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A Prognostic Model Predicting Autologous Transplantation Outcomes in Children, Adolescents and Young Adults with Hodgkin Lymphoma

Prakash Satwani, MBBS, MD[1], **Kwang Woo Ahn, PhD**[2,3], **Jeanette Carreras, MPH**[2], **Hisham Abdel-Azim, MD**[4], **Mitchell S. Cairo, MD**[5], **Amanda Cashen, MD**[6], **Andy I. Chen, MD, PhD**[7], **Jonathon B. Cohen, MD, MS**[8], **Luciano J. Costa, MD, PhD**[9], **Christopher Dandoy, MD**[10], **Timothy S. Fenske, MD, MS**[11], **César O. Freytes, MD**[12], **Siddhartha Ganguly, MD, FACP**[13], **Robert Peter Gale, MD, PhD, DSc(hon), FACP**[14], **Nilanjan Ghosh, MD, PhD**[15], **Mark S. Hertzberg, MD, PhD**[16], **Robert J. Hayashi, MD**[17], **Rummurti T. Kamble, MD**[18], **Abraham S. Kanate, MD**[19], **Armand Keating, MD**[20], **Mohamed A. Kharfan-Dabaja, MD**[21], **Hillard M. Lazarus, MD**[22], **David I. Marks, MD, PhD**[23], **Taiga Nishihori, MD**[21], **Richard F. Olsson, MD, PhD**[24,25], **Tim D. Prestidge, BHB, MBChB, FRACP, FRCPA**[26], **Juliana Martinez Rolon, MD**[27], **Bipin N. Savani, MD**[28], **Julie M. Vose, MD**[29], **William A. Wood, MD, MPH**[30], **David J. Inwards, MD**[31], **Veronika Bachanova, MD, PhD**[32], **Sonali M. Smith, MD**[33], **David G. Maloney, MD, PhD**[34], **Anna Sureda, MD, PhD**[35,36], and **Mehdi Hamadani, MD**[2]

[1]Division of Pediatric Hematology, Oncology and Stem Cell Transplantation, Department of Pediatrics, Columbia University Medical Center, New York, NY [2]CIBMTR® (Center for International Blood and Marrow Transplant Research), Medical College of Wisconsin, Milwaukee, WI [3]Division of Biostatistics, Institute for Health and Society, Medical College of Wisconsin, Milwaukee, WI [4]Division of Hematology, Oncology and Blood & Marrow Transplantation, Children's Hospital Los Angeles, University of Southern California Keck School of Medicine, Los Angeles, CA [5]Pediatric Hematology/Oncology and Stem Cell Transplantation, New York Medical College, New York, NY [6]Division of Oncology, Washington University School of Medicine, St. Louis, MO [7]Oregon Health and Science University, Portland, OR [8]Department of Hematology and Medical Oncology, Winship Cancer Institute, Emory University School of Medicine, Atlanta, GA

Corresponding author: Mehdi Hamadani, MD, Center for International Blood and Marrow Transplant Research, Medical College of Wisconsin, 9200 W. Wisconsin Avenue, Suite C5500, Milwaukee, WI 53226, USA; Phone: 414-805-0643; Fax: 414-805-0714; mhamadani@mcw.edu.

Author Contributions:

Conception and design: Praskash Satwani & Mehdi Hamadani

Collection and assembly of data: Kwang Woo Ahn, Jeanette Carreras and Mehdi Hamadani

Data analysis: Kwang Woo Ahn, Jeanette Carreras with final approval on fidelity of analysis by CIBMTR statistical center in Milwaukee, WI.

Data Interpretation: Prakash Satwani, Kwang Woo Ahn, Jeanette Carreras and Mehdi Hamadani. All remaining authors provided written comments on interpretation of data.

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Final approval of manuscript: All authors.

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[9]Division of Hematology/Oncology, Department of Medicine, University of Alabama at Birmingham, Birmingham, AL [10]Cincinnati Children's Hospital Medical Center, Cincinnati, OH [11]Division of Hematology and Oncology, Medical College of Wisconsin, Milwaukee, WI [12]South Texas Veterans Health Care System and University of Texas Health Science Center San Antonio, San Antonio, TX [13]Blood and Marrow Transplantation, Division of Hematology and Oncology, University of Kansas Medical Center, Kansas City, KS [14]Hematology Research Centre, Division of Experimental Medicine, Department of Medicine, Imperial College London, London, United Kingdom [15]Department of Hematologic Oncology and Blood Disorders, Levine Cancer Institute, Carolinas Healthcare System, Charlotte, NC [16]Department of Haematology, Prince of Wales Hospital, Randwick NSW, Australia [17]Division of Pediatric Hematology/Oncology, Department of Pediatrics, Washington University School of Medicine in St. Louis, St. Louis, MO [18]Division of Hematology and Oncology, Center for Cell and Gene Therapy, Baylor College of Medicine, Houston, TX [19]Osborn Hematopoietic Malignancy and Transplantation Program, West Virginia University, Morgantown, WV [20]Department of Medical Oncology and Hematology, Princess Margaret Hospital, University of Toronto, Toronto, ON, Canada [21]Department of Blood and Marrow Transplantation, H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL [22]Seidman Cancer Center, University Hospitals Case Medical Center, Cleveland, OH [23]Pediatric Bone Marrow Transplant, University Hospitals Bristol NHS Trust, Bristol, United Kingdom [24]Division of Therapeutic Immunology, Department of Laboratory Medicine, Karolinska Institutet, Stockholm, Sweden [25]Centre for Clinical Research Sörmland, Uppsala University, Uppsala, Sweden [26]Blood and Cancer Centre, Starship Children's Hospital, Auckland, New Zealand [27]Bone Marrow Transplante Unit, FUNDALEU, Buenos Aires, Argentina [28]Division of Hematology/Oncology, Department of Medicine, Vanderbilt University Medical Center, Nashville, TN [29]Department of Internal Medicine, The Nebraska Medical Center, Omaha, NE [30]Division of Hematology/Oncology, Department of Medicine, University of North Carolina, Chapel Hill, NC [31]Division of Hematology, Mayo Clinic, Rochester, MN [32]Bone and Marrow Transplant Program, University of Minnesota Medical Center, Minneapolis, MN [33]Section of Hematology/Oncology, The University of Chicago, Chicago, IL [34]Fred Hutchinson Cancer Research Center, Seattle, WA [35]Servei d'Hematologia, Institut Català d'Oncologia, Hospital Duran i Reynals, Barcelona, Spain [36]Secretary, European Group for Blood and Marrow Transplantation

