

Clinical Study

High-Dose Therapy and Autologous Hematopoietic Progenitor Cells Transplantation for Recurrent or Refractory Hodgkin's Lymphoma: Analysis of King Hussein Cancer Center Results and Prognostic Variables

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Purpose. to evaluate the outcome of patients with Hodgkin's lymphoma who underwent autologous transplantation at KHCC bone marrow transplant program. **Patients and Methods.** Over 6 years, 63 patients with relapsed or refractory Hodgkin's lymphoma underwent high dose chemotherapy followed by autologous transplant. There were 25.4% patients in complete remission (CR), 71.4% with chemotherapy responsive disease at the time of transplant. Prior to conditioning regimen, 56% received two chemotherapy lines, and, 44% received more than two lines. **Results.** The main outcomes of the study are the rate of complete remission at day 100, overall survival (OS), relapse-free survival (RFS), The impact of the following variables on OS and RFS: (a) disease status at the time of transplant, (b) number of chemotherapy lines prior to conditioning, (c) age group, (d) time of relapse < or >12 months were investigated. The CR at day 100 was 57%. The median overall survival for the whole group was 40.6 months; the median RFS was 20 months. The only factor which significantly impacts the study outcomes was the number of chemotherapy lines prior to conditioning on OS in favor of patients received two lines. **Conclusion.** In our study only the number of chemotherapy lines received before conditioning had statistically significant impact on OS.

1. Introduction

Among patients with early-stage Hodgkin's lymphoma (HL) the rate of relapse ranges from 10 to 15% [1] and in patients with advanced stage HL the relapse rate ranges from 30 to 40% [2–6]. In addition, approximately 10–15% of patients experience progression of disease after an initial partial response.

High-dose chemotherapy (HDCT) followed by hematopoietic stem cell transplantation can achieve sustained remission in patients with advanced refractory or recurrent HL [7–14]. Several factors can predict survival and RFS after high-dose chemotherapy and autologous transplant. One of these factors is the number of chemotherapy lines patients received

prior to transplant [15–19]. Another factor which was shown in previous studies to predict the risk of relapse was the disease status at the time of transplant, with superior outcomes in patients who were in complete remission (CR), or minimal residual disease in comparison to those with bulky disease [14, 17, 20], and the last factor which was shown to influence the outcome is the time to initial relapse (TTR) >12 months versus <12 months which is measured from the date of diagnosis to that of proven relapse [21]. At the King Hussein Cancer Center (KHCC) bone marrow and stem cell transplantation program, Amman, Jordan, we performed stem cell transplantation for 63 patients with HL between the years 2003 and 2008. We report herein the outcome of these patients. Since our program is combined for adult and

pediatric patients, our study includes, as one of its objectives, the comparison between the two age groups in treatment outcome. To our knowledge there is no data available on the impact of age on transplantation outcome of HL. (Adult patients at our center are defined as 18 years or older.)

2. Patients and Method

The outcome of sixty-three patients who underwent HSCT at KHCC between January 2003 and December 2008 was studied through retrospective chart review after obtaining IRB approval.

The diagnosis was confirmed for all patients at KHCC by pathology review, and they all met the standard criteria to be eligible for autologous transplant. We included all patients who underwent transplant if all data required for the study was available in their files.

We reviewed 70 files for patients with relapsed/refractory HL who underwent transplant at KHCC during the study period. Data about disease status at the time of transplant, number of chemotherapy lines received before transplant, evaluation at day 100, vital status, and disease status at last followup was available for sixty-three patients (90%), so this group composed our study population.

2.1. Treatment. Prior to the conditioning regimen 56% of the patients received only two lines of chemotherapy, and 44% received more than two lines. Chemotherapy and GCSF mobilization followed by stem cell collection was used in 89% of patients, while GCSF alone followed by stem cell collection was used in 11% of cases. The source of stem cells was peripheral blood in all cases.

