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Original paper

Aim of the study: The aim of the study was to determine the incidence of second malignancies among patients with Hodgkin lymphoma (HL) treated with autologous haematopoietic stem cell transplantation (ASCT) following a modified BEAM (BCNU, etoposide, cytarabine, melphalan, dexamethasone) regimen between 1992 and 2012 at our department. We also intended to define the risk factors for the occurrence of second neoplasm after ASCT.

Material and methods: The long-term outcomes after transplant were evaluated in 170 patients, median age 31 years (range 17–61), who received a median of two pre-transplant chemotherapy lines (range 1–5).

Results: MOPP (mechlorethamine, vincristine, procarbazine, prednisone) or MOPP-type regimens were given to 12% of patients prior to ASCT. The median follow-up of the survivors was 73 (12–242) months. The 7-year overall survival and progression-free survival were 75% and 64%, respectively. Second malignancies occurred in 7 of the 170 patients, including 5 haematological malignancies, and 2 solid tumors. They developed at a median of 8 years (range 0.4–13.5) from ASCT. The 10-year and 15-year cumulative incidence of developing a second malignancy were 7% and 13%, respectively. In multivariate analysis, age ≥ 40 years at transplant (HR = 8.8; $p = 0.008$) and pre-transplant MOPP-type chemotherapy (HR = 5.6; $p = 0.030$) were the only factors significant for developing a second malignancy.

Conclusions: Our results indicate that age of patient and the type of pre-transplant chemotherapy contribute to the risk of the development of a second neoplasm after ASCT in patients with HL. We believe that better characterization of second malignancies and associated risk factors may be useful for clinicians who care for these patients.

Key words: Hodgkin lymphoma, autologous haematopoietic stem cell transplantation, BEAM, second malignancy.

Second malignancies after autologous haematopoietic stem cell transplantation following modified BEAM conditioning regimen in patients with Hodgkin lymphoma – characteristics and risk factor analysis

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Introduction

High-dose therapy (HDT) followed by autologous haematopoietic stem cell transplantation (ASCT) is considered the treatment of choice for patients with relapsed Hodgkin lymphoma (HL) and an effective treatment option for patients who did not adequately respond to conventional therapy. Approximately half of patients treated with ASCT are likely to be long-term survivors, since this treatment provides long-term disease-free survival in over 50–60% of patients [1, 2].

Second malignant neoplasms are a well recognized and serious late complication in HL survivors. Several studies have been reported which proved the increased incidence of second malignancies for patients with HL treated with conventional therapy, especially those who were exposed to alkylating agents, such as mechlorethamine and procarbazine in the MOPP (mechlorethamine, vincristine, procarbazine, prednisone) regimen [3–6]. Moreover, there are available data indicating that lymphoma patients treated with HDT and ASCT are at increased risk for second neoplasms including therapy-related acute myeloid leukaemia/myelodysplastic syndrome (t-AML/MDS) [7–10]. However, the potential contribution of ASCT to second malignancy development remains controversial [11–13]. Studies investigating the contribution of pre-transplant therapy and transplant procedures in the development of second malignancies in HL patients have yielded inconsistent results [7, 11, 14, 15]. Since deaths due to second malignancies are the most common cause of non-relapse mortality among long-term survivors of HL, better characterization of second malignancies and the identification of Hodgkin lymphoma patients with high risk of developing second malignancy after ASCT may be useful for clinicians who care for these patients.

To enhance the published experience, we conducted a retrospective review of patients who underwent ASCT following a modified BEAM preparative regimen for refractory or relapsed HL at our centre. We intended to determine the incidence of second malignancies and associated pre-transplant and transplant-related risk factors. Herein, we report the results of this analysis.

