Outcomes of High Dose Therapy and Autologous Haematopoietic Stem Cell Transplantation for Non-Hodgkin Lymphoma: A Retrospective Analysis of Two Centres in Malaysia

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Abstract

There is scarce information available in regards to the survival outcome of non-Hodgkin lymphoma (NHL) in South East Asia regions. Reports on the outcome of High dose therapy followed by autologous haematopoietic stem cell transplantation (AHSCT) were mainly from developed countries. In this study, we present the outcome of NHL patients treated with AHSCT from year 1997 to 2016 in two urban hospitals in Malaysia. A total of 140 patients were identified, majority of whom had B cell lymphoma (54.3%). Majority of patients (89.3%) were in complete remission at AHSCT. The overall survival (OS) and event-free survival (EFS) at 3 years were 70.7% and 62.1% respectively. The transplant-related mortality was 3.4%.

KEYWORDS

Autologous hematopoietic stem cell transplantation, High dose therapy, Non-Hodgkin lymphoma, Resource limited country, Retrospective

WHAT'S KNOWN?

- Autologous hematopoietic stem cell transplantation (AHSCT) was first used as frontline, consolidative treatment for aggressive non-Hodgkin lymphoma (NHL) in the early '90s.

- In selected centres, upfront AHSCT has also been considered a feasible form of management for poor risk patients.

-There is scarce information available in regards to the survival outcome of NHL in South East Asia regions. Reports on the outcome of high dose therapy followed by AHSCT were mainly from developed countries.

WHAT'S NEW?

- In this study, we present the outcome of NHL patients treated with AHSCT in Malaysia (the very first report from Malaysia), where data in resource limited countries within South East Asian region are lacking

- Our study illustrates the outcomes of HDT and AHSCT in NHL patients in a resource limited country with a comparable transplant related mortality.

- Due to the higher incidence of aggressive lymphomas, this article also highlighted upfront AHSCT as a possible cost-effective strategy to reduce the risk of relapse.

1. INTRODUCTION

Non-Hodgkin lymphoma (NHL) is a pathologically and prognostically diverse group of hematological malignancies with variable clinical outcomes. NHL accounted for approximately 80% of all lymphoid neoplasms and in Malaysia, lymphoma is the sixth most common cancer and accounted for about 4.3% of all cancers. Survival had improved significantly for NHL in the past decades in many countries including Asian regions. Risk stratification based on prognostic indices for each subtype of NHL is an important tool which has been validated to predict outcomes (1). Diffuse large B-cell lymphoma (DLBCL) is the most common form of aggressive lymphoma (2), accounting for 30–40% of newly diagnosed NHL globally. In patients with DLBCL, the international prognostic index (IPI), which includes variables such as age, performance status (PS), lactate dehydrogenase (LDH), number of extra-nodal involvement and staging is used to prognosticate patients (1, 3).

Autologous hematopoietic stem cell transplantation (AHSCT) was first used as frontline, consolidative treatment for aggressive NHL in the early '90s (4). Subsequently, high dose therapy (HDT) followed by AHSCT has been widely adopted for cases of relapsed or refractory NHL (RR-NHL). In selected centres, upfront AHSCT has also been considered a feasible form of management for poor risk patients (5, 6). Prior to rituximab being introduced, many studies have demonstrated the role of AHSCT in improving event-free survival (EFS) and overall survival (OS) in patients who had RR-NHL (7, 8). One such trial, PARMA, has established HDT-AHSCT as the standard of care for relapsed or refractory DLBCL (RR-DLBCL). The trial demonstrated a significantly better five-year EFS and OS for the AHSCT group compared to the salvage therapy group(8). Hence, the role of HDT-AHSCT as a standard treatment in RR-DLBCL was recommended by the US National Comprehensive Cancer Network (NCCN) (9).

In pre-rituximab era, survival benefit was demonstrated with ASHCT in patients who had achieved CR after salvage chemotherapy (8). Other studies have reported that about a third of patients who achieved partial remission (PR) also experienced better long-term EFS with ASHCT when compared with chemotherapy alone (7, 10).

In the post Rituximab era, a registry study done recently in the United States concluded there has been limited improvement in the survival of adult patients with DLBCL beyond the introduction of rituximab (11). An international retrospective multicohort non-Hodgkin lymphoma research study (SCHOLAR-1) also demonstrated the poor outcomes in patients with refractory DLBCL. These data are particularly important because it represents a large cohort with refractory DLBCL, which supported the need for more effective therapies (12). Novel agents such as bendamustine and polatuzumab are used for aggressive and relapsed cases in many developed countries, however these therapies are expensive and not easily available to many resource-limited countries such as Malaysia. Therefore, effective upfront therapy would likely benefit to reduce relapse and become the mainstay treatment in RR-DLBCL especially in a resource limited country.

