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ORIGINAL PAPER

Effects of chemotherapy dose reductions in overweight patients with acute myeloid leukaemia: A Danish nationwide cohort study

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Summary

Overweight patients with cancer are frequently reduced in chemotherapy dose due to toxicity concerns, although previous studies have indicated that dose reduction (DR) of overweight patients results in comparable toxicity but may compromise overall survival (OS). Current evidence regarding DR in patients with acute myeloid leukaemia (AML) is limited. To investigate the association between DR and outcome among overweight patients with AML we analysed a Danish nationwide cohort of overweight adult AML patients treated with remission induction chemotherapy. Among 536 patients identified, 10.1% were categorized as DR defined as 95% or less of full body surface area (BSA)-based dose. Risk factors for DR were high body mass index (BMI) and BSA, therapy-related AML and favourable cytogenetics. No significant differences were observed for rates of complete remission (CR), 30- and 90-day mortality between DR and non-DR patients. Furthermore, DR did not affect median relapse-free survival (RFS) [DR, 14.5 (95% confidence interval, 9.0–41.7) months; non-DR, 15.0 (12.3–19.3)] with an adjusted difference in five-year restricted mean survival time (Δ5y-RMST) of 0.2 (−8.4 to 8.8) months nor median OS (DR, 17.0 [11.9 to 45.5] months; non-DR, 17.5 [14.8 to 20.5]) with an adjusted Δ5y-RMST of 0.8 (−5.7 to 7.3) months. In conclusion, we found no statistically significant association between DR and outcomes among overweight patients with AML. However, we acknowledge the limited sample size and encourage further studies in this important subject.

KEYWORDS
acute leukaemia, chemotherapy, dose reduction, overweight and obesity, survival

INTRODUCTION

Acute myeloid leukaemia (AML) is an aggressive neoplasia resulting in clonal expansion and accumulation of immature myeloid cells in the bone marrow. High-intensity antineoplastic treatment, so called remission induction chemotherapy (IC), is currently the best treatment option to induce complete remission (CR) followed by consolidation therapy

to maintain CR and sustain long-term survival. However, IC comes with severe toxicity and risk of treatment-related mortality influenced by patient-related factors such as age, comorbidity and performance status.[1,2] Several studies have associated being overweight with increased risk of cancer[3,4] including AML.[5,6] Furthermore, overweight among cancer patients has been associated with inferior overall survival (OS).[3,4] While being overweight has been correlated with adverse clinical outcomes in acute promyelocytic leukaemia (APL), this association is more vague and conflicting for patients with non-APL AML.[5–8]

Most antineoplastic agents are dosed according to an anthropometric parameter. In AML, dosing of IC has traditionally been calculated based on body surface area (BSA).[9] Dose reduction (DR) of antineoplastic drugs is a common phenomenon in overweight patients with solid cancers due to concerns of treatment-related toxicity and overdosing.[10,11] Even though overweight may affect the pharmacokinetic properties of antineoplastic agents, there is no evidence showing increased toxicity of full dosing in overweight and obese patients compared to normal-weight patients.[12,13] Rather, DR or dose capping of antineoplastic agents to for example BSA 2.0 m^2 or <95% of actual weight-based dose, has been shown to result in inferior OS indicating a potential disadvantage of DR for overweight patients.[10–12,14] At present, the most widely used guidelines provide no specific recommendations on IC dosing in overweight patients with AML.[9,15,16] A clinical practice guideline provided by the American Society of Clinical Oncology (ASCO), does not recommend up-front DR based on body mass index (BMI) or BSA in overweight or obese patients with solid cancers.[12,17] Recently, evidence for acute leukaemia, specifically AML, has been included in an updated ASCO guideline; however, evidence is sparse and little efforts have focused specifically on obese and overweight patients.[17]

The objectives of this study were to (i) describe the frequency and risk factors for DR in adult overweight AML patients receiving IC in a real-world setting; (ii) investigate if DR affects rates of CR, 30- or 90-day mortality as surrogates for efficacy and toxicity; and (iii) investigate if DR is associated with differences in OS and relapse-free survival (RFS).

MATERIALS AND METHOD

Patients and setting

We conducted a Danish nationwide retrospective cohort study. The study population was identified utilizing the Danish National Acute Leukaemia Registry (DNLR) covering >99% of patients diagnosed with AML in Denmark (Appendix S1).[18] Eligible patients had to fulfil the following inclusion criteria: (i) diagnosed with AML (excluding acute promyelocytic leukaemia) according to World Health Organization (WHO) criteria (Swerdlow et al., 2008) between 1 January 2000 and 31 December 2012; (ii) treated with IC defined as cytarabine (≥200 mg/m^2/day) administered for a minimum of 5 days in combination with an anthracycline (i.e., idarubicin or daunorubicin) or anthracycline-related compound (i.e., mitoxantrone); (iii) a BMI of 25 kg/m^2 or above; (iv) aged 18–75 years; and (v) had available information on weight, height and a registered BSA (rBSA) on chemotherapy dosing forms. We excluded patients receiving less than 100% chemotherapy dosing according to the rBSA on chemotherapy dosing forms to avoid inclusion of patients who received DR due to organ impairment (i.e., percentage reduction due to cardiac, hepatic, or renal insufficiency) and thus introducing confounding by indication.

