Second primary non-myeloid malignancies following intensive treatment for adult acute myeloid leukaemia: a Danish population-based cohort study

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Summary

Background Second primary malignancies (SPMs) are a well-known, long-term complication of antineoplastic treatment. This nationwide cohort study examined the risk of non-myeloid SPMs in survivors of adult acute myeloid leukaemia (AML) treated with intensive chemotherapy and, in some cases, allogeneic stem cell transplantation (alloSCT), compared to a matched general population.

Methods Patients with incident AML between 2000 and 2018, alive and aged 18–70 years two years after start of intensive chemotherapy, were included and matched 1:10 to comparators from the general Danish population on sex, age, and the Nordic Multimorbidity Index. Exclusion criteria were non-myeloid SPMs for both AML survivors and comparators.

Findings A total of 750 AML survivors and 7500 comparators were followed for a median of 10.6 years. The hazard ratio (HR) of non-myeloid SPMs was 1.55 (95% confidence interval [CI] 1.27–1.89) for AML survivors compared to comparators, driven by non-melanoma skin cancer (HR 2.52, 95% CI 1.90–3.35), not of solid cancer (HR 1.14, 95% CI 0.87–1.49). The 10-year cumulative incidences of any non-myeloid SPM were 13.5% (95% CI 10.6–16.5%) in AML survivors and 11.9% (95% CI 11.1–12.8%) in matched comparators. Additionally, AML survivors consolidated with alloSCT had a higher hazard rate of non-myeloid SPMs compared to non-transplanted AML survivors (adjusted HR 1.50, 95% CI 1.00–2.26).

Interpretation The increased rate of non-myeloid SPMs observed in this population-based cohort study of AML survivors was almost entirely driven by non-melanoma skin cancer and is thus outweighed by the importance of intensive chemotherapy.

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Keywords: Acute myeloid leukaemia; Second primary non-myeloid malignancies; Long-term toxicities; Intensive chemotherapy; Allogeneic stem-cell transplantation

Introduction

Second primary malignancies (SPMs) are a well-established and feared late complication of antineoplastic treatment.[1,2] Currently, high-dose antineoplastic combination treatment is needed to overcome and secure long-term survival for acute myeloid leukaemia (AML), an aggressive, haematological malignancy. AML is characterized by clonal proliferation of malignant haematopoietic stem and progenitor cells, thereby disrupting the healthy bone marrow.[3] Treatment of AML

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Research in context

Evidence before this study

A systematic search of PubMed and Embase was performed on September 17, 2023, and again on June 21, 2024, to identify previously published studies investigating the incidence of second primary malignancies (SPMs) in patients with acute myeloid leukaemia (AML) treated with intensive induction chemotherapy (and allogeneic stem cell transplantation [alloSCT]). For the search, the combination of the following MESH/Emtree terms and free-text were used to identify the population ("acute myeloid leukaemia" OR "adult acute myeloid leukaemia") AND the exposure ("chemotherapy" OR "induction chemotherapy" OR "antineoplastic agents" OR "allogeneic stem cell/bone marrow transplantation" OR "haematopoietic stem cell transplantation") AND the outcome ("second primary malignancy/cancer/neoplasm" OR "secondary malignancy/cancer/neoplasm" OR "therapy/treatment related malignancy/cancer/neoplasm" OR "long-term adverse effects" OR "chemotherapy/transplantation late effects"). Relevant synonyms and abbreviations were also used. The search results consisted of 3880 studies, which primarily investigated the occurrence of SPMs in survivors of childhood leukemia or in adult patients with lymphoma, solid cancers, or hematological malignancies other than AML. Some of the studies were included as background information and as material for discussion and comparison, since we identified only a few studies investigating the risk of SPMs in adult patients with AML. Several studies explored the incidence of acute leukemia or other haematological malignancies secondary to cancer therapy and were excluded. Only articles published in English were included.

Added value of this study

With this Danish nationwide study, we present a detailed analysis of the risk of developing SPM subsequent to treatment with intensive chemotherapy in survivors of AML, and the added effect of consolidation with alloSCT, including the effect of consolidation intensity. To study this, we utilized the validated and high-quality Danish nationwide registries to identify the study participants, covariates, and outcome, which enabled a long and complete follow-up of 10.6 years. Ten leukemia-free comparators from the general Danish population were randomly selected to compare the association between AML treatment and the development of non-myeloid SPMs to the risk in a matched background population. We estimated hazard ratios (HRs), cumulative incidences with death as a competing event, and incidence rates of different non-myeloid SPM subtypes.

Implications of all the available evidence

Our study demonstrates increased hazard rates and cumulative incidences of any non-myeloid SPM in survivors of AML, which was primarily driven by a higher risk of non-melanoma skin cancer (NMSC). However, the cumulative incidence of non-myeloid SPMs, including solid cancers, increased continuously throughout the entire follow-up period of more than a decade, calling for an even longer follow-up period in future studies to assess the true long-term effect. Furthermore, our study indicates that consolidation with alloSCT has an added effect on the risk of non-myeloid SPMs, particularly NMSCs, although these findings were not statistically significant.

consists of intensive combination chemotherapy and, for selected patients, consolidation with allogeneic stem cell transplantation (alloSCT), which includes whole-body radiation therapy and myeloablative chemotherapy.[4] Radiotherapy and chemotherapy are known to be carcinogenic,[1,2] but the etiology of SPMs is multifactorial and complex. Etiological factors may include patient's age, environmental exposures, lifestyle (e.g., tobacco and alcohol use), genetic susceptibility, and therapy-related factors.[1,2,5,6] The occurrence of SPMs is well-described in long-term survivors of lymphoma, breast cancer, bladder cancer, colon cancer, and childhood leukaemia, among others.[1,2,5,7–10] As an increasing number of patients with AML become long-term survivors, the magnitude of this late effect is only becoming more apparent, but the risk of SPMs in adult survivors of AML is not yet well-described.