Although evidence regarding the use of AHSCT in NHL are widely available, data in resource limited countries within South East Asian (SEA) region are lacking, despite incidence of aggressive lymphoma subtypes such as T cell and DLBCL being higher in such populations (13-15). This is especially pertinent when the novel agents for treatment of relapsed refractory NHL are expensive and are not freely accessible to many patients. Therefore, it is crucial that we have local data to establish the effectiveness of AHSCT, which is relatively less expensive when compared to novel agents, and to determine the possible predictive factors which can translate to better outcome.

2. METHODOLOGY

2.1. Study population

All adult NHL patients who had undergone AHSCT from October 1997 to November 2016 in two hospitals in Klang Valley, Malaysia were identified. Patients with primary central nervous system lymphoma were excluded from this study. This study was approved by the local institutional ethical review boards of both participating hospitals.

2.2. Study demographics and clinical data

Demographic data and clinical information were collected. Clinical information collected includes age at diagnosis, gender, stage of the disease, number of sites of extra-nodal involvement, serum LDH at diagnosis, performance status and remission status during transplantation. Disease staging was assessed according to the Ann Arbor classification. Clinical staging was performed using positron emission tomography or computed tomography scanning of the neck, thorax, abdomen, and pelvis; bone marrow biopsy; cerebrospinal fluid examination if available; and other tools, such as magnetic resonance imaging if available.

Remission status was assessed using the International Working Group criteria. International prognostic index (IPI) (which includes age, performance status, stage, extranodal involvement, and LDH level) were used as clinical prognostic factors. Index values of 0 and 1 are classified as low risk (L), 2 as low-intermediate risk (L/I), 3 as high-intermediate risk (H/I) and both 4 and 5 factors as high risk (H). The risk groups were further categorized into 2 groups; where an IPI score of 0-2 was defined as low risk, whereas 3-5 was considered high risk.

Other transplant data such as total CD 34^+ stem cell dose infused, type of conditioning regimens, days to engraftment, transplant related complications and outcome were also recorded. Patients were followed up until December 2017 for the incidence of relapse and death. OS was measured from the date of diagnosis until death from any cause, with surviving patients censored at the last follow-up date. EFS was defined from the date of diagnosis to the date of disease progression, relapse or death from any cause.

2.3. Statistical Analysis

Descriptive statistics were used for the analysis of patients' characteristics including demographic factors such as age, gender, diagnosis, stage, status at transplant, number of relapses, number of deaths, cause of death, and conditioning regime. The Kaplan–Meier method with the log-rank test was used to estimate OS and EFS, and prognostic risk factors were analyzed using univariate analysis. All reported p-values were for two-sided testing, and a p-value of [?]0.05 was considered statistically significant for all analyses. All statistical analyses were performed using SPSS for Windows, version 24.

3. RESULTS

3.1 Patient characteristics

A total of 148 patients were included in this study. The median age of patients was 45 years. Majority of the patients had underlying B cell lymphoma. The median age at diagnosis and at transplantation were 43.5 (IQR 14 to 67) and 45.5 (IQR 15 to 69) years respectively. The median period between diagnosis and AHSCT was 9.5 (IQR 2-112) months. Forty seven percent of patients were transplanted in first remission. The transplant related mortality was 3.4%. The summary of patients' characteristics is shown in Table 1.

3.2. Factors associated with Outcome

Three-year OS and EFS of all patients were 70.7% and 62.1% respectively. Patients who were transplanted in CR1 had significantly better three-year OS (84.8%), than patients transplanted in CR2 (66.1%) and PR (26.7%), p=0.000 (Figure 1). Similarly, three-year EFS of patients who were transplanted in CR1 (78.8%) was significantly better than patients transplanted in CR2 (52.5%) and PR (26.7%), p=0.000. Patients who had marrow involvement had a significantly poorer three-year OS (50%) than patients who had no bone marrow involvement (75.9%), p=0.008. Similarly, three-year EFS of patients (68.8%) who had no marrow involvement was significantly better than patients with bone marrow involvement (35.7%), p=0.000. There was no significant difference in OS and EFS in patients with high risk IPI and low risk IPI group. Age, gender, and types of NHL were also not found to have significantly affected OS and EFS. With multiple variate analysis, patients who were transplant in CR1 had better compared to patients who were transplant in CR2 regardless of outcome, as shown in Table 2.

3.3. Causes of Mortality

A total of 45 patients (30%) passed away during this study period. Majority of patients (27%) were due to progression of disease and only 3.4% were due to transplant related mortality. The most common cause of transplant related mortality was infection.

