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Risk of acute myeloid leukemia and myelodysplastic syndrome among older women receiving anthracycline-based adjuvant chemotherapy for breast cancer on Modern Cooperative Group Trials (Alliance A151511)

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Compliance with ethical standards

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Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors. The manuscript only includes secondary analysis of pre-existing data that were collected as part of the included clinical trials.

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Abstract

Purpose—We examined acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS) events among 9679 women treated for breast cancer on four adjuvant Alliance for Clinical Trials in Oncology trials with >90 months of follow-up in order to better characterize the risk for AML/MDS in older patients receiving anthracyclines.

Methods—We used multivariable Cox regression to examine factors associated with AML/MDS, adjusting for age (≥65 vs. <65 years; separately for ≥70 vs. <70 years), race/ethnicity, insurance, performance status, and anthracycline receipt. We also examined the effect of cyclophosphamide, the interaction of anthracycline and age, and outcomes for those developing AML/MDS.

Results—On Cancer and Leukemia Group B (CALGB) 40101, 49907, 9344, and 9741, 7290 received anthracyclines; 15% were in the age ≥65 and 7% were ≥70. Overall, 47 patients developed AML/MDS (30 AML [0.3%], 17 MDS [0.2%]); 83% of events occurred within 5 years of study registration. Among those age ≥65 and ≥70, 0.8 and 1.0% developed AML/MDS (vs. 0.4% for age <65), respectively. In adjusted analyses, older age and anthracycline receipt were significantly associated with AML/MDS (adjusted hazard ratio [;HR] for age ≥65 [vs.<65] = 3.13, 95% confidence interval [CI] 1.18–8.33; HR for anthracycline receipt [vs. no anthracycline] = 5.16, 95% CI 1.47–18.19). There was no interaction between age and anthracycline use. Deaths occurred in 70% of those developing AML/MDS.

Conclusions—We observed an increased risk for AML/MDS for older patients *and* those receiving anthracyclines, though these events were rare. Our results help inform discussions surrounding anticipated toxicities of adjuvant chemotherapy in older patients.

Keywords

Breast cancer; Older patients; Leukemia; Myelodysplastic syndrome; Chemotherapy

Introduction

There are an estimated 20,830 cases of acute myeloid leukemia (AML) annually, representing 1.3% of all new cancer cases, with an approximate lifetime risk of 0.5–1% [1]. According to registry data, 14.7 women per 100,000 (0.01%) develop AML annually once they reach the age 65 years or older (vs. 1.8 women per 100,000 for ages <65) and the risk increases with age, with 20.2 women per 100,000 (0.02%) developing AML during ages 80–84 [1, 2]. Although myelodysplastic syndrome (MDS) is also a disease of aging, the incidence and lifetime risk for MDS is more challenging to define because of difficulties and/or delays in diagnosing MDS in some patients (e.g., unexplained anemia). As a result, there is a range of incidence rates reported in the literature (i.e., 20–50 cases per 100,000 for patients age >70 per year [0.02–0.05% of patients in this age group]) [3, 4]. According to recent registry data, 22.3 and 42.3 cases of MDS are diagnosed annually per 100,000 U.S.

women ages 70–79 and ≥80, respectively [1, 5]. Collectively, a new diagnosis of AML or MDS occurs annually in approximately 0.16% of U.S. women in the age 60 and older, translating into 0.8% of women in this age group over a 5-year period [1, 2, 5].

Although serious long-term sequelae of adjuvant chemotherapy for breast cancer are rare, malignant hematologic complications such as AML/MDS have been consistently demonstrated in patients receiving anthracycline-based chemotherapy. Prior studies have also shown that increasing age is associated with a higher risk for both AML/MDS compared with younger patients receiving treatment. However, assessments of therapy-related complications in older patients are limited by low numbers of older patients on studies, the small number of studies available within older populations specifically [6, 7], inclusion of dated adjuvant trials [7–9], or restriction to single institution [10], registry [11] or claims-based data [12]. Although claims-based studies are informative because of their large sample sizes, these analyses do not contain details on individual patient characteristics.