Sixty (95%) of 63 patients received BEAM (BCNU, Etoposide, Ara-C, and Melphalan) as conditioning. One patient received CBV (Cytosan, BCNU, VP16), and two patients received TEAM (Thiotepa, Etoposide, Ara-C, and Melphalan). The median CD34 dose delivered was $5.6 \times 10^6/\text{kg}$ ($1.51\text{--}12.1$). All patients received routine prophylaxis with acyclovir, fluconazole, and trimethoprim/sulfamethoxazole.

Patients had followup CT scan at day 30, and CT scan or PET-CT scan at day 100. RECIST criteria were used to assess response by CT scan. The majority of patients had only CT scan for followup.

2.2. End Points. The primary end points were

- (i) the rate of complete remission at day 100,
- (ii) overall survival (OS),
- (iii) relapse-free survival (RFS),
- (iv) overall survival and RFS according to disease status at the time of transplant, number of chemotherapy lines, age group, and TTR.

The secondary end points were

- (i) day 100 nonrelapse mortality (NRM),
- (ii) incidence of grade 3-4 mucositis.

TABLE 1: Characteristics of 63 patients with HL who underwent autologous stem cell transplantation.

		Count (%)
Gender	Male	38 (60.3%)
	Female	25 (39.7%)
Age	Adult	54 (85.7%)
	Pediatric	9 (14.3%)
Number of previous Chemotherapy lines received	2 lines	35 (55.6%)
	>2 lines	28 (44.4%)
Disease status at transplant	Complete remission	16 (25.4%)
	Responsive disease	45 (71.4%)
	Stable disease	2 (3.2%)
Time to relapse (TTR)	≤ 12 months	30 (48%)
	>12 months	33 (52%)
Mobilization regimen	Chemotherapy + GCSF	57 (90.5%)
	GCSF only	6 (9.5%)
Stem cell source	Peripheral	63 (100%)
Stem cell dose	Median (range)	$5.6 \times 10^6/\text{kg}$ ($1.51\text{--}12.1 \times 10^6/\text{kg}$)
	BEAM*	60 (95.2%)
Conditioning regimen	TEAM**	2 (3.2%)
	CBV***	1 (1.6%)

* BEAM: BCNU, etoposide, Ara-C, melphalan.

** TEAM: thiotepa, etoposide, Ara-C, melphalan.

*** CBV: cyclophosphamide, BCNU, VP16.

2.3. Statistical Analysis. The rate of complete remission at day 100, as well as the overall survival, and relapse-free survivals were the primary outcomes of this study. Furthermore, day 100 nonrelapse mortality (NRM) and incidence of grade 3, 4 mucositis are secondary outcomes to be investigated in this study. Outcome comparison between groups categorized by disease status at the end of treatment, number of lines of chemotherapy, time to relapse, and age groups was carried out. Kaplan-Meier method was used to present survival curves. Comparison between groups in survival was carried out using Log Rank test.

3. Results

3.1. Patients' Characteristics. The characteristics of the 63 patients at the time of autologous stem cell transplant are listed in Table 1.

Only 16 (25.4%) of the 63 patients were in complete remissions (CRs) at the time of transplantation; the majority of patients in this series had responsive disease, 45 patients (71.4%), and 2 patients (3%) had stable disease. All patients had successful engraftment, with a median time of 10 days for white blood cells and 12 days for platelets engraftment.

3.1.1. Overall Survival. All 63 patients were followed with a median follow-up time of 34.89 months. The median overall

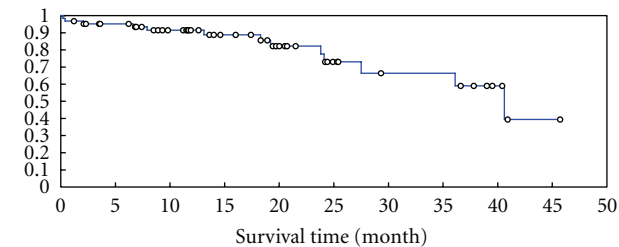


FIGURE 1: Overall survival of 63 patients received autologous transplantation for HL.

