2009

Autologous Stem Cell Transplantation in Elderly Patients with Non-Hodgkin's Lymphoma

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A Thesis Submitted to the

Yale University School of Medicine

in Partial Fulfillment of the Requirements for the

Degree of Doctor of Medicine

By

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2009

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Abstract

Clinical trials investigating autologous stem cell transplantation (ASCT) have historically excluded elderly patients due to the risk of treatment-related morbidity related to the administration of high dose chemotherapy. While the availability of this procedure continues to expand, the elderly still represent a population for which the role of ASCT needs to be fully defined. 201 patients who underwent autologous stem cell transplantation (ASCT) for Non Hodgkin's lymphoma (NHL) at a single institution following BEAM conditioning between January 1, 2000 and December 31, 2007 were retrospectively identified from the Yale University School of Medicine Bone Marrow Transplant Database. 67 patients were older than 60 years at the time of transplantation (median age 65, range 60 – 75) and were compared to a matched group of 134 patients transplanted during the same time period. These groups were extremely well-matched for all demographics such as gender, NHL histology, performance status, and comorbidities. Most patients had advanced stage disease at diagnosis and were transplanted at first or second remission. Diffuse large B-cell and mantle cell lymphoma were the most common subtypes but other subtypes were represented. The elderly group experienced significantly more serious toxicities within the first 100 days (63%) when compared to the control group (42%). However, there were no statistical differences ($p<0.0001$) between the groups regarding specific organ system toxicities. The 1-year non-relapse mortality (3%) was not significantly different when compared to the younger cohort (1%). At a median follow-up of 31 months the median overall survival is 85 months in the elderly group and at a median follow up of 33 months in the younger group the median overall survival has not yet been reached. The overall survival at 3 years is 74% and 75% respectively ($p=0.91$). The disease-free survival at 3 years is 48% in the elderly group compared to 58% in the control group ($p=0.66$). By univariate analysis, age >60 years (RR 3.1, 95% CI 1.7 – 5.7, $p=0.004$) was the only factor predictive of developing a serious toxicity from ASCT within the first 100 days. HCT-CI score (RR 2, 95% CI 1 – 4, $p=0.043$) was the only factor associated with significantly worse overall survival. Autologous stem cell transplantation can be safely performed in selected patients older than 60 years with chemosensitive NHL. Although elderly patients appear more likely to develop acute toxicities, the outcomes are similar to that of younger patients with respect to non-relapse mortality, disease-free survival, and overall survival.

Acknowledgements

Thanks to Dr. Stuart Seropian for his efforts and support. Thanks to Dr. Dan Zelterman for statistical analysis. Thanks to the Yale Oncology Medical Records staff for their assistance. Thanks to my family for their love and encouragement in helping me achieve my dreams.

Introduction

The Non-Hodgkin's Lymphomas (NHL) are a diverse group of malignancies arising from lymphoid tissues. They have been classified into greater than forty distinct disease entities with variable clinical and biological features. There are types that have a gradual onset while others progress quite rapidly. Some are mostly contained to the lymph nodes while others predominantly involve extranodal sites. Aggressive types require intensive treatment regimens initially while more indolent types may require no initial treatment at all. Consequently, due to great variety of the clinical behavior among the subtypes, much time and effort has been spent concerning the proper classification of the distinct entities that encompass the Non-Hodgkin's Lymphomas.

The process of classifying NHL began over fifty years ago with the Rappaport classification which was first described in 1956, before the differences between B-cells and T-cells were understood. This classification system established four categories: well-differentiated lymphocytic lymphoma, poorly-differentiated lymphocytic lymphoma, mixed lymphocytic and histiocytic, and histiocytic lymphoma.(1) The Rappaport classification was replaced by the Lukes-Collins classification, established in 1974, which first distinguished B-cell and T-cell lymphomas using immunophenotyping. During the 1970s, advances were being made both in the treatment and the clinical behavior of many lymphomas. Published clinical trials were difficult to interpret as clinicians used different classification schemes. In order to reconcile this confusion, The Working Formulation was developed in 1982. The Working Formulation was based on morphological appearance and clinical behavior and divided NHL into three groups, low grade, intermediate grade, and high grade. (2) However, The Working Formulation was designed more to guide treatment decisions and served as a transition to the era when science would take a larger role in the classification of NHL.

Throughout the 1980s and 1990s, immunologic, cytogenetic and molecular techniques were utilized to further characterize and distinguish NHL. With that knowledge, a group of hematopathologists established The Revised European-American Lymphoma (REAL) classification in 1994. The REAL classification is comprised of four major categories (B-cell neoplasms, T-cell and Natural Killer (NK) cell neoplasms, and Hodgkins lymphoma) with several distinct sub-types within each major category.(3) The latest classification system, first published in 2001, is the World Health Organization (WHO) classification which identifies forty-three disease subtypes that are divided into five categories: Precursor B- and T-cell neoplasms, Mature B-cell neoplasms, Mature T- and NK cell neoplasms, Hodgkin's lymphoma, and Immunodeficiency associated lymphoproliferative disorders.(2) The WHO classification is currently used today as the standard guide to classifying NHL.

NHL is the most commonly occurring hematological malignancy in the United States. There were an estimated 66,120 new cases and 19,160 deaths in the United States in 2008. Of the new cases in 2008, there was a slight male predominance (35,450 males, 30,670 females). The new cases of NHL represent 4.6% of all new cases of cancer in the US and deaths from NHL account for 3.4% of all cancer deaths. In 2008, NHL was the 6th most commonly diagnosed cancer and accounted for the 6th leading cause of cancer deaths.(4) Worldwide, the highest incidence rates occur in the US along with Europe and Australia while T-cell lymphomas are more common in Asian countries.(5) Over the past four decades there has been a steady increase in the incidence of NHL. An aging population, better diagnostic techniques, increase in HIV infections, and increased immunosuppressive states due to increased organ transplantation have all been implicated to explain the increase in frequency, but do not completely explain the increase. (6) The incidence and mortality of NHL varies greatly by age. NHL is far more common and results in more deaths in the elderly as compared with younger counterparts. The

incidence and mortality rates by age are listed in Table 1. The median age at diagnosis is 67 years of age. (7) The majority of all cases of NHL are diagnosed in patients 65 years or older, and nearly three out of every four deaths from NHL occur in those 65 or older.

Table 1: NHL Incidence & Mortality Rates by Age (7)

Age	Incidence (%)	Deaths (%)
Under 20 yrs	1.7	0.5
20 – 34 yrs	4.1	1.6
35 – 44 yrs	7.4	3.0
45 – 54 yrs	14.0	7.3
55 – 64 yrs	18.5	13.9
65 – 74 yrs	22.3	23.3
75 – 84 yrs	23.4	33.5
Over 85 yrs	8.5	17.0

The cause of most cases of NHL is unknown; however, genetic diseases, environmental exposures, infectious agents, and immunodeficiency states have all been implicated. Rare genetic disorders such as Severe Combined Immunodefiency (SCID), Wiscott-Aldrich, and Ataxia-Telangiectasia have been associated with a 25% risk of developing lymphoma. (8) Furthermore, immunocompromised states also are predisposed to developing NHL. This includes HIV infections, iatrogenic immunosuppression following organ transplantation, and certain autoiummune disorders such as Rheumatoid Arthritis (RA), Systemic Lupus Erythematosus (SLE), and Sjogren's syndrome. Infectious agents also play a etiologic role, HIV/AIDS infections are strongly associated with B-cell lymphomas, Epstein-Barr virus (EBV) is associated with 95% of

endemic Burkitt's lymphoma, Human T-cell Lymphotropic virus (HTLV-1) is responsible for adult T-cell lymphoma, and *Helicobacter pylori* is the causative agent for the vast majority of gastric MALT lymphoma. Additionally, Human Herpes virus (HHV-8), Hepatitis C, and *Borrelia burgdorferi* infections have also been associated with increased rates of lymphoma. (9, 10) Finally, certain environmental exposures including pesticides, hair dyes, tobacco, etc. have been associated with an increased risk of developing NHL. These causal relationships are difficult to assess as studies designed to determine these risks are quite heterogeneous and have reported contradictory conclusions. (10)

NHL comprises greater than 40 distinct pathological diagnoses with great variation in presentation, clinical course, and appropriate therapy. Thus, it is essential that clinicians become knowledgeable about the characteristic features of the most common subtypes to ensure the correct diagnosis is made and the proper treatment is administered. The next section will review the pertinent background of the most common NHL subtypes included in this study.

NHL Disease Subtypes

Diffuse large B-cell lymphoma (DLBCL) is the most common subtype of NHL accounting for roughly 31% of all cases. (11) DLBCL is a malignant proliferation of large B-cells with variable morphology, molecular, and clinical findings. Regarding the pathology, there are three major morphological subtypes of DLBCL: centroblastic, immunoblastic, and T-cell rich. Despite the established variation in morphology, these distinctions are largely academic as there have yet to be unique therapies or clinical outcomes for each subtype. Typically there is a diffuse proliferation of cells that destroys the normal lymph node architecture. All types of DLBCL

express pan-B-cell markers, CD 19+, CD 20+, and CD79a +, while Bcl-2 and Bcl-6 are expressed in 50 – 75% of cases. (12)

DLBCL primarily involves the lymph nodes or extranodal tissue, and the majority of patients will have extranodal involvement at diagnosis. While any organ may be involved, the most common sites are the gastrointestinal tract, bone marrow, and central nervous system. Nearly half of patients present with localized (stage I or II) disease and half present with disseminated disease.(6) Currently, studies have established 3 – 4 cycles of Rituximab and cyclophosphamide, doxorubicin, vincristine, prednisone (R-CHOP) with or without involved field radiation as the recommended treatment for localized DLBCL. Advanced-stage DLBCL is potentially a curable disease when treated with 6 – 8 cycles of R-CHOP. This regimen has a 70% complete response (CR) rate and 50 – 70% of those will be cured. Relapsed or refractory disease should be accompanied with a biopsy to confirm disease progression. Typically relapsed/ refractory disease is treated with second-line combination chemotherapeutic regimens, such as ifosfamide, carboplatin, and etoposide (ICE) with rituximab followed by an autologous stem cell transplant (ASCT). (12) The PARMA International trial demonstrated that ASCT produced higher rates of 5-year disease-free (51% v. 12%) and overall survival (53% v. 32%) as compared to salvage chemotherapy alone. (13)

Follicular lymphoma (FL) is the second most common type of NHL accounting for 22% of cases. (11) The neoplasm is composed of a combination of small, cleaved cells known as centrocytes and large, non-cleaved cells known as centroblasts. The proportion of these cells varies greatly and FL is subclassified as small cell/mixed cell or large cell based on the predominance of cell type. This subclassification does not have prognostic significance, but typically clinical aggressiveness, as evidenced by more rapid proliferation and poorer response

to chemotherapy, increases with higher proportion of large cells. (14) By immunohistochemistry, FL cells express pan-B-cell markers, CD20 and CD79a, and most express follicle center B-cell antigens, CD10 and Bcl-6. The genetic hallmark is the t(14;18) translocation which results in the overexpression of Bcl-2, an antiapoptotic protein. This translocation occurs in 80 – 90% of cases of FL and thus, Bcl-2 expression is highly suggestive of FL. (15) Additionally, Bcl-6 translocation occurs in 15% of cases and is associated with an increased risk of transformation to DLBCL. (16)

FL most commonly presents with painless lymphadenopathy in the elderly with a slight female preponderance. Upon presentation, the lymphadenopathy usually is widespread involving multiple sites. Only a minority present with constitutional symptoms such as fever, night sweats, or weight loss; known as B symptoms. Although FL is primarily confined to the lymph nodes, most have advanced stage disease with bone marrow and splenic involvement, while other extranodal sites such as peripheral blood are rarely involved. While the clinical course is variable, the majority of cases are characterized by an indolent course that may include unpredictable periods of waxing and waning lymphadenopathy. (15)

Typically, asymptomatic patients are not treated and followed closely for evidence of symptoms and disease progression. This treatment strategy is known as “watch and wait”. Approximately 15 – 20% of patients with FL did not require treatment 10 or more years after the initial diagnosis in one observation study. (17) The advent of rituximab has prompted a reevaluation of the appropriateness of watchful waiting given that it is very well tolerated and can be given effectively multiple times over many years. Studies currently are underway to address this question. However, when there is change in the pace of the disease and systemic symptoms arise signifying progressive disease, it becomes clear that treatment is indicated. (15)

Multiple cycles of combination chemotherapy plus rituximab are effective and typically achieve a CR in the majority of patients. (17) The optimal regimen is the source of a debate, and while many options are available, R-CHOP is a common regimen for the initial treatment. Although most cases are advanced stage, radiation therapy can be used if disease is localized. Currently, FL is not curable and regardless of the response to the initial treatment, most will relapse within 2 years. However, 20% will have a remission of greater than 10 years. (6) Many options exist for second-line chemotherapy, including the initial chemotherapeutic regimen, in the treatment of relapsed disease. Additionally, radioimmunotherapy, the use of radiolabeled antibodies against CD20, can also be utilized to treat relapsed FL particularly if it has become refractory to rituximab. The optimal role of stem cell transplantation in the treatment of FL is still being investigated. Currently, ASCT is reserved for younger patients with poor prognostic factors and those that have an early recurrence to the initial regimen. The treatment of FL remains an area of active research since it continues to be an incurable disease.

Mantle cell lymphoma (MCL) was first recognized as a separate entity in the REAL classification system and currently represents approximately 6% of all NHL cases. (11) It is a B-cell neoplasm that arises from the pre-germinal center B-cells that occupy the mantle zones surrounding the germinal center. The tumor is composed of small- to medium-sized lymphoid cells with irregularly notched nuclei. MCL cells express pan-B-cell markers, CD20 and CD79a, but does not express follicle center B-cell antigens, CD10 and Bcl-6. It is one of a few tumor cells that expresses CD5, a pan-T-cell antigen, but does not express CD23 thereby helping to distinguish it from chronic lymphocytic leukemia (CLL). The cytogenetic hallmark is the t(11;14) translocation that results in an overexpression of cyclin D1, a cell cycle regulating protein. Thus, nuclear staining of cyclin D1 is diagnostic of MCL. (18) MCL is far more common in the elderly and is 3 -4 times more likely in males than in females. Patients most commonly present with

palpable lymphadenopathy and constitutional B symptoms. Approximately 70% of patients have stage IV disease at diagnosis and nearly 90% have extranodal involvement. The most frequent extranodal sites include the bone marrow, peripheral blood, gastrointestinal tract, and the liver. The clinical course is usually aggressive and is associated with a poor prognosis. One study estimated the 10-year failure-free survival at 8% . (19) Patients are usually treated with intensive combination chemotherapy such as R-CHOP or rituximab plus twice daily cyclophosphamide, vincristine, doxorubicin, dexamethasone, cytarabine, and methotrexate (R-hyperCVAD), but no regimen has demonstrated an obvious superiority or an ability to cure. (18) The chemotherapy regimens are usually followed by an ASCT to consolidate the treatment. Unfortunately, even with intensified treatment relapses still occur, but ASCT does appear to prolong survival as well as remission time. Currently many studies are underway to establish the optimal role of ASCT in the management of MCL.