Clinical information

Baseline clinicopathological information was retrieved from DNLR.[18] Performance status was grouped according to WHO score (WHO-PS).[19] Information on AML subtype (de novo, secondary and therapy-related) was classified according to WHO.[20] Cytogenetic risk category was grouped according to Medical Research Council (MRC) criteria (favourable, intermediate and adverse).[21]

Data on anthropometric variables and lifestyle factors (smoking history and comorbidities) for patients fulfilling the inclusion criteria were retrieved from medical records registered during routine clinical practice (either electronic or paper records). Weight and height at the time of diagnosis were retrieved from medical records and rBSA from day one of the first cycle of chemotherapy serving as basis for chemotherapy dosing was retrieved from paper chemotherapy dosing forms. We calculated BMI as weight/height^2 and actual BSA (cBSA) using the DuBois formula.[22,23] Comorbidities included a previous history of diabetes mellitus, chronic obstructive pulmonary disease, ischaemic heart disease, rheumatological disease, hypertension and hypercholesterolaemia. Smoking status was categorized as never or ever as previously described.[24]

Chemotherapy dosing and regimens

Information on IC regimens were retrieved from DNLR (for treatment regimens see the Appendix S1). All chemotherapy doses in IC were calculated based on rBSA by the prescribing physician and checked by the pharmacist prior to production. Dose reduction (DR) was defined as $100 \times (\text{cBSA} - \text{rBSA})/\text{cBSA} \geq 5\%$ corresponding to chemotherapy reduction of at least 5% compared to full cBSA-based dosage based on previous reports in solid cancers.[10,11,14] Examples of calculation are provided in the Appendix S1.

Outcomes

The primary outcome was OS, which was defined as the time from diagnosis until death, emigration, or end of follow-up (April 2015) where vital status of all patients was assessed using the Danish civil registration system ensuring complete follow-up.[25] Secondary end-points were 30- and 90-day

mortality, rate of CR assessed by morphological bone marrow examination following up to two cycles of IC according to international criteria[26] and RFS was measured from time of CR achievement according to European LeukemiaNet (ELN) criteria until relapse, death, emigration, or end of follow-up.[9]

Statistical analysis

Patient characteristics were described for the total cohort and by dose reduction strata (DR and non-DR). Categorical variables were presented as percentage and continuous variables as median and interquartile range (IQR). Differences in baseline variables were compared using the chi-squared test for categorical variables and the Wilcoxon rank-sum test for continuous variables.

The relative risk (RR) for DR was computed using univariable Poisson regression models including the following covariates: sex, age, BMI, height, weight, cBSA, WHO-PS, smoking status, number of comorbidities, AML subtype (de novo [dn-AML], secondary [sAML] or therapy-related [tAML]) and cytogenetic risk category.

To compare toxicity between DR strata we calculated crude and adjusted RRs of death within 30- and 90-days following diagnosis (30- and 90-day mortality) as a surrogate of early toxicity from IC. To compare the efficacy of IC between DR strata we calculated crude and adjusted RRs for the achievement of CR after first-line IC.

Crude OS and RFS were calculated using the Kaplan–Meier method and the median OS and RFS were computed as the time point where the respective curve reaches 50%. The log-rank test was used to test for differences in crude OS and RFS. OS and RFS were also compared using crude and adjusted [for age, sex, comorbidity, WHO-PS, BMI, cytogenetic risk category, AML subtype, and white blood cell count (WBC)] 5-year restricted mean survival time (5y-RMST) estimates, and should be visualized as the area under the survival curve until 5 years after diagnosis and interpreted as the average survival from diagnosis to 5 years. Differences in 5y-RMST (Δ5y-RMST) were obtained using a pseudo-observation approach, where appropriate confidence intervals were computed using generalized estimating equations, setting non-DR as reference.[27] The Δ5y-RMST should be interpretated as the difference in average survival from diagnosis until 5 years.[28] Only patients with complete data on covariates were included in adjusted analyses. Median follow-up estimates were calculated using the reverse Kaplan–Meier method.

As a supplemental analysis, we performed two case-matched analyses (one for OS and one for RFS), where each DR patient was matched to a non-DR patient on age, sex, AML subtype and BMI by genetic matching scheme.[29] This was performed for the overall cohort (to compare CR rates, 30- and 90-day mortality and OS) and for patients achieving CR (to compare RFS) separately. An additional analysis using a DR of 5% or more as cut-off and stratified on age (18–59 years and 60–75 years) was performed to investigate the effect of age.