In this nationwide cohort study of AML survivors, alive two years after initiation of intensive induction chemotherapy, we first aimed to assess the hazard rate, cumulative incidence, and incidence rates of non-myeloid SPMs following intensive therapy compared to that of a matched general population. Secondly, we aimed to estimate if consolidation with alloSCT (including both radiation and chemotherapy) resulted in an additional risk of developing non-myeloid SPMs compared to patients with AML consolidated with chemotherapy only.

Methods

Study population and data sources

Patients diagnosed with AML were identified using the Danish National Acute Leukaemia Registry.[3,11] Patients fulfilling the following criteria were eligible for this study: (a) diagnosed with AML (excluding acute promyelocytic leukaemia), (b) first-line treatment with intensive chemotherapy between January 1, 2000, and December 31, 2018, (c) aged 18–70 years, alive, and living in Denmark two years after initiation of intensive

induction chemotherapy (index date), and (d) no non-myeloid malignancies prior to the index date (Fig. 1). The two-year delay from treatment initiation to start of follow-up was implemented to include AML survivors, exclude concurrent malignancies diagnosed near the time of AML diagnosis, and reduce the impact of mortality on the results. Treatment information was retrieved from the Danish National Acute Leukaemia Registry and categorized into four groups: 1) DA-like (treatment regimens consisting of daunorubicin or an anthracycline-related compound in combination with cytarabine), 2) DA-like + add-on (DA-regimens with a supplementary cytotoxic agent, tyrosine-kinase inhibitor or anti-CD33 antibody-drug-conjugate), 3) FLAG-Ida (treatment with fludarabine, high dose cytarabine, idarubicin, and granulocyte-colony stimulation factor), and 4) Other (various other intensive treatment regimens) (Table S1). Information on intensive induction regimens is reported for descriptive purposes only. Information on alloSCT was retrieved from the Danish National Acute Leukaemia Registry and verified using the Danish National Patient Registry.[12,13]

A comparator cohort, free of AML, was created from the Danish general population using the Danish Civil Registration System.[14] Ten random comparators from the general population were included on the index date for each index patient using exact matching on sex, birth year, and comorbidities using the Nordic Multimorbidity Index (NMI),[15] calculated 180 days prior to the AML diagnosis. The NMI is a multimorbidity measure, developed on the general Danish population during the follow-up period 2013–2018 to predict 5-year mortality based on several predictors including specific diagnoses and drug prescriptions, originally published in 2022.[15] The NMI were used to decrease the risk of confounding. Comparators had to be alive, living in Denmark, and without prior AML and non-myeloid malignancies at the index date (Fig. 1). Data on previous malignancies for patients and comparators were obtained from the Danish Cancer Registry[16] (detailed information on the data sources can be found in the Supplementary).

Outcome and definitions

The primary outcome was incident non-myeloid SPMs, defined as the first primary non-myeloid malignancy after the index date of AML survivors or the first-ever non-myeloid malignancy after the index date in matched comparators. SPMs were identified in the Danish Cancer Registry using the International Classification of Diseases, version 10 (ICD-10 codes) (Table S2). Malignancies were stratified into solid cancers, non-myeloid haematological malignancies, and non-melanoma skin cancer (NMSC). Selected solid cancers were further stratified into breast cancer, respiratory cancer, and gastrointestinal cancer, thus covering the three most frequent occurring forms of solid cancers in Denmark (i.e., female breast cancer, lung cancer, and colon cancer). Classification of NMSC into basal cell carcinoma (BCC), squamous cell carcinoma (SCC) and otherwise unspecified was made using the Danish Pathology Register[17] (see Supplementary).

Statistical analysis

Baseline characteristics for AML survivors and matched comparators were presented with continuous variables reported as medians and interquartile ranges (IQRs), and categorical variables as frequencies and percentages. The primary endpoint was the first non-myeloid

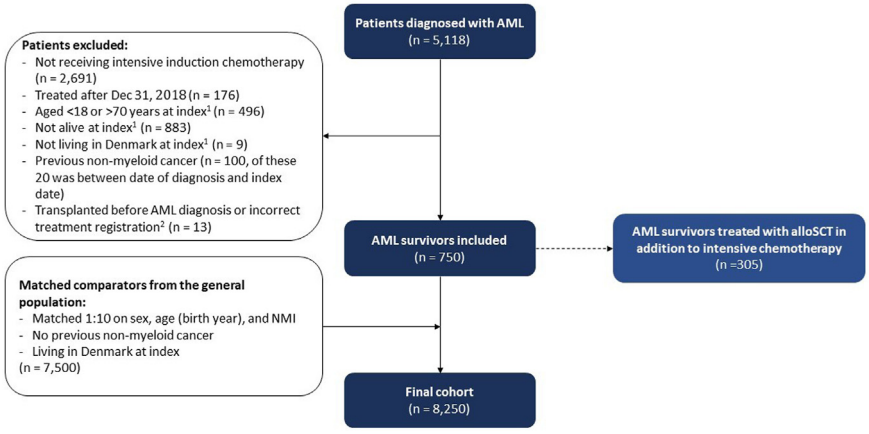

***Fig. 1:* CONSORT diagram of the study population**. Inclusion of patients with AML, who were alive two years after receiving intensive induction chemotherapy, and matched comparators from the general population, and further stratification of AML survivors additionally treated with alloSCT before index.[1] At index' is equivalent to the time of inclusion two years after the date of initiation of induction chemotherapy. [2]Includes patients receiving alloSCT for previous haematological malignancies and patients not registered with a valid type of intensive treatment for AML. Abbreviations: AlloSCT, allogeneic stem cell transplantation; AML, acute myeloid leukaemia; NMI, nordic multimorbidity index.

