Conditional survival and excess mortality after high-dose therapy with autologous stem cell transplantation for adult refractory or relapsed Hodgkin lymphoma in Norway

The prognosis for patients with Hodgkin lymphoma (HL) under 60-65 years is very good, with 5-year overall survival (OS) of 88%-95% with modern combined modality therapy, even in advanced stages.[1] However, in some patients, the disease will be refractory to or relapse soon after first-line therapy. For these patients, the prognosis is worse, and high-dose therapy with autologous stem cell transplantation (HDT-ASCT) has been shown to be the optimal salvage therapy for patients with chemo-sensitive disease and without major co-morbidities.[2-4] Patients with HL treated with HDT-ASCT are at increased risk of premature death compared to the general population,[5-7] mainly due to relapse of their primary disease, but also because of treatment-related complications and late effects.[5-9] Survival estimates are traditionally reported from time of HDT-ASCT.[3,4,10] However, the mortality rate decreases over time from treatment, as most relapses occur within the first few years. Hence, presenting survival estimates conditioned on being alive after different periods of time after HDT-ASCT is more applicable to patients who have already survived some time after therapy. This population-based study included the complete unselected cohort of adult Norwegian patients with HL treated with HDT-ASCT from 1987-2008. We found that 63% were alive after ten years. The cohort had 17-fold increased mortality compared to the general population. However, the conditional survival improved steadily for each additional year, and while still elevated beyond five years, there was no excess mortality after ten years.

VanderWalde et al. examined conditional relative survival after HDT-ASCT for all hematologic malignancies (n=2388) treated in a single institution from 1986-2006.[7] For HL (n=466), they reported a 5-year relative survival of 59%, with a standardized mortality ratio (SMR) of 29.4. Conditioned on having survived 1-10 years after HDT-ASCT, the 5-year survival probability increased to 67%-91%, and the mortality approached, but did not reach, that of the general population (SMR=2.7) after ten years. Others have reported estimates of 10-year OS for 2-year survivors after HDT-ASCT ranging from 66%-77%.[6,8,9] Earlier reports on relative survival for 2-year survivors ten years after HDT-ASCT are conflicting, with findings of no excess mortality,[5] but also up to 15-fold increased risk compared to the general population, even after ten years.[6] Nevertheless, conditional survival after HDT-ASCT for HL specifically has yet to be studied in a population-based national sample.

The aims of this population-based multi-center study were to investigate conditional OS and SMR in a national cohort of HL-patients treated with HDT-ASCT, and secondly to analyze cause of death and incidence of second malignancies.