Furthermore, we performed a sensitivity analysis defining DR as 10% or more dose reduction to explore the threshold of 5% used in previous studies. Statistical analyses were performed in R version 4.1.2 (R Core Team, 2021). p values of at most 0.05 were considered statically significant. The study was approved by the Danish Data Protection Agency (jr. nr. 2008-58-0028).

RESULTS

Patient characteristics

The study population included 536 patients fulfilling the inclusion criteria (Figure S1) with a median follow-up of 102.4 (IQR: 63–134) months. Patient characteristics for the total cohort and according to DR strata are listed in Table 1. The median age at diagnosis was 59 (IQR: 48–66) years and the median BMI, cBSA and rBSA of the cohort were 28.1 (IQR: 26.4–30.7) kg/m^2, 2.0 (IQR: 1.9–2.1) m^2 and 2.0 (IQR: 1.9–2.1) m^2, respectively (Table 1 and Figure 1A–C). Patients who had received DR IC had a higher median BMI of 30.7 (IQR: 28.3–35.5) kg/m^2 and a median cBSA of 2.2 (IQR: 2.1–2.3) m^2 compared to non-DR patients at 28.0 (IQR: 26.3–30.4) kg/m^2 and 1.98 (IQR: 1.9–2.1) m^2, respectively (Figure 1A,B and Figure S2). Characteristics and an overview of the matching balance for the two case-matched cohorts are available in the Appendix (Table S1 and Figure S3).

Risk of dose capping

In total, 10.1% (54/536) of the patients were DR to 95% or less of the expected chemotherapy dosing relative to cBSA. The mean dose reduction according to full-BSA-based dose of DR patients was 11.2% compared to 0.4% for non-DR patients (Figure 1C).

An univariable regression model (Figure 2) revealed increasing cBSA as a risk factor for DR [2.0–2.2 m^2: RR, 4.61 (95% CI: 1.85–12.47); ≥2.2 m^2: RR, 15.21 (95% CI: 6.30–36.73); $p < 0.01$ for both]. Increasing BMI was also associated with increased RR of DR [BMI 30–34.9 kg/m^2: RR, 2.52 (95% CI: 1.34–4.75); BMI ≥35 kg/m^2: RR, 4.66 (95% CI: 2.42–8.98); $p < 0.01$ for both]. Furthermore, the tAML subtype [RR, 2.85 (95% CI: 1.12–7.24); $p = 0.03$] and favourable cytogenetic risk category [RR, 2.20 (95% CI: 1.08–4.49); $p = 0.03$] were associated with an increased risk of DR.

Efficacy and toxicity of dose reduction

Crude and adjusted RRs for 30- and 90-day mortality and CR following first-line IC for the DR group for the total cohort and the case-matched cohort are provided in Table 2. The 30-day mortality for non-DR patients was 8.9% and 13.0% for DR patients [RR of 1.45 (95% CI: 0.60–3.03, $p = 0.36$)]. The 90-day mortality for non-DR patients was 16.0% compared to 20.4%

TABLE 1 Selected baseline characteristics of the total study cohort and stratified by dose-reduction status

Variable	Total (n = 536)	DR (n = 54)	Non-DR (n = 482)	p value*
Sex, male, n (%)	309 (57.6)	38 (70.4)	271 (56.2)	0.064
Age, median, years (IQR)	59 (48–66)	59 (48–64)	59 (48–66)	0.369
<60years, n (%)	281 (52.4)	28 (51.9)	253 (52.5)	
WHO-PS, n (%)				0.799
0–1	445 (83.0)	46 (85.2)	399 (82.8)	
≥2	91 (17.0)	8 (14.8)	83 (17.2)	
Comorbidity, n (%)				0.078
0	308 (57.5)	28 (51.9)	280 (58.1)	
1	114 (21.3)	16 (29.6)	98 (20.3)	
≥2	79 (14.7)	10 (18.5)	69 (14.3)	
cBSA, median, m^2, (IQR)	2.0 (1.9–2.1)	2.2 (2.1–2.3)	1.98 (1.9–2.1)	<0.001
cBSA <2.0m^2, n (%)	264 (49.3)	6 (11.1)	258 (53.5)	
cBSA ≥2.0m^2, n (%)	272 (50.7)	48 (88.9)	224 (46.5)	
rBSA, median, m^2, (IQR)	2.0 (1.9–2.1)	2.0 (2.0–2.0)	2.0 (1.9–2.1)	<0.001
rBSA <2.0m^2, n (%)	236 (44.0)	8 (14.8)	228 (47.3)	
rBSA ≥2.0m^2, n (%)	300 (56.0)	46 (85.2)	254 (52.7)	
BMI, median, kg/m^2 (IQR)	28.1 (26.4–30.7)	30.7 (28.3–35.5)	28.0 (26.3–30.4)	<0.001
BMI 25–29.9, n (%)	369 (68.8)	22 (40.7)	347 (72.0)	
BMI 30–34.9, n (%)	113 (21.1)	17 (31.5)	96 (19.9)	
BMI ≥35, n (%)	54 (10.1)	15 (27.8)	39 (8.1)	
Smoking status, n (%)				0.778
Ever-smokers	250 (46.6)	27 (50.0)	223 (46.3)	
Never-smokers	200 (37.3)	20 (37.0)	180 (37.3)	
AML subtype, n (%)				0.035
De novo AML	433 (80.8)	38 (70.4)	395 (82.0)	
sAML	83 (15.5)	11 (20.4)	72 (14.9)	
tAML	20 (3.7)	5 (9.3)	15 (3.1)	
BM blast, median %, (IQR)	58.0 (35.0–80.0)	45.0 (35.0–70.0)	61.5 (35.0–81.0)	0.051
PB blast, median %, (IQR)	29 (6.2–65.0)	20 (2.0–51.5)	30 (7.5–67.0)	0.084
LDH, median, U/L, (IQR)	405 (241–732)	450 (236–1055)	399 (242–699)	0.544
Platelets, median, ×10^9/L, (IQR)	50 (27–67)	40 (22–70)	51 (28–92)	0.101
WBC, median, ×10^9/L, (IQR)	11.0 (2.2–50.0)	8.6 (2.4–61.1)	11.2 (2.2–50.0)	0.937
Cytogenetics performed, n (%)	502 (93.7)	50 (92.6)	452 (93.8)	0.965
Cytogenetic risk[a], n (%)				0.138
Favourable risk	52 (9.7)	10 (18.5)	42 (8.7)	
Intermediate risk	355 (66.2)	31 (57.4)	324 (67.2)	
Adverse risk	80 (14.9)	8 (14.8)	72 (14.9)	
Treatment regimen, n (%)				0.451
DA	360 (67.2)	34 (63.0)	326 (67.6)	
FLAG-Ida	50 (9.3)	8 (14.8)	42 (8.7)	
ADE	104 (19.4)	9 (16.7)	95 (19.7)	
Other	22 (4.1)	3 (5.6)	19 (3.9)	