SPM; with follow-up defined from two years after initiation of intensive induction chemotherapy (index date) for both AML survivors and matched comparators until the first non-myeloid SPM, death from any cause, emigration, or December 31, 2021, whichever came first. For the analyses with endpoints defined as a non-myeloid SPM from a specific subgroup of cancers (Table S2), the occurrence of a prior non-myeloid SPM from another subgroup was not considered an event and was not accounted for. Median follow-up time was calculated as the median of all the potential follow-up times for all participants, defined as time from index date to end of study.

Cause-specific hazard ratios (HRs) including 95% confidence intervals (95% CIs) for first non-myeloid SPMs were computed using Cox proportional hazards regression, with matched comparators as reference. Cumulative incidences of first non-myeloid SPMs were calculated, with death as a competing event (including both non-relapse and relapse mortality), using the Aalen-Johanson estimator, including pointwise 95% CIs. Differences in the cumulative incidences over the entire follow-up period were tested using Gray's test. Incidence rates (IRs) of first non-myeloid SPMs per 1000 person-years and incidence rate ratios (IRRs) between AML survivors and matched comparators were estimated using Poisson regression. In the secondary analysis, the effect of alloSCT and conditioning intensity (myeloablative conditioning [MAC] vs reduced-intensity conditioning [RIC]) were assessed using cause-specific hazard ratios computed by Cox proportional hazards regression with adjustments for sex, age, and NMI, and the Aalen-Johansen estimator for cumulative incidences (see Supplementary for further details on statistical analyses).

p-values ≤0.05 were considered statistically significant in all analyses. Results from subgroup analyses with few SPM events are not shown due to models not converging. The statistical analyses were conducted in SAS version 9.4 and R version 4.2.2. This study is in accordance with the General Data Protection Regulation and is a part of North Denmark Region's record of processing activities (F2023-111) and is approved by the Danish Clinical Registries (ALD-2023-08-01).

Role of the funding source

Svend Andersen, Heinrich Kopps, and Karen Elise Jensen's Foundation had no **role** in study design, data collection, data analysis, data interpretation or preparation of the manuscript.

Results

Population characteristics and second primary malignancies

A total of 750 AML survivors, alive two years after first line intensive induction chemotherapy, were included and matched to 7500 comparators (Table 1). The median age was 54 years (IQR 43–62 years) and 52.5% were male. Initial induction therapy of patients with AML included DA-like (57.2%), DA-like + add-on (21.1%), FLAG-Ida (14.4%) or Other (7.3%) (Table S1, Figure S1). A total of 305 (40.7%) patients were consolidated with alloSCT; 136 (44.6%) with MAC and 169 (55.4%) with RIC. The median follow-up time was 10.6 years (IQR 5.8–15.6 years). The five-year overall survival was 71.6% (95% CI 68.3–75.0%) for AML survivors and 97.0% (95% CI 96.6–97.4%) for comparators (Figure S2).

Among the 750 AML survivors, 107 (14.3%) developed at least one non-myeloid SPM during the follow-up period and 15 (2.0%) patients developed multiple SPMs. Of all AML survivors, 7.5% developed solid cancers, <0.7% non-myeloid haematological SPMs, and 7.5% NMSCs (76.8% BCC and 23.2% SCCs including not

	AML survivors (n = 750)	Matched comparators (n = 7500)
Age at index date, median (IQR)	54 (43–62)	54 (43–62)
Sex, n (%)		
Female	356 (47.5%)	3560 (47.5%)
Male	394 (52.5%)	3940 (52.5%)
Nordic Multimorbidity Index[a], n (%)		
≤0	493 (65.7%)	4930 (65.7%)
1–7	205 (27.3%)	2050 (27.3%)
>7	52 (6.9%)	520 (6.9%)
Performance status[b], n (%)		
0-1/missing[c]	680 (90.7%)	–
2–4	70 (9.3%)	–
Risk stratification[d], n (%)		
Favorable	95 (19.6%)	–
Intermediate	337 (69.5%)	–
Adverse	53 (10.9%)	–
Missing/deficient metaphases	265	–
First course intensive treatment, n (%)		
DA-like	429 (57.2%)	–
DA-like + add-on	158 (21.1%)	–
FLAG-IDA	108 (14.4%)	–
Other	55 (7.3%)	–
Receiving alloSCT, n (%)		
No	445 (59.3%)	–
Yes	305 (40.7%)	–
alloSCT subtype, n (%)		
MAC	136 (44.6%)	–
RIC	169 (55.4%)	–

Abbreviations: AlloSCT, allogeneic stem cell transplantation; AML, acute myeloid leukaemia; DA, daunorubicin/cytarabine; FLAG-Ida, fludarabine/high dose cytarabine/idarubicin/granulocyte colony stimulating factor; IQR, interquartile range; MAC, myeloablative conditioning; RIC, reduced-intensity conditioning. [a]Calculated 180 days prior to time of AML diagnosis. [b]From time of AML diagnosis. [c]Includes a small number of patients with missing information on performance status. [d]Risk stratification is based on Grimwade et al.[18]

Table 1: **Baseline characteristics.**

otherwise specified) (Table 2). Among 7500 matched comparators, 986 (13.2%) developed at least one primary malignancy and 122 (1.6%) comparators developed multiple primary malignancies (Tables 2 and 3). Of all comparators, 9.1% developed solid cancers, 0.6% non-myeloid haematological malignancies, and 4.3% NMSCs (80.8% BCCs and 19.2% SCCs including not otherwise specified) (Table 2).

