-microglobulin.[16] In our study gender, IPI scoring, tumor stage, presence of B-symptoms and period of transplantation (2000-2009 vs. 2010-2015) did not influence the outcome parameters significantly. As the performance status was always evaluated as good, this factor could not be compared. Serologic tests, sites of lymphoma involvement, bulky disease and extranodal manifestations were not analyzed.

### Transplant-related mortality

TRM if defined as mortality within 100 days post transplantation counted for 12 events of death or 6.7% of all transplanted patients. In the study of Yi-Bin et al. the TRM in ASCT after BEAM regimen was 4% (95% CI 3-5%), which is slightly better than TRM in our study.[5] In the study of Puig *et al.* the influence of conditioning regimen on TRM was evaluated.[4] The group with BEAM as conditioning regimen had a TRM of 7%.

IPA as post-transplant complication was significantly associated with a higher mortality rate and especially a higher transplant-related mortality. There was no significant association with DLCO prior to transplantation, nor with other possible prognostic factors such as age, type of lymphoma, ECOG performance status or period of transplantation.

### Time of transplantation

The choice of time of transplantation is based on type of lymphoma and prognostic factors. There are still no accepted guidelines regarding indications for ASCT and recommendations differ between transplant centers. For FL and HL recommendations are clear, transplantation is indicated in case of RR disease. For PTCL the tendency had changed over the last couple of

years.[3] Current results are demonstrating a benefit for transplantation already after first line of chemotherapy, especially in PTCL with negative prognostic factors. Also in MCL the tendency is shifting towards transplantation already after first line of treatment.[1]

Recommendations in DLBCL support more and more the transplantation in RR disease over transplantation in first CR. Five out of 6 patients diagnosed with DLBCL in this cohort study were transplanted after first line of treatment, but their transplantation took place between 2000 and 2006, probably a period were sufficient information was missing to create well established recommendations.

### Final conclusion

Over the last decades transplantation of stem cells is gaining a more and more important role in the management of Hodgkin and non-Hodgkin lymphoma. At the transplant center of the University Hospitals of Leuven we present good rates of long term overall and progression free survival, and an average transplant-related mortality. The present study confirms results reported in literature.

A lower overall survival was reported in aggressive lymphoma, especially the T-cell lymphoma. The negative prognostic value was demonstrated for active disease on FDG PET-CT prior to transplantation, chemotherapy-resistant lymphoma and age at transplantation older than 50 years.

Negative aspects of our study consist in the retrospective character, the analysis of only one transplant center and the heterogeneity of the total population. When dividing the population in more homogeneous groups, the samples were smaller and of low significance. Further investigation by systematic reviews or meta-analysis combining results of multiple transplant centers remain interesting issues for future assessments.

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