Abbreviations: ADE, cytarabine + daunorubicin + etoposide; AML, acute myeloid leukaemia; BM, bone marrow; BMI, body mass index; BSA, body surface area; cBSA, calculated BSA; DA, daunorubicin + cytarabine; DR, dose reduction; FLAG-Ida, fludarabine + cytarabine + idarubicin + granulocyte colony-stimulating factor; IQR, interquartile range (25th–75th percentiles); LDH, lactate dehydrogenase; PB, peripheral blood; rBSA, registered BSA; sAML, secondary AML; tAML, therapy-related AML; WBC, white blood cell count; WHO-PS, World Health Organization performance status score.

[a]Risk according to the Medical Research Council (Grimwade et al, 2010). Fifteen patients were unclassifiable due to no mitosis (n = 6) or missing karyotype (n = 9).

*p value from comparison between DR and non-DR.

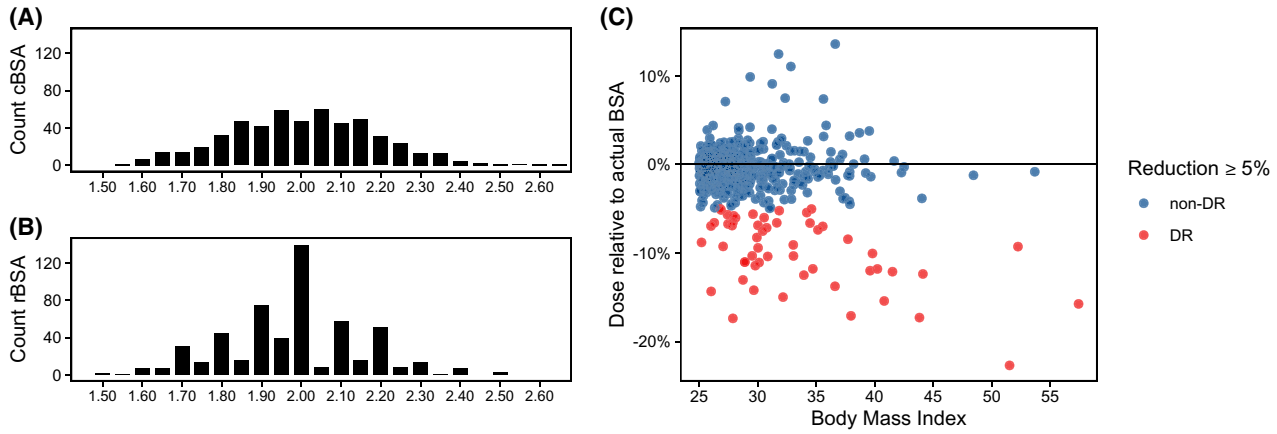

FIGURE 1 Distribution of (A) calculated body surface area (cBSA); (B) registered body surface area (rBSA); and (C) body mass index (BMI) related to percentage dose reduction of actual weight-based dose among 536 patients with acute myeloid leukaemia (AML). [Colour figure can be viewed at wileyonlinelibrary.com]