Intensive chemotherapy

The hazard rate of developing any type of non-myeloid SPM in AML survivors was significantly higher compared to matched comparators (HR 1.55, 95% CI 1.27–1.89, Table 2), but no differences were found in the cumulative incidences of non-myeloid SPMs between patients and comparators during the entire follow-up period (p = 0.36, Fig. 2a, and Table S3 for 5-, 10-, 15-year cumulative incidences). There were no differences in the hazard rates of solid cancers (HR 1.14, 95% CI 0.87–1.49, Table 2) or in the cumulative incidences during the entire follow-up period (p = 0.15, Fig. 2b, and Table S3) between AML survivors and matched comparators. Additionally, there were no significant differences in the hazard rates or cumulative incidences of breast cancer, respiratory cancer, or gastrointestinal cancer (Table 2, Figure S3, Table S3). Likewise, we observed no differences in the hazard rates or cumulative incidences of non-myeloid haematological SPMs (Table 2, Fig. 2d, Table S3). The hazard rate of NMSC was significantly higher for AML survivors (HR 2.52, 95% CI 1.90–3.35, Table 2), and the cumulative incidences were significantly elevated during the entire follow-up period compared to matched comparators (p < 0.0001, Fig. 2c, and Table S3).

The IR of any type of non-myeloid SPM per 1000 person-years was 21.24 for AML survivors and 14.08 for matched comparators with a corresponding IRR of 1.51 (95% CI 1.24–1.84, Table 3). When assessing the IRRs for specific non-myeloid SPM subtypes, AML survivors had a higher IR of NMSC than comparators (IRR 2.41, 95% CI 1.82–3.20, Table 3), a higher IR of melanoma (IRR 2.60, 95% CI 1.22–5.54, Table 3), and a lower IR of SPMs in male genital organs (IRR 0.26, 95% CI 0.08–0.82, Table 3). The IRs for all other non-myeloid SPM subtypes did not differ significantly between AML survivors and comparators (Table 3).

AlloSCT and conditioning intensity

AML survivors receiving consolidation with alloSCT before the index date had a higher overall hazard rate of non-myeloid SPMs compared to non-transplanted AML survivors (adjusted HR 1.50, 95% CI 1.00–2.26, adjusted for sex, age, and NMI, Table S4). This was mainly driven by an increased hazard rate of NMSCs among transplanted AML survivors (adjusted HR 1.73, 95% CI 0.99–3.02, Table S4). Overall, there were no differences in the hazard rate of solid cancers (adjusted HR 1.28, 95% CI 0.72–2.27, Table S4), or specific cancer types including breast cancer, respiratory cancer, and gastrointestinal cancer (Table S4).

Non-myeloid SPMs	Strata	n/events/%	HR (95% CI)	p-value
Overall	Matched comparators	7500/986/13.1	1.00 (reference)	–
	AML survivors	750/107/14.3	1.55 (1.27–1.89)	<0.0001
Solid cancers[a]	Matched comparators	7500/682/9.1	1.00 (reference)	–
	AML survivors	750/56/7.5	1.14 (0.87–1.49)	0.36
Respiratory cancer	Matched comparators	7500/106/1.4	1.00 (reference)	–
	AML survivors	750/13/1.7	1.69 (0.95–3.01)	0.075
Gastrointestinal cancer	Matched comparators	7500/167/2.2	1.00 (reference)	–
	AML survivors	750/12/1.6	1.01 (0.56–1.82)	0.96
Breast cancer	Matched comparators	7500/111/1.5	1.00 (reference)	–
	AML survivors	750/11/1.5	1.34 (0.72–2.48)	0.36
NMSC	Matched comparators	7500/323/4.3	1.00 (reference)	–
	AML survivors	750/56/7.5	2.52 (1.90–3.35)	<0.0001
Non-myeloid haematological malignancies[b]	Matched comparators	7500/48/0.6	1.00 (reference)	–
	AML survivors	750/<5/<0.7	0.84 (0.26–2.68)	0.76

Comparison of non-myeloid SPM hazard rates between AML survivors and matched comparators from the general population, with matched comparators used as the reference group. Abbreviations: AML, acute myeloid leukaemia; CI, confidence interval; HR, hazard ratio; HTLV-1, human T-lymphotropic virus 1; NMSC, non-melanoma skin cancer; SPM, second primary malignancy. [a]Includes all solid cancers. [b]Includes lymphoma, multiple myeloma and other plasma cell neoplasms, chronic lymphoblastic leukaemia of B-cell type, hairy-cell leukaemia, adult T-cell lymphoma/leukaemia (HTLV-1-associated), and mature B-cell leukaemia of Burkitt-type.

Table 2: **Hazard ratios (HRs) of non-myeloid SPMs in AML survivors compared to matched comparators; with matched comparators as reference group.**

AML survivors receiving alloSCT had a higher cumulative incidence of any type of non-myeloid SPMs during the entire follow-up period compared to that of matched comparators from the general population (p = 0.039, Fig. 3b, and Table S5 for 5-, 10-, and 15-year cumulative incidences). There were no differences in the cumulative incidences of solid cancers in transplanted AML survivors compared to matched comparators during the entire follow-up period (p = 0.97, Fig. 3d, and Table S5). However, the cumulative incidences of NMSC were higher among AML survivors treated with alloSCT during the entire follow-up period (p < 0.0001, Fig. 3f, and Table S5).

In comparison, among non-transplanted AML survivors, there were no differences in the cumulative incidences of any type of non-myeloid SPMs during the entire follow-up period compared to matched comparators (p = 0.54, Fig. 3a, and Table S5). The cumulative incidence of solid cancers was lower in non-transplanted AML survivors compared to matched comparators during the entire follow-up period (p = 0.062, Fig. 3c, and Table S5). The cumulative incidences of NMSCs were higher in non-transplanted AML survivors compared to matched comparators during the entire follow-up period (p = 0.029, Fig. 3e, and Table S5).