T-cell NHL comprise 16 major subtypes and account for 10 – 15% of NHL cases. Peripheral T-cell lymphoma (PTCL) is a heterogeneous group of aggressive neoplasms and represents 7% of all NHL cases. (11) Most express CD4. PTCL typically presents with generalized lymphadenopathy, constitutional B symptoms, and commonly hepatosplenomegaly or pruritic skin rash. Since PTCL is associated with poor prognostic factors and usually has a poor response to treatment, stem cell transplantation is usually considered early in the course. The 5-year survival for all therapies is 25%. (20) Angioimmunoblastic T-cell lymphoma is a major subtype of PTCL and accounts for roughly 2% of all NHL cases. (11) Neither the role for transplantation nor the optimal therapy for this disease has been clearly defined.

Anaplastic large T-cell lymphoma is yet another type of T-cell NHL and represents 2% of NHL cases. The discovery of CD30 antigen and t(2;5) translocation resulting in overexpression of

anaplastic lymphoma kinase (ALK) established the existence of a distinct entity. Anaplastic large T-cell lymphoma typically affects younger male patients. The average age at diagnosis is 33 years old and males account for 70% of those afflicted. The skin is frequently involved and some patients only have disease confined to the skin which is known as cutaneous anaplastic T-cell lymphoma. The ALK status of patients with anaplastic lymphoma is an important prognostic factor and guides treatment. ALK-positive disease has a favorable 5-year survival of 70% and usually is treated with an anthracycline-based regimen while ALK-negative disease has a worse prognosis, similar to PTCL, and is more likely to be treated with ASCT. (20, 21)

Autologous Stem Cell Transplantation

Hematopoietic stem cell transplantation is feasible because of three remarkable qualities of the hematopoietic stem cell: great regenerative capability, the ability to target the bone marrow when administered intravenously, and the capability to be cryopreserved and thawed without loss of function. (6) Hematopoietic stem cell transplantation is used primarily to treat hematologic cancers but can also treat other disorders such as aplastic anemia, amyloidosis, etc. Stem cell transplantation is classified based on the relationship of the donor to the recipient. Allogeneic transplantation involves the harvesting and transfer of cells from a person who is immunologically different than the recipient. A syngeneic transplant occurs when the donor is a twin sibling. Autologous transplantation involves the removal and subsequent reinfusion of the patient's own stem cells.

Autologous and allogeneic transplants have different goals. In an allogeneic transplant, the goal is for the donor cells to attack the tumor. This is known as the graft-versus-tumor (GVT) effect. Unfortunately, since the donor cells are immunologically different from the host tissue, there is a risk for the donor cells to also attack host tissues, which is known as graft-versus-host

disease (GVHD). In contrast, in autologous transplants, the harvested stem cells augment hematopoietic recovery following high dose chemotherapy. Since the stem cells were harvested prior to the administration of high dose chemotherapy, there is a risk that they are contaminated with tumor cells. However, syngeneic transplants carry no risk of GVHD or risk of contaminated tumor cells in the graft, but only 1% of patients have identical twins.(6)

The transplant procedure begins with the administration of a combination of high-dose chemotherapeutic agents, known as the preparative regimen. The purpose is to eliminate existing cancer cells. Historically, the preparative regimen combined total-body irradiation (TBI) with high-dose chemotherapy in order to reach all cancer cells, but TBI has fallen out of favor for autologous transplants because of toxicities and availability. (22) Currently, there are two types of preparative regimens commonly used. The first type is based on carmustine (BCNU) which is an alkylating agent, and examples include BEAM (carmustine, etoposide, cytarabine, melphalan) and BEAC (carmustine, etoposide, cytarabine, cyclophosphamide). The most serious toxicity with this type of preparative regimen is carmustine- induced interstitial pulmonary fibrosis. The other type of regimen is based on busulfan, also an alkylating agent, and examples include busulfan/cyclophosphamide and busulfan/etoposide. For busulfan containing regimens, busulfan can also cause an interstitial pulmonary fibrosis as well as veno-occlusive disease. (23)

Prior to the administration of the preparative regimen stem cells are collected and then given back at the completion of the preparative regimen to augment the recovery from the high-dose chemotherapy. Historically, stem cells were collected from the bone marrow via multiple aspirations of the posterior iliac crests. Obtaining stem cells from the marrow requires the use of general anesthesia and occurs in the operating room since it involves 100 – 200 punctures of the iliac crests. This is an extremely painful procedure and patients usually do not

have complete resolution of their hip pain for 2 – 3 weeks. In addition to the pain, there are also risks of infection, bleeding, and those associated with general anesthesia. (24, 25) These considerable risks of bone marrow harvesting contributed to age restriction of ASCT in the past.

Since stem cells are constantly detaching from the marrow and entering the circulation, it is possible to collect stem cells from the peripheral blood. In contrast to bone marrow harvesting, peripheral blood stem cell (PBSC) collection is 3 – 4 hour outpatient procedure that does not require the use of general anesthesia. Patients receive granulocyte colony stimulating factor (G-CSF) via subcutaneous injection following myelosuppressive chemotherapy for 7 – 10 days prior to the collection. G-CSF increases the numbers of stem cells in the marrow and also induces mobilization into the peripheral blood by disrupting the interaction with a certain chemokine receptor, CXRC4, and by stimulating the release of various proteolytic enzymes. (25) Growth factors are very effective and PBSC typically results in 2 – 4 times more $CD34^+$ cells than bone marrow harvesting. (26) Although, the risks associated with PBSC collection are far less severe than those associated with bone marrow harvesting, the procedure is not risk free. Most associated complications are attributed to G-CSF. Patients commonly experience bone pain, headache, and fatigue, but severe side-effects and hospitalizations rarely occur. (24) The administration of G-CSF does cause a temporary splenic enlargement and there have been reports of splenic rupture. However, the estimated risk of splenic rupture is 1 in 10,000. (25)

Immediate clinical outcomes in ASCT mainly are directly related to the number of stem cells infused, and consequently, the time required to recover neutrophils and platelets. The infusion of more stem cells results in a more rapid hematopoietic recovery with a low probability of graft failure. (27) PBSC collection results in significantly higher numbers of stem cells, and is associated with more rapid engraftment and lower probability of graft failure than

bone marrow harvesting. (25) In the 1990s, most centers switched from bone marrow to peripheral blood as the source for stem cells because it was associated with less severe risks, fewer hospitalizations, higher numbers of stem cells, and more rapid engraftment. This switch in addition to a move away from TBI-containing conditioning regimens reduced mortality and expanded the availability of ASCT allowing populations previously excluded to become eligible for this therapy. Peripheral blood stem cell collection has now emerged as the standard of care and occurs in greater than 95% of all ASCT. (25)

ASCT is frequently used to treat and potentially cure many types of NHL. The most established use of ASCT is in patients with relapsed chemosensitive aggressive NHL. In 1995, the PARMA International trial compared ASCT to conventional chemotherapy plus radiotherapy for relapsed aggressive NHL. 109 patients, aged between 18 and 60 years, were randomized to receive either chemotherapy plus radiotherapy or ASCT after responding to an initial two cycles of salvage chemotherapy. With a median follow-up of 63 months, the response rate (86% v. 44%), the 5-year event free survival (46% v. 12%), and the overall survival (53% v. 32%) was superior in the group that received ASCT as compared the conventional chemotherapy group. (28) ASCT has also been studied in patients with primary refractory disease or disease that does not respond to salvage chemotherapy since these patients almost always have very poor outcomes. (29) Kewalramani reported the outcomes of 85 patients, 12% were older than 60, with primary refractory disease who were treated with ICE followed by ASCT if they had chemosensitive disease. 42 patients received ASCT and had 3-year event free survival and overall survival of 44.2% and 52.5% respectively, which were similar to rates achieved in relapsed chemosensitive disease. (30)

Milpied undertook a similar randomized trial for aggressive subtypes of NHL . This trial of 197 randomized patients, all less than 60 years old, compared standard chemotherapy (CHOP) with chemotherapy (CEEP) followed by ASCT as a first-line therapy. With a median follow-up of 4 years, the ASCT group had a higher estimated 5-year event free survival (55% v. 37%) but not a statistically significant higher estimated 5-year overall survival (71% v. 56%). The differences in overall survival between groups were dramatically more pronounced in those patients with poor prognostic factors (74% v. 44%). (31) However, a meta-analysis of 15 randomized controlled trials that included over 3,000 patients comparing ASCT to conventional chemotherapy as a first-line therapy reported that ASCT produced higher complete response rates but no statistical benefit to survival. (32) The role of front-line ASCT for aggressive subtypes of NHL has not been definitively established and is currently being investigated in various clinical trials.

MCL is an aggressive type of NHL with a distinct natural history from DLBCL. Standard-dose chemotherapy can achieve remissions but relapses almost always occur within the first 2 years. ASCT may provide more durable responses and prolong survival, but the utilization and indications remain a source of controversy and active debate. A number of retrospective phase II studies have been published that have reported differing results; some showing a survival benefit in certain subsets, while others suggest no benefit at all. (33) Dreyling recently published a prospective randomized trial that compared chemotherapy followed by ASCT to interferon-α maintenance therapy in patients in first remission. 122 patients, between 18 and 65 years of age, after receiving 4 – 6 cycles of CHOP or CHOP-like regimens with chemosensitive disease were randomized to the two arms. The ASCT arm experienced longer median progression free survival (39 months v. 17 months) but similar three-year overall survival (83% v. 77%). (34) To date this is the only published prospective randomized control trial for ASCT in

MCL patients. Clearly, further investigation and more evidence is required to identify which patients and in what settings ASCT is most appropriate for the treatment of MCL.

The indications for ASCT in indolent forms of NHL are less well established. The natural history of indolent forms of NHL, such as FL, involves multiple remissions followed by recurrences with progressively shorter disease-free periods. Consequently, most cases of FL are believed to be incurable. The fact that the majority of FL patients are elderly further complicates the role and utilization of ASCT within treatment strategies. Since patients with indolent forms of NHL can have considerable asymptomatic periods of time prior to the unpredictable transition to more aggressive disease progression, it is important to identify those patients who will most benefit from ASCT given the associated risks including developing myelodysplastic syndromes (MDS) or even acute myelogenous leukemia (AML). Furthermore, with the advent of rituximab, a highly effective and well-tolerated therapy that can be used as maintenance therapy for several years, judicious patient selection for ASCT is even more essential.

The International Prognostic Index (IPI), developed in 1993, was utilized to assign patients with aggressive forms of NHL into 4 different prognostic groups (low, low/intermediate, high/intermediate, high risk) based on the presence of certain risk factors (age, disease stage, performance status, extranodal disease, serum LDH level). IPI score has been used to guide treatment decisions for aggressive forms of NHL. (6) However, when applied to patients with indolent forms, the IPI was less successful and underestimated the numbers of high risk patients. Consequently, in 2004, the Follicular Lymphoma International Prognostic Index (FLIPI) was developed to assist in identifying FL patients with worse prognoses. The FLIPI score is also determined by five risk factors (age, disease stage, hemoglobin level, number of nodal areas,

serum LDH level), identifies low, intermediate, and high risk patients, and can be used to improve treatment decisions for FL. (35) Recently, researchers have begun investigating whether the presence of certain pre-transplant comorbid diseases can aid in the prediction of outcomes, and therefore, guide patient selection of intensive therapies. Building on earlier comorbidity indices, Sorror identified chronic medical conditions that were important in predicting non-relapse mortality (NRM) in stem cell transplants and created a unique scoring system that could be utilized to assess survival probabilities after allogeneic transplant. (36) More recently it has been applied to autologous transplants and was able to demonstrate that high-risk patients experienced a higher mortality. (37)

This scoring system is known as the Hematopoietic cell transplantation-specific comorbidity index (HCT-CI) and was applied to all patients in the present study using pre-transplant laboratory values. The index assigns weighted scores, from 1 to 3, to various pre-existing as well as active diseases requiring treatment at the time of transplant. Conditions such as atrial fibrillation, prior myocardial infarction, obesity, depression, insulin-dependent diabetes are examples of diseases that have a score of 1. Chronic renal insufficiency and moderate dyspnea on exertion as evidenced by abnormal pulmonary function tests are examples diseases that score 2 points, while prior solid tumor, cirrhosis, and valvular disease are examples of conditions that score 3 points. When all relevant comorbidities are scored and added together, patients are separated into three groups that predict a low, intermediate, and high risk of poor outcomes. In the validating study, the intermediate risk group was shown to have a NRM of 21% and a survival of 60% whereas the high-risk groups had a NRM of 41% and a survival of 34%. (36)

As with aggressive forms of NHL, ASCT has been more extensively studied in relapsed FL. Schouten undertook a randomized control trial to investigate whether ASCT (purged or un-purged cells) was more effective than standard chemotherapy in relapsed NHL. Patients, aged between 29 and 64 years, that responded to an initial course of chemotherapy were randomized to receive purged ASCT, un-purged ASCT, or further chemotherapy. Both the 2-year progression-free survival (PFS) (55% v. 58% v. 26%) and 4-year overall survival (OS) (77% v. 71% v. 46%) were higher in the purged and un-purged ASCT groups as compared with further chemotherapy. However, there was not a statistical difference between the purged ASCT and un-purged ASCT groups. (38) Numerous single-center phase II trials have also examined the role of ASCT in relapsed FL. One such trial showed that ASCT can produce durable remissions in those that respond. Of the 153 patients who received ASCT, the 8-year PFS and OS were estimated at 42% and 66% respectively. (39) These studies indicate that ASCT is effective in relapsed FL and may extend survival.