Variable	Stratification	N	Relative risk of DR	Estimate (95%CI)	P-value
Sex	Female	227		Reference	
	Male	309		1·74 (0·97, 3·13)	0·062
Age	18-59	281		Reference	
	60-75	255		1·02 (0·60, 1·75)	0·933
Body Mass Index	25-29·9	369		Reference	
	30-34·9	113		2·52 (1·34, 4·75)	0·004
	>= 35	54		4·66 (2·42, 8·98)	<0·001
Body Surface Area	< 2·0	264		Reference	
	2·0-2·2	191		4·61 (1·85, 11·47)	0·001
	>= 2·2	81		15·21 (6·30, 36·73)	<0·001
WHO performance	0-1	445		Reference	
	2-4	91		0·85 (0·40, 1·80)	0·672
Smoking status	Never-smoker	200		Reference	
	Ever-smoker	250		1·08 (0·61, 1·93)	0·794
No. of Comorbidities	0	308		Reference	
	1	114		1·54 (0·84, 2·85)	0·166
	2+	79		1·39 (0·68, 2·87)	0·369
AML subtype	De novo AML	433		Reference	
	sAML	83		1·51 (0·77, 2·95)	0·229
	tAML	20		2·85 (1·12, 7·24)	0·028
Cytogenetic	Intermediate risk	355		Reference	
	Adverse risk	80		1·15 (0·53, 2·49)	0·732
	Favourable risk	52		2·20 (1·08, 4·49)	0·030

FIGURE 2 Relative risk (RR) for dose reduction of remission-induction chemotherapy derived from univariate Poisson regression analysis for 536 patients with acute myeloid leukaemia (AML).

for DR patients yielding a RR of 1.28 (95% CI: 0.64–2.29, $p = 0.45$). The adjusted RR for 30-day was 1.24 (95% CI: 0.42–3.11, $p = 0.67$) and 1.11 (95% CI: 0.48–2.28, $p = 0.79$) for 90-day mortality. The 30-day mortality in the case-matched cohort was 11.1% for non-DR patients and 13.0% for DR patients [RR 1.17 (95% CI: 0.39–3.62, $p = 0.78$)] and 90-day mortality was 20.4% in both groups [RR 1.0 (95% CI: 0.43–2.33, $p = 1.0$)].

A total of 333 patients achieved CR following first-line IC. The rate of CR was 61.8% in non-DR patients compared to 64.8% among DR patients corresponding to a RR of 1.05 (95% CI: 0.73–1.47, $p = 0.79$) (Table 2). After adjustment the estimate was similar with a RR of 1.04 (95% CI: 0.68–1.55, $p = 0.84$). In the case-matched cohort, 63.0% of non-DR patients and 64.8% of DR patients achieved CR, corresponding to a RR of 1.03 (95% CI: 0.64–1.65, $p = 0.9$) (Table 2).

Effect of dose capping on overall survival and relapse-free survival

The median OS for the entire cohort was 17.5 (95% CI: 14.8–20.2) months. Median OS for non-DR patients was 17.5 (95%