Within the subgroup of AML survivors consolidated with alloSCT, the HRs showed no significant

Non-myeloid SPM subtype	Strata	n/events/%	IR (per 1000 py)	IRR (95% CI)	p-value
Overall	Matched comparators	7500/986/13.1	14.08	1.00 (reference)	–
	AML survivors	750/107/14.3	21.24	1.51 (1.24–1.84)	<0.0001
Lip, pharynx and oral cavity	Matched comparators	7500/18/0.2	0.24	1.00 (reference)	–
	AML survivors	750/<5/<0.7	0.55	2.26 (0.66–7.66)	0.19
Gastrointestinal organs	Matched comparators	7500/167/2.2	2.26	1.00 (reference)	–
	AML survivors	750/12/1.6	2.19	0.97 (0.54–1.74)	0.92
Respiratory organs	Matched comparators	7500/106/1.4	1.43	1.00 (reference)	–
	AML survivors	750/13/1.7	2.37	1.66 (0.93–2.95)	0.086
NMSC	Matched comparators	7500/323/4.3	4.44	1.00 (reference)	–
	AML survivors	750/56/7.5	10.71	2.41 (1.82–3.20)	<0.0001
Melanoma	Matched comparators	7500/42/0.6	0.57	1.00 (reference)	–
	AML survivors	750/8/1.1	1.47	2.60 (1.22–5.54)	0.013
Breast	Matched comparators	7500/111/1.5	1.51	1.00 (reference)	–
	AML survivors	750/11/1.5	2.02	1.34 (0.72–2.50)	0.35
Female genital organs	Matched comparators	7500/35/0.5	0.47	1.00 (reference)	–
	AML survivors	750/<5/<0.7	0.55	1.16 (0.36–3.77)	0.80
Male genital organs	Matched comparators	7500/154/2.1	2.09	1.00 (reference)	–
	AML survivors	750/<5/<0.7	0.55	0.26 (0.08–0.82)	0.021
Urinary tract	Matched comparators	7500/52/0.7	0.70	1.00 (reference)	–
	AML survivors	750/<5/<0.7	0.55	0.78 (0.24–2.49)	0.67
Central nervous system	Matched comparators	7500/13/0.2	0.17	1.00 (reference)	–
	AML survivors	750/<5/<0.7	0.55	3.12 (0.89–10.96)	0.075
Haematological[a]	Matched comparators	7500/48/0.6	0.65	1.00 (reference)	–
	AML survivors	750/<5/<0.7	0.55	0.84 (0.26–2.71)	0.78

Abbreviations: AML, acute myeloid leukaemia; CI, confidence Intervals, IR, incidence rate; IRR, incidence rate ratio; NMSC, non-melanoma skin cancer; SPM, second primary malignancy. [a]Non-myeloid haematological malignancies.

Table 3: **Incidence rates (IRs) of non-myeloid SPM subtypes per 1000 persons-years (py) and incidence rate ratios (IRRs) among AML survivors and matched comparators, with matched comparators as reference group.**

differences in hazard rates of any type of non-myeloid SPMs (adjusted HR 0.88, 95% CI 0.41–1.91), solid cancers (adjusted HR 0.40, 95% CI 0.14–1.19), or NMSCs (adjusted HR 1.17, 95% CI 0.42–3.28) between patients conditioned with MAC compared to RIC, when adjusting for sex, age, and NMI (Table S6).

Discussion

This study showed a higher hazard rate of non-myeloid SPMs in AML survivors following intensive treatment, with or without alloSCT, compared to matched comparators from the general population. This observation was driven by higher rates of NMSCs, whereas no differences in solid cancers were found. The cumulative incidences of NMSCs, with death as a competing event, were higher in AML survivors than in matched comparators, which was not the case for solid cancers. The IRs of any type of non-myeloid SPM per 1000 person-years was 21.24 for AML survivors and 14.08 for matched comparators, and the study demonstrated higher IRs of NMSC and melanoma, but not of any other type of non-myeloid SPM. Notably, we observed a lower IR of malignancies in the male genital organs of AML survivors compared to matched comparators. This may be explained by surveillance bias as newly diagnosed patients with AML initially undergo excessive testing, potentially identifying an underlying elevated prostate-antigen. This could lead to a prostate cancer diagnosis earlier for the AML survivors compared to the general population, and before the index date, which would exclude them from this study. However, the sample size is small for the analysis of specific SPM subtypes, and the observed IRRs should be interpreted with caution.

The literature on SPMs for patients with AML is sparse. To our knowledge, this is the first matched population-based cohort study on non-myeloid SPMs for survivors of adult AML. However, a US population-based study investigating the risk of SPMs for adult patients diagnosed with AML between 1992 and 2010 using the Surveillance, Epidemiology and End Results (SEER) database[19] estimated a 17% relative increase of SPMs in patients with AML (standardized incidence ratio [SIR] 1.17, 95% CI 0.99–1.36) compared to the general population and an excess risk of 15.5 per 10,000 individuals with a median follow-up time of 4.21 years.[19] The study demonstrated an increased risk of oral cavity and pharyngeal cancer in patients with AML aged 18–60 years (SIR 4.34, 95% CI 1.74–8.94), which was not replicated in our study. The excess risk of NMSCs observed in our study was not demonstrated in the US