All patients aged 18 years or over treated with HDT-

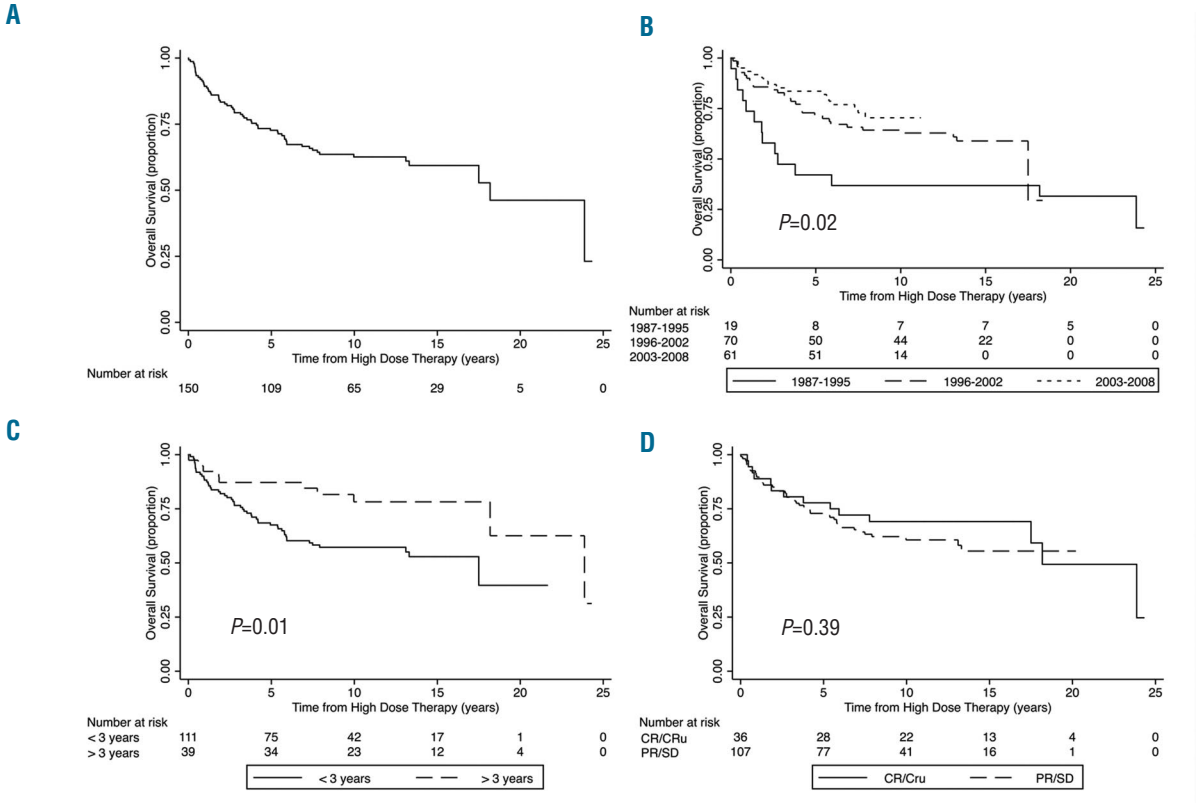

Figure 1. Kaplan-Meier curves showing overall survival after high-dose therapy with autologous stem cell transplantation (HDT-ASCT) for relapsed/refractory Hodgkin lymphoma for the entire cohort (n=150) (A), and by treatment period (B), time from diagnosis to HDT-ASCT (C) and disease status at HDT-ASCT (D). Observation time are calculated from time of HDT-ASCT to death or cut off at June 30th 2014. *P*-values are obtained from log rank tests. CR: complete remission; CRu: complete remission unconfirmed; PR: partial remission and SD: stable disease.

ASCT for HL in Norway in the period 1987-2008 were included. Clinical data collected from patients' charts were linked with national registries for information about date and cause of death (Statistics Norway) and data on second malignancies (the Cancer Registry of Norway) by using the 11-digit personal identification number given to all Norwegian citizens. The Cancer Registry of Norway contains information on all new cancers occurring in Norway

Table 1. Patients' characteristics and Cox regression analysis.

			Univariate Cox-regression			Multivariate Cox-regression		
	n	%	HR	95 % CI	P	HR	95 % CI	P
Age at diagnosis (years)								
Median (range)	31 (10-64)							
<25	50	33 %	0.53	0.25-1.15	0.11			
25-44	80	53 %	0.69	0.35-1.38	0.30			
≥45	20	14 %	Ref					
Age at HDT-ASCT (years)								
Median (range)	33 (18-65)							
<25	34	23 %	0.71	0.33-1.52	0.38	0.54	0.24-1.21	0.13
25-44	87	58 %	0.71	0.38-1.31	0.28	0.84	0.44-1.59	0.58
≥45	29	19 %	Ref			Ref		
Sex								
Male	87	58 %	1.03	0.61-1.73	0.92	1.15	0.64-2.05	0.64
Female	63	42 %	Ref			Ref		
Histological subtype								
Classical HL	131	87 %	1.39	0.34-5.73	0.65			
NLPLH	7	5 %	Ref					
Missing/not specified	12	8 %						
Ann Arbor stage at diagnosis								
I	14	9 %	0.93	0.36-2.38	0.87			
II	55	37 %	0.77	0.39-1.51	0.44			
III	45	30 %	0.88	0.45-1.74	0.72			
IV	35	23 %	Ref					
Missing	1	1 %						
High-dose regimen								
TBI + HD cyclophosphamide	16	11 %	1.76	1.03-4.37	0.13			
BEAM	134	89 %	Ref					
Primary chemotherapy								
ABVD-like	113	75 %	1.41	0.51-3.93	0.51			
MOPP-like	15	10 %	2.97	0.65-7.16	0.21			
CHOP-like	12	8 %	Ref					
Other incl. BEACOPP	5	3 %						
None/missing	5	3 %						
Radiotherapy								
Mediastinal	105	70 %	1.12	0.52-2.38	0.77			
Other	23	15 %	1.00	0.37-2.66	0.99			
None	22	15 %						
Treatment period								
1987-1995	19	13 %	2.88	1.35-6.15	0.01	8.60	3.24-22.83	<0.01
1996-2002	70	47 %	1.44	0.79-2.63	0.24	1.82	0.94-3.53	0.08
2003-2008	61	40 %	Ref			Ref		
Time from diagnosis to HDT-ASCT								
Median months (range)	21 (3-272)							
< 3 years	111	74 %	2.44	1.19-4.99	0.01	3.99	1.75-9.11	<0.01
≥ 3 years	39	26 %	Ref			Ref		
Treatment lines before HDT-ASCT								
2	123	82 %	1.89	0.86-4.18	0.12			
≥ 3	27	18 %	Ref					
Disease status at HDT-ASCT								
PR/SD	107	71 %	1.32	0.70-2.50	0.39	2.72	1.24-5.93	0.01
CR/CRu	36	24 %	Ref			Ref		
Missing	7	5 %						