Abstract

Autologous hematopoietic cell transplantation (AutoHCT) is a potentially curative treatment modality for relapsed/refractory Hodgkin lymphoma (HL). However, no large studies have evaluated pre-transplant factors predictive of outcomes of AutoHCT in children, adolescents and young adults (CAYA, age <30 years). In a retrospective study, we analyzed 606 CAYA patients (median age 23 years) with relapsed/refractory HL who underwent AutoHCT between 1995–2010. The probabilities of progression free survival (PFS) at 1, 5 and 10 years were 66% (95% CI: 62–70), 52% (95% CI: 48–57) and 47% (95% CI: 42–51), respectively. Multivariate analysis for PFS demonstrated that at the time of AutoHCT patients with Karnofsky/Lansky score ≥90, no extranodal involvement and chemosensitive disease had significantly improved PFS. Patients with time from diagnosis to first relapse of <1 year had a significantly inferior PFS. A prognostic model for PFS was developed that stratified patients into low, intermediate and high-risk groups,

predicting for 5-year PFS probabilities of 72% (95% CI: 64–80), 53% (95% CI: 47–59) and 23% (95% CI: 9–36), respectively. This large study identifies a group of CAYA patients with relapsed/refractory HL who are at high risk for progression after AutoHCT. Such patients should be targeted for novel therapeutic and/or maintenance approaches post-AutoHCT.

Keywords

CAYA; Autologous transplantation; Hodgkin lymphoma

Introduction

Hodgkin Lymphoma (HL) is the most common cancer in children, adolescents and young adults (CAYA) with a peak incidence between the ages of 20 and 34[1]. With the use of chemotherapy alone or with the addition of radiotherapy, the overall survival (OS) rate of newly diagnosed HL in CAYA is approximately 80–90%[1,2]. However, a subset of CAYA patients with HL have refractory disease to first line therapies or experience disease relapse[2]. For these patients, conventional salvage therapies, followed by autologous hematopoietic cell transplantation (AutoHCT) is often considered the standard of care. Even with the addition of AutoHCT, many patients will not achieve long-term remission[3]. The outlook for such patients remains poor. A small prospective study by Baker et al., demonstrated that the 5-year probability of failure-free survival in CAYA patients with relapsed/refractory HL following AutoHCT was only 31%[4].

Various factors influence the outcome of patients with relapsed/refractory HL. Long-term survival of patients with HL is age dependent; patients <15 years and 15–29 years have better long-term survival probability than do patients 30–44 years old. Patients older than 45 years of age tend to fare less well[5]. In a handful of small CAYA AutoHCT studies the following have been shown to be associated with inferior outcomes: time to relapse[6–8], primary refractory disease[4,6, 9–12], response to salvage chemotherapy[7,9,11–13], extranodal involvement[10,14], mediastinal mass[10] and high serum lactate dehydrogenase (LDH) levels at the time of relapse[4]. While the findings in these studies are compelling, their small sample sizes and inconsistent evaluation methodology make the above prognostic indicators difficult to generalize across larger CAYA population.

In adult patients with HL, various prognostic models have identified and validated various disease and patient-specific variables present either at diagnosis[15] or prior to AutoHCT [16–18] that are associated with inferior outcomes. These identified predictive factors in older adults may not be applicable to CAYA, as older adults potentially have more co-morbidity. However, differences in disease biology, if any, among CAYA and older adults are yet to be elucidated.

To date, there are no published large-scale studies looking at risk factors or prognostic indicators in CAYA patients with relapsed/refractory HL undergoing AutoHCT. Thus, in this Center for International Bone Marrow Transplant Research (CIBMTR) analysis, we evaluated various risk factors that might be prognostic in CAYA patients undergoing AutoHCT for relapsed/refractory HL.

Materials and Methods

Data sources

The CIBMTR is a working group of more than 450 transplantation centers worldwide that contribute detailed data on HCTs to a statistical center at the Medical College of Wisconsin. Centers report HCTs consecutively with compliance monitored by on-site audits. Patients are followed longitudinally with yearly follow-up. Observational studies by the CIBMTR are performed in compliance with federal regulations with ongoing review by the institutional review board of the Medical College of Wisconsin.