Material and methods

Study population

We retrospectively reviewed the data of all patients with refractory or relapsed HL who were treated with a modified BEAM regimen followed by ASCT between

January 1992 and January 2012 at our centre. Patients records were reviewed to obtain patient characteristics and treatment details (sex, clinical stage according to the Ann Arbor system, presence of B symptoms, the type of first line chemotherapy, the number and type of salvage chemotherapy lines, radiotherapy, disease status at transplant, age at transplant). All patients were treated initially with chemotherapy with or without radiotherapy. The treatment practices varied during the study period, including type of first line and salvage regimens, and the indications for radiotherapy. The disease status at transplant was defined using standard criteria of response [16]. With regard to transplant procedures, patients underwent haematopoietic cell collection either by bone marrow harvest or leukapheresis following stem cell mobilization. Stem cell mobilization was performed using salvage chemotherapy or cyclophosphamide (4 g/m^2) ± etoposide (600 mg/m^2) with G-CSF stimulation. The stem cells were cryopreserved without further manipulation. The modified BEAM conditioning consisted of carmustine (300 mg/m^2), etoposide (800 mg/m^2), cytarabine (6000 mg/m^2), melphalan (140 mg/m^2) and dexamethasone (168 mg/m^2).

After ASCT, all patients were routinely observed by a haematologist in the outpatient clinic of our institution. Recommended evaluation included physical examination, cell blood count and biochemistry every 3 months during the first year, and every 6 months thereafter. Computed tomography, or X-ray of chest and abdomen ultrasonography was performed once per year.

Statistical analysis

Survival curves were estimated according to the method of Kaplan and Meier. Overall survival (OS) was measured from the time of transplantation until death of any cause and progression-free survival (PFS) was measured from the time of transplantation until documented progression or relapse or death. Non-relapse mortality (NRM) was defined as death of other causes than lymphoma relapse/progression. The probabilities of non-relapse mortality, relapse and second malignancy were calculated with the cumulative incidence estimator. The cumulative incidence of NRM and relapse were calculated with either relapse or non-relapse related mortality treated as competing risk. The cumulative incidence of second malignancy was calculated in the survivors' group, with death from any reason other than second neoplasm treated as competing risk. The time at risk for the development of a second malignancy was calculated from the date of ASCT.

Cox regression analysis for second malignancy incidence included potential prognostic factors, age at transplant, sex, clinical stage, presence of B symptoms, total number of chemotherapy lines before ASCT, MOPP or MOPP-type chemotherapy prior to transplant, radiotherapy, and disease status at transplant. *P*-values < 0.05 were considered significant.

SPSS version 14.0 (SPSS, Chicago, IL) was used for all statistical analyses except for cumulative incidence curve analyses, which were calculated using the statistical package NCSS version 2007 (NCSS, Kaysville, Utah).

Results

Patients' characteristics, prior treatment and transplantation procedure details

From January 1992 to January 2012, the 170 patients (90 men and 80 women) with refractory (n = 111) or relapsed (n = 59) HL underwent ASCT following a modified BEAM conditioning regimen.

In our study group 73.5% (125/170) of patients were treated according to the ABVD (adriamycin, bleomycin, vinblastine, dacarbazine) regimen as a frontline chemotherapy. The majority of patients (76%) received a cisplatin-based regimen, DHAP (dexamethasone, cytarabine, cisplatin) or ESHAP (etoposide, methylprednisolone, cytarabine, cisplatin), as second

Table 1. Patient characteristics and treatment details

Characteristics	Number (%)
Total number of patients	170 (100)
Age (years) at transplant	
median 31, range 17–61	
< 40 years	136 (80)
≥ 40 years	34 (20)
Gender	
male	90 (53)
female	80 (47)
Clinical stage	
II	32 (19)
III	54 (32)
IV	79 (46)
unknown	5 (3)
Constitutional symptoms	
absent	45 (26.5)
present	118 (69.5)
unknown	7 (4)
Induction chemotherapy	
ABVD	125 (73.5)
BEACOPP or escalated BEACOPP	16 (9.5)
MOPP or MOPP-type	15 (9)
other regimens	14 (8)
Second line chemotherapy	
ESHAP or DHAP	130 (76)
Escalated BEACOPP	11 (7)
ABVD	9 (5)
MOPP or MOPP-type	5 (3)
other regimens	15 (9)
Number of pre-transplant chemotherapy regimens	
2	102 (60)
> 2	59 (35)
unknown	9 (5)
Radiotherapy prior to ASCT	
yes	75 (44)
no	86 (51)
unknown	9 (5)
Disease status at ASCT	
CR	72 (42)
PR	81 (48)
less than PR	17 (10)