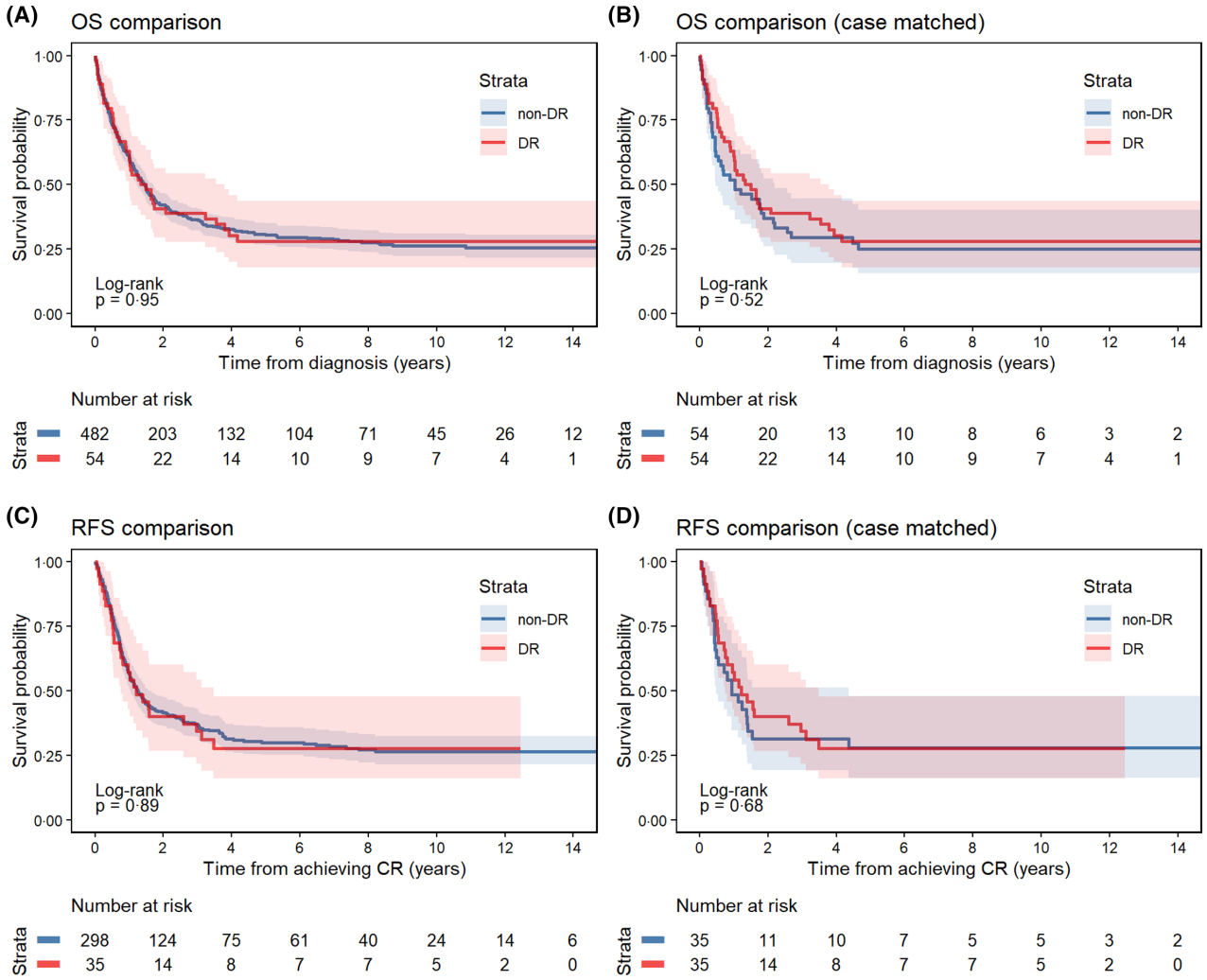

FIGURE 3 Crude overall survival (OS), relapse-free survival (RFS), and 95% confidence interval (CI) for patients with acute myeloid leukaemia (AML) by dose reduction status. (A) OS for the total cohort ($n = 536$), (B) OS for the case matched cohort ($n = 116$), (C) RFS for the total cohort ($n = 333$), and (D) RFS for the case matched cohort ($n = 76$). Survival time is displayed as time after diagnosis (OS) or time after achieving complete remission (CR) (RFS). p value from log-rank test. [Colour figure can be viewed at wileyonlinelibrary.com]

CI: 14.8–20.5) months and 17.0 (95% CI: 12.3–45.5) months for DR patients with a crude Δ5y-RMST of −0.2 (95% CI: −7.1 to 6.7) months (Figure 3A and Table 3). After adjustment for age, sex, comorbidity, WHO-PS, BMI, cytogenetic risk category, AML subtype and WBC the adjusted Δ5y-RMST remained non-significant at 0.8 (95% CI: −5.7 to 7.3) months. In the case-matched cohort, the median OS for non-DR patients was 12.3 (95% CI: 5.5–26.3) months compared to 17.0 (95% CI: 11.9–45.5) months for DR patients with a crude Δ5y-RMST of 3.1 (95% CI: −5.9 to 12.1) months (Figure 3B and Table 3).

Among 333 patients achieving CR, the median RFS in the non-DR cohort was 15.0 (95% CI: 12.3–19.3) months compared to 14.5 (95% CI: 9.0–41.7) months for DR patients, corresponding to a Δ5y-RMST of −1.3 (95% CI: −9.7 to 7.1) months and an adjusted Δ5y-RMST of 0.2 (95% CI: −8.4 to 8.8) months (Figure 3C and Table 3). In the case-matched cohort, median RFS was 11.3 (95% CI: 5.8–52.2) and 14.5 (95% CI: 9.0–41.7) months for the non-DR and DR groups respectively, with a Δ5y-RMST of 2.1 (95% CI: −9.1 to 13.3) months (Figure 3D and Table 3).

Sensitivity analyses

We did the full analysis using a threshold of 10% or higher for DR (Table S2, S3 and Figure S4). In total, 25 patients (4.7%) were defined as DR using this threshold. Furthermore, an analysis using a DR of 5% or more as cut-off stratified on age 18–59 and 60–75 years revealed no statistically significant differences for OS, RFS or median OS (Figure S5). Our sensitivity analyses did not alter our overall conclusion.