Patients

There is no universally accepted definition of AYA. The National Cancer Institute Adolescent and Young Adult Oncology Progress Review Group include patients from 15 to 39 years of age. However, Surveillance, Epidemiology, and End Results (SEER) and Children's Oncology Group's Adolescents and Young Adults Committees define AYA as 15 to 29 years of age[19]. In the current study we defined AYA as patients from 15–29 years old.

CAYA (age <30 years) with a histologically proven diagnosis of relapsed or refractory HL, undergoing first peripheral blood AutoHCT reported to the CIBMTR between 1995 and 2010 were included in this study. Patients achieving a complete remission (CR) with 1st line therapy and then undergoing upfront AutoHCT consolidation (n=23), without any evidence of relapsed or refractory disease before transplantation were excluded. Subjects undergoing a planned tandem HCT (tandem AutoHCT, n=14; or AutoHCT followed by tandem allogeneic HCT, n=1), those with nodular lymphocyte predominant HL (n=6), and human immunodeficiency virus positive cases (n=10) were also excluded.

Definitions and Endpoints

To assess disease status at AutoHCT, (chemo-) sensitive disease on CIBMTR forms is define as ≥50% reduction in greatest diameter of all disease sites, with no new sites of disease on radiographic assessment, while (chemo-) resistant disease is defined as <50% reduction in the diameter of all disease sites, or development of new disease sites. Positron emission tomography (PET scan) data were not available for response assessment during the era of this study, the CIBMTR database.

Primary outcomes in this study were non-relapse mortality (NRM), progression/relapse, progression-free survival (PFS) and OS. NRM was defined as death without evidence of disease progression/relapse; relapse was considered a competing event. Progression/relapse was defined as progressive disease after AutoHCT or disease recurrence after a CR; NRM was considered a competing event. For PFS, a patient was considered a treatment failure at the time of progression/relapse or death from any cause. Patients alive without evidence of disease relapse or progression were censored at last follow-up. The OS was defined as the interval from the date of AutoHCT to the date of death or last follow-up.

Statistical analysis

Probabilities of PFS and OS were calculated using the Kaplan-Meier estimator. Probabilities of NRM, disease progression/relapse, and hematopoietic recovery were calculated using cumulative incidence curves to accommodate for competing events[20]. Associations among patient, disease and transplant-related variables and outcomes of interest were analyzed using Cox proportional hazards regression. A stepwise selection was used to identify covariates that influenced outcomes. Covariates with a $p<0.01$ were considered significant. The proportionality assumption for Cox regression was tested by adding a time-dependent covariate for each risk factor and each outcome. Interactions among significant variables were examined. Results are expressed as relative risk (RR) of occurrence of the event. The variables considered in multivariate analysis are shown in Table 1.

Prognostic Model for PFS

To develop a prognostic model of PFS in the CAYA population post-AutoHCT a Cox regression method was used to identify potential risk factors associated with treatment failure (failure event of PFS). This was done using a forward stepwise model with $p<0.01$ to enter and remove contributing factors from the model. Results were then confirmed using a backward elimination procedure and then a forward selection. The risk factors considered in the model-building procedure are shown in Table 1. Based on the final multivariate model and relative risk of significant prognostic factors, each factor was assigned a score of 1. All statistical analyses were performed using SAS version 9.3 (SAS Institute, Cary, NC).

Results

Patient Characteristics

Between 1995 and 2010, 606 CAYA with the median age of 23 years (3–29 years) were included in this study. Patient characteristics are described in Table 2. Briefly, the majority of patients in this analysis were Caucasian/white (77%), the most common histological subtype was nodular sclerosis (77%), at diagnosis disease stage was I–II in 50% and III–IV in 48%, while 53% patients had B-symptoms and 32% patients had extranodal involvement at the time of diagnosis. The median number of lines of therapy before AutoHCT was two, and 60% of patients received first line ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine) or ABVD-like chemotherapy with or without radiation. Extranodal involvement at AutoHCT was reported in 18% patients. The majority of the patients (79%) had chemosensitive disease prior to AutoHCT. The most commonly utilized conditioning regimen (67%) was BEAM (BCNU, etoposide, cytarabine and melphalan).

Univariate Outcomes

For the total cohort, the probabilities of NRM at 1, 3, 5 and 10 years were 6% (95% CI: 4–8), 6% (4–8), 7% (95% CI: 5–9) and 9% (95% CI: 6–12), respectively (Figure 1A). The probabilities of disease progression/relapse at 1, 3, 5 and 10 years were 28% (95% CI: 24–32), 38% (95% CI: 34–42), 41% (95% CI: 37–45) and 45 % (95% CI: 40–49) (Figure 1B). The probabilities of PFS at 1, 3, 5 and 10 years were 66 % (95% CI: 62–70), 57% (95% CI: 53–61), 52% (95% CI: 48–57) and 47% (95% CI: 42–51), respectively (Figure 1C). The

probability for OS were 87% (95% CI: 84–89), 74% (95% CI: 70–78), 68% (95% CI: 63–71) and 58% (95% CI: 53–63), respectively (Figure 1D).