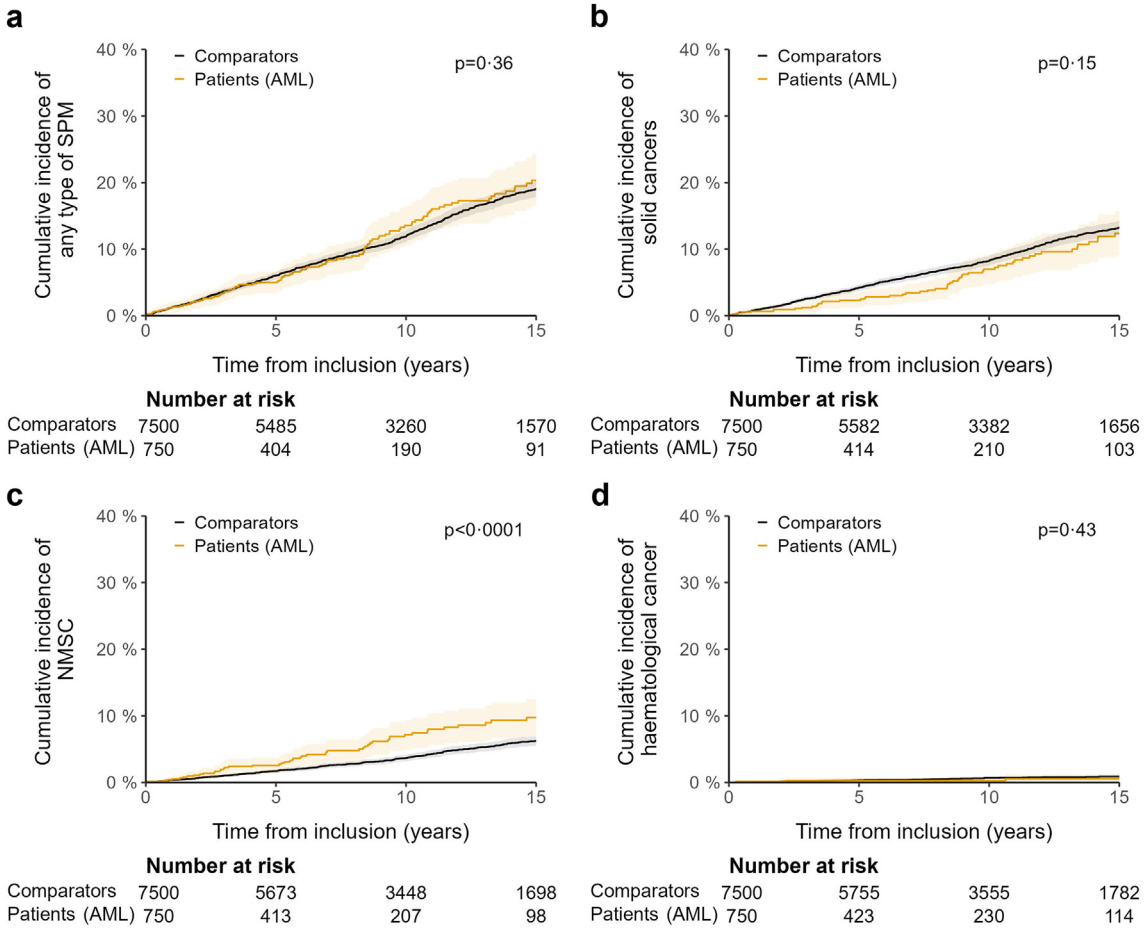

***Fig. 2:* Cumulative incidences of non-myeloid SPMs in AML survivors, alive two years after initiation of intensive induction chemotherapy, and matched comparators, with death as a competing event**. (a) Cumulative incidence of any type of non-myeloid SPM. (b) Cumulative incidence of solid cancers. (c) Cumulative incidence of NMSCs. (d) Cumulative incidences of non-myeloid haematological malignancies. Abbreviations: AML, acute myeloid leukaemia; NMSC, non-melanoma skin cancer; SPM, second primary malignancy.

study, which may be explained by a possible lack of registration of NMSCs historically in national cancer registries in the US.[20] The present study demonstrates a median follow-up time of 10.6 years in which the cumulative incidence of any type of non-myeloid SPMs increased continuously without reaching a plateau. This observation was also demonstrated in a retrospective study of pediatric patients with acute lymphoblastic leukaemia (ALL) in complete remission treated between 1962 and 1998 at St. Jude Children's Research Hospital with a median follow-up of 18.7 years,[9] suggesting the necessity for even longer follow-up in future studies concerned with estimation of the risk of SPMs.[9]

The observed increased rates of non-myeloid SPMs in the present study were primarily driven by an excess risk of NMSCs. Innate and extrinsic risk factors for the development of NMSC include genetic susceptibility, sex, age, natural and artificial UV exposure, alcohol consumption, radiotherapy, and immunosuppression.[21] In addition to these risk factors, a study of 124 pediatric or adolescent patients diagnosed with NMSC identified an association between chemotherapy and the development of BCC in children.[22] In another study of 2415 recipients of alloSCT, aged 18–71 years, SPMs were identified in 209 patients. Of these, 58 (27.8%) were NMSCs.[23] These studies concur with our findings of increased hazard rates and cumulative incidences of NMSC in adult patients with AML, alive two years after treatment with intensive chemotherapy with or without alloSCT, which furthermore underscores the importance of sun protection during and after treatment. The same association was also demonstrated in a recent population-based cohort study of 803 patients with lymphoma in Denmark treated with high-dose chemotherapy and autologous stem cell transplantation,[7] followed from date of transplantation until first SPM. The