Patients' characteristics and uni- and multivariate Cox-regression analyses of potential prognostic factors for overall survival after high-dose therapy with autologous stem cell transplantation (HDT-ASCT) for relapsed/refractory Hodgkin lymphoma (HL) (n=150). HR: Hazard Ratio; CI: confidence intervals; NLPHL: nodular lymphocyte predominant Hodgkin lymphoma; TBI: total body irradiation; BEAM: BCNU, etoposide, cytarabin and melphalan; ABVD-like: doxorubicin, bleomycin, vinblastine, dacarbazine and dexamethasone and similar regimens; MOPP-like: chlorambucil, vinblastine, procarbazine and prednisolone; CHOP-like: cyclophosphamide, doxorubicin, vincristine and prednisolone and similar; BEACOPP: bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine and prednisolone; CR: complete remission; CRu: complete remission unconfirmed; PR: partial remission (n=103); SD: stable disease (n=4).

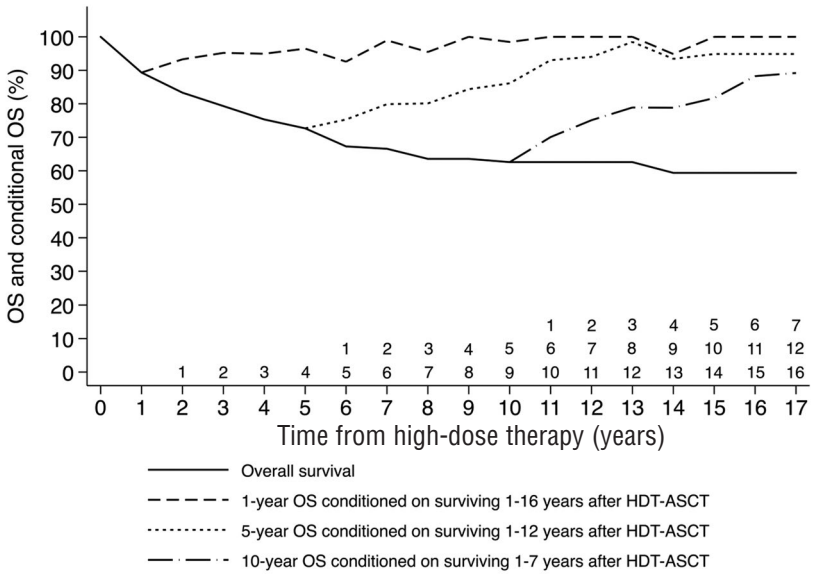

Figure 2. Conditional overall survival after high-dose therapy with autologous stem cell support (HDT-ASCT) for Hodgkin lymphoma (calculated using the life-table method). Curves are given if 10 or more patients were alive at start of follow-up year. HDT: high dose therapy; OS: overall survival.

based on compulsory reporting for all hospitals, laboratories and physicians (98.8% overall completeness).[11] Observation time for survival analyses was calculated from time of HDT-ASCT to death or cut off at 30th June 2014. Data on second cancer were available only until end of 2011. Details on statistical analysis, methods and treatment are given in the *Online Supplementary Appendix*.

In total, 150 patients were included in the cohort (Table 1). With a median observation time from HDT-ASCT of 8.9 years (range 0.02-24.3), the 5-, 10- and 15-year OS were 73% (95%CI: 65%-79%), 63% (95%CI: 54%-70%) and 59% (95%CI: 50%-62%), respectively (Figure 1). Treatment period 1987-1995 versus 2003-2008 (P<0.01), time from diagnosis to HDT-ASCT of less than three years (P<0.01) and not achieving complete remission (CR) before HDT-ASCT (P=0.01) were associated with poorer survival in multivariate analysis (Table 1). This is in line with previous findings among HL patients treated with HDT-ASCT[10,12] and for 2-year survivors of HDT-ASCT for all lymphomas.[6] In recent years, methods available for assessing treatment response after induction therapy have improved. Most of our patients were treated before positron emission tomography (PET) became widely available, and biopsies to decide if any residual lesions were biologically active were less frequently performed. Our categorization of disease status is, therefore, not fully comparable to current PET-based criteria. Age at HDT-ASCT has previously been described as a predictor for survival after HDT-ASCT,[5-7,10,12] but did not affect the outcomes in our cohort.