Multivariate Outcomes

On multivariate analysis for NRM, the single significant factor associated with higher NRM was utilization of non-ABVD regimens as a first line therapy compared to ABVD/ABVD-like regimens (RR=2.47; 95% CI=1.32–4.62: p=0.004) [Table 3]. Multivariate analysis for disease progression/relapse demonstrated that patients with Karnofsky/Lansky performance score (KPS/LPS) <90 (RR=1.46; 95% CI=1.08–1.98: p=0.01), utilization of CBV (cyclophosphamide, BCNU and etoposide) conditioning regimen (RR=1.72; 95% CI=1.21–2.45: p=0.003), presence of extranodal involvement at AutoHCT (RR=1.67; 95% CI=1.23–2.29: p=0.001) and chemoresistant disease (RR=1.75; 95% CI=1.29–2.36; p=0.0003) were associated with a higher risk of relapse/progression post-AutoHCT, while **t**ime from **d**iagnosis to **f**irst **r**elapse (TDFR) interval of ≥1 year was associated with a reduced risk of progression/relapse (RR= 0.65; 95% CI=0.48–0.88: p=0.006).

Patients who had a KPS/LPS <90 (RR–1.45; 95% CI=1.10–1.92: p=0.008), extranodal involvement at AutoHCT (RR=1.59; 95% CI=1.19–2.12: p=0.001) and chemoresistant disease (RR=1.84; 95% CI=1.40–2.42: p<0.0001) had a higher risk of therapy failure (i.e. inferior PFS). Patients with TDFR interval of ≥1 year had a lower risk of therapy failure (i.e. superior PFS) (RR=0.71; 95% CI=0.54–0.93: p=0.01) [Table 3].

On multivariate analysis a higher risk of mortality (inferior OS) was associated with first line therapy with non-ABVD compared to ABVD/ABVD-like regimens (RR=1.64; 95% CI=1.21–2.22: p=0.001), the presence of extranodal involvement at AutoHCT (RR=1.81; 95% CI=1.29–2.52: p=0.0005), and chemoresistance disease (RR=2.27; 95% CI=1.64–3.13: p=<0.0001). In contrast, patients with a TDFR interval of ≥ 1 year had a lower risk of mortality (i.e. superior OS) (RR=0.62; 95% CI=0.44–0.86: p=0.004) [Table 3].

Prognostic Model for PFS

The four significant adverse prognostic factors, each assigned a score of 1, included in the final model were (i) KPS/LPS <90%, (ii) TDFR of <1 year, (iii) extranodal involvement at AutoHCT and (iv) chemoresistant disease at AutoHCT. The score for any individual patient using the 4 significant prognostic factors, ranged from 0 to 4. Table 4 summarizes the prognostic model's performance. Distribution of patients by total risk score was as follows: 126 patients had a total risk score of 0 (reference category), 192 patients had a total risk score of 1 (RR=1.81 range, 1.25 to 2.62), 129 patients had a total risk score of 2 (RR=2.11 range, 1.42 to 3.13), 38 patients had a total risk score of 3 (RR=3.92 range, 2.42 to 6.36) and 4 patients had a total risk score of 4 (RR=11.33 range, 4.03 to 31.82).

Based on the range of RR and the distribution of patients across the total risk score categories, we classified each patient into three prognostic risk groups: low-risk group (score = 0), intermediate-risk group (score = 1 or 2), or high-risk group (score = 3 or 4). Statistical significance was reached when we compared the PFS between low and intermediate group (p=0.0002), low and high risk group (p<0.0001) and intermediate and high risk group

(p<0.0001). The 3-year PFS probabilities for the low, intermediate and high risk groups are 75% (95% CI=67–82), 56% (95% CI=51–62) and 29% (95% CI=15–43), respectively. The probability for 5-year PFS were 72% (95% CI: 64–80), 53% (95% CI: 47–59) and 23% (95% CI: 9–36) respectively, for the three prognostic groups (Figure 2).

Cause of Death and Secondary Malignancies

At a median follow-up of 64 months 209 patients were no longer alive. The primary causes of death post-AutoHCT were recurrent HL (N=154, 74% of all deaths), organ failure (N=12, 6%), second malignancy (N=4, 2%), infection (N=7, 3%) or other/indeterminate (N=32, 15%). At a median follow-up of 64 months, 16 patients (3%) developed secondary malignancies. New malignancies reported included one case each of basal cell carcinoma, breast cancer, chronic lymphocytic leukemia, prostate cancer, oligodendroglioma, carcinoma of the pleural cavity and two cases each of acute myeloid leukemia, myelodysplastic syndrome and thyroid cancer. There were 3 cases of genitourinary cancer and one missing second malignancy subtype.

Discussion

To our knowledge, this is the largest study describing the outcomes of CAYA with relapsed/refractory HL following AutoHCT. For the first time, we propose a prognostic model specifically for CAYA patients undergoing AutoHCT for relapsed/refractory HL. Previous HL models included older patients and therefore may not be as relevant for the CAYA population. Our large CAYA data set enabled us to develop a simple-to-use, clinically relevant prognostic model identifying 4 risk factors easily available at the time of AutoHCT.