TABLE 2	
Summary statistics	
Total observed	63
Total failed	13
Total censored	50
Mean survival time	
Mean survival time (survival < 40.9)	32.550
Standard deviation	2.070
Lower bound (95%)	28.492
Upper bound (95%)	36.608
Quantiles estimation	
Quantile	50%
Estimate	40.600
Lower bound (95%)	27.500
Upper bound (95%)	

survival was 40.6 months, with projected 3-year overall survival of 64.6% as shown in Figure 1 and Table 2.

The overall survival of patients who received two lines before transplant was significantly better than that of those who received more than two lines, 73% versus 43% ($P = 0.049$) Figure 2 and Table 3. However, there was no statistically significant difference between those who were in complete remission versus those with responsive disease. Also, there was no statistical difference in the survival of children or adults who received autologous transplant and no difference in survival according to TTR >12 months or <12 months.

3.1.2. Relapse-Free Survival. The median RFS for the whole group was 20 months. The projected 3-year RFS is 42.3% Figure 3 and Table 4. Exploring the impact of disease status at transplant, number of lines of chemotherapy age group, and TTR on relapse-free survival, it was found that none of these factors significantly affected the time to relapse. It is worth mentioning here that there was a trend for improvement in RFS for patients who received two lines in comparison to those who received more than two (P value = 0.095) as seen in Figure 4 and Table 5.

3.2. Day 100 Mortality and Incidence of Grade 3-4 Mucositis. Only three patients died in the first 100 days (4.8%), after transplant. The cause of death was sepsis in all of the three

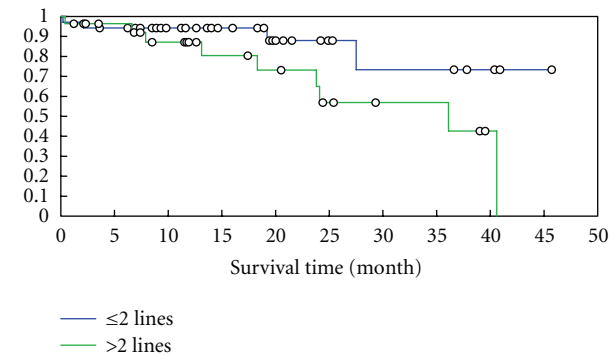


FIGURE 2: Overall survival of 63 patients with HL according to number of lines of chemotherapy received before transplantation.

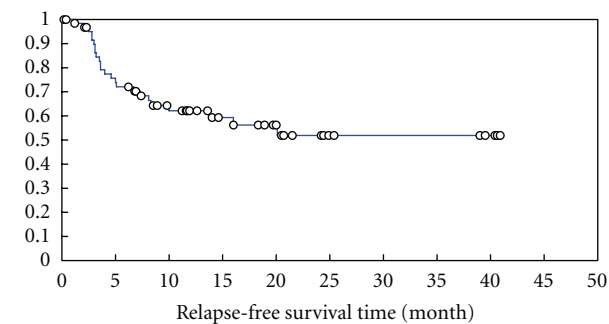


FIGURE 3: Relapse free-survival of 63 patients received autologous transplantation for HL.

TABLE 3	
Summary statistics (≤ 2 line)	
Total observed	35
Total failed	4
Total censored	31
Quantiles estimation (≤ 2 line)	
Quantile	50%
Estimate	
Lower bound (95%)	
Upper bound (95%)	
Quantiles estimation (> 2 lines)	
Total observed	28
Total failed	9
Total censored	19
Quantile	50%
Estimate	36.100
Lower bound (95%)	23.800
Upper bound (95%)	40.600
Statistic	Log-rank
P value	0.050

cases. This is comparable to the acceptable international figures. As for grade 3-4 mucositis, its occurrence reached 50%.

