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Hospitalizations in Long-term Survivors of Childhood AML Treated with Allogeneic HCT - an Adult Life after Childhood Cancer in Scandinavia (ALiCCS) Study

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To the Editor:

Allogeneic hematopoietic cell transplantation (allo-HCT) in first complete remission (CR1) increases the disease-free survival in childhood acute myeloid leukemia (AML) but it does not seem to have significant impact on the overall survival [1] and the risk for severe late morbidity may be increased. Considering that the indications for allo-HCT in CR1 are under continuous discussion and revision, the long-term consequences for survivors following different treatment strategies deserve a more thorough evaluation.

Whether the long-term consequences differ after receiving allo-HCT in first or second complete remission (CR2) is largely unknown. We aimed to reveal toxicity after allo-HCT in childhood AML survivors by comparing hospitalization rates in transplanted survivors and in the background population and used a similar approach for non-transplanted childhood AML survivors.

In this large population-based register study, first time hospitalization rates in 5-year survivors of childhood AML treated either with allo-HCT or without allo-HCT with chemotherapy only were assessed by using high-quality national hospital registries and a population comparison cohort. Hospitalization rates in long-term survivors were analyzed with respect to conditioning regimen (total body irradiation [TBI]/no TBI) and disease status at transplant (CR1/CR2). To our knowledge, this is the largest population-based study on disease-specific hospitalization rates in long-term survivors of childhood AML treated with allo-HCT.

Treatment data from the NOPHO-AML registry was used in combination with data on somatic diseases from comprehensive nationwide and population-based health registries in the 'Adult Life after Childhood Cancer in Scandinavia' study (AliCCS; http://www.aliccs.org). The nationwide hospital registries contain information on virtually all non-psychiatric hospital

admissions in the four participating countries. The design and characteristics of the ALiCCS study have been described previously [2]. The population-based NOPHO-AML registry includes clinical data on all patients diagnosed with AML in the participating countries who have been treated according to the common NOPHO-AML protocols.

All 5-year survivors of childhood AML diagnosed before 18 years of age from July 1, 1984 to December 31, 2005 and who received treatment according to the NOPHO-AML protocols 84, 88, 93, or 2004 [3,4] in Denmark, Finland, Iceland or Sweden were identified in the NOPHO-AML registry. A randomly sampled comparison cohort of individuals of the same sex, age, and country was selected from the population registries. The final AML cohort constituted of 196 5-year survivors identified in the NOPHO-AML registry and 152,231 population comparisons. Survivors and comparisons were followed in the national hospital registers for a primary discharge diagnosis within 120 disease-specific categories classified according to ICD-8, ICD-9 or ICD-10.

Follow-up for first time hospitalizations among the AML survivors started 5 years from AML diagnosis and at least one year from allo-HCT, if performed, and for the population controls, on the corresponding date, or the start of the hospital registries, whichever occurred first. The follow-up ended on the date of death, the date of emigration, or the end of study in each country: 2008 (Iceland), 2009 (Finland and Sweden) and 2010 (Denmark), whichever occurred first.

First-time hospital admissions for a given disease category among the AML survivors were compared with hospitalization rates in the population comparison cohort. Standardized hospitalization rate ratios (RRs; observed-to-expected numbers of hospitalizations) with 95% confidence intervals (CI) were computed using Fieller's theorem assuming that the observed numbers of first hospital contacts followed a Poisson distribution. Absolute excess risks

(AERs) of survivors first hospital contact were calculated for each disease category and main diagnostic group by subtracting the expected number of first hospitalization rates from the observed hospitalization rates per 100,000 person-years of follow-up with corresponding 95% confidence interval (CI), in other words, the additional risk of hospitalization exceeding the background level.

Out of the 196 childhood AML survivors, 97 (49%) had received allo-HCT and 99 (51%) were treated with chemotherapy only (CT). The median follow-up time from AML diagnosis was 12 years (range 5–28) among allo-HCT recipients and 11 years (range 5–28) among CT survivors. Fifty-nine (61%) of the allo-HCT survivors had received TBI and 37 (38%) had received allo-HCT in CR2. Almost one third of the 196 AML survivors had been hospitalized at least once for a somatic disease. With 56 observed hospitalizations instead of the expected 27, the AML survivors had an overall two-fold RR 2.1 (95% CI, 1.6–2.7) and an overall AER of 2.3 (95% CI, 1.2–35) per 100 person-years, translating into two excess hospital admissions for every 10 survivors during 10 years of follow-up.

