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

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Treatment

HDT-ASCT has been a treatment option for relapsed/refractory HL in Norway since 1987.[1,2] In general, only patients without major co-morbidities, and who responded to induction chemotherapy (i.e. at least PR) were considered eligible for transplantation. Patients with progressive disease were therefore excluded, but the cohort still included 4 patients with SD. Excluding these from the analyses did not alter the results (data not shown). In the period 1987-1995 HDT-ASCT was given at the Norwegian Radium Hospital (Oslo) only, whereas from 1996 the treatment has been given at the five Norwegian university hospitals: Oslo University Hospital (formerly Norwegian Radium Hospital and Ullevål University Hospital), Haukeland University Hospital (Bergen), St. Olav University Hospital (Trondheim) and the University Hospital of North Norway (Tromsø). Until 1996 the high dose regimen consisted of total body irradiation (TBI) and high dose cyclophosphamide, and from 1996 of chemotherapy only (BEAM: carmustine, etoposide, cytarabine and melphalan). From 1994, the stem cell source changed from bone marrow to peripheral blood progenitor cells.

Only 19 patients with HL (13%) were treated with HDT-ASCT in the first time period (1987-1995). Of these 78% were male, compared to 55% in the period 1996-2008 (p=0.05). There was no statistically significant difference in the age distribution between the two time periods.

Patient identification

The patients were identified through treatment records and registries at each hospital, and cross-checked against reports from HDT-ASCT meetings, the clinical quality register for lymphomas at Oslo University Hospital and radiotherapy registers.

Statistics

OS was calculated by Kaplan-Meier method with p-values obtained from log-rank tests. Cox proportional hazard regression models (univariate and multivariate) were fitted to evaluate the effect of factors potentially influencing OS. The assumption of proportional hazards was verified graphically and checked using test of proportional hazard assumption. Conditional survival was calculated using the life-table method, and 1-, 5- and 10-year OS were computed conditioned upon having survived each additional year from HDT-ASCT.

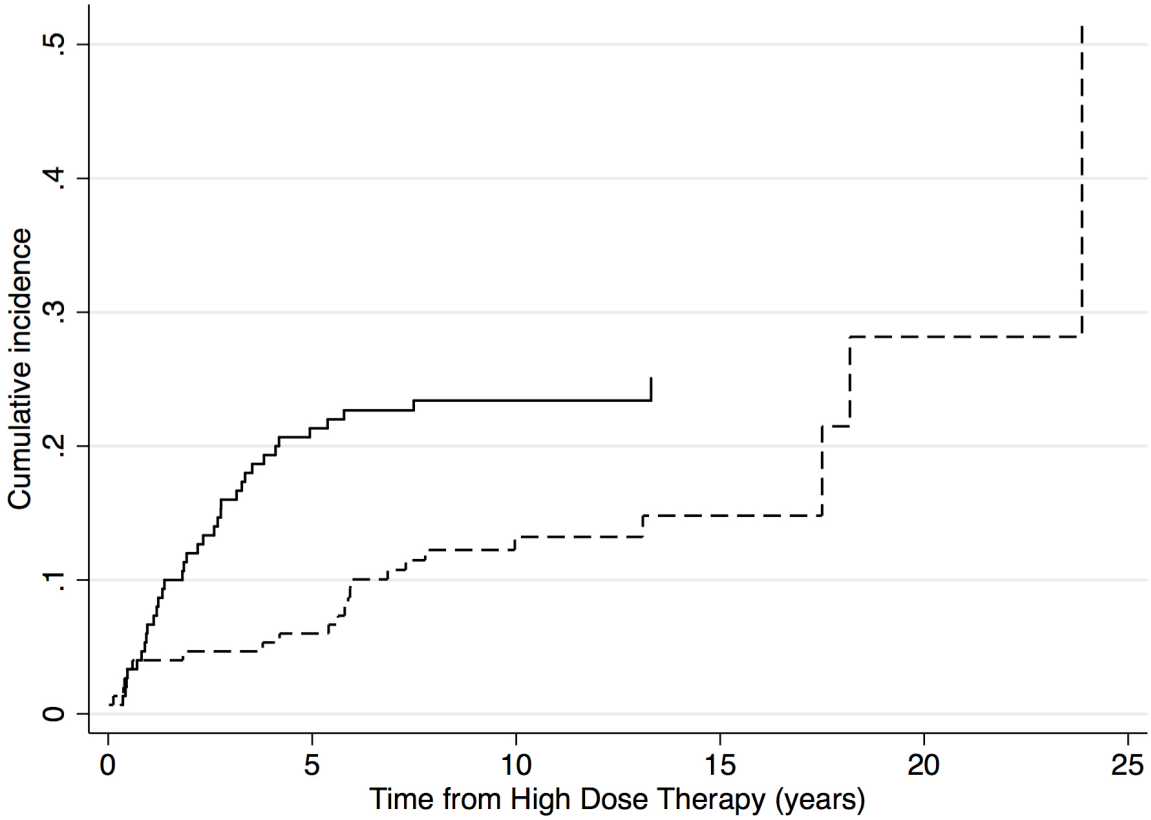
Standardized mortality ratios (SMRs) were calculated as the ratio of observed to expected mortality. Death statistics for the Norwegian population were extracted from Statistics Norway. Reference rates were computed for 3-year calendar periods and 5-year age-

groups for each sex. Expected mortality rates were computed by applying the period-, sex- and age-specific mortality to the observed person-years in the cohort.

A p-value ≤0.05 (two-sided) was considered statistically significant. Analyses were performed using SPSS 18 and Stata 13.[3,4]

Definitions and measurements

Time periods were divided in three based on time of HDT-ASCT: 1987-1995, 1996-2002 and 2003-2008. Time from HL-diagnosis to HDT-ASCT was dichotomized: more or less than 3 years. Disease status at HDT-ASCT was defined according to standard treatment response criteria after induction chemotherapy: complete remission (CR), complete remission unconfirmed (CRu), partial response (PR) and stable disease (SD).[5] Treatment related mortality was defined as death from a direct complication to HDT-ASCT in tumor free patients, determined from patient charts. Otherwise, the cause of death registered in Statistics Norway was used as cause of death. Second malignancy (SPM) was defined as any new malignancy other than HL-relapse (non-melanoma skin cancer excluded) diagnosed after HDT-ASCT, until cut-off at December 31th 2011.



Supplementary figure S1: Cumulative incidence of deaths caused by Hodgkin lymphoma (solid line) after high dose therapy with autologous stem cell support (HDT-ASCT) for relapsed/refractory Hodgkin lymphoma, with deaths of other causes (dashed line) as competing event.

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