TABLE 4

Summary statistics	
Total observed	63
Total failed	24
Total censored	39
Quantiles estimation	
Quantile	50%
Estimate	
Lower bound (95%)	NA
Upper bound (95%)	NA

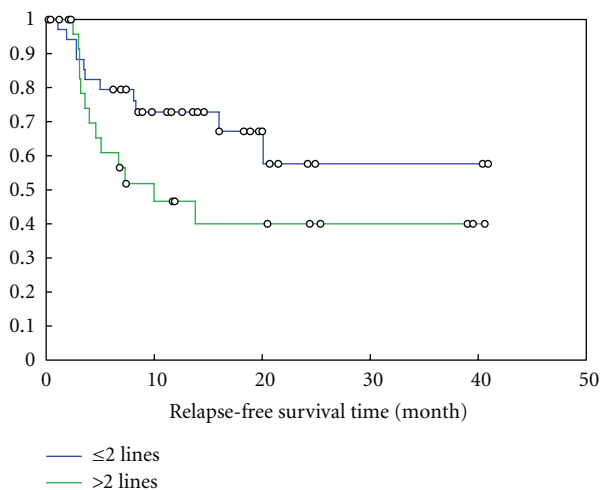


FIGURE 4: Relapse-free survival of 63 patients with HL according to number of lines of chemotherapy received before transplantation.

4. Discussion

High-dose chemotherapy with autologous stem cell transplantation is a well-established potentially curative therapy for relapsed/refractory Hodgkin's lymphoma.

At KHCC sixty-three patients underwent high-dose chemotherapy with autologous transplant from 2003 to 2008. At the time of transplantation 25% of patients were in CR, and at day 100 the number rose to 57%. Prior to the conditioning regimen, 55.6% received two lines of chemotherapy and 44.4% received more than two lines.

The median survival for the whole group was 40.6 months, with projected 3-year overall survival of 64.6%, and the median RFS was 20 months, with projected 3-year RFS of 42.3%.

These results were close to the 5-year OS and RFS published by Engelhardt et al. [21].

All patients engrafted on time. The incidence of grade 3-4 mucositis was 50%, and the day 100 mortality was 4.8%.

The correlation between the numbers of chemotherapy lines received prior to conditioning and survival was statistically significant. This is consistent with some previously published studies [15–19], although this was not shown in the study published by Engelhardt et al. [21]. In our study

TABLE 5

Summary statistics (≤ 2 line)	
Total observed	35
Total failed	11
Total censored	24
Quantiles estimation (≤ 2 line)	
Quantile	50%
Estimate	NA
Lower bound (95%)	
Upper bound (95%)	
Summary statistics (> 2 lines)	
Total observed	28
Total failed	13
Total censored	15
Quantiles estimation (> 2 lines)	
Quantile	50%
Estimate	10.000
Lower bound (95%)	4.600
Upper bound (95%)	
Test of equality of the survival distribution functions (DF = 1)	
Statistic	Log-rank
P value	0.094

there was a trend towards improvement in RFS in patients who received two lines of chemotherapy in comparison to those who received more than two lines, but this was not statistically significant, probably due to the small sample size.

The disease status at the time of transplant (CR versus RD) did not affect the OS or RFS, and this is consistent with Engelhardt et al. study [21], but contradicting other studies [14, 17, 20]. We believe that the main reason for this is the small sample size in our study, as there was a trend towards improvement in patients who were in CR over those who had RD, with P values of 0.10 and 0.15 for RFS and OS, respectively.

There was no difference in outcome between the two age groups in term of OS and RFS, with the caveat of the small number of pediatric patients. There was no difference in OS and RFS according to TTR.

5. Conclusion

We can therefore conclude from our study that the number of chemotherapy lines received prior to the conditioning regimen is the most important predictor of survival.

Our patients who proceeded to autologous transplantation had to have chemosensitive disease; otherwise changing the chemotherapy line was recommended in case progression or no response after two cycles of therapy. This supports the hypothesis that the tumor biology is the most important predictor of OS, with tumors that were sensitive to the first line of salvage chemotherapy having a better outcome than

those that were not, even if the latter responded to further salvage chemotherapy.