Given the success of ASCT in relapsed indolent NHL, trials have also been established to determine if ASCT given up-front to consolidate therapy after first remission can prolong PFS and OS and disrupt the natural history of recurrent remissions and relapses. The German Low-Grade Lymphoma Study Group (GLSG) compared conventional chemotherapy to ASCT in patients younger than 60 years with previously untreated indolent NHL. This phase III trial randomly assigned patients who responded to an initial course of chemotherapy to receive consolidation with ASCT or maintenance interferon-α therapy. The ASCT group achieved a higher 5-year PFS (65% v. 33%) as compared with the interferon-α group. Overall survival was not evaluable because median follow-up was too short at the time of publication. While acute toxicities were more frequent in ASCT group, the treatment-related mortality was similar in both groups. (40) Additionally, GOELAMS undertook a phase III trial investigating whether

doxorubicin-containing chemotherapy or ASCT would improve survival in untreated FL. Patients less than 60 years were randomly assigned to receive high-dose therapy followed by ASCT or standard doxorubicin-containing chemotherapy plus interferon-α. While the ASCT group had a higher PFS (60% v. 48%), the conventional chemotherapy group had a higher, although not statistically significant, 5-year overall survival (78% v. 84%). Furthermore, there was a higher incidence of secondary malignancies in ASCT group. Given the conflicting OS results, these studies reveal the difficulty in determining the optimal timing and the optimal patient population for ASCT. (41) Moreover, both of these studies occurred in the pre-rituximab era, so it is unclear how rituximab would impact the survival of ASCT. Thus, more studies are needed to more clearly define the role of ASCT in the treatment of indolent forms of NHL.

Treatment of Elderly NHL Patients

Although many studies have outlined and identified a standard of care of most NHL subtypes, there are still unanswered questions. One such area of uncertainty that currently needs more investigation is the effective treatment of elderly patients with NHL. The treatment of this population has become increasingly more relevant as both life expectancy and incidence of NHL continue to increase. If current trends continue, it is predicted that 70% of all cancers will occur in those aged 65 years and greater by 2020. (42)

Currently, cancer is the second most common cause of all deaths in patients older than 65 years and furthermore, approximately half of all cancers occur in this population. (43) Animal studies have provided clues as to why cancers are more common in the elderly as compared to their younger counterparts. First, carcinogenesis is a slow process that can require decades to develop. Second, older tissues are more susceptible to the effects of carcinogens due to preexisting damage, such as DNA hypomethylation and point mutations that occur with

age. (44) Thus, an older individual may develop a neoplasm sooner than a younger individual exposed to the same carcinogen. Additionally, there is evidence that tumors in older individuals behave different clinically than those in younger individuals. For example, regarding DLBCL, shorter periods of remission in elderly patients have been associated with increased levels of IL-6. IL-6 production increases with age and is increased in certain geriatric diseases such as dementia and osteoporosis. (45) Acute myeloid leukemia (AML) tumor cells in the elderly have been shown to have increased expression of multidrug resistance-1 (MDR-1) gene and increased cytogenetic abnormalities which may explain the poorer prognosis in this population. (46) Research is currently ongoing to continue to identify and further characterize age-related biological differences in cancers.

Epidemiological studies have shown that the stage of cancers at presentation varies with age. Breast, bladder, and colon cancers are diagnosed at more advance stages in the elderly while lung cancers generally present at an earlier stage. (47) This variation may be explained by age-related differences in aggressiveness of the tumor, delay in the recognition of early signs and symptoms, decreased use of preventative services such as mammograms and colonoscopies, and limited access to care. (48) Pain commonly is the symptom that prompts evaluation that leads to the diagnosis of cancer. However, in the elderly, pain may be attributed to a concomitant chronic medical condition or trivialized as a common manifestation of old age and not trigger a thorough investigation. (49)

As was previously mentioned, 54% of all cases of NHL occur in those aged 65 years and greater. (7) The prevalence of NHL in those greater than 60 years old continues to increase likely because this group is a growing population. Thus, providers treating NHL will have a substantial proportion of elderly patients in their practices. Elderly patients can develop any

subtype of NHL, although, epidemiological studies have shown that DLBCL and PTCL developed more frequently while anaplastic large cell and Burkitt's lymphoma were less commonly observed. No significant differences in the morphology and clinical presentation of NHL between younger and older individuals have been described. (50) In other words, DLBCL tumor cells should appear and present clinically in a similar way regardless of the age of the patient. Nevertheless, numerous studies have shown that older age is associated with shorter disease-free and overall survival, particularly with aggressive subtypes, due to the presence of concomitant medical problems, decreased organ function, and altered pharmacokinetics and pharmacodynamics. (51)

Although the elderly are the largest group of users of pharmaceuticals, most clinical trials include patients who are 55 years and younger. (52) The elderly have stark differences with their younger counterparts in pharmacokinetics and pharmacodynamics. Consequently, it may be very difficult for providers to select and dose chemotherapeutic agents to treat NHL in older patients. Drug absorption in the elderly is reduced due to decreased gastrointestinal motility, splanchnic blood flow, and digestive enzyme secretion. (52, 53) However, these differences do not have considerable effects on most chemotherapy since they are administered parenterally. (54) Since both liver size and perfusion decrease with age, elderly patients may have lower clearance of certain drugs. (54, 55) Furthermore, because older patients regularly take other concomitant medications, there is an increased risk of drug-drug interactions that alter P450-mediated metabolism. (56) Additionally, excretion also declines with age due to gradual loss of renal mass and decrease in glomerular filtration rate (GFR). After age 40, GFR decreases by roughly 1mL/min each subsequent year. (57)

In addition to declines in hepatic, renal, and cardiovascular function, elderly patients have decreased hematopoietic reserve. Myelotoxicity is a common complication of many chemotherapeutic regimens. Thus, given the reduced reserve, myelotoxicity is more likely to occur and can be induced with lesser doses as compared with therapy in younger patients. Myelotoxicity is a concern because febrile neutropenia and other infectious complications commonly can develop and ultimately may lead to disseminated sepsis and death. (58) This may be one explanation for why providers historically treated older patients with sub-therapeutic chemotherapy regimens. However, poorer outcomes are associated with sub-therapeutic doses and older patients should receive full doses for optimal treatment. In order to reduce the risk of myelotoxic complications, it is now recommended that G-CSF be administered. (51)

Aging is extremely individualized, and the clinical response of a given elderly patient should not be predicted based solely on age. The progressive reduction of functional reserve that characterizes aging occurs at a variable rate and course. As individuals age, different organs lose functional reserve at different rates and in different patterns. (59) In fact, the greatest diversity in terms of rates of decline occurs in those aged 70 to 85 years. (60) Thus, assessing the elderly patient has become a challenge for which the standard history and physical exam is grossly inadequate. Historically, investigators of experimental trials have not viewed the aging process as one of great variation and diversity. Elderly was defined by age alone, and the threshold age dividing the “elderly” from the “non-elderly” appeared to be somewhat arbitrary. Most studies excluded patients older than 60 years of age, but some used 65 and others used 55 as the cutoff. These exclusions were likely appropriate 15 – 20 years ago, before advances had been made to the supportive care for intensive therapies allowing more patients to tolerate and benefit from them. This convention has remained, however, and currently, studies with elderly

patients generally involve patients greater than 60 or 65 years of age. In this study we defined elderly as anyone who received their transplant after their 60th birthday.

Unfortunately, only a few published studies have addressed the treatment of older patients with NHL. One such phase III trial randomly assigned 148 patients greater than 60 years of age, with intermediate and high grade NHL, to either a CHOP treatment arm or a CNOP treatment arm, in which mitoxantrone was substituted for the more toxic doxorubicin. The CHOP arm had a better median and 3-year overall survival, and the toxicity was similar in both groups. (61) As in younger patients, these results support the use of CHOP to treat aggressive subtypes of NHL. Another phase II trial compared treatment with standard dose CHOP administered in the standard schedule, every 21 days, to a weekly administration of 33% of the standard dose for 3 weeks in patients greater than 65 years of age. At 2 years, the standard dose CHOP arm produced a superior overall survival when compared to the low dose CHOP arm. (62) Both of these studies confirmed the administration of the full dose of CHOP as the standard treatment of the elderly with aggressive NHL. Because of its effectiveness and low toxicity profile, rituximab typically is added to CHOP and now is the standard treatment for DLBCL. Recently, a study evaluated the use of R-CHOP in elderly patients with DLBCL. 399 patients between the ages of 60 and 80 were randomly assigned to receive 8 cycles of CHOP or R-CHOP. Those assigned to the R-CHOP arm achieved a significantly higher CR rate, longer progression-free survival, and overall survival with no significant difference in toxicity as compared with the CHOP arm. (63) Thus, this study confirmed that R-CHOP is the optimal treatment for DLBCL in the elderly.

As was previously discussed, ASCT has an integral role in the treatment of many aggressive subtypes of NHL. While the utilization of ASCT continues to expand in recent times,

the elderly represent a population for which the role of ASCT in treatment still needs to be fully defined. Most trials have excluded this population and consequently many providers are reluctant to consider ASCT as a viable treatment option. Questions remain regarding elderly patients' ability to mobilize adequate numbers of stem cells, capability to tolerate the high dose chemotherapy, and most importantly the efficacy and clinical benefits of the treatment.

Hematopoietic production of bone marrow varies with age. (64) In one study, younger individuals (mean age 23 yrs) were able to increase the production of granulocyte-macrophage colony-forming units threefold in response to low dose (30 μg) G-CSF while older individuals (mean age 74 yrs) were not able to significantly increase production. However, at a standard dose (300 μg) of G-CSF, although the younger group produced twice that of the older group, both groups were able to significantly increase production of granulocyte-macrophage colony-forming units. (65) Thus, while marrow function and responsiveness to growth factors does decline with age, older patients are still able to generate adequate numbers of stem cells in preparation for transplantation. Questions regarding the elderly patients' ability to tolerate ASCT as well as the efficacy of this treatment in this age group are harder to answer. One study designed to evaluate cardiac toxicities of elderly patients (≥60 yrs) undergoing ASCT found that the elderly were more susceptible to cardiac toxicities but had similar response rates and survival when compared to younger counterparts. (66) Recent publications suggest that older patients treated with curative intent with aggressive therapy and modern supportive measures may have a similar outcome to younger patients. (67) There remains however, a relative paucity of clinical data regarding the use of high-dose therapy and ASCT in elderly NHL patients.

Numerous studies have shown that ASCT results in a survival benefit and potential cure in relapsed and refractory patients younger than 60 years when compared with conventional

chemotherapy. (28 – 34, 38 – 41) The median age of the patients included in these studies was considerably younger than the median age of all patients with NHL. Earlier series have reported early treatment-related mortality (TRM) for all adults at 10 – 15%. (68) More recently, the use of mobilized peripheral blood stem cells (PBSC) and G-CSF support, in conjunction with more effective antibiotic and antifungal drugs, has reduced the toxicity associated with the procedure and has expanded its availability allowing the transplantation of elderly patients to be evaluated. Currently, early TRM has been greatly reduced and now is reported between 2 – 3%, with infection being the cause one third of the time. (69)

Recent publications have sought to improve this scarcity of information and suggest that older patients treated with curative intent with aggressive therapy and modern supportive measures may have a similar outcome to younger patients. To date, a series of retrospective analyses have attested to the feasibility of ASCT in selected patients over age 60 without undue treatment related morbidity or significantly worse survival. (70 – 86) However, common to these reports are several shortcomings, including small numbers of subjects, heterogeneity of transplant conditioning regimens, and short term follow-up duration.

One of the earliest studies, published in 1994, noted an equivalent progression-free (33% v. 37%) and overall survival (38% v. 39%) in elderly patients (≥55 years) with intermediate and high grade NHL but a higher early TRM rate (13% v. 5%) when compared with younger patients with matched prognostic factors. (70) In this study, the records of 901 patients transplanted between 1980 and 1993 at 94 European and American centers were retrospectively reviewed. Of the 901 patients, 82 were older than 55 years at the time of transplant and, for this study, represented the elderly group. There were only 23 patients older than 60 years at transplant, so 55 years was used as the cutoff to increase the numbers of the

elderly group. Since the patients were from 94 different centers, there was substantial heterogeneity with respect to disease status at transplant and to conditioning regimens. TBI was a component of the conditioning regimen of patients in both groups, although, significantly fewer in the elderly group. The relatively higher TRM was likely result of both the TBI-containing regimens and that bone marrow was the source of stem cells for all transplants. Additionally, the study period was 13 years in duration, and there was a considerable difference between the groups regarding when patients were transplanted. The median date of transplant for the control group was December 1985, but was July 1991 for the elderly group. This likely indicates a reluctance for centers to transplant older patients until improvements to supportive care had been made. Consequently, the median follow-up for the elderly group was 20 months as compared to 71 months for the control group. Additionally, it is unclear how the included patients were chosen and given the retrospective nature of this study and extended study period, selection bias impacts the strength of the conclusions. Nonetheless, despite these flaws, this was one of the first published reports to demonstrate that a selected group of patients older than 55 could undergo ASCT and experience a similar long-term survival to their younger counterparts. (70)

Moreau reported that ASCT could be performed in selected elderly patients as an initial treatment. 11 patients, aged between 61 and 65 years, with intermediate and high-grade NHL were transplanted and found to have a median survival of 28 months with an estimated progression-free survival of 50% at 3.5 years and an estimated overall survival of 45.7%. (71) Stamatoullas concluded that ASCT was feasible in elderly patients with relapsed or refractory aggressive NHL. This study included 9 patients, aged 61 to 72 years, and had very short follow-up, the longest of which was 14 months. (72) While these studies were performed at single-centers and included homogeneous populations transplanted under the same protocols, they

had a small sample size with a relatively short follow-up, were retrospective in nature, and lacked a comparative control group. Furthermore, the authors of most of these reports did not explicitly comment on how the elderly patients were selected for their respective studies. Those that did list selection criteria often used performance status (73, 74), which can be argued is the most subjective factor of the IPI.

Several subsequent trials increased the numbers of the study populations by grouping patients with different malignancies together. (74 – 79) Villela reported the results of ASCT in 49 patients aged from 60 to 71 years. The diagnoses of these patients included multiple myeloma, acute myelogenous leukemia, chronic myelogenous leukemia, chronic lymphocytic leukemia, Hodgkin's disease, amyloidosis, as well as NHL. (75) While a larger sample size can buttress the findings, these trials were limited by the considerable variation in the diagnosis, disease status, and conditioning regimen, however. With such heterogeneous populations, it becomes difficult to widely apply these findings and consequently influence the management of elderly patients with NHL.