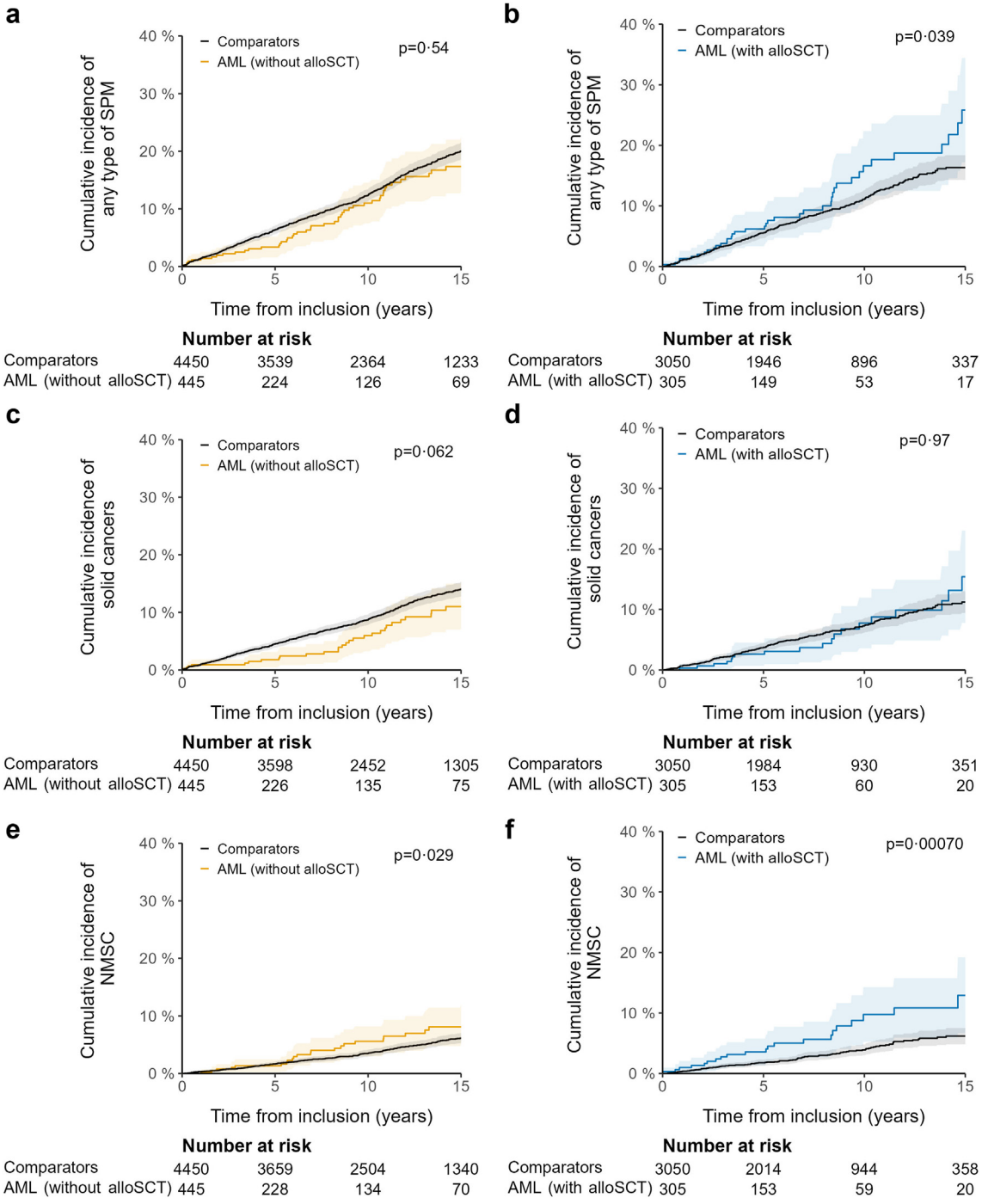

Fig. 3: **Cumulative incidences of SPMs, with death as a competing event, in AML survivors treated with alloSCT in addition to intensive chemotherapy compared to matched comparators, and in non-transplanted AML survivors compared to matched comparators. AML patients were alive and cancer free two years after initiation of induction chemotherapy.** **(a)** Cumulative incidence of any type of non-myeloid SPM in non-transplanted AML survivors and their matched comparators. **(b)** Cumulative incidence of any type of non-myeloid SPM in AML survivors treated with alloSCT and their matched comparators. **(c)** Cumulative incidence of solid cancers in non-transplanted AML survivors and their matched comparators. **(d)** Cumulative incidence of solid cancers in AML survivors treated with alloSCT and their matched comparators. **(e)** Cumulative incidence of NMSC in non-transplanted AML survivors and their matched comparators. **(f)** Cumulative incidence of NMSC in AML survivors treated with alloSCT and their matched comparators. Abbreviations: AlloSCT, allogeneic stem cell transplantation; AML, acute myeloid leukaemia; NMSC, non-melanoma skin cancer; SPM, second primary malignancy.

study showed a higher rate of NMSCs in patients with lymphoma than in matched comparators (adjusted HR 2.94, 95% CI 1.83–3.57),[7] which are comparable to our findings with a HR of 2.52 (95% CI 1.90–3.35). In contrast to patients with lymphoma, patients with AML often undergo alloSCT which includes radiation therapy. In our cohort of AML patients, 41% received alloSCT on top of chemotherapy. In addition to NMSC, the study demonstrated higher rates of MDS or AML (adjusted HR 41.13, 95% CI 15.77–107.30) in patients with lymphoma compared to matched controls.[7] In contrast, the present study did not include acute leukaemias, myelodysplastic syndrome (MDS), or myeloproliferative neoplasms as events after a primary AML diagnosis. The myeloid cancers are an integrated part of the pathogenesis of certain AML types and including myeloid malignancy as outcomes would introduce misclassification of exposure as outcomes.