Relapse after autologous transplant for HL remains a significant problem with more than 50% of patients relapsing as projected from our study, so it is important to focus on treatment strategies after relapse.

There is a potential durable response with reduced-intensity allogeneic transplant for HL patients relapsed after autologous transplant as shown by the study of Peggs et al. [22].

Novel agents like Brentuximab Vedotin are promising with phase II studies showing response rate as high as 75% in relapse/refractory HL. It is currently under investigation in phase III trial for patients with HL at high risk for residual disease following autologous stem cell transplantation [23].

References

- [1] L. Specht, R. G. Gray, M. J. Clarke, and R. Peto, "Influence of more extensive radiotherapy and adjuvant chemotherapy on long-term outcome of early-stage Hodgkin's disease: a meta-analysis of 23 randomized trials involving 3,888 patients," *Journal of Clinical Oncology*, vol. 16, no. 3, pp. 830–843, 1998.
- [2] A. M. Oza, T. S. Ganesan, M. Leahy et al., "Patterns of survival in patients with Hodgkin's disease: long follow up in a single centre," *Annals of Oncology*, vol. 4, no. 5, pp. 385–392, 1993.
- [3] G. P. Canellos, J. R. Anderson, K. J. Propert et al., "Chemotherapy of advanced Hodgkin's disease with MOPP, ABVD, or MOPP alternating with ABVD," *New England Journal of Medicine*, vol. 327, no. 21, pp. 1478–1484, 1992.
- [4] R. Somers, P. Carde, M. Henry-Amar et al., "A randomized study in stage IIIB and IV Hodgkin's disease comparing eight courses of MOPP versus an alternation of MOPP with ABVD: a European organization for research and treatment of cancer lymphoma cooperative group and Groupe Pierre-et-Marie-Curie controlled clinical trial," *Journal of Clinical Oncology*, vol. 12, no. 2, pp. 279–287, 1994.
- [5] J. A. Radford, D. Crowther, A. Z. S. Rohatiner et al., "Results of a randomized trial comparing MVPP chemotherapy with a hybrid regimen, ChlVPP/EVA, in the initial treatment of Hodgkin's disease," *Journal of Clinical Oncology*, vol. 13, no. 9, pp. 2379–2385, 1995.
- [6] S. Viviani, G. Bonadonna, A. Santoro et al., "Alternating versus hybrid MOPP and ABVD combinations in advanced Hodgkin's disease: ten-year results," *Journal of Clinical Oncology*, vol. 14, no. 5, pp. 1421–1430, 1996.
- [7] S. Jagannath, J. O. Armitage, K. A. Dicke et al., "Prognostic factors for response and survival after high-dose cyclophosphamide, carmustine, and etoposide with autologous bone marrow transplantation for relapsed Hodgkin's disease," *Journal of Clinical Oncology*, vol. 7, no. 2, pp. 179–185, 1989.
- [8] C. E. Desch, M. R. Lasala, T. J. Smith, and B. E. Hillner, "The optimal timing of autologous bone marrow transplantation in Hodgkin's disease patients after a chemotherapy relapse," *Journal of Clinical Oncology*, vol. 10, no. 2, pp. 200–209, 1992.
- [9] R. Chopra, A. K. McMillan, D. C. Linch et al., "The place of high-dose BEAM therapy and autologous bone marrow transplantation in poor-risk Hodgkin's disease. A single-center eight-year study of 155 patients," *Blood*, vol. 81, no. 5, pp. 1137–1145, 1993.
- [10] J. Yahalom, S. C. Gulati, M. Toia et al., "Accelerated hyperfractionated total-lymphoid irradiation, high-dose chemotherapy, and autologous bone marrow transplantation for refractory and relapsing patients with Hodgkin's disease," *Journal of Clinical Oncology*, vol. 11, no. 6, pp. 1062–1070, 1993.