Most of the published reports analyzing ASCT in the elderly list a median age at transplant between 62 and 63 years. (71, 72, 74, 75, 77, 78, 80, 81, 83, 86) There have been a few studies in which the median age at the time of transplant ranged from 65 to 68, and one study included a patient that was as old as 82 years at the time at transplant. (73, 74, 77, 84, 85) Zallio transplanted 20 NHL patients with a median age of 67 years and reported an estimated 5-year overall survival of 59%. (82) While some of these trials suffer from the same limitations mentioned above, heterogeneous population, small sample size, selection bias, etc., they do provide evidence that selected patients older than 70 and even older than 80 can safely undergo ASCT.

Fortunately, recent studies have not contained many of the design flaws that have weakened previous reports. They have begun to provide the data needed to change the historical perceptions held regarding the role of ASCT in elderly patients. Buadi examined the outcomes of ASCT in 93 NHL patients, aged 60 to 76 years, and compared them to a matched group of 178 younger patients, aged 18 to 59 years, at a single center transplanted with the same protocol guidelines. The elderly group was found to have a significantly shorter median survival (25 months v. 56 months), but a similar estimated 4-year progression-free survival (38% v. 42%) and TRM (5.4% v. 2.8%). (84) Unlike the earlier smaller studies, this study was conducted a single center, has a much larger and homogeneous sample size, contains a matched control group, and has an extended follow-up period. Although it appears clear from the published data that ASCT may be safely performed in selected patients older than 60 years of age, evidence regarding the long term efficacy, and a precise understanding of the differences in age groups with regard to treatment related toxicity remain limited. More large-scale studies are needed to further evaluate ASCT in the elderly in order to remove the perception that age alone is an absolute contraindication for intensive and potentially curative therapies such as ASCT.

Purpose of the Thesis

This study aims to add to the existing clinical evidence regarding elderly patients with NHL who have received ASCT. It examines all patients transplanted at one medical center with an identical conditioning regimen and with long-term follow-up. This study will test the hypothesis that elderly patients (>60 years) undergoing ASCT when compared to similar population of younger patients (<60 years), treated with the same protocol, will not experience

clinically significant differences in overall survival, progression-free survival, incidence of acute serious toxicities, early treatment-related mortality, or non-relapse mortality.

Methods

213 patients who underwent autologous stem cell transplantation (ASCT) for NHL at a single institution following BEAM conditioning between January 1, 2000 and December 31, 2007 were retrospectively identified from the Yale University School of Medicine Bone Marrow Transplant Database. 7 patients were excluded due to inadequate documentation in the medical records. 5 patients received ibritumomab (Zevalin), a radioimmunotherapeutic agent, as a part of the conditioning regimen and were excluded from this study. During this time period, 67 patients older than 60 years of age at the time of transplant and 134 patients younger than 60 years of age received ASCT at Yale. Patients in both groups were primarily referred from community oncologists for treatment of relapsed or high risk NHL in first partial or complete remission. Patients were determined to be eligible for transplantation based on an adequate performance status and medical evaluation for organ function.

Data were collected from review of patient records. Pre-transplant laboratory values, pulmonary function tests, and MUGA evaluations were used to determine hematopoietic cell transplantation comorbidity index (HCT-CI) scores. In order to investigate the tolerability of ASCT, toxicities occurring between day 0 and day 100 were graded retrospectively using the NCI Common Toxicity Criteria v3.0. Only toxicities graded 3 and above were recorded.

Peripheral blood stem cells (PBSC) were obtained during recovery from mobilizing chemotherapy. PBSC collection was started when the white blood cell count recovered from a

nadir to greater than 3000/μL and/or when peripheral $CD34^+$ cells were greater than 10/ μL. Filgrastim (granulocyte colony stimulating factor) was continued until the last day of collection. The target progenitor cell dose was ≥5.0 x 10^6 $CD34^+$ cells/kg with a minimal acceptable dose of ≥2.0 x 10^6 $CD34^+$ cells/kg. All products were cryopreserved using standard techniques.

The preparative regimen comprised BEAM (carmustine [BCNU] 300 mg/m^2 on day minus-6, etoposide 200 mg/m^2 every 12 hours on days minus-5 to minus-2, cytarabine 100 mg/m^2 every 12 hours on days minus-5 to minus-2, and melphalan 140 mg/m^2 on day minus-1. The cumulative doses of the drugs were carmustine 300 mg/m^2, etoposide 1200 mg/m^2, cytarabine 800 mg/m^2, and melphalan 140 mg/m^2. Doses were given according to the patient's actual weight except in obese patients, in which case an adjustment was made. 4 elderly patients received dose reductions of the preparative regimen. On the day of transplant (day 0), cryopreserved stem cell products were warmed to 37^{o}C and infused through a central line.

Patients were considered eligible for ASCT in the outpatient setting if they lived within a 45-minute travelling distance of the oncology clinic and with an able care provider, and had adequate insurance coverage. These patients were seen and assessed for toxicities daily in the outpatient clinic and received intravenous fluids and blood products as indicated.

On day 0, filgrastim 5–10 mg/kg subcutaneously, ciprofloxacin 500 mg p.o. twice daily and fluconazole 200 mg p.o. once daily were started and continued until engraftment. Acyclovir, 200 mg p.o. five times daily was administered to all patients. CMV-negative, irradiated blood products were given to all patients. Platelets were transfused for counts below 20000/ μL or at higher counts if evidence of bleeding was present. In 2003, the administration of ceftriaxione, 1 g daily, was adopted as an additional Gram-positive organism prophylaxis and was started upon the first day of documented neutropenia. Patients were given intravenous

antibiotics for oral temperatures greater than 38.0°C or if the patient had a change in clinical status suggestive of infection following cultures of the peripheral blood, central lines, and urine. Once intravenous antibiotics were started, ciprofloxacin was discontinued, but fluconazole was maintained until the neutrophil count was greater than 500/ µL. The choice of initial empiric antibiotics was left to the discretion of the admitting physician and in the majority of cases included a third generation cephalosporin, typically ceftazidime. Vancomycin was added initially if clinical evidence of a gram-positive infection was present or after 24–48 h for persistent fevers or positive cultures for gram positive organisms.

Complete response (CR) was defined as the disappearance of all clinical evidence of lymphoma for a minimum of 4 weeks with no persisting symptoms related to the disease. Any residual masses had to remain unchanged for 6 months or longer. Partial response (PR) was defined as at least a 50% decrease in the sum of the products of the two longest diameters of all measurable lesions for at least 4 weeks. Additionally, no lesion could increase in size and no new lesion could appear. Progressive disease (PD) was defined as greater than 25% increase in the sum of the products of the two longest diameters of any measurable lesion or the appearance of a new lesion. Patients who achieved at least a PR with salvage chemotherapy administered before transplantation were considered to have chemosensitive disease and those that achieved less than a PR were considered to have chemoresistant disease.

Disease-free survival (DFS) was defined as the time from transplant to recurrence or death from any cause. Overall survival (OS) was defined as the time from transplant to death from any cause. Treatment-related mortality (TRM) was defined as death unrelated to relapse within the first 100 days following ASCT. Non-relapse mortality (NRM) was defined as death from any cause except for progression of disease. Days to neutrophil recovery, determined when absolute neutrophil count (ANC) was greater than 500/mm^3, were calculated from the

date of transplant. Platelet engraftment, defined as the time until the platelet count was greater than 20,000/μL for consecutive days without platelet transfusion, was followed for all patients but not measured in this study as the precise day of engraftment was not regularly recorded.

Comparisons between groups were performed with X^2 for categorical variables or *t*-test for continuous variables. Survival analyses were performed using the method of Kaplan and Meier and comparisons of survival curves were performed with log-rank analysis or the Breslow (Generalized Wilcoxon) test. Cox proportional hazard regression was used to analyze the effect of age, cell type (B-cell v. T-cell), number of prior regimens, pre-transplant disease status, HCT comorbidity score and performance status on survival. The proportionality of baseline hazard functions was assessed for selected variables by examination of the log-minus-log survival plot. Binary logistic regression was performed to examine the effect of age, cell type (B –cell v. T-cell), number of prior regimens, pre-transplant disease status, HCT comorbidity score and performance status on the incidence of grade 3 or greater toxicity occurring at any time point between day +0 and day +100. All analyses were performed using SPSS for Mac, version 16.0 (SPSS, Chicago, IL, USA)

Results

A total of 201 consecutive patients were included; patient characteristics are presented in Table 1. 67 patients were older than 60 years of age (median age 65, range 60 – 75) and 134 patients were younger than 60 years of age (median age 51.1, range 18 – 59) at the time of transplantation. The two groups were well-matched for demographics and disease-related

characteristics. Males outnumbered females in both groups but with a similar distribution. Diffuse large B-cell lymphoma was the most common histological type in both the elderly and the control group. Although not significant, there was a difference with regard to histological subtype (p=.054). The control group contained 15 patients (11%) with anaplastic lymphoma, while the elderly group only contained 2 patients with anaplastic lymphoma. Furthermore, the elderly group contained more patients with mantle cell lymphoma. This difference between the groups is consistent with the epidemiology of these two types, as anaplastic lymphoma is more common is younger patients, while mantle cell lymphoma is more common in elderly patients. The majority of patients in both groups had advanced stage disease at diagnosis and most were transplanted in first or second remission. There was a minority of patients transplanted in the third or greater remission, but all patients in both groups had chemosensitive disease. The comorbidities of both groups, as measured by the HCT-CI score, had a similar distribution of the three risk groups. A similar proportion in both groups was transplanted in the outpatient setting.

Table 2: Patient Characteristics

	Elderly Group (N=67)	Control Group (N=134)	p-Value
Median age at transplant, (range)	65 (60 – 75)	51 (18 – 59)	
Elderly Group by Age (%)	60 – 64 yrs: 45% (30) 65 – 69 yrs: 45% (30) ≥ 70yrs: 10% (7)		
Gender: Male (%) Female (%)	60% (40) 40% (27)	63% (84) 37% (50)	0.682
Histology: Disease type	DLBCL: 46% (31) Mantle Cell: 25% (17) Foll.-Transformed: 9% (6) Follicular: 8% (5) T-cell: 6% (4) Anaplastic: 3% (2) Other: 3% (2)	DLBCL: 43% (58) Mantle Cell: 13% (17) Foll.-Transformed: 8% (11) Follicular: 8% (11) T-cell: 7% (9) Anaplastic: 11% (15) Other: 10% (13)	0.054
Histology: B-cell v. T-cell	B-cell: 91% (61) T-cell: 6% (4) Anaplastic: 3% (2)	B-cell: 82% (110) T-cell: 7% (9) Anaplastic: 11% (15)	0.134
Histology: Aggressive v. Indolent	Aggressive: 94% (63) Indolent: 6% (4)	Aggressive: 93% (124) Indolent: 7% (10)	0.695
Stage III – IV (%)	90% (64)	89% (120)	0.737

	Elderly Group (N=67)	Control Group (N=134)	p-Value
Disease status at transplant	1st CR/PR: 43% (29) 2nd CR/PR: 43% (29) >2nd CR/PR: 13% (9)	1st CR/PR: 47% (62) 2nd CR/PR: 45% (60) >2nd CR/PR: 8% (11)	0.514
HCT-CI Score	0 : 37% (22) 1 – 2: 35% (21) >2: 28% (17)	0: 32% (40) 1 – 2: 40% (50) >2: 28% (35)	0.768
ECOG PS	0 – 1: 92% (60) >2: 7% (5) Unknown: 1% (2)	0 – 1: 93% (124) >2: 7% (9) Unknown: <1% (1)	0.604
Transplanted as an outpatient	64% (43)	69% (93)	

The mean numbers of $CD34^+$ cells collected and infused as well as the time to neutrophil engraftment are listed in Table 3. There were no significant differences in the number of CD34+ cells collected or the time to recover neutrophils between the two groups. Additionally, both groups received a similar number of $CD34^+$ cells reinfused.

Table 3: Stem cells and engraftment

	Elderly Group (N=67)	Control Group (N=134)	p-Value
Mean number of $CD34^+$ cells collected (x 10^6/kg)	7.48 ± 5.57 (range: 3.2 – 34. 7 x 10^6)	6.95 ± 4.14 (range: 2.8 – 28.9 x 10^6)	0.45
Mean number of $CD34^+$ cells infused (x 10^6/kg)	5.90 ± 2.21 (range: 3.2 – 13.5 x 10^6)	5.09 ± 1.77 (range: 0.9 – 13.2 x 10^6)	0.17
Mean time to ANC engraftment (range)	9 days ± 0.95 (range: 8 – 13 days)	9 days ± 0.73 (range: 7 – 11 days)	0.4

Serious regimen-related toxicities are listed in Table 4. In the elderly group, 93% of patients required hospitalization within the 1st 100 days post-transplant and 10% required an intensive care unit admission, whereas 84% of patients in the control group required hospitalization within the 1st 100 days post-transplant and 5% required an intensive care unit admission. In both groups, neutropenic fever was the most common reason for admission. . Besides neutropenic fever, the most common serious toxicities within the first 100 days post-transplant in both groups were mucositis and diarrhea. The elderly group experienced significantly more acute serious toxicities as compared to the control group ($p<0.0001$). However, there were no statistical differences between the groups regarding specific organ system toxicities.

Table 4: Serious toxicities (>Gr.2) within 1st 100 days post-transplant

	Elderly Group (N=67)	Control Group (N=134)	p-Value
Any toxicities (> Gr. 2)	67% (44)	40% (53)	**<0.0001 ***
Mucositis	33% (22)	36% (48)	0.73
Nausea/Vomiting	9% (6)	12% (16)	0.375
Diarrhea	33% (22)	31% (42)	0.900
Cardiovascular	14% (9)	7% (9)	0.107
Pulmonary	12% (8)	7% (9)	0.209
Infectious Disease	21% (14)	18% (24)	0.575
Neutropenic Fever	68% (48)	72% (97)	0.594
Neurological	8% (5)	5% (7)	0.500
Renal	3% (2)	1% (1)	1.000
Hepatic	2% (1)	2% (2)	0.530
ICU Admissions	10% (7)	5% (7)	0.211

* indicates significant difference between groups

The 3 and 5-year overall and disease-free survival, 100-day NRM, and 1-year NRM were compared between groups and are listed in Table 5. With a median follow-up 35 months, the 5-year overall survival for all patients included in this study was 65% (Figure 1) Figures 2 and 4 display the OS and DFS by age group respectively. The 3 and 5-year OS were very similar between the two groups (p=0.91). Figure 3 presents the DFS for all patients. The DFS at 3 and 5 years was slightly higher in the control group but, these differences were not statistically significant (p=0.66). Furthermore, the median OS and DFS were lower in the elderly group when compared to the controls. Additionally, the elderly group had a higher, but not statistically significant (p=0.19), 100-day and 1-year NRM (Figure 5).