Due to the improvement in upfront treatment strategies for newly diagnosed HL, the outcome for patients with HL has improved such that approximately 80% of HL patients become long-term survivors now [21]. However, for those who have relapsed or refractory disease, outcomes are variable, with some patients achieving long-term remission after AutoHCT and others responding poorly. Improved prognostic tools are needed to identify such high-risk patients. Various prognostic factors have been identified from a series of clinical studies that are frequently small. Such studies often lack statistical power to definitively define prognostic factors, which has led to a lack of consistency and consensus across studies[2,22]. Because of this, accurately determining risk of treatment failure for CAYA patients undergoing AutoHCT remains a challenge, which makes identification of patients suitable for intensified or investigational therapies difficult. CIBMTR data are uniformly collected with rigorous quality control and has large number of patients with contemporary and generalizable data. Hence, in this large analysis we were able to identify the prognostic factors associated with poor outcomes in CAYA patients with HL post-AutoHCT.

Previously published studies with small number of patients (highest n=70)[12], prognostic factors that have been studied in CAYA are primary refractory disease (3–10 year OS/EFS/DFS: 35–47%)[6,9–12], early relapse within one year of diagnosis (3–10 years OS/DFS: 34–67%)[6–8], poor response to salvage therapy (2–5 year OS/DFS/EFS: 6–30%)[7,9,11–13], extranodal involvement at relapse (8 year EFS-7%)[14] and B-symptoms at relapse (2yr

OS-27%)[9]. In our large CAYA study, the probabilities of PFS at 1 and 5 years following AutoHCT were 66% and 52%, respectively. Patients with TDFR of <1 year, extranodal involvement at AutoHCT, chemoresistant disease and KPS/LPS <90 at the time of AutoHCT all had inferior PFS. Of interest, according to our analysis, age, time from diagnosis to AutoHCT, disease stage at diagnosis and relapse, B-symptoms, bulky disease at the time of AutoHCT, LDH at the time of AutoHCT, number of chemotherapy regimens prior to AutoHCT and radiation therapy prior to AutoHCT were not associated with PFS.

Our analysis of 606 HL CAYA patients, with relapse/refractory HL who were treated with AutoHCT found three prognostic factors consistently associated with relapse/progression, PFS and OS. These prognostic indicators were as follows: TDFR <1 year, extranodal involvement at relapse and chemoresistant disease at the time of AutoHCT.

This study has limitations of being retrospective, patients were reported to the CIBMTR over the period of 15 years, and PET scan data were not collected. Over that last decade PET scan has emerged as an important prognostic factor in adults with relapsed HL as patients with negative PET study prior to AutoHCT have been shown to have superior outcomes[23–24]. With regard to our study, PET data was not uniformly captured during the era in question. We therefore were not able to determine the impact of PET status pre-AutoHCT. Our data suggest that the extent of exposure to specific cytotoxic chemotherapy agents during salvage therapy does not directly correlate with PFS. However, knowing that PET-avid disease prior to AutoHCT has been associated with inferior outcomes in other studies[23–24], reasonable efforts should be made to achieve PET negative status prior to AutoHCT, whether that be using conventional therapy[25] or novel therapies such as brentuximab vedotin[26] or bendamustine[27].

Various conditioning regimens have been utilized for patients with relapsed HL. In our study BEAM, busulfan-based and CBV were the most frequently utilized regimens. In multivariate analysis, the incidence of NRM did not differ across various conditioning regimens. We did find, however, that compared to BEAM, CBV conditioning was associated with a higher-risk of progression/relapse (RR-1.72, p=0.002). Similar results were reported by William et al[28]. NRM in our study was 6% and 7% at 1 and 5 years respectively which is comparable to the studies published in adults with relapsed/refractory HL receiving AutoHCT [29–31]. However, incidence of NRM in a prospective COG study that utilized CBV conditioning regimen for AutoHCT in children with relapsed/refractory lymphoma was 13% (5/38)[7]. In the current study, utilization of non-ABVD regimens as a first line therapy was associated with higher NRM and lower OS. It is plausible that patients treated with a more intensive first line non-ABVD regimen have less risk of primary relapse. However, few patients who relapse experience higher NRM resulting in lower OS.

The CAYA population with HL is a unique and challenging, despite excellent outcomes, still includes a subset of patients whose survival is unacceptably low. Because they are younger at diagnosis, they are at risk of long-term complications and significant morbidity later in life as a result of disease treatment. The prognostic model developed in our study identifies a group of high-risk patients, who have suboptimal outcomes despite AutoHCT salvage. Investigation of novel conditioning approaches or post-AutoHCT therapies e.g.

maintenance brentuximab vedotin[26], reduced-intensity allogeneic HCT[35], cellular therapy[36] or incorporation of PD-1 inhibitors[37], for these CAYA with poor prognosis is warranted.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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*Corporate Members