When exploring the effect of alloSCT on the SPM risk, the present study observed an increased hazard rate of non-myeloid SPMs in transplanted vs non-transplanted AML survivors, driven by a higher hazard rate of NMSCs in recipients of alloSCT. We observed higher cumulative incidences of overall non-myeloid SPMs and of NMSCs in transplanted AML survivors compared to a matched background population, but not of solid cancers. In comparison, the cumulative incidences of any non-myeloid SPM were not higher in non-transplanted AML survivors compared to matched comparators. This might indicate that the additional treatment related to transplantation, including conditioning regimens and subsequent immunosuppression, is associated with higher risk of developing non-myeloid SPMs, particularly NMSC. Here, it must be taken into consideration that transplanted patients are possibly more fit than non-transplanted patients, since recipients of alloSCT must be fit enough to withstand the adverse effects of the treatment (Table S7). The development of SPMs following alloSCT is excessively documented in the literature and several risk factors for post-alloSCT SPMs have been identified, including total body irradiation, immunosuppression, and advanced age.[24–28] A retrospective, multicenter study from British Columbia of 926 recipients of alloSCT between 1985 and 2003 found a 10-year cumulative incidence of second solid cancers of 3.1%, including BCC and carcinoma in situ.[26] This is notably lower than the 10-year cumulative incidence of solid cancers of 7.8% observed in recipients of alloSCT in our study. The study participants in the British Columbia study included recipients of alloSCT for various haematological diseases, including both multiple myeloma, acute leukaemia, myelodysplastic neoplasms, and less aggressive leukaemias, such as chronic myeloid leukaemia. This combination of diseases is of different nature regarding prognosis and treatment, which may not reflect the more homogenous population in our study of AML survivors treated with intensive chemotherapy. Furthermore, the median follow-up time of the British Columbia study was only 1.8 years (IQR 0–19.2 years),[26] which is too low to establish a relation between alloSCT and SPMs due to the long latency of SPMs. In comparison, the AML survivors included in our study were alive two years after initiation of induction chemotherapy, hence mortality would not be expected to affect the SPM risk extensively. Similarly, Ringdén et al. found a 10-year cumulative risk of second solid cancers in recipients of RIC alloSCT of 1.71% (excluding NMSC) at a median follow-up of 72 months.[25] The study also compared the SPM risk in recipients of RIC vs MAC and found no significant difference between these two treatment strategies.[25] This correlates with our findings; the adjusted analysis of hazard rates of non-myeloid SPMs showed no significant difference between the two treatment groups when adjusting for age, sex, and NMI (HR 0.88, 95% CI 0.41–1.91).

This study presents several strengths. The population of Denmark includes 5.9[29] million residents with free access to tax-supported medical care, and all contacts with the public health care system are registered by health care personnel, linked by a unique social security number. These nationwide registers are of high coverage and validity and contain high-quality individual-level data on patient- and disease characteristics. This contributed to minimal selection bias and a high generalizability, further achieved by matching on sex, age, and comorbidities (NMI). The use of registry-data also enabled a long follow-up and minimal loss to follow-up since patients were not requested to answer questionnaires or participate in follow-up examinations. The long and complete follow-up of this study was essential when studying the occurrence of non-myeloid SPMs, in particular second solid cancers with a latency period often exceeding ten years.[2] Furthermore, identification of SPMs in the Danish Cancer Registry by morphology contributed to minimal information bias. Finally, by including patients with AML who survived at least two years from treatment initiation, we attempted to minimize the effect of mortality on the results.

Some limitations of this study require highlighting. The cause of SPM is multifactorial, and a full overview of potential confounders would incorporate genetic and molecular factors, detailed information regarding lifestyle (e.g., smoking habits, alcohol consumption, exercise, and UV-exposure), and innate or iatrogenic immunosuppression prior to inclusion. True data on this information are difficult to obtain and were not included in this study. Furthermore, part of the higher hazard rate and cumulative incidence of NMSC in AML survivors could be a result of surveillance bias, as patients are followed more intensively compared to the general population, in particular after alloSCT. This might lead to more

aggressive diagnostics when patients present with suspect skin lesions. Thus, it is difficult to isolate the true effect of intensive chemotherapy and alloSCT on the SPM risk and hereby draw a causal conclusion from the associations found in this study. However, the two-year landmark set up in our study may have underestimated the true risk of non-myeloid SPMs in patients with AML, if development of SPM occurred within the two-year period. Finally, this study suffers from relatively small sample sizes, in particular regarding events of specific SPM subtypes, which implies that some caution has to be taken when drawing final conclusions and interpreting the results for those subtypes of cancers that are in general relatively rare.

In summary, in this matched population-based cohort study of 750 AML survivors, alive two years after treatment with intensive induction chemotherapy, we found significantly higher rates of any non-myeloid SPMs and higher rates and cumulative incidences of NMSCs compared to a matched general population. No increased rates or cumulative incidences of solid cancers were found, except for an increased incidence rate of melanoma. Furthermore, we observed an association between alloSCT and a higher hazard rate of non-myeloid SPMs among AML survivors receiving alloSCT compared to non-transplanted AML survivors, although there was no strong evidence of such an association. We believe these results underscore that, except for an increased risk of NMSC, AML treatment including consolidation with alloSCT is not associated with an increase in non-myeloid SPMs and should not be a concern for optimal AML treatment. Nevertheless, patients should be made aware of the potential risk of NMSC and encouraged to consult their general practitioner if noticing dermatological changes.

Contributors

NNN, JFJ, DTK, JB, TT, TCEG, and MTS designed and conceptualised the study. NNN, JFJ, and MTS conducted the management and coordination of responsibilities. All authors collected and assembled the data. NNN, JFJ, DTK and MTS performed the data analysis. NNN, JFJ, DTK and MTS drafted the manuscript. All authors contributed to the interpretation of results and to revision of the manuscript. All authors had access to the data and have read and approved the final manuscript.

Data sharing statement

We are not allowed to share individual participant data from Statistics Denmark, according to rules set forth by the Danish Authorities. Therefore, data used in this study are not available.

Declaration of interests

JB has received research support from Gilead Sciences Denmark. TT has received travel grant from Immedica and research support from Janssen. HBO has a consulting/advisory role for Abbvie, Bristol Myers Squibb, Daiichi Sankyo Nordics, Celgene, and Sanofi and has received research support from Jazz Pharmaceuticals and a travel grant from Beigene. DTK has a consulting/advisory role for AbbVie, Astellas Pharma, Atheneum, and Immedica and has received travel grants from Swedish Orphan Biovitrum. CS has a consulting/advisory role for Incyte and has received a travel grant from Abbvie, Norton Healthcare Limited and Swedish Orphan biovitrum. No further conflicts of interest to be reported.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.lanepe.2024.101204.

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