Table 5: Survival (OS, DFS, NRM)

	Elderly Group (N=67)	Control Group (N=134)	p-Value
Median follow-up	31 months	35 months	
3-year OS	74%	75%	0.91
5-year OS	62%	67%	0.91
Median OS	85 months	Not reached	
3-year DFS	48%	58%	0.66
5-year DFS	48%	54%	0.66
Median DFS	38 months	82 months	
100 –day NRM	1.5%	0%	0.19
1-year NRM	3%	1%	0.19

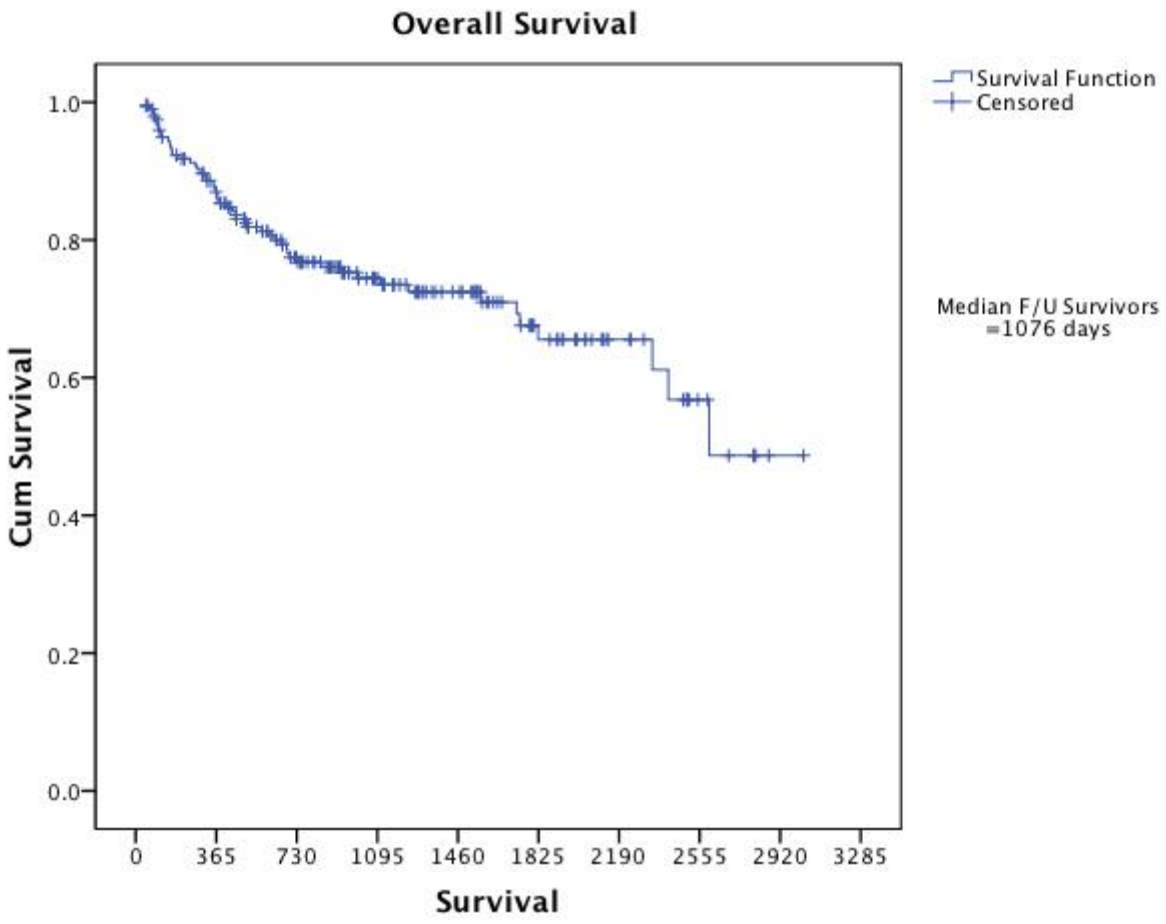

Figure 1: Overall Survival (all patients) with median follow-up of 35 months

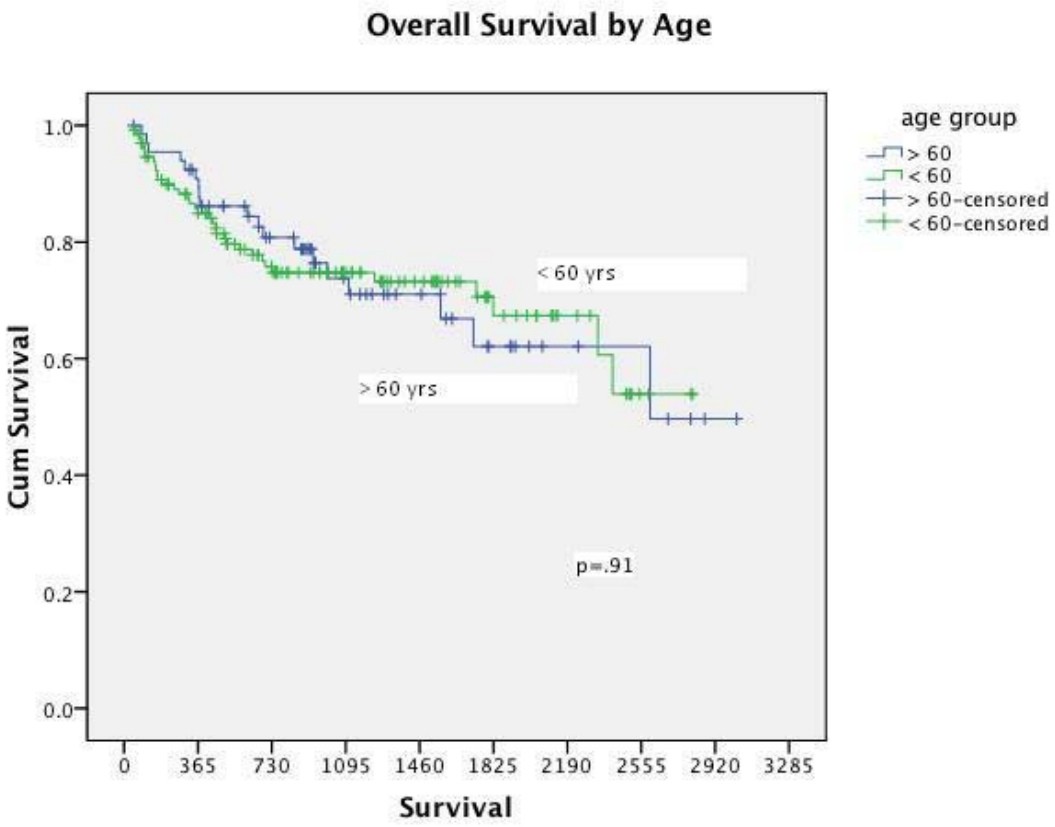

Figure 2: Overall survival by age group (median follow-up 31 months for elderly and 35 months for control)

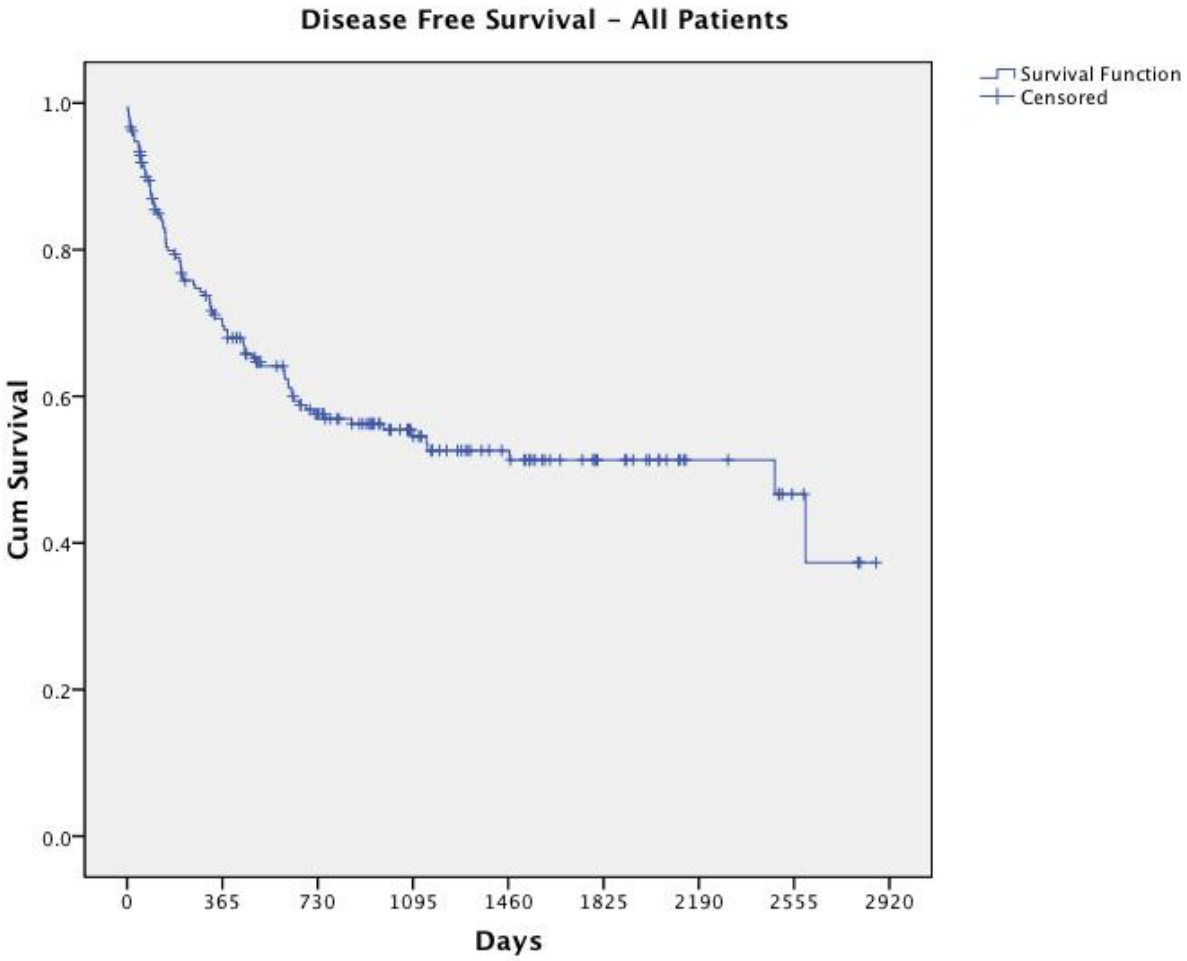

Figure 3: DFS (all patients)