- [11] D. E. Reece, J. M. Connors, J. J. Spinelli et al., "Intensive therapy with cyclophosphamide, carmustine, etoposide \pm cisplatin, and autologous bone marrow transplantation for Hodgkin's disease in first relapse after combination chemotherapy," *Blood*, vol. 83, no. 5, pp. 1193–1199, 1994.
- [12] A. Nademanee, M. R. O'Donnell, D. S. Snyder et al., "High-dose chemotherapy with or without total body irradiation followed by autologous bone marrow and/or peripheral blood stem cell transplantation for patients with relapsed and refractory Hodgkin's disease: results in 85 patients with analysis of prognostic factors," *Blood*, vol. 85, no. 5, pp. 1381–1390, 1995.
- [13] A. R. Yuen, S. A. Rosenberg, R. T. Hoppe, J. D. Halpern, and S. J. Horning, "Comparison between conventional salvage therapy and high-dose therapy with autografting for recurrent or refractory Hodgkin's disease," *Blood*, vol. 89, no. 3, pp. 814–822, 1997.
- [14] S. J. Horning, N. J. Chao, R. S. Negrin et al., "High-dose therapy and autologous hematopoietic progenitor cell transplantation for recurrent or refractory Hodgkin's disease: analysis of the Stanford University results and prognostic indices," *Blood*, vol. 89, no. 3, pp. 801–813, 1997.
- [15] M. E. R. O'Brien, S. Milan, D. Cunningham et al., "High-dose chemotherapy and autologous bone marrow transplant in relapsed Hodgkin's disease—a pragmatic prognostic index," *British Journal of Cancer*, vol. 73, no. 10, pp. 1272–1277, 1996.
- [16] J. C. Lavoie, J. M. Connors, G. L. Phillips et al., "High-dose chemotherapy and autologous stem cell transplantation for primary refractory or relapsed Hodgkin lymphoma: long-term outcome in the first 100 patients treated in Vancouver," *Blood*, vol. 106, no. 4, pp. 1473–1478, 2005.
- [17] L. J. Burns, K. A. Daniels, P. B. McGlave et al., "Autologous stem cell transplantation for refractory and relapsed Hodgkin's disease: factors predictive of prolonged survival," *Bone Marrow Transplantation*, vol. 16, no. 1, pp. 13–18, 1995.
- [18] A. Nademanee, M. R. O'Donnell, D. S. Snyder et al., "High-dose chemotherapy with or without total body irradiation followed by autologous bone marrow and/or peripheral blood stem cell transplantation for patients with relapsed and refractory Hodgkin's disease: Results in 85 patients with analysis of prognostic factors," *Blood*, vol. 85, no. 5, pp. 1381–1390, 1995.
- [19] P. J. Bierman, R. G. Bagin, S. Jagannath et al., "High dose chemotherapy followed by autologous hematopoietic rescue in Hodgkin's disease: long term follow-up in 128 patients," *Annals of Oncology*, vol. 4, no. 9, pp. 767–773, 1993.
- [20] M. Crump, A. M. Smith, J. Brandwein et al., "High-dose etoposide and melphalan, and autologous bone marrow transplantation for patients with advanced Hodgkin's disease: importance of disease status at transplant," *Journal of Clinical Oncology*, vol. 11, no. 4, pp. 704–711, 1993.
- [21] B. G. Engelhardt, D. W. Holland, S. J. Brandt et al., "High-dose chemotherapy followed by autologous stem cell transplantation for relapsed or refractory Hodgkin lymphoma: prognostic features and outcomes," *Leukemia and Lymphoma*, vol. 48, no. 9, pp. 1728–1735, 2007.
- [22] K. S. Peggs, A. Hunter, R. Chopra et al., "Clinical evidence of a graft-versus-Hodgkin's-lymphoma effect after reduced-intensity allogeneic transplantation," *Lancet*, vol. 365, no. 9475, pp. 1934–1941, 2005.
- [23] K. V. Foyil and N. L. Bartlett, "Brentuximab vedotin for the treatment of CD30⁺ lymphomas," *Immunotherapy*, vol. 3, no. 4, pp. 475–485, 2011.