ASCT – autologous haematopoietic stem cell transplantation, CR – complete response, PR – partial response

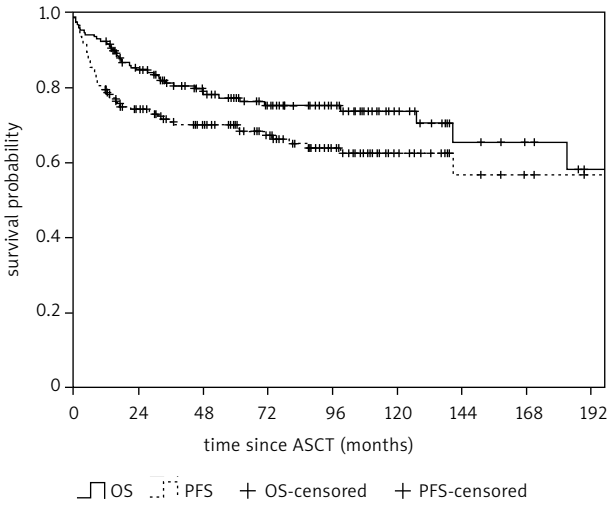

Fig. 1. Kaplan-Meier estimates of overall survival (OS) and progression-free survival (PFS) for all patients

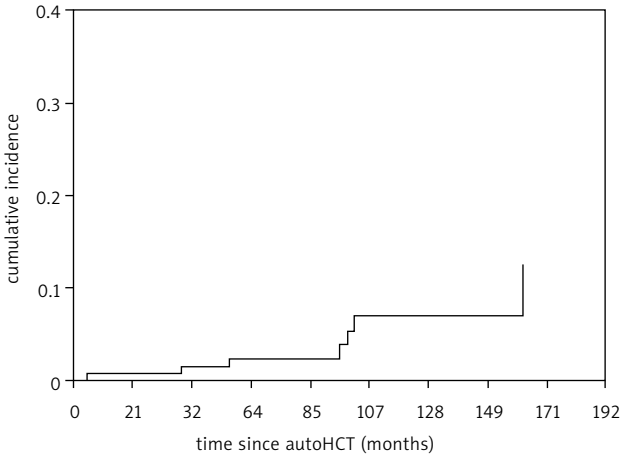

Fig. 2. Cumulative incidence of second malignancy development for all patients

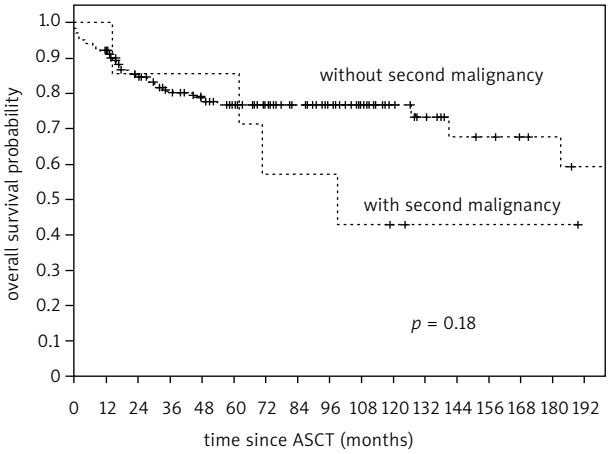

Fig. 3. Kaplan-Meier estimates of overall survival stratified by the post-transplant development of second malignancy

line chemotherapy. Twenty patients (12%) received MOPP or MOPP-type regimen as either an upfront or second line chemotherapy. Subsequent lines of salvage treatment included IVE (ifosfamide, etoposide, epirubicin), ICE (ifosfamide, carboplatin, etoposide), dexaBEAM (dexamethasone, carmustine, etoposide, cytarabine, melphalan) or gemcitabine-based regimens. The patients received a median of 2 (range 1–5) chemotherapy lines prior to ASCT. Seventy-five patients (44%) received radiotherapy prior to transplant. Finally, 72 patients were in CR and 81 in PR at ASCT, respectively. Seventeen patients did not respond to the salvage chemotherapy and they underwent ASCT in less than PR.

The mobilized peripheral blood in 63%, and bone marrow in 31% of all cases were used as the autologous graft source. Six percent of patients received both bone marrow and mobilized peripheral blood as a source of stem cells.