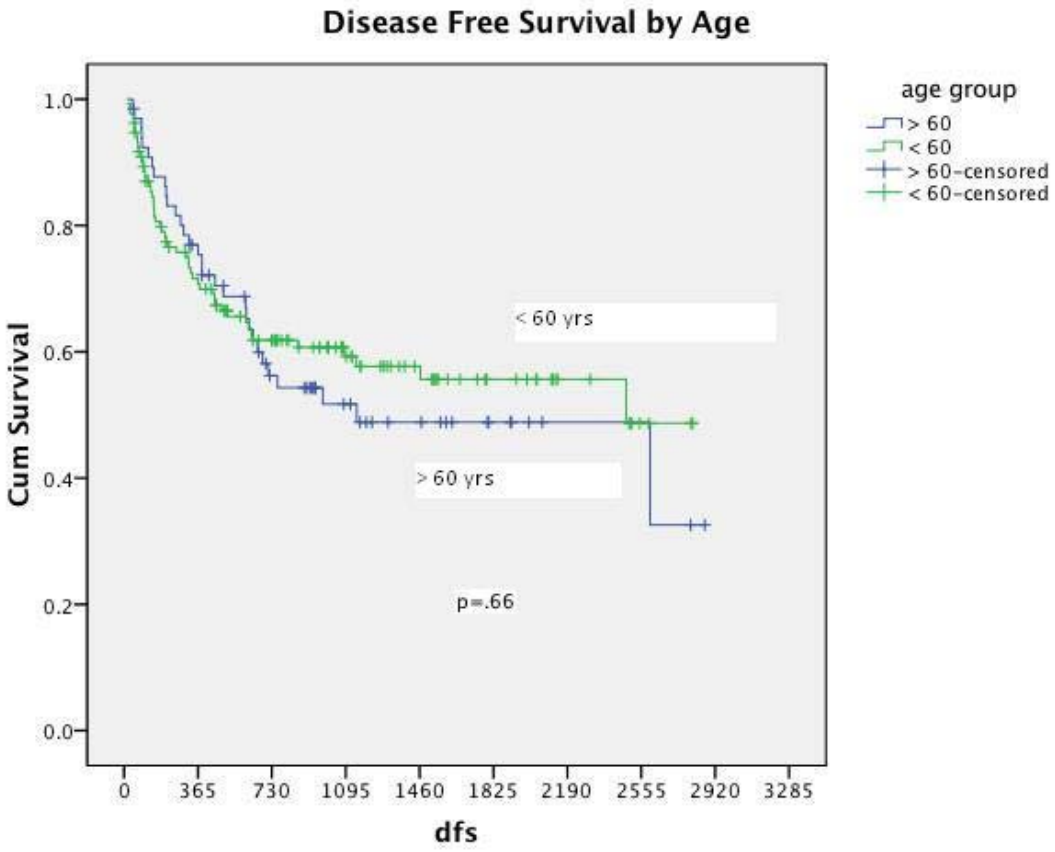

Figure 4: DFS by age group

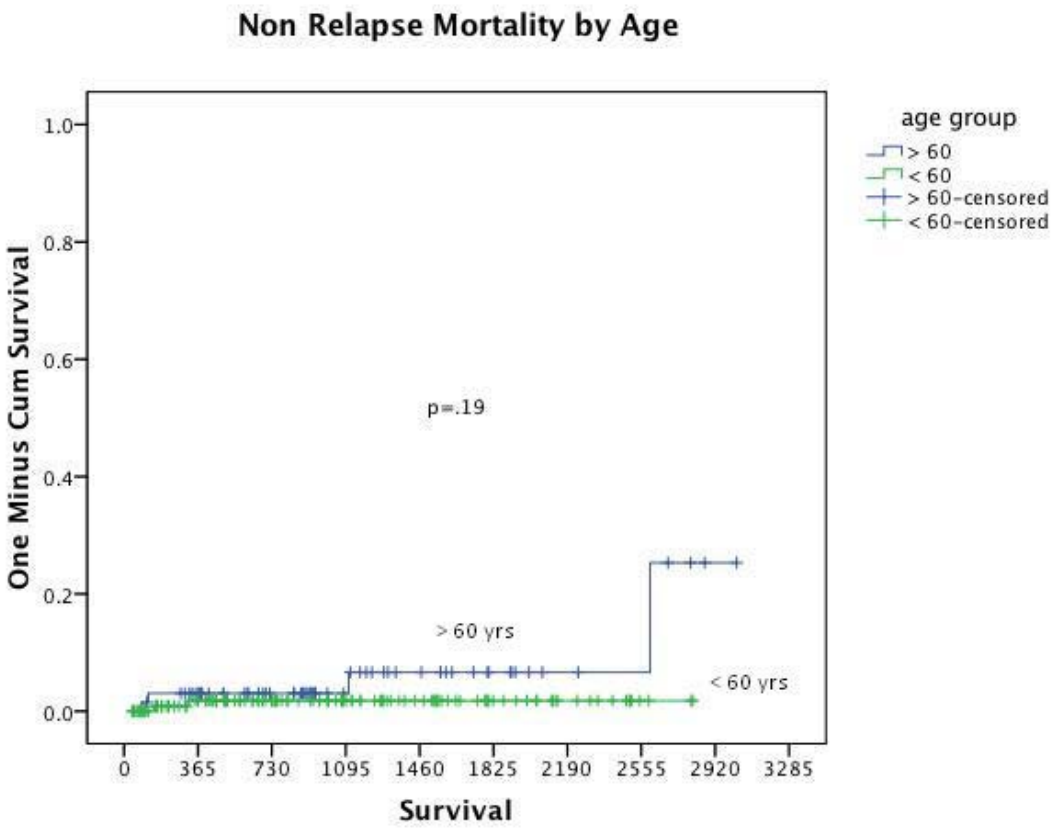

Figure 5: NRM by age

In the univariate analysis of all patients, the only factor that was statistically significant in predicting the likelihood of developing an acute serious toxicity from ASCT was age >60 years (RR 3.1, 95% CI 1.7 – 5.7, p=0.004). Cell type (B-cell v. T-cell), histology (aggressive v. indolent), disease status, ECOG performance status, HCT-CI score, and number of $CD34^{+}$ cells administered

all were not significantly associated with experiencing a serious toxicity. With respect to OS, in the univariate analysis of all patients, HCT-CI score > 2 (RR 2, 95% CI 1 – 4, p=0.043) was the only factor associated with significantly worse OS. Although, with a weighted pair-wise comparison of disease status ranks, there was a significant difference with regards to OS between patients transplanted at 1^{st} CR/PR and patients transplanted at 2^{nd} CR/PR (p=0.021) (Figure 6). Age at transplant, sex, disease stage, histology (aggressive v. indolent), ECOG performance status, number of prior treatment, number of $CD34^{+}$ cells administered, and ICU admission, all were analyzed and determined not to be significantly associated with worse OS.

A similar univariate analysis was applied exclusively to the elderly group with regard to toxicity and survival. There were no significant factors predictive of toxicity or OS. However, disease status at the time of transplant (1^{st} CR/PR v. $>2^{nd}$ CR/PR) was significantly associated with DFS in the elderly group (p=0.041) (Figure 7).

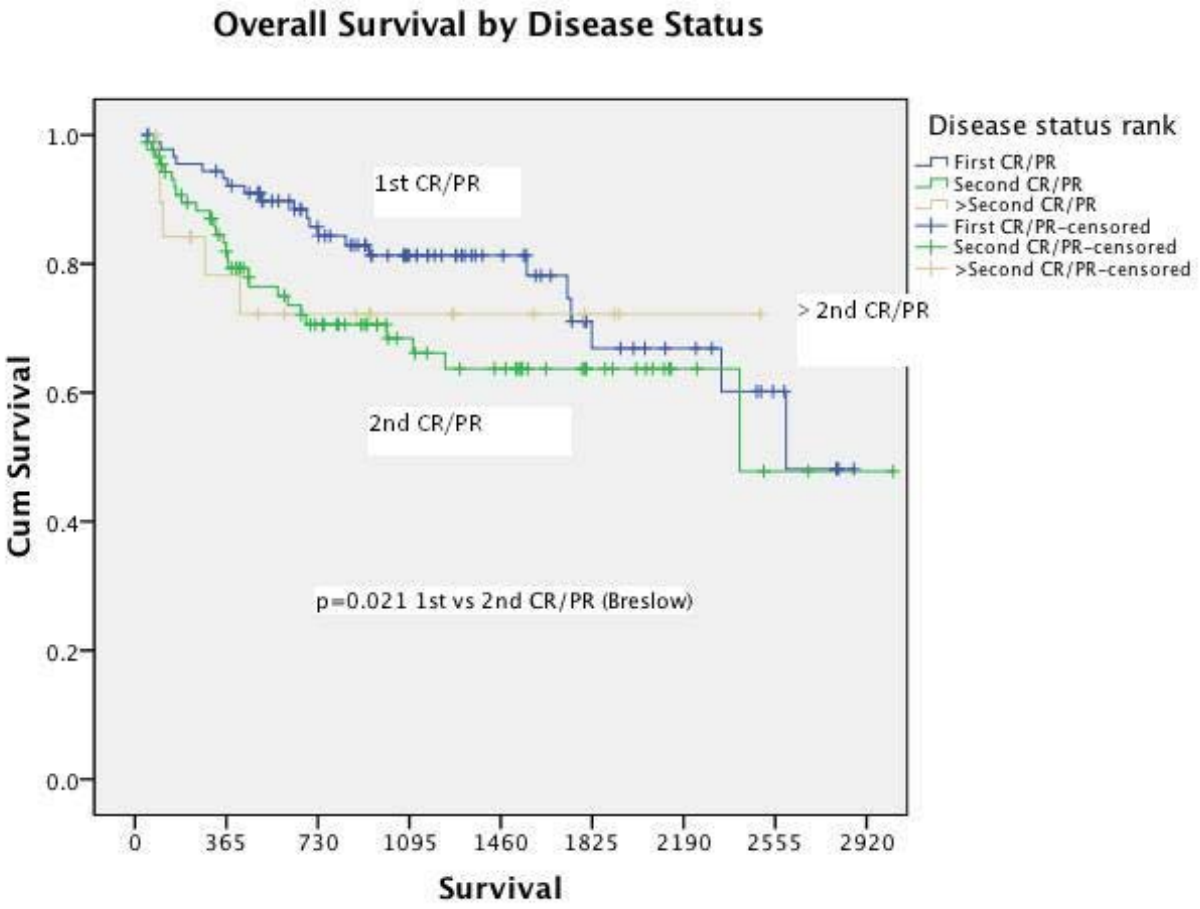

Figure 6: Overall survival by disease status (1st CR/PR v. 2nd CR/PR)

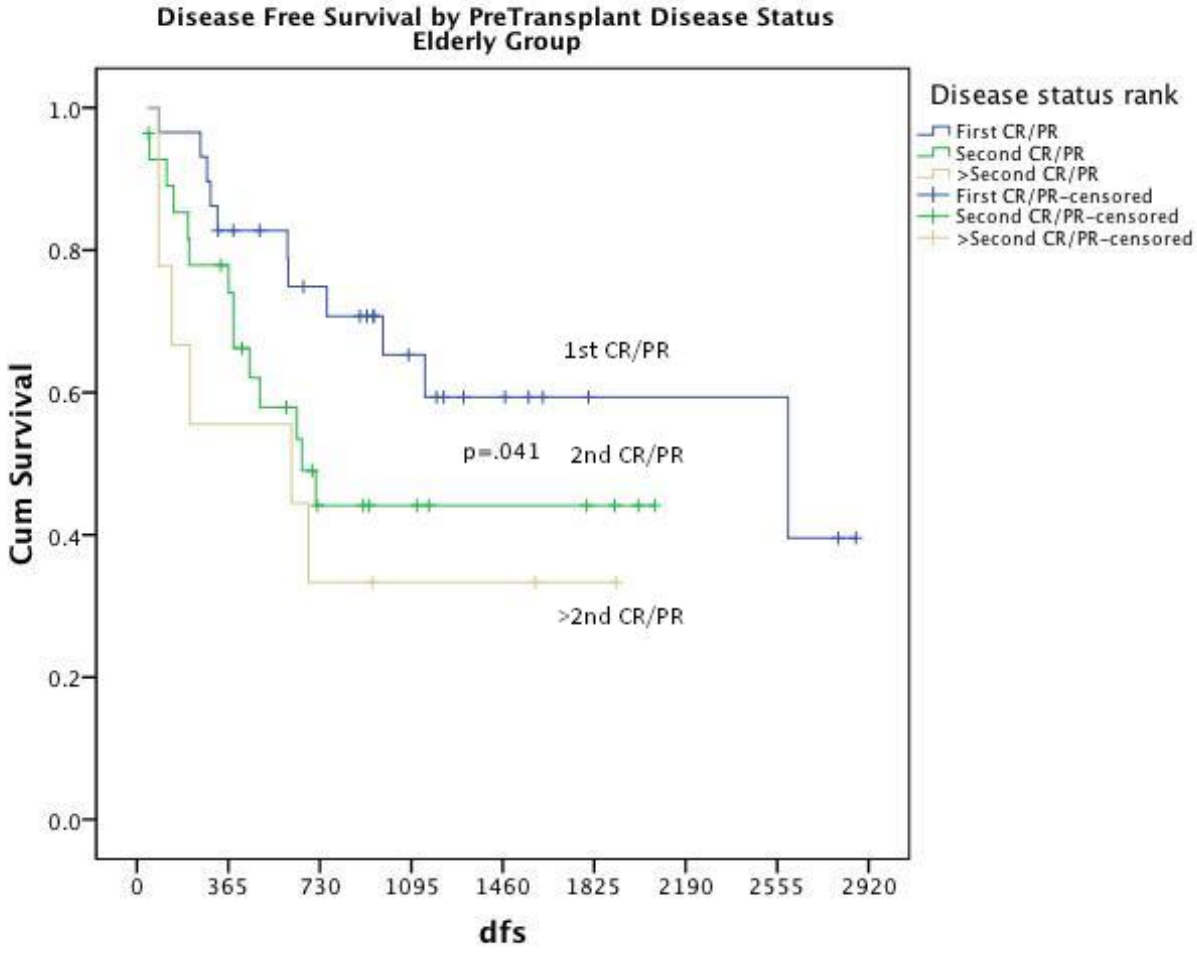

Figure 7: Disease-free survival by disease status in the elderly group

DLBCL and MCL were the most common NHL subtypes represented in this study. Figures 8 and 9 present the OS and DFS for DLBCL by age group. The outcomes for DLBCL patients are nearly identical when the two age groups are compared. In a subgroup analysis of all DLBCL patients, disease status (1^{st} CR/Pr v. 2^{nd} CR/PR, and 1st CR/PR v. $>2^{nd}$ CR/PR) was found to be predictive of OS (p=0.044 and 0.05, respectively) (Figure 10). Similarly, when only elderly patients with DLBCL are analyzed, disease status was not significant (p=0.3) for OS, but the survival curves appear quite separate (Figure 11). It likely did not reach significance due to

smaller numbers. Figures 12 and 13 display the OS and DFS for MCL by age group. Both the OS and DFS do appear to be lower for elderly patients with MCL when compared to controls, but these differences were not statistically significant potentially due to the smaller number of patients.