Survivors treated with allo-HCT had a significantly increased risk for hospitalizations with an overall 2.8-fold RR and an overall AER of 3.8 per 100 person-years with 35 out of 97 (36%) survivors having been hospitalized at least once. The overall risk for hospitalizations for CT survivors was not significantly increased when compared with population comparisons (RR 1.4 [95% CI, 0.9–2.2]). Hence, it was mainly survivors who had received allo-HCT as part of their treatment who contributed to the increased risk of hospitalizations (Figure 1A).

Allo-HCT survivors had significantly increased hospitalization rates in all survivor subgroups but the survivors transplanted in CR2 had the highest risk for any hospitalization: 18 out of 37 survivors (49%) had been hospitalized at least once (RR 6.3; 95% CI, 4.0–10) whereas the

risk was lower after allo-HCT in CR1 with 17 (28%) having been hospitalized (RR 1.8; 95% CI, 1.1–2.9).

Among the 60 allo-HCT survivors transplanted in CR1, increased risks were observed for endocrine (RR 14; 95% CI, 6.8–27), cardiovascular (RR 9.8; 95% CI, 4.1–24), and respiratory disease (RR 2.4; 95% CI 1.1–5.0), as well as for diseases affecting the gastrointestinal tract and digestive organs (RR 2.7; 95% CI, 1.3–5.6) (Figure 1B). Survivors transplanted in CR2 had an increased risk for hospital admissions due to infectious disease (RR 9.1; 95% CI, 3.4–24), diseases involving the nervous system (RR 9.9; 95% CI 4.1–24), bone, joints and soft tissue (RR 6.1; 95% CI, 2.3–16), respiratory organs (RR 4.5; 95% CI 2.0–10), the gastrointestinal tract and the digestive system (RR 7.3; 95% CI 3.6–15), and endocrine disease (RR 9.5; 95% CI 3.1–29) (Figure 1B).

Twenty-seven (46%) of the allo-HCT survivors conditioned with TBI had been hospitalized yielding a 3-fold risk (RR; 95% CI, 3.0, 2.1–4.1) for ever being hospitalized. Among those who had received allo-HCT without TBI, the corresponding number was lower, 8 (21%), but nevertheless significantly increased (RR 2.4; 95% CI, 1.2–4.8).

Allo-HCT survivors with TBI-based conditioning was associated with the highest risk for hospitalizations due to endocrine disease (RR 14; 95% CI, 8–27) (Figure 1C). The allo-HCT survivors without TBI had an increased risk for being hospitalized for cardiovascular disease (RR 18; 95% CI, 5.7–55), respiratory disease (RR 5.5; 95% CI, 2.3–13), diseases involving the gastrointestinal tract and digestive system (RR 4.1; 95% CI, 1.6–11), and diseases involving the nervous system (RR 4.7; 95% CI, 1.8–19) (Figure 1C).

Allo-HCT was associated with an increased overall risk for hospitalizations in 5-year survivors of childhood AML irrespective of conditioning regimen when compared with the background population. Although allo-HCT is the treatment with the strongest anti-leukemic

effect in childhood AML, allo-HCT is associated with severe long-term effects [5]. Due to the diversity of AML and small patient numbers, no uniform risk group definition has been established and protocols use different risk stratification algorithms to identify patients at high risk of relapse and no consensus exists on indications for allo-HCT in CR1 [1]. Waiting with allo-HCT until after relapse may spare many patients the late toxicities associated with allo-HCT, but in case of relapse only approximately 40% can be salvaged [6] and the risk for late morbidities may be increased.