Patients' baseline characteristics with treatment details are presented in Table 1.

Survival data

The median follow-up time of surviving patients was 73 months (range 12–242 months). After 7 years following transplantation, estimated overall survival (OS) and progression-free survival (PFS) were 75.3% (95% CI: 67.6–81.6%) and 63.9% (95% CI: 55.6–71.5%), respectively (Fig. 1).

Forty-one (24%) patients in our study died. The cause of death in 24 patients was relapse/progression of Hodgkin lymphoma. Three other patients who relapsed after ASCT died from complications after subsequent allogeneic (n = 2) or autologous (n = 1) haematopoietic stem cell transplantation. Fourteen patients (8%) died from causes not related to lymphoma relapse/progression. Eight patients died within 3 months of ASCT from infection (n = 7) and primary graft failure (n = 1). Causes of late non-relapse mortality included hepatic veno-occlusive disease (n = 1), cardiac disease (n = 1), ischaemic stroke (n = 1), and second malignancy (n = 3). The 1-year and 5-year cumulative incidence of NRM was 4% (95% CI: 2–8%) and 5% (95% CI: 3–10%), respectively.

Second malignancy characteristics, incidence and risk factors

Second malignancy occurred in 7 of the 170 patients, including one myelodysplastic syndrome, two acute myeloid leukaemias, two aggressive non-Hodgkin lymphomas and two solid tumors. With regard to solid tumors, one bladder cancer was diagnosed 8 years after ASCT, and one thyroid cancer occurred 13.5 years after transplant. Second haematological malignancy developed at a median of 4.7 years (range, 0.4–8.4 years) from ASCT. The median time of occurrence any second malignancy was 8 years (range 0.4–13.5). The 10-year and 15-year cumulative incidence of developing a second malignancy were 7% (95% CI: 3–16%) and 13% (95% CI: 5–33%) (Fig. 2). Four of the seven patients with post-transplant diagnosed second neoplasm died. Three of them died from progression of second malignancy. One patient diagnosed with non-Hodgkin lymphoma and subsequently treated with chemotherapy died from cardiac disease. The median survival calculated from the diagnosis of the second malignancy was 32 months. The 10-year OS estimates for patients with post-transplant diagnosed second neoplasm and without second neoplasm calculated from ASCT were 43% and 73%, respectively (Fig. 3). Despite the observed trend for shorter

survival of patients with second malignancy, the survival difference did not reach statistical significance ($p = 0.18$).

The median age of the patients with second malignancy at transplant was 44 years (range 23–50). Of the seven patients developing second neoplasm, four patients received MOPP-type chemotherapy prior to ASCT, and two patients received both radiotherapy and chemotherapy. In univariate analysis, age at ASCT (< 40 vs. ≥ 40 years; $p = 0.001$) and pre-transplant MOPP-type chemotherapy (MOPP vs. other; $p = 0.056$) were the only significant factors for the development of the second malignancy. Both of those two factors remained statistically significant in multivariate analysis (Table 2).

Table 2. Cox regression analysis of cumulative incidence of second malignancy at 7 years after autologous haematopoietic stem cell transplantation

	Cumulative incidence % (95% CI)	HR (95% CI)	*P*
Age at transplant			
< 40 years	1 (1–5)	1.0	0.008
≥ 40 years	8 (2–31)	8.8 (1.8–43.6)	
Prior MOPP-type chemotherapy			
no	1 (0–8)	1.0	0.030
yes	10 (3–37)	5.6 (1.2–26.5)	

CI – confidence interval, HR – hazard ratio

Discussion

Despite satisfactory 7-year survival rates of 75% for patients with refractory and relapsed HL treated with HDT followed by ASCT reported in the present retrospective study, our results confirm that second malignancies are one of the major concerns in long-term HL survivors, since deaths of second malignancies were the leading cause of late non-relapse mortality in our analysis. Four of a total of six late deaths not related to HL relapse/progression were associated with second malignancy.