DISCUSSION

Non-Hodgkin lymphoma is a heterogenous disease that has been reported to be consistently increasing in many parts of the world. Amongst the NHL, DLBCL is one of the most frequent types of aggressive NHL that accounts for 41% of the newly diagnosed adult NHL in Asia (14, 16). Although CR was achievable in 60% to 80% of patients, the durable remission was only seen in 35-45% of patients (17, 18). With AHSCT, the OS has improved, especially in RR-NHL (5, 8, 19, 20). AHSCT is now widely used as standard therapy in relapsed NHL (8) and most guidelines recommended it as consolidation following salvage chemotherapy (9, 21).

Several studies have reported good outcomes following HDT-ASHCT (20, 22). In this study, the three-year OS and EFS of 70.7% and 62.1% respectively is comparable to that of other centres worldwide, where the OS rate ranges from 68-74%, and the progression-free survival rate of 60-69% (5, 19). The low transplant-related mortality of AHSCT, which is comparable to other centres (16, 26), implied that supportive care in our centres was non-inferior.

In this study, AHSCT at CR expectedly yielded better OS and EFS when compared to those who were transplanted in PR and is consistent with other studies (23, 24). Patients who were transplanted in CR1 appeared to have better OS and EFS and this is especially evident in high-risk patients who were transplanted in CR1. Our findings were consistent to what was reported by Caballero et al. (2003), Nakaya et al. (2017), and Zhao et al. (2017). Similarly, a study by Kansai Medical University Hospital showed that upfront AHSCT provided better outcomes compared to those who did not undergo ASHCT (16), and this is further supported by a meta-analysis which found that high risk patients may benefit from upfront AHSCT (4). However, appropriate timing in transplantation remains debatable. Its role in the upfront setting remains controversial.

IPI scoring had been used as a clinical tool for risk stratification of patients with DLBCL and is considered valuable as a prognosis indicator in aggressive lymphoma (1, 28, 29).Through the revised IPI score, patients with high-risk IPI with DLBCL continue to have sub-optimal outcomes with a predicted five-year survival of 50–55% (3). Accurate molecular classification is extremely important for precision medicine in malignant lymphomas. Increasing, molecular and genotyping cell of origin (COO) are methods being used but limited as needs cost for Next-Generation Sequencing (NGS). In the early 2000, a study demonstrated that DLBCL could be differentiated based on gene expression profiling methods (GEP) into distinct molecular subtypes through their cell of origin (COO) (33), coupled with many other studies confirming the prognostic significance for molecular subtyping of COO subtypes of ABC DLBCLs having a poorer PFS (1,33 – 36) . In this study, IPI was not found to be predictive and this may be due to the relatively small number of DLBCL in this cohort, with a significant proportion of lymphomas were not classifiable. This raised the issue of the importance of the mutation profiling besides the possible downfall when using the clinical prognostic score alone in malignant lymphomas.

The limitations of this study are the sample size is relatively small and there is a relatively significant proportion of lymphoma were not classified according to the new WHO classification. The follow up period is also relatively short.

Despite these limitations, our study illustrates the outcomes of HDT and AHSCT in NHL patients in a resource limited country with a comparable TRM. Due to the higher incidence of aggressive lymphoma in Asian population, there is a need for Asian countries to construct multicentre databases to spur the kind of research demonstrated in developed countries, to find the most feasible treatment modalities such as upfront AHSCT which may be a cost-effective strategy to reduce the risk of relapse. Moving forward, we recommend larger studies in randomized and selected cohort with longer duration of follow up to be conducted to validate our findings.

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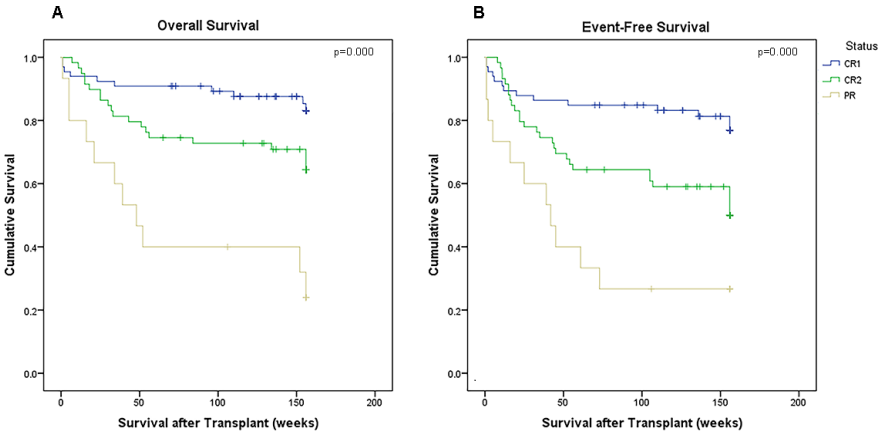

Figure 1. Kaplan-Meier three-year survival analysis for (A) overall survival and (B) event-free survival of patients transplanted in different remission status.