The strengths of our study include the large cohort of AML patients treated according to common Nordic treatment protocols, access to unique resources, including the large population-based cohort of Nordic childhood cancer survivors in ALiCCS with matched population comparisons, and data that does not rely on self-reports and is hence free of recall bias. Our cohort is still young, with the oldest survivors being in their late thirties, which may have contributed to the low observed numbers of hospitalizations in our cohort. Conditions not requiring inpatient care may have been missed as data from outpatient clinics is not included in our study. However, this is not expected to affect the estimated relative risks.

Our results mainly reflect the cost of long-term survival and in many cases, long-term survival would not have been achieved without an allo-HCT. TBI and relapse were risk factors for higher hospitalization rates after allo-HCT, but even allo-HCT without TBI was associated with significantly increased hospitalization rates. Allo-HCT is the treatment of choice for relapsed AML, and a carefully selected high-risk group of AML, in whom the increase in survival outweighs the negative long-term effects of HCT. Our findings underline the necessity of long-term follow-up after allo-HCT that facilitates early detection of late morbidities and targeted life-style and medical interventions regardless of which conditioning-regimen is used.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The registry data that support the findings of this study are available from the following authorities: Denmark: Research services at Sundhedsdatastyrelsen (forskerservice@sundhedsdata.dk); Finland: TLH National Institute for Health and Welfare in Finland (Service telephone for research authorization applications: tel. +358 29 524 6677); Iceland: The Icelandic Cancer Registry (skra@krabb.is); The Directorate of Health (mottaka@landlaeknir.is); Statistics Iceland www.statice.is/services (rannsoknathjonusta@hagstofa.is); and Sweden: The National Board of Health and Welfare (registerservice@socialstyrelsen.se). National legal regulations apply to the availability of these data. For further information regarding the ALiCCS study data, please contact Professor Jeanette Falck Winther, MD, DMSc (jeanette@cancer.dk).

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FIGURE LEGENDS:

Figure 1

Forest plot for first-time standardized hospitalization rate ratios (RRs) by twelve main diagnostic groups in 5-year survivors of childhood AML:

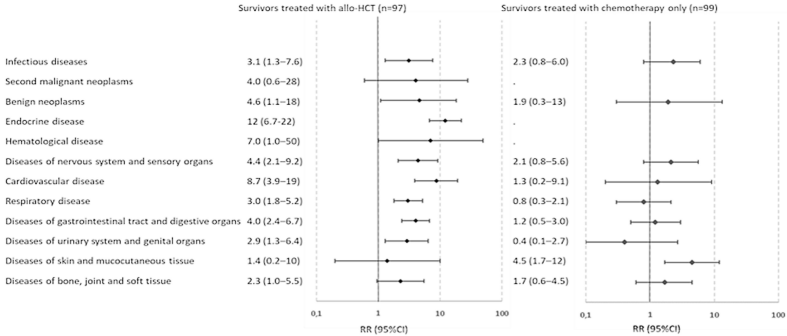
A. treated either with allo-HCT (n=97) or with chemotherapy only (n=99),

B. who received allo-HCT either in CR1 (n=60) or in CR2 (n=37),

C. who received allo-HCT either with total body irradiation (TBI) (n=59) or without TBI (n=38).

Abbreviations: AML, acute myeloid leukemia; allo-HCT, allogeneic hematopoietic cell transplantation.

A



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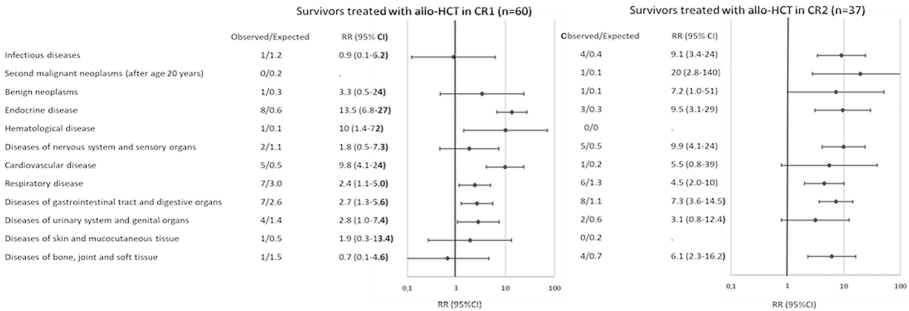

C