DISCUSSION

In this Danish nationwide study, we found that approximately 10% of overweight and obese AML patients

TABLE 2 Crude and adjusted relative risk for complete remission, 30- and 90-day mortality for the total cohort and case-matched cohort stratified by dose-reduction status

Outcome	Strata	Total cohort ($n = 536$)					Case-matched cohort ($n = 108$)		
		n/events/%	RR (95% CI)	*p*	*n*/events/%	aRR (95% CI)[a]	*p*	*n*/events/%	RR (95% CI)	*p*
30-day mortality	Non-DR	482/43/8.9	1 (reference)	—	401/37/9.2	1 (reference)	—	54/6/11.1	1 (reference)	—
	DR	54/7/13.0	1.45 (0.60–3.03)	0.36	47/6/12.8	1.24 (0.42–3.11)	0.67	54/7/13.0	1.17 (0.39–3.62)	0.78
90-day mortality	Non-DR	482/77/16.0	1 (reference)	—	401/66/16.5	1 (reference)	—	54/11/20.4	1 (reference)	—
	DR	54/11/20.4	1.28 (0.64–2.29)	0.45	47/9/19.1	1.11 (0.48–2.28)	0.79	54/11/20.4	1.00 (0.43–2.33)	1.0
CR[b]	Non-DR	482/298/61.8	1 (reference)	—	401/254/63.3	1 (reference)	—	54/34/63.0	1 (reference)	—
	DR	54/35/64.8	1.05 (0.73–1.47)	0.79	47/30/63.8	1.04 (0.68–1.55)	0.84	54/35/64.8	1.03 (0.64–1.65)	0.90

Abbreviations: AML, acute myeloid leukaemia; aRR, adjusted relative risk; BMI, body mass index; CI, confidence interval; CR, complete remission; dn AML, de novo AML; DR, dose reduction; RR, relative risk; sAML, secondary AML; tAML, therapy-related AML; WBC, white blood cell count; WHO-PS, World Health Organization performance status score.

[a]Adjusted for age (continuous), sex (male and female), comorbidity (0, 1 and ≥2), WHO-PS (0–1, ≥2), BMI (continuous), cytogenetic risk category (favourable, intermediate, and adverse), AML subtype (dn-AML, sAML and tAML), and WBC (continuous).

[b]Complete remission following first-line therapy.

treated with IC were dose-reduced relative to full BSA-based dosing with a mean reduction of 11.2%. Factors associated with increased risk of DR were increasing BSA and BMI but also tAML and favourable cytogenetic risk; however, due to the retrospective nature of the study we do not know the exact clinical rationale for the DR. Importantly, we found no statistically significant association between DR (using 5% and 10% cut-offs for DR) and 30- and 90-day mortality, rates of CR, RFS, or OS.

Due to increasing prevalence worldwide, overweight and obesity in cancer patients is an increasing public health challenge, and continuous and robust research in this field to optimize cancer treatment for this group is highly needed.[12,30] The care for overweight and obese cancer patients remains challenging since treatment-related toxicities and mortality are closely related to pre-existing comorbidities, such as cardiovascular diseases, which are more prevalent in this patient group.[31,32]

Several other studies have assessed this question and the results are conflicting; where some find a negative survival effect of DR or dose capping,[33,34] others find no effect or better outcomes in overweight receiving DR or dose capping.[35–39] Notable differences between studies are study population, cytogenetic risk, and age. Crysandt et al. and Cahu et al.[33,34] retrospectively analysed data from the prospective clinical trials AML2003 and GOELAMS 2001 including younger adults (≤60 years) with higher proportions of favourable cytogenetic risk, and found either a univariate association to inferior survival[33] or a trend towards inferior survival but no differences in event-free survival.[34] Other studies included older patients (>60 years) mostly from single institution experiences have not been able to associate DR or dose capping to inferior survival.[35–39] However, none of the afore-mentioned studies adjust for known powerful covariates. We acknowledge that the present study cannot provide the optimal dosing strategy within the narrow therapeutic index of chemotherapy, and it is likely that further reductions, that is, 75% of full BSA-based doses may impact outcomes more profoundly.

Dose reduction in overweight and obese patients may originate from concerns regarding excessive toxicity when administering full-weight-based chemotherapy doses. However, for solid cancers, these concerns are not supported by the literature, and DR may compromise cure.[12] A limitation of our study is the lack of registered side effects and toxicities from our cohort due to the retrospective design; however, we did not find any excess 30- or 90-day mortality, which can be considered surrogates for treatment-related mortality. Previous studies investigating rate of haematological and non-haematological toxicities, and treatment-related mortality among overweight and obese AML patients receiving IC according to adjusted body weight or full dose, have not reported excessive toxicity in patients receiving full doses.[36,38]

To the best of our knowledge, this is the largest nationwide study conducted on real-world patients with a complete follow-up allowing a true population-based design. Still, only

TABLE 3 Crude and adjusted overall and relapse-free survival and five-year restricted mean survival for the total cohort and for case-matched cohort according to dose-reduction strata