Our retrospective analysis reports 13% incidence of second malignancy at 15 years from ASCT. This incidence rate is comparable to those reported by other authors. The 5-year cumulative incidence (CI) of second malignancies reported by Sureda was 4.3% [2] and the 15-year CI reported by Forrest and Goodman were 8% and 15.3% [11, 17], respectively. We identified age at ASCT and pre-transplant MOPP-type therapy as risk factors for second malignancy development in univariate and multivariate model. Available published studies investigating different potential risk factors associated with pre-transplant therapy and transplant procedures have shown inconsistent results. Therapy-related factors and clinical features that were reported as predictors of second malignancy development after ASCT included patient age, the number of pre-transplant therapy lines, prior extended-field radiation therapy, prior treatment with rituximab, use of the second harvest peripheral blood haematopoietic stem cell for autograft, disease status at ASCT, and post-transplant radiotherapy [7, 11, 14, 15]. Among these factors, age is the best known risk factor for the development of second malignancies in long-term HL survivors. Our results confirm the strong and independent impact of this factor on the incidence of second neoplasm after ASCT. We have also shown that pre-transplant MOPP-type chemotherapy contribute to risk of second neoplasm after ASCT. There have been several reports documenting that patients with HL treated with conventional chemotherapy and exposed to DNA-breaking alkylating agents such as mechlorethamine and procarbazine in the MOPP regimen, and topoisomerase II inhibitors, such as etoposide are at increased long-term risk of developing t-AML/MDS [18–20]. Our results confirm that pre-transplant MOPP-type chemotherapy plays a critical role in development of post-transplant second malignancies. In contrast, we did not find that clinical stage of the disease, disease status at transplant, number of prior chemotherapy lines or radiotherapy significantly affected incidence of second neoplasms. In conclusion, the results of the present analysis support the previously published evidence that the introduction of the ABVD regimen substantially reduced the risk of second malignancy in HL survivors [21, 22] and indicate the major role of pre-transplant chemotherapy with alkylating agents in the post-transplant development of second malignancies after ASCT.

We believe that the characteristics of second malignancies diagnosed in patients with HL who were treated with ASCT, as well as the results of risk factors analysis reported in our study may be useful in optimization of second malignancy screening in these patients.

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The authors declare no conflict of interest.

References

1. Moskowitz CH, Nimer SD, Zelenetz AD, et al. A 2-step comprehensive high-dose chemoradiotherapy second-line program for relapsed and refractory Hodgkin disease: analysis by intent to treat and development of a prognostic model. Blood 2001; 97: 616-23.
2. Sureda A, Arranz R, Iriondo A, et al.; Grupo Español de Linfomas/Transplante Autólogo de Médula Osea Spanish Cooperative Group. Autologous stem-cell transplantation for Hodgkin's disease: results and prognostic factors in 494 patients from the Grupo Espanol de Linfomas/Transplante Autologo de Medula Osea Spanish Cooperative Group. J Clin Oncol 2001; 19: 1395-404.
3. Tucker MA, Coleman CN, Cox RS, Varghese A, Rosenberg SA. Risk of second cancers after treatment for Hodgkin's disease. N Engl J Med 1988; 318: 76-81.
4. Dores GM, Metayer C, Curtis RE, et al. Second malignant neoplasms among long-term survivors of Hodgkin's disease: a population-based evaluation over 25 years. J Clin Oncol 2002; 20: 3484-94.
5. Ng AK, Bernardo MV, Weller E, et al. Second malignancy after Hodgkin disease treated with radiation therapy with or without chemotherapy: long-term risks and risk factors. Blood 2002; 100: 1989-96.
6. Travis LB, Gospodarowicz M, Curtis RE, et al. Lung cancer following chemotherapy and radiotherapy for Hodgkin's disease. J Natl Cancer Inst 2002; 94: 182-92.
7. Milligan DW, Ruiz De Elvira MC, Kolb HJ, Goldstone AH, Meloni G, Rohatiner AZ, Colombat P, Schmitz N. Secondary leukaemia and myelodysplasia after autografting for lymphoma: results from the EBMT. EBMT Lymphoma and Late Effects Working Parties. European Group for Blood and Marrow Transplantation. Br J Haematol 1999; 106: 1020-6.
8. Darrington DL, Vose JM, Anderson JR, et al. Incidence and characterization of secondary myelodysplastic syndrome and acute myel-