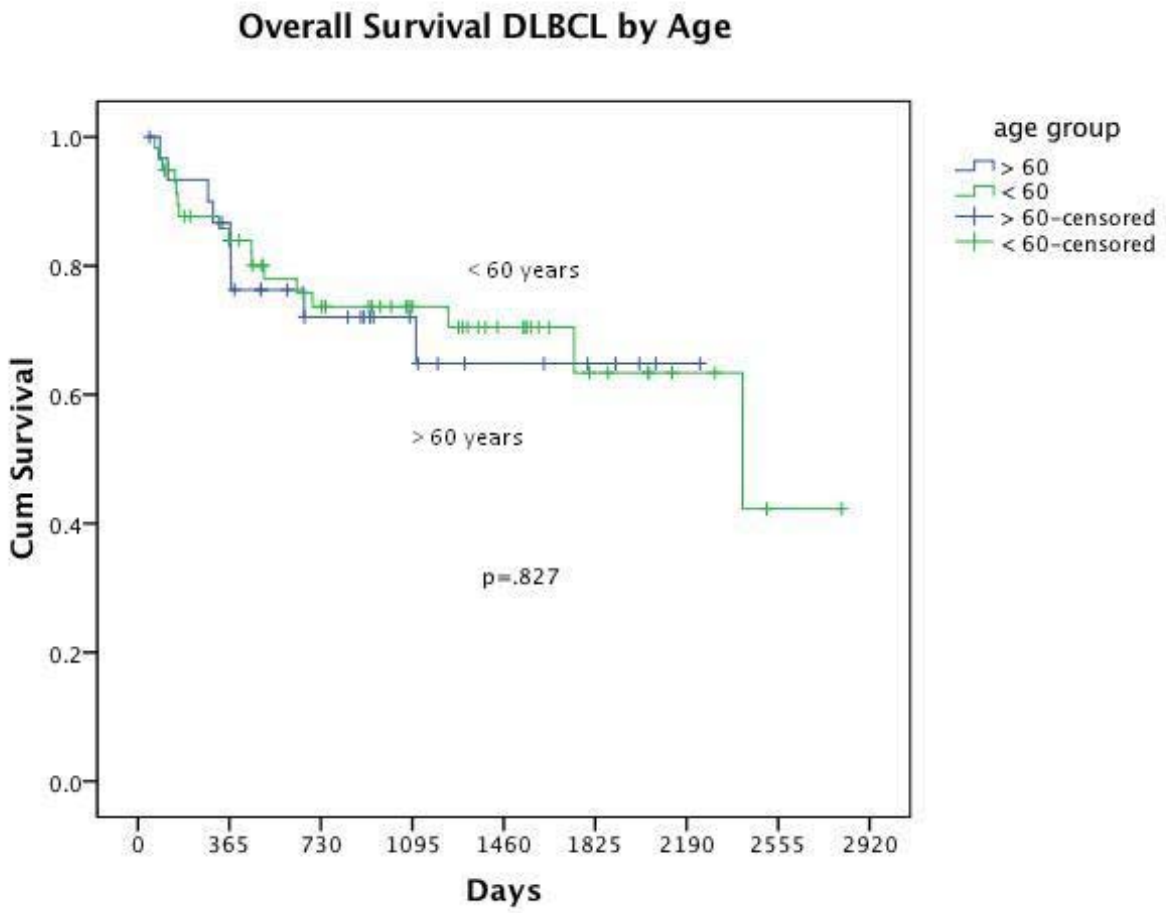

Figure 8: Overall survival of DLBCL by disease age

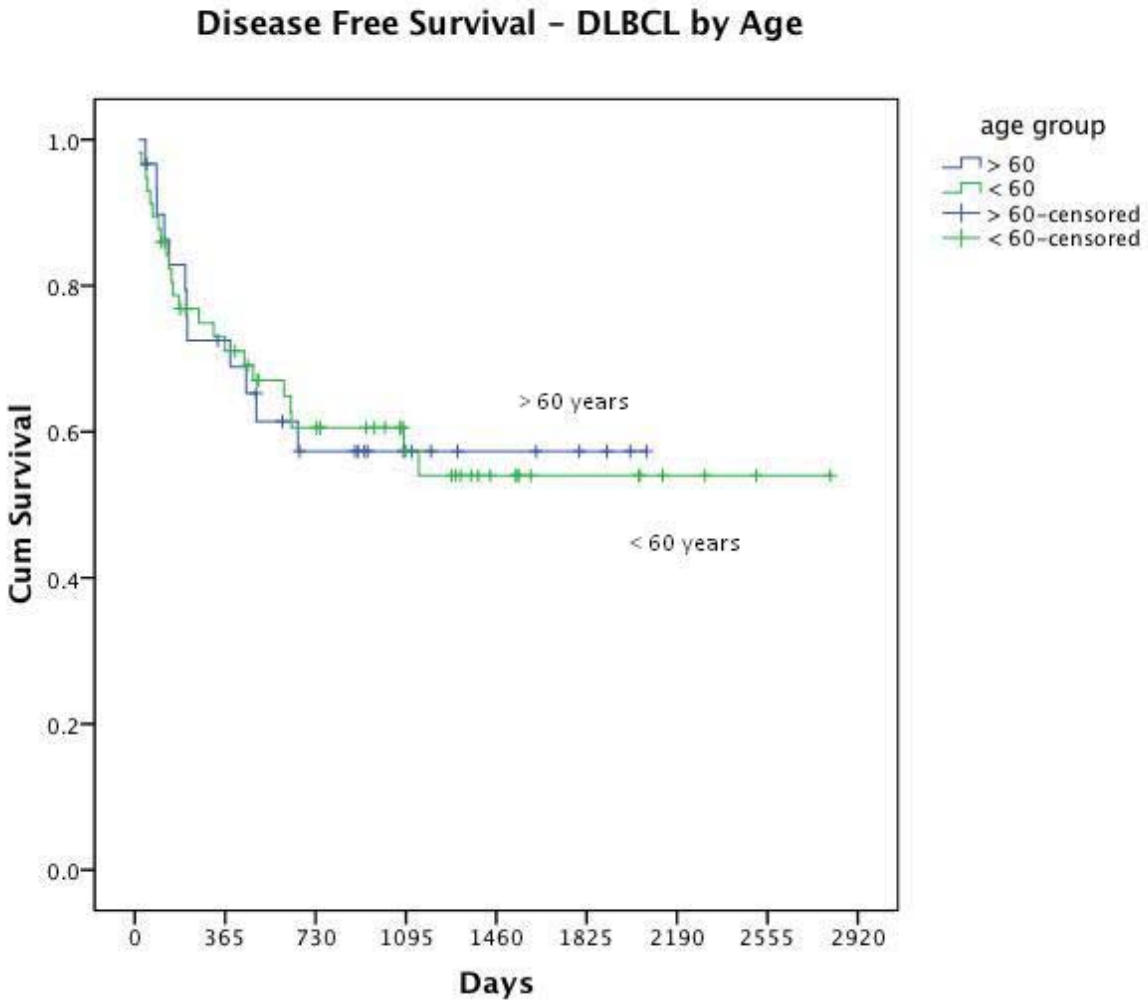

Figure 9: Disease-free survival of DLBCL by disease stage

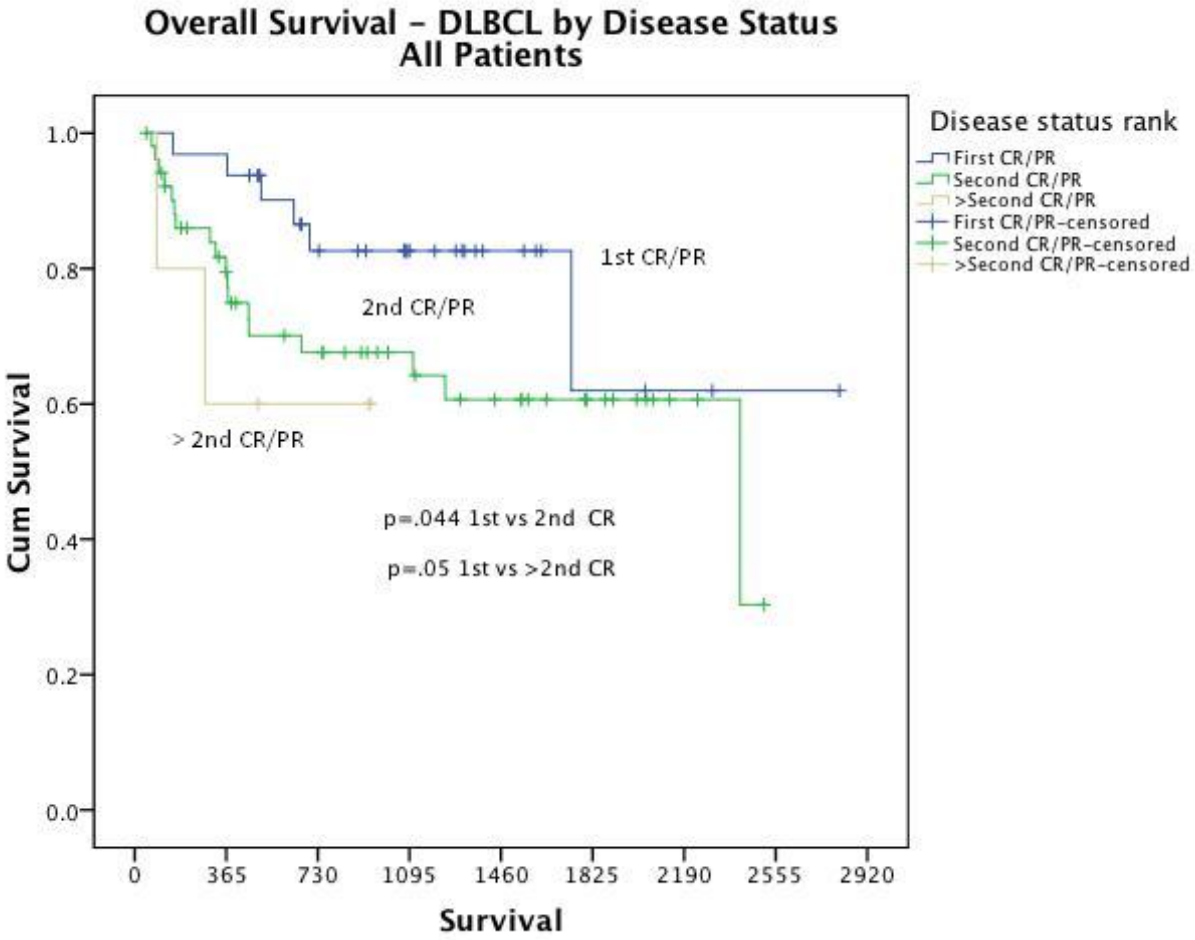

Figure 10: Overall survival of DLBCL by disease status (1st CR/PR v. 2nd CR/PR and 1st CR v. >2nd CR/PR)