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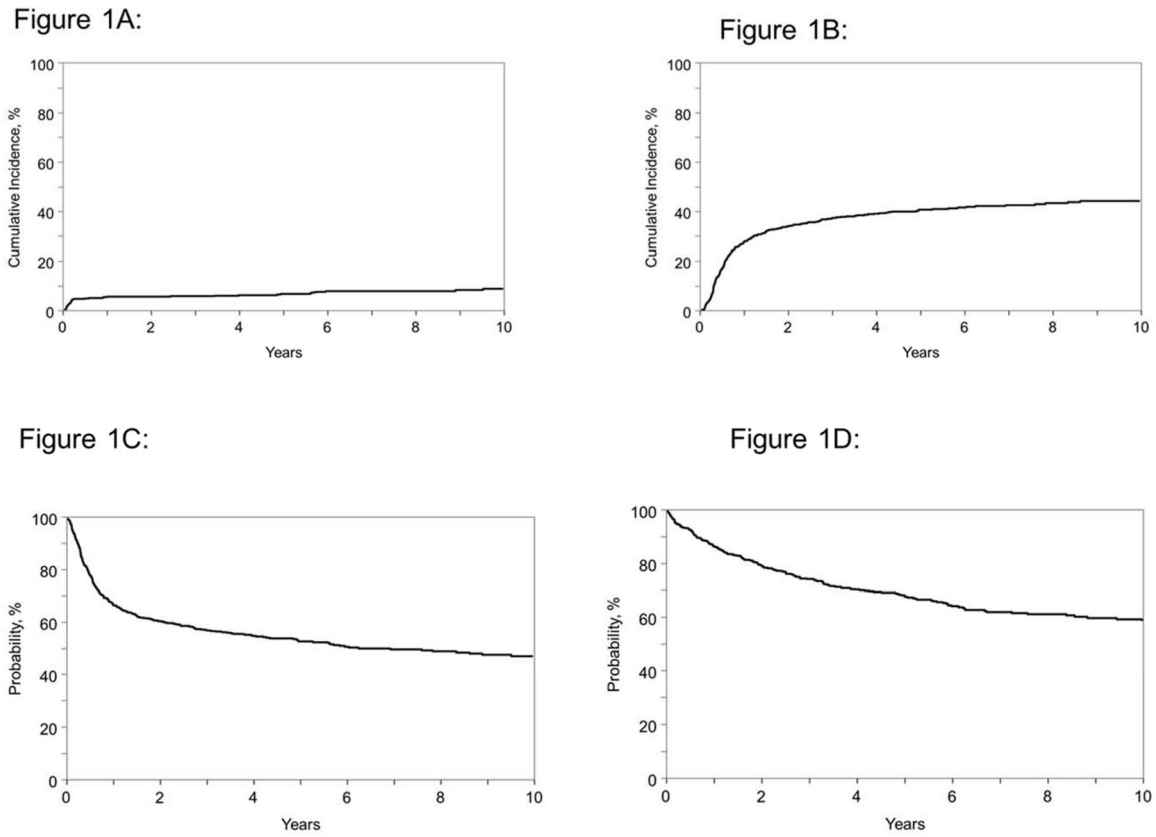

Figure 1.

Autologous hematopoietic cell transplantation outcomes for children, adolescents and young adults with Hodgkin lymphoma

1A: Non-relapse related mortality.

1B: Progression/relapse.

1C: Progressions free survival.

1D: Overall survival.

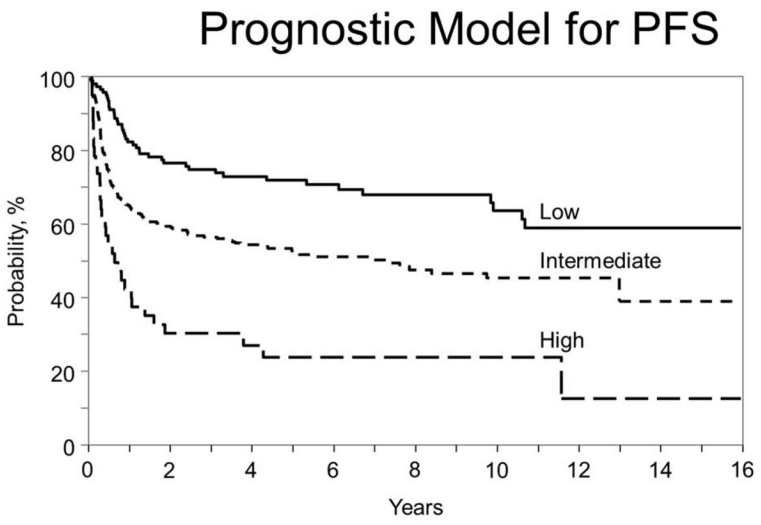

Figure 2.

Prognostic model predicting progression free survival for children, adolescents and young adults with Hodgkin lymphoma with low, intermediate and high risk scores [low vs. intermediate score ($p=0.0002$), low vs. high score ($p<0.0001$) and intermediate vs. high score ($p<0.0001$)].

Table 1

Variables tested in Cox proportional hazards regression models for relapse/progression, non-relapse mortality, overall survival and progression free survival.