ogenous leukemia following high-dose chemoradiotherapy and autologous stem-cell transplantation for lymphoid malignancies. J Clin Oncol 1994; 12: 2527-34.
9. André M, Henry-Amar M, Blaise D, et al. Treatment-related deaths and second cancer risk after autologous stem-cell transplantation for Hodgkin's disease. Blood 1998; 92: 1933-40.
10. Miller JS, Arthur DC, Litz CE, Neglia JP, Miller WJ, Weisdorf DJ. Myelodysplastic syndrome after autologous bone marrow transplantation: an additional late complication of curative cancer therapy. Blood 1994; 83: 3780-6.
11. Forrest DL, Hogge DE, Nevill TJ, et al. High-dose therapy and autologous hematopoietic stem-cell transplantation does not increase the risk of second neoplasms for patients with Hodgkin's lymphoma: a comparison of conventional therapy alone versus conventional therapy followed by autologous hematopoietic stem-cell transplantation. J Clin Oncol 2005; 23: 7994-8002.
12. Pedersen-Bjergaard J, Pedersen M, Myhre J, Geisler C. High risk of therapy-related leukemia after BEAM chemotherapy and autologous stem cell transplantation for previously treated lymphomas is mainly related to primary chemotherapy and not to the BEAM-transplantation procedure. Leukemia 1997; 11: 1654-60.
13. Harrison CN, Gregory W, Hudson GV, et al. High-dose BEAM chemotherapy with autologous haemopoietic stem cell transplantation for Hodgkin's disease is unlikely to be associated with a major increased risk of secondary MDS/AML. Br J Cancer 1999; 81: 476-83.
14. Kalaycio M, Rybicki L, Pohlman B, Sobecks R, Andresen S, Kuczkowski E, Bolwell B. Risk factors before autologous stem-cell transplantation for lymphoma predict for secondary myelodysplasia and acute myelogenous leukemia. J Clin Oncol 2006; 24: 3604-10.
15. Tarella C, Passera R, Magni M, et al. Risk factors for the development of secondary malignancy after high-dose chemotherapy and autograft, with or without rituximab: a 20-year retrospective follow-up study in patients with lymphoma. J Clin Oncol 2011; 29: 814-24.
16. Cheson BD, Horning SJ, Coiffier B, et al. Report of an international workshop to standardize response criteria for non-Hodgkin's lymphomas. NCI Sponsored International Working Group. J Clin Oncol 1999; 17: 1244.
17. Goodman KA, Riedel E, Serrano V, et al. Long-term effects of high-dose chemotherapy and radiation for relapsed and refractory Hodgkin's lymphoma. J Clin Oncol 2008; 26: 5240-47.
18. Brusamolino E, Anselmo AP, Klersy C, et al. The risk of acute leukemia in patients treated for Hodgkin's disease is significantly higher after combined modality programs than after chemotherapy alone and is correlated with the extent of radiotherapy and type and duration of chemotherapy: a case-control study. Haematologica 1998; 83: 812-23.
19. van Leeuwen FE, Chorus AM, van den Belt-Dusebout AW, et al. Leukemia risk following Hodgkin's disease: relation to cumulative dose of alkylating agents, treatment with teniposide combinations, number of episodes of chemotherapy, and bone marrow damage. J Clin Oncol 1994; 12: 1063-73.
20. Koontz MZ, Horning SJ, Balise R, Greenberg PL, Rosenberg SA, Hoppe RT, Advani RH. Risk of therapy-related secondary leukemia in Hodgkin lymphoma: the Stanford University experience over three generations of clinical trials. J Clin Oncol 2013; 31: 592-8.
21. Valagussa P, Santoro A, Fossati-Bellani F, Banfi A, Bonadonna G. Second acute leukemia and other malignancies following treatment for Hodgkin's disease. J Clin Oncol 1986; 4: 830-7.
22. Brusamolino E, Gotti M, Fiaccadori V. The Risk of Therapy-Related Myelodysplasia/Acute Myeloid Leukemia in Hodgkin Lymphoma has Substantially Decreased in the ABVD Era Abolishing Mechlorethamine and Procarbazine and Limiting Volumes and Doses of Radiotherapy. Mediterr J Hematol Infect Dis 2012; 4: e2012022.

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