		Kaplan–Meier (months)			Restricted mean survival time (months)		
Cohort	**Outcome**	**Strata**	***n*/events**	**Median survival (95% CI)**	**Crude Δ5y-RMST (95% CI)**	***n*/events**	**Adjusted Δ5y-RMST[a] (95% CI)**
Total	OS	Non-DR	482/344	17.5 (14.8–20.5)	1 (reference)	401/295	1 (reference)
		DR	54/38	17.0 (11.9–45.5)	−0.2 (−7.1–6.7)	47/32	0.8 (−5.7–7.3)
	RFS	Non-DR	298/211	15.0 (12.3–19.3)	1 (reference)	254/182	1 (reference)
		DR	35/25	14.5 (9.0–41.7)	−1.3 (−9.7–7.1)	30/20	0.2 (−8.4–8.8)
Case matched	OS	Non-DR	54/40	12.3 (5.5–26.3)	1 (reference)	—	—
		DR	54/38	17.0 (11.9–45.5)	3.1 (−5.9–12.1)	—	—
	RFS	Non-DR	35/25	11.3 (5.8–52.2)	1 (reference)	—	—
		DR	35/25	14.5 (9.0–41.7)	2.1 (−9.1–13.3)	—	—

Abbreviations: AML, acute myeloid leukaemia; BMI, body mass index; CI, confidence interval; dn AML, de novo AML; DR, dose reduction; OS, overall survival; RFS, relapse-free survival; RMST, restricted mean survival time; sAML, secondary AML; tAML, therapy-related AML; WBC, white blood cell count; WHO-PS, World Health Organization performance status score; Δ5y-RMST, difference in five-year RMST.

[a]Adjusted for age (continuous), sex (male and female), comorbidity (0, 1 and ≥2), WHO-PS (0–1, ≥2), BMI (continuous), cytogenetic risk category (favourable, intermediate, and adverse), AML subtype (dn-AML, sAML and tAML), and WBC (continuous).

a minor fraction of analysed patients were DR, thus limiting the statistical power of the current study. A substantial number of patients were excluded due to missing information on key variables. This exclusion was mainly due to missing chemotherapy dosing forms from earlier time periods occurring at a random pattern. Furthermore, we cannot exclude the possibility of residual confounding, or the existence of other covariates not captured or analysed resulting in unbalance between our groups. For example, the lack of mutational status because studies suggest that overweight could influence the mutational landscape including a lower frequency of high-risk mutations such as *TP53*; however studies have previously shown that overweight does not influence survival in AML.[8,40] Additionally, we had no available information on cumulative doses contained in IC. This could potentially mask DR in our dataset since shortening of IC, for example, from daunorubicin plus cytarabine (DA) '7 + 3' to '5 + 2' also results in dose reductions. Furthermore, chemotherapy regimens like fludarabine, cytarabine, idarubicin and granulocyte colony-stimulating factor (FLAG-Ida) may include dose reductions for older patients (i.e., cytarabine reduction from 2 g/m^2 to 1 g/m^2); however, this reduction is not done by decreasing rBSA but reflects an age-standardized reduction captured in our adjustment and age-stratified analysis.

In the present study we define overweight based on BMI; however, a high BMI does not reflect body composition, that is, the distribution of adipose and muscle tissue. The distinction between excessive muscle and adipose tissue as a cause of high BMI may be important since emerging evidence suggests a complex interplay between bone marrow adipose tissue, leukaemic cells and antineoplastic agents such as anthracyclines.[41]

In conclusion, the results of this nationwide study showed that approximately 10% of Danish overweight or obese patients with newly diagnosed AML treated with IC in the period 2000–2012 received reduced chemotherapy dose during remission induction therapy. Importantly, we did not observe a significant difference between patients receiving full dose and patients receiving a reduced dose. Our results need to be interpreted with caution due to the small number of patients treated with a reduced dose and therefore the limited power to reject the presence of clinically relevant differential outcomes.

AUTHOR CONTRIBUTIONS

Conception and design: Daniel T. Kristensen, Lars B. Nielsen, Marianne T. Severinsen. Administrative support: Marianne T. Severinsen. Provision of study materials or patients: Daniel T. Kristensen, Tove-Christina C. Kristensen, Lene Ø. Jepsen, Claudia Schöllkopf, Kim Theilgaard-Mönch, Tarec C. El-Galaly, Anne S. Roug, Marianne T. Severinsen. Collection and assembly of data: Daniel T. Kristensen, Lars B. Nielsen, Tove-Christina C. Kristensen, Anne S. Roug, Marianne T. Severinsen. Data analysis and interpretation: Daniel T. Kristensen, Lars B. Nielsen, Lasse H. K. Jakobsen, Tarec C. El-Galaly, Anne S. Roug, Marianne T. Severinsen. Manuscript writing: all authors. Final approval of manuscript: all authors. Accountable for all aspects of the work: all authors.

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CONFLICTS OF INTEREST

The authors declare no competing financial interests in relation to the present study. Tove-Christina C. Kristensen received travel grant from AbbVie (2021). Tarec C. El-Galaly was previously employed by Roche Ltd (Basel) (2019–2021) and has received a speaker fee from Abbvie (2021) and

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DATA AVIVALIBILITY STATEMENT

By Danish law the data cannot be shared directly; however, they can be assessed through application. E-mail to the corresponding author for additional information or see www.rkkp.dk/in-english/.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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