Patient-related:
Age at transplant, years: continuous; and <21 vs. ≥21 year
Gender: Male vs. Female
Karnofsky or Lansky performance status ≥90 vs. <90 vs. missing
Race: Caucasian/White vs. Black vs. others
Disease-related:
Histology: nodular sclerosis vs. lymphocyte-rich vs. mixed cellularity vs. lymphocyte depleted vs. HL, not otherwise specified
Time from diagnosis to first relapse after 1st line therapy: continuous & <1 year (including refractory to first line) vs. ≥1 year
Time from diagnosis to transplant: continuous
Disease stage at diagnosis: I/II vs. III/IV
B symptoms: No vs. Yes
LDH at AutoHCT: normal vs. high
Number of lines of therapy prior to transplant: continuous & <3 vs. ≥3 lines
First line therapy: ABVD or ABVD-like [±Radiation] vs. All other regimens [± Radiation] vs. Unknown/Missing
Extranodal involvement at AutoHCT: No vs. Yes
Bulky disease at AutoHCT: No vs. Yes
Prior history of radiation therapy: Yes vs. No
Disease status at Auto: sensitive vs. resistant
Transplant-related:
Conditioning regimen: BEAM vs. CBV vs. other
Year of transplantation: continuous and 1995–2000 vs. 2001–2005 vs. 2006–2010

HL-Hodgkin lymphoma, ABVD-doxorubicin, bleomycin, vinblastine, dacarbazine, AutoHCT-Autologous hematopoietic cell transplant, BEAM-BCNU, etoposide, cytarabine, melphalan, CBV-cyclophosphamide, carmustine, etoposide.

Table 2

Characteristics of <30 years old patients who underwent AutoHCT for relapsed/refractory HL from 1995–2010 reported to the CIBMTR.

Variable	N (%)
Total number of patients	**606**
Age at AutoHCT, years	
Median	23 (3–29)
<21	208 (34)
≥21	398 (66)
Male Sex	332 (55)
KPS/LPS	
<90%	124 (20)
90–100%	454 (75)
Race	
Caucasian/White	464 (77)
Black	57 (9)
Asian/Pacific Islander	14 (2)
Hispanic	58 (10)
Others	13 (2)
HL subtype	
Lymphocyte-rich	26 (4)
Nodular sclerosis	468 (77)
Mixed cellularity	57 (9)
Lymphocyte depleted	10 (2)
Not specified	45 (7)
Time from diagnosis to first relapse (TDFR) pre-AutoHCT, months	
Median (range)	22 (5–229)
<12 (including patients refractory to 1st line therapy)	322 (53)
≥12	213 (35)
Missing	71 (12)
Time from diagnosis to AutoHCT, months (range)	19 (3–238)
Disease stage at diagnosis	
I–II	300 (50)
III–IV	293 (48)
Unknown	13 (2)
B-Symptoms at diagnosis	
Present	323 (53)
Elevated LDH concentration prior to AutoHCT	158 (26)
Number of chemotherapy lines	2 (1–5)
First line chemotherapy	
ABVD or ABVD-like ± radiation	361 (60)
BEACOPP-like ± radiation	23 (4)

Variable	N (%)
CHOP-like ± radiation	15 (2)
MOPP/ABV(±D) or COPP/ABV (±D) Hybrid ± radiation	88 (15)
COPP or MOPP ± radiation	32 (5)
Stanford V	2 (<1)
Radiation alone or other chemotherapy ± radiation	85 (14)
Bone marrow involvement at diagnosis	40 (7)
Bone marrow involvement at AutoHCT	9 (1)
Total number of patients	**606**
Extranodal involvement at diagnosis	196 (32)
Extranodal involvement at AutoHCT	107 (18)
Bulky disease at AutoHCT	73 (12)
Radiation prior to AutoHCT	276 (46)
Chemosensitive disease prior to AutoHCT	
Sensitive	479 (79)
Resistant	113 (19)
Missing *(Untreated relapse/unknown (n=11) included)*	14 (2)
Disease status prior to AutoHCT	
PIF sensitive	90 (15)
PIF resistant	53 (9)
CR1	35 (6)
Relapsed sensitive	209 (34)
Relapsed resistant	60 (10)
CR2+	145 (24)
Untreated relapse/unknown	11 (2)
Missing	3 (<1)
Conditioning regimens	
TBI-based	33 (5)
BEAM and similar	406 (67)
CBV or similar	77 (13)
BuMEL/BuCy	42 (7)
Others*	48 (8)
Year of AutoHCT	
1995–2000	325 (54)
2001–2005	127 (21)
2006–2010	154 (25)
Planned radiation post-AutoHCT	183 (30)
Median follow-up of survivors median (range)	64 (4–216)

ABVD-like=include omission of either bleomycin or dacarbazine from standard ABVD or substitution of doxorubicin with epirubicin. PIF *resistant*= primary induction failure sensitive resistant: never in CR but with stable or progressive disease on treatment; PIF *sensitive*=primary induction failure sensitive: never in CR but with partial remission.

HL-Hodgkin lymphoma, KPS/LS-Karnofsky/Lansky performance status, TDFR-Time from diagnosis to first relapse, LDH- lactate dehydrogenase, ABVD- doxorubicin, bleomycin, vinblastine, dacarbazine, BEACOPP-Bleomycin, etoposide, Adriamycin, cyclophosphamide, oncovin, procarbazine, prednisone, COPP- , cyclophosphamide, oncovin, procarbazine, prednisone, MOPP-mechlorethamine, oncovin, procarbazine,

prednisone CHOP- Cyclophosphamide, daunorubicin, oncovin, prednisone AutoHCT- Autologous hematopoietic cell transplant, TBI-total body irradiation, BEAM- BCNU, etoposide, cytarabine, melphalan, CBV- cyclophosphamide, carmustine, etoposide. BUMEL/BuCy- busulfan-melphalan/busulfan-cyclophosphamide

* Bu alone (n=1), Bu+Thio (n=1), Carboplatin+Mito+Thio (n=4), Carboplatin+Thio (n=3), Carboplatin+VP16+ Ifos (n=5), Carboplatin +VP16+LPAM (n=8), Cy+Carboplatin+Thio (n=5), CY+mito/nitro+thio (n=2), Cy+Thio (n=6), Cy+Thio+Mesna (n=2), LPAM alone (n=8), LPAM+Mito (n=1), VP16 (n=1), unknown (n=1)

Table 3

Multivariate analyses for NRM, progression/relapse, PFS and OS.