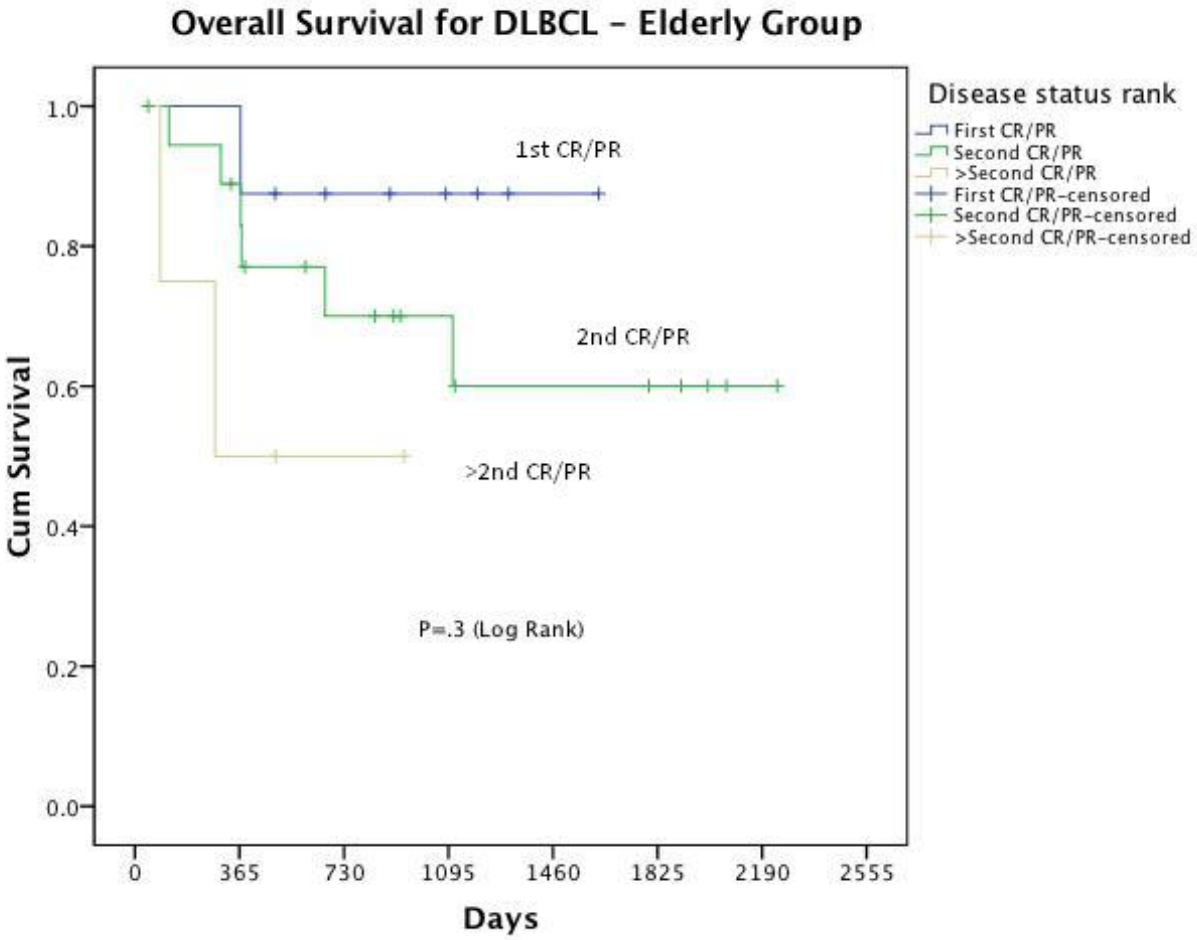

Figure 11: Overall survival of elderly with DLBCL by disease stage

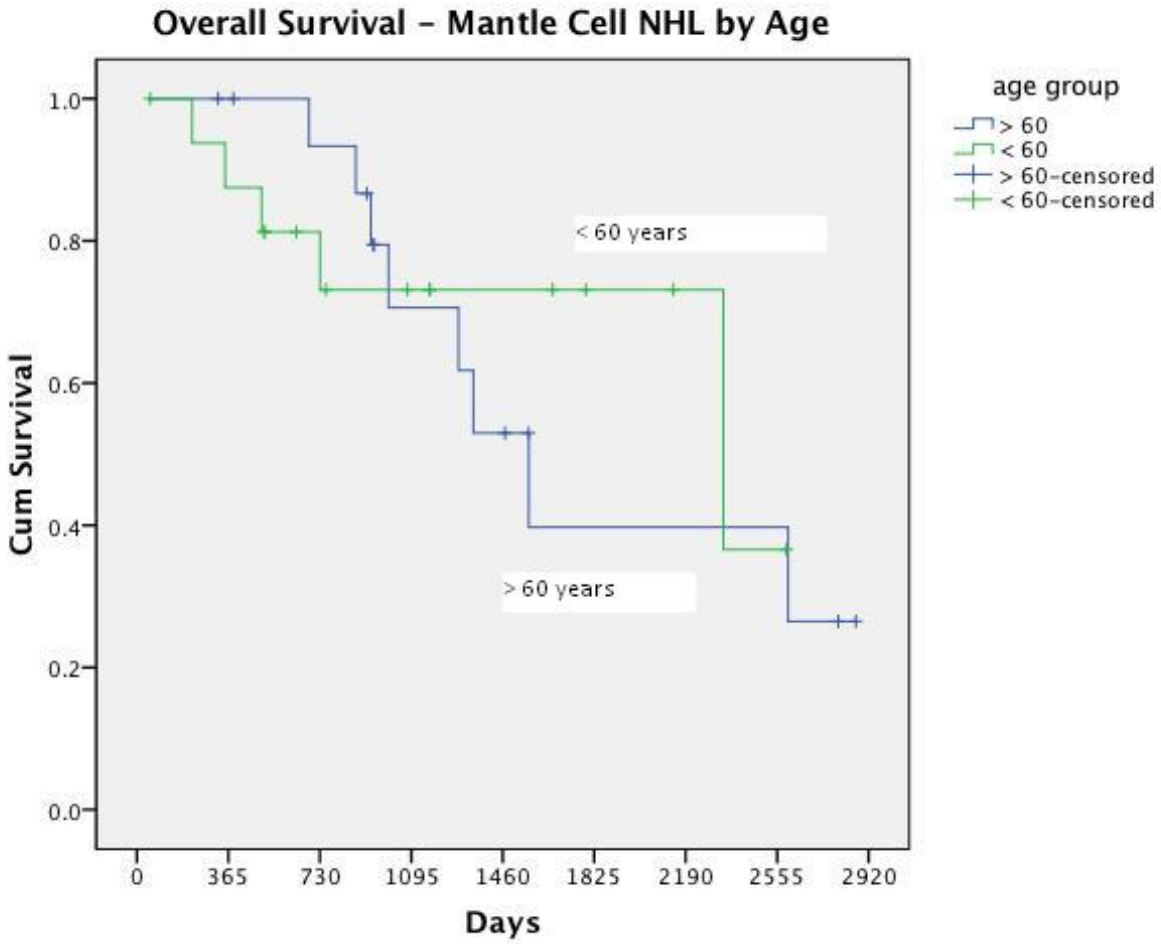

Figure 12: Overall survival of MCL by disease age

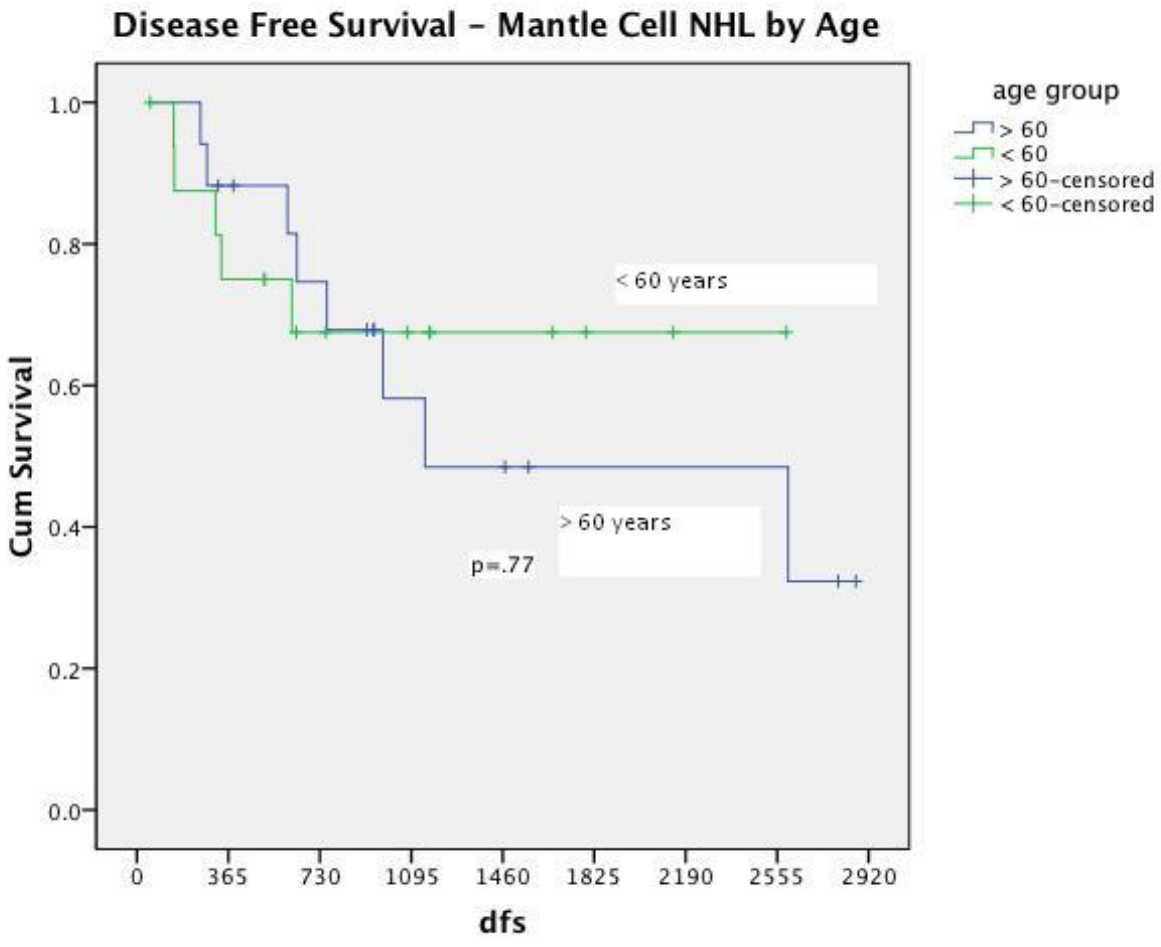

Figure 13: Disease-free survival of MCL by disease age

Discussion

This retrospective study examines the outcomes of 201 patients with NHL who were all transplanted at a single institution using a uniform protocol with a median follow-up of nearly 3 years. There were 67 patients who were older than 60 years at the time of transplant included in this study, which makes this one of the larger single-center studies to evaluate elderly patients' experiences with ASCT. The main observations were a significantly higher rate of serious toxicities within the first 100 days (67% v. 40%, $p<0.0001$) but a similar OS (at 3 years 74% v. 75%, $p=0.91$), DFS (at 3 years 48% v. 58%, $p=0.66$), and NRM (at 1 year, 3% v. 1%, $p=0.19$) in patients older than 60 years. Additionally, the outcomes for DLBCL and MCL show encouraging results indicative of the promising application of ASCT in the treatment of the subtypes in elderly patients.

Acute serious toxicities were closely followed in this study. An acute serious toxicity is defined as a toxicity that occurred within the first 100 days and was graded 3 or above by the NCI Common Toxicity Criteria v3.0. Despite the nearly identical distribution of HCT-CI scores between groups, interestingly, the elderly were found to experience more acute serious toxicities. Furthermore, HCT-CI score was not predictive of toxicity in the univariate analysis. There have been few studies analyzing the factors significantly associated with post-transplant toxicities. In one such study of 99 elderly (> 65 years) patients with NHL who underwent ASCT, Hosing reported that having a HCT-CI score > 2 predicted a higher incidence of grades 3 – 5 toxicities. Additionally, age > 68 years and receiving TBI with cyclophosphamide were also predictive. (85)

Although the elderly group endured more acute serious toxicities, there was not a particular organ system for which toxicities were statistically significantly increased. Nevertheless,

pulmonary and cardiac toxicities were more common in the elderly group. In this series, the control group had a higher frequency of abnormal pre-transplant pulmonary function tests (PFTs) (43%) when compared to the elderly group (34%). However, the post-transplant experience was reversed as 12% of elderly patients experienced acute serious pulmonary toxicities as compared with only 7% in the control group. Additionally, the elderly group had more pre-existing cardiac comorbidities (24% v. 12%) and also more post-transplant serious cardiac toxicities (14% v. 7%) than the control group. The value of pre-transplant testing in predicting post-transplant outcomes is controversial. Although, obstructive and restrictive ventilatory defects as well as reductions in diffusing lung capacity have been documented after transplantation, the predictive value and clinical usefulness of pre-transplant PFTs are in doubt. (87, 88) Similarly, there is a debate regarding the role of pre-transplant cardiac evaluation in predicting the likelihood of post-transplant cardiac toxicities. Some reports have shown an increased incidence of post-transplant cardiac toxicities in patients with abnormal (<50%) pre-transplant ejection fractions (EFs), while others have not found a correlation. (89) Fortunately, the higher incidence of toxicities in this study did not portend a worse survival.

The rate of 100-day NRM among elderly patients (1.5%) in this series is low and is comparable to the reported rates (4%) of similar earlier studies and to the reported rates of patients younger than 60. (68, 84, 85) The median overall survival for elderly patients was 85 months which is longer than recently published studies, but this result likely is a consequence of the patients included. The vast majority of patients were transplanted in first or second remission and all patients had chemosensitive disease. Additionally, all patients were transplanted after January 2000 while previous reports have included elderly patients transplanted over a longer time period before many improvements to supportive care had become routinely available. For example, bone marrow harvested stem cells were the source of

stem cells for ASCT and conditioning regimens were TBI-containing for a minority of patients in earlier reports.

In the univariate analysis, HCT-CI score was the only factor that influenced overall survival in this present study. This conclusion supports the value of the HCT-CI as a pre-transplant predictor of outcomes. Although it was applied retrospectively, with more supportive data from other trials, it may become a routine part of the pre-transplant screening process. However, similar studies have concluded that factors other than HCT-CI score impacted OS. Hosing found that disease status and lactate dehydrogenase (LDH) were predictive of overall survival while Buadi reported that age-adjusted IPI predicted survival. (84, 85) Unfortunately, in this study, LDH values as well as the age-adjusted IPI could not be reliably extracted from the medical records, so these factors could not be evaluated. Another report of 59 elderly patients (≥ 60 years) with advanced NHL who underwent ASCT found that comorbidities significantly influenced early NRM and OS. (90) This study utilized the Charlson comorbidity index (CCI) to assess comorbidities. The CCI was developed before the HCT-CI, but similarly is a weighted scale that is based on the relative risk of death attributable to certain conditions. (91)

Disease status at transplant was important but not significant in the present study for the entire population of patients, possibly because all patients included had chemosensitive disease and were mostly transplanted in first or second remission. In Hosing's series, some patients had chemoresistant disease, and the percentage transplanted in first or second remission was not explicitly reported. (85) However, in subgroup analyses of our data, disease status was found to be significant for OS in certain settings. In a weighted pair-wise comparison between 1^{st} CR/PR and second CR/PR ($p=0.044$) and between 1^{st} CR/PR and $> 2^{nd}$ CR/PR ($p=0.05$), OS was higher for patients in first remission. Additionally, in the analysis of all DLBCL patients, disease

status was significant for OS. Finally, when all elderly patients in this study were analyzed, disease status significantly influenced DFS. Disease status was found to be a major factor in terms of outcome, but it did not reach significance when all patients were analyzed. Nonetheless, patients will have better outcomes of they are treated in first remission than if they are treated later in their disease course. Thus, it is important for studies, like this one, to show that elderly can safely tolerate and respond to ASCT, so providers will no longer be reluctant to consider ASCT as a viable therapy early in the disease course (e.g. 1st remission) and offer elderly patients the best opportunity to achieve favorable outcomes.

DLBCL and MCL accounted for nearly 75% of the histological NHL subtypes in the elderly group. Both the overall and disease-free survival curves for DLBCL patients are virtually indistinguishable when compared by age group. Age was not important, but disease status was with regards to outcomes. In this study, the elderly patient in first remission achieved a better outcome than control patients in second or third remission. The MCL survival curves appear more separate when compared by age group, but the differences were not significant. It is unclear if they would become significant if there were more patients in the analysis. These results demonstrate potential success and support the indication of ASCT in the treatment of these aggressive subtypes in elderly patients.

Another encouraging finding of this study was that a majority (64%) of elderly patients were transplanted in the outpatient setting. A few studies have described the experience of outpatient ASCT of patients with multiple myeloma and follicular lymphoma. These studies have reported low rates of early NRM (<2%) and have concluded that ASCT in the outpatient setting is safe and feasible. (92, 93, 94) If future studies are also able to show that elderly patients can be safely transplanted as outpatients, the outdated perception that ASCT is too

intense for frailer populations like the elderly will hopefully be abandoned. Hopefully, providers will become less fearful to refer patients older than 60 years for transplant because it offers them a better chance for long-term survival.

Although this study reports an equivalent NRM, OS, and DFS, there are limitations to the broad application of this conclusion to all elderly patients with NHL. The elderly patients included in this study represent a highly-selected population. Most of the elderly patients, as well as the control patients, were referred by community oncologists. Consequently, there were essentially two levels of selection in this study; first from the patient's own local oncologists on whether to refer and second from the oncologist at the transplant center on whether to transplant. Additionally, due to the conventional view that elderly patients would have poor outcomes from ASCT, at both levels, the elderly likely received greater scrutiny than their younger counterparts. Both the referring and transplanting oncologist inherently selected relatively "healthy" patients older than 60 years whom they predicted would have favorable outcomes, which may explain in part why 64% were able to be transplanted as outpatients. It is unknown how many patients were not offered a referral or the basis for which that decision was made. Thus, the degree of selection bias cannot be measured. Nevertheless despite the bias, this study was able to reveal that elderly patients with a certain comorbidity profile could not only tolerate transplant but also could achieve equivalent results to their younger counterparts. Therefore, other elderly patients with the same comorbidity profile may experience similar success.

All retrospective studies are subject to bias and confounding factors. A heterogeneous population, small sample size, short follow-up, and lack of a matched comparative control group are examples of limitations in earlier studies investigating elderly patients and ASCT. This study

attempted to minimize these design flaws by including a matched control group of patients transplanted at the same center with the same guidelines during the same time period. Unlike previous reports, all patients in this study received BEAM as the conditioning regimen and all patients received peripheral blood stem cell grafts. Furthermore, to reduce the degree of selection bias, all elderly patients with NHL transplanted between 2000 and 2007 were included and similarly, the control group comprised all patients younger than 60 years transplanted within the same period with the same regimens. Only a small number of patients for which the medical records were inadequate were excluded. The control group was very well matched in this study, there were no differences with respect to gender, disease stage, disease status at transplant, performance status, or HCT-CI risk groups. There was a difference, not statistically, between the groups with regard to the histological type. The elderly group contained a higher percentage of mantle cell lymphoma and very few patients with anaplastic lymphoma. Conversely, 10% of the control group had anaplastic lymphoma. Mantle cell lymphoma is a disease of the elderly while anaplastic lymphoma is more common in younger patients, and typically has a good prognosis. (21) But, the patients with anaplastic lymphoma in this study likely had poor prognostic factors since they were considered for transplantation in first or second remission in most cases.

Since many of the patients were referred, patients eventually returned to the care of their local oncologist and would return every three to six months to yearly depending on the length of time from their transplant. Patients included in this study were closely followed during the first 100 days, and data extracted during this time period was accurate and reliable. Thus, this study concludes that elderly patients are more likely to experience acute serious toxicities, but cannot attest to the incidence of toxicities after day 100. On the other hand, patients did return at least once a year, and consequently, survival data was recorded consistently

throughout the 8-year study period. The median follow-up for all patients was nearly 3 years and some patients were followed for as long as 8 years allowing survival curves to be very accurate for a considerable duration.

In conclusion, this retrospective analysis indicates that selected patients older than 60 years with chemosensitive NHL can safely undergo high-dose chemotherapy and autologous stem cell transplantation. Although elderly patients appear more likely to develop more acute serious toxicities, they experience equivalent outcomes with respect to NRM, OS, and DFS to their younger counterparts. Patients older than 60 should be considered for high-dose chemotherapy and ASCT and should be included in future clinical trials to further define the role of ASCT in the management of NHL.

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