The 1-, 5- and 10-year conditional OS are shown in Figure 2. The conditional survival increased steadily for each additional year survived. One-year OS increased from 89% after HDT-ASCT to 95% conditioned on surviving the first two years after HDT-ASCT, and reached 100% conditioned on surviving the first eight years. The 5-year OS conditioned on having survived two, five and ten years after ASCT-HDT were 80%, 86% and 95%, respectively. The 10-year OS conditioned on having survived two and five years was 75% and 82%, respectively.

Standardized mortality ratio for the entire cohort was 16.9 (95%CI: 13.0-22.0). For patients having survived two, five and ten years after HDT-ASCT, the SMRs decreased to 9.5 (95%CI: 6.6-13.4), 4.8 (95%CI: 2.9-8.0) and 1.6 (95%CI: 0.6-4.3), respectively. There was, thus, no increased mortality after ten years compared to the general Norwegian population. While this is consistent with a previous study,[5] others have reported increased mortality even beyond ten years.[6,7]

Among deceased patients (n=60), the cause of death was HL in 36 cases (60% of deaths). Treatment-related mortality occurred in 3 cases, on days 7, 47 and 147. Second malignancies (n=9) was the most common non-relapse-related cause of death (non-Hodgkin lymphoma (n=2), leukemia/myelodysplastic syndrome (MDS) (n=5), solid cancers (n=2), confirming previous findings.[5-9] The remaining causes of death were heart disease (n=3), sudden death of unknown cause (n=4), other (n=4), and missing (n=1). The 10-year cumulative incidence of HL-deaths and deaths from other causes were 24.6 (95%CI: 18.3%-32.6%) and 16.0 (95%CI: 10.4%-24.1%), respectively (*Online Supplementary Figure S1*). A higher relapse-related death rate of 78% after HDT-ASCT has previously been reported.[7] However, since that study also included other hematologic malignancies with higher risk of relapse and poorer survival after HDT-ASCT than HL,[13] a higher proportion of relapse-related deaths would be expected compared to our cohort. Studies including only patients alive and in CR two years after HDT-ASCT, and thus excluding any relapses occurring in the first two years, report the proportion of relapse-related deaths to approximately 60%.[5,8,9]

With median observation time of seven years from HDT-ASCT (9 years for patients alive 31st December 2011), a second malignancy was diagnosed in 9 patients (6%) after a median five years (range 1-13): non-Hodgkin lymphoma (n=4), acute leukemia/MDS (n=3) and solid cancers (n=2). Three of these patients had received prior MOPP-like chemotherapy and 8 had received prior radiotherapy, including 3 with total body irradiation (TBI). A population-based Australian study (n=7765) reported a similar 10-year incidence of second malignancies after HDT-ASCT for any cancer (5%),[14] which is lower than reports on HL survivors specifically after HDT-ASCT.[8-10] Some of these studies, however, had a median follow-up time of over ten years from HDT-ASCT. We only have information from the Cancer Registry until the end of 2011, and it is likely that the number of cases of second malignancies will increase

with longer observation time. This is also indicated by the fact that, of the 8 deaths registered after 2011, 5 were caused by second malignancies [NHL (n=1), leukemia/MDS (n=2) and solid cancer (n=2)]. These were all diagnosed after the cut off for second malignancies, and could, therefore, not be included in the analysis on second malignancies.

The median observation time for survival analysis of nine years from HDT-ASCT and 11 years from diagnosis is also most likely to be too short to estimate the true risk of mortality due to late effects such as cardiovascular disease and second malignancies, especially for patients who have received RT.[15] To detect any such increased mortality that might occur 20 years or longer after diagnosis or HDT-ASCT, the cohort will be observed further. Nevertheless, the relatively low risk of death from causes other than HL is encouraging in this heavily treated cohort, but may be expected due to less toxic treatment during later decades and improved treatment outcomes both from cancers and cardiovascular diseases. In addition, increased awareness of treatment-related morbidity might have led to earlier detection.

While conditional survival after HDT-ASCT for all hematologic malignancies, including HL, has been investigated in a large single center study,[7] to our knowledge this is the first report on conditional survival and SMR in a national cohort of patients with HL specifically. Despite a relatively small sample size, the major strength of our study is the national population-based design including all patients with HL treated with HDT-ASCT in a homogenous population, with well-characterized data from high-quality national registries combined with detailed treatment data from each hospital.

In conclusion, the majority of patients with relapsed/refractory HL are cured after HDT-ASCT. The expected survival rapidly improves after having survived the first few years. Although survivors are at increased risk of premature death beyond five years after HDT-ASCT, the mortality eventually reaches that of the general population after ten years.

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