Non-relapse related mortality					
First line therapy	**N**	**RR**	**95%CI Lower Limit**	**95%CI Upper Limit**	**p-value**
ABVD or ABVD like	359	1			
Other regimens	221	2.47	1.32	4.62	0.004
Missing	24	6.41	2.63	15.60	<0.0001
Progression/relapse					
Karnofsky/Lansky score					
≥90	453	1			
<90	124	1.46	1.08	1.98	0.01
Missing	27	1.63	0.94	2.84	0.08
TDFR					
< 1 year	321	1			
≥1 year	212	0.65	0.48	0.88	0.006
Missing	71	1.35	0.98	1.99	0.13
Extranodal involvement at AutoHCT					
No	476	1			
Yes	107	1.67	1.23	2.29	0.001
Missing	21	1.19	0.60	2.36	0.62
Disease status					
Chemosensitive	478	1			
Resistant	112	1.75	1.29	2.36	0.0003
Missing	14	2.14	1.05	4.40	0.04
Conditioning regimen					
BEAM	404	1			
CBV	77	1.72	1.21	2.45	0.003
Other	123	1.3	0.95	1.78	0.10
Therapy failure (inverse of PFS)					
Karnofsky/Lansky performance score					

Non-relapse related mortality					
First line therapy	**N**	**RR**	**95%CI Lower Limit**	**95%CI Upper Limit**	**p-value**
≥90	453	1			
<90	124	1.45	1.10	1.92	0.008
Missing	27	1.57	0.95	2.59	0.08
TDFR					
< 1 year	321	1			
≥1 year	212	0.71	0.54	0.93	0.01
Missing	71	1.35	0.95	1.91	0.09
Extranodal involvement					
No	476	1			
Yes	107	1.59	1.19	2.12	0.001
Missing	21	1.50	0.85	2.66	0.16
Disease status					
Chemosensitive	478	1			
Resistant	112	1.84	1.40	2.42	<0.0001
Missing	14	2.06	1.05	4.05	0.03
Mortality (overall survival)					
TDFR					
< 1 year	322	1			
≥1 year	213	0.62	0.44	0.86	0.004
Missing	71	1.20	0.79	1.83	0.39
First line therapy					
ABVD or ABVD like	361	1			
Other regimens	221	1.64	1.21	2.22	0.001
Missing	24	2.30	1.23	4.32	0.01
Extranodal involvement					
No	478	1			
Yes	107	1.81	1.29	2.52	0.0005
Missing	21	1.91	1.03	3.55	0.04

Non-relapse related mortality					
First line therapy	**N**	**RR**	**95%CI Lower Limit**	**95%CI Upper Limit**	**p-value**
Disease status					
Chemosensitive	479	1			
Resistant	113	2.27	1.64	3.13	<0.0001
Missing	14	0.90	0.32	2.50	0.84

ABVD- doxorubicin, bleomycin, vinblastine, dacarbazine, ABVD-like=include omission of either bleomycin or dacarbazine from standard ABVD or substitution of doxorubicin with epirubicin. TDFR- Time from diagnosis to first relapse, AutoHCT- Autologous hematopoietic cell transplant, BEAM- BCNU, etoposide, cytarabine, melphalan, CBV- cyclophosphamide, carmustine, etoposide. BUMEL/ BuCy- busulfan-melphalan/busulfan-cyclophosphamide.

Table 4

Prognostic Model for progression-free survival

			95% CI	95% CI		Overall
Prognostic Score	**N**	**RR**	**Lower Limit**	**Upper Limit**	**p-value**	**p-value**
0	126	1				<0.0001
1	192	1.81	1.25	2.63	0.002	
2	129	2.11	1.42	3.13	0.0002	
3	38	3.93	2.42	6.36	<0.0001	
4	4	11.33	4.03	31.82	<0.0001	
Contrast						
1 vs. 2		0.86	0.62	1.19	0.36	
1 vs. 3		0.46	0.30	0.71	0.0004	
1 vs. 4		0.16	0.06	0.44	0.0004	
2 vs. 3		0.54	0.34	0.84	0.006	
2 vs. 4		0.19	0.07	0.51	0.001	
3 vs. 4		0.35	0.12	0.99	0.05	
PFS Risk Groups						
			95% CI	95% CI		Overall
Risk Group	N	RR	Lower Limit	Upper Limit	p-value	p-value
Low (Score=0)	126	1				<0.0001
Intermediate (Score=1 or2)	321	1.92	1.36	2.72	0.0002	
High(Score=3 or 4)	42	4.27	2.68	6.79	<0.0001	
Contrast						
Intermediate vs. High		0.45	0.31	0.66	<0.0001	

PFS-progression-free survival