Up to 1% of patients have been reported to develop AML or MDS after receipt of anthracyclines [6–8, 12, 13], with a potential twofold increase for older (vs. younger) patients [7]. According to a recent report within National Comprehensive Cancer Network (NCCN) centers, patients receiving anthracyclines had a doubling of risk for developing a hematologic malignancy above baseline. In this NCCN analysis [6], the 5- and 10-year cumulative incidence for developing any marrow neoplasm in patients with breast cancer having surgery alone (i.e., baseline risk) were 0.05% (95% confidence interval [CI] 0–0.14) and 0.20% (95% CI 0–0.51), respectively. In contrast, those receiving trimodality therapy (surgery, chemotherapy, and radiation) had a 5- and 10-year incidence of 0.32% (95% CI 0.19–0.46) and 0.51% (95% CI 0.29–0.74), respectively. However, this NCCN study only evaluated age thresholds of <50 and ≥50 years, included myeloproliferative diagnoses other than AML and MDS, and did not specifically evaluate the effect of older age or performance status on event rates [6].

In this study of four Alliance for Clinical Trials in Oncology adjuvant chemotherapy trials for breast cancer, which now have extended follow-up, we characterized the rates, timing, and outcomes for AML/MDS events by age and evaluated the factors associated with development of these malignant complications. We compared AML/MDS event rates in anthracycline and non-anthracyline arms of each trial and in older versus younger patients. In addition, we separately examined risk for AML/MDS for those age ≥65 and age ≥70 at study entry.

Methods

Patients and data

We pooled data from four adjuvant trials enrolling patients during 1994–2010 which administered an anthracycline-containing regimen in at least one treatment arm: Cancer and Leukemia Group B (CALGB, now part of the Alliance for Clinical Trials in Oncology) 40101, CALGB 49907, CALGB 9344, and CALGB 9741 (N9831 was excluded because long-term adverse event hematologic toxicity data were not available). The agents administered, key eligibility and accrual dates, study sample sizes, and median follow-up

time for each study are shown in Table 1. Each study administered an anthracycline-containing regimen in at least one treatment arm. Eligible patients included any woman enrolled on these selected adjuvant studies.

Outcomes of interest

The primary endpoint of interest was any reported outcome of AML and/or MDS at any time during the follow-up period for patients enrolled on all included studies. We separately examined the occurrence of AML, MDS, and a combined event of AML/MDS for those in the age ≥65 and ≥70 compared to younger trial participants (age < 65). As secondary endpoints, for those who developed AML or MDS, we explored (a) the time from study registration date to AML/MDS report, (b) vital status (alive or dead at last follow-up), and (c) survival time from the AML/MDS report until death or last follow-up.

Independent variables

Independent variables of interest were age, defined as age ≥65 and age ≥70, and anthracycline receipt (yes/no). Control variables varied by model. The base model included race, ethnicity, Eastern Cooperative Oncology Group (ECOG) performance status (PS), and insurance status. Baseline body surface area (BSA) was initially considered as a covariate (as an additional marker of health status) but was not significantly associated with AML/MDS ($p = 0.4$), and was not included in models. An additional model included an interaction term for anthracycline*age to examine associations with AML/MDS events. A final model also included a variable to delineate whether a participant received anthracycline (as part of doxorubicin and cyclophosphamide [AC]), cyclophosphamide given without anthracycline (cyclophosphamide-methotrexate-5-fluorouracil [CMF]), or ‘other’ (paclitaxel or capecitabine monotherapy, combined as one group because of smaller sample sizes). All variables were categorized as per Table 2.

Statistical Analysis

Patient characteristics by age and clinical trial were compared using Chi square testing. We examined the overall frequency (reported as a proportion of the entire study population) of AML, MDS, or either event for each protocol by age ≥65 (vs. <65) and age ≥70 (vs. <70) and by other patient characteristics such as treatment received, BSA, and ECOG PS. Aside from BSA, comorbid conditions were not consistently collected and were not included. To better understand the timing of hematologic events and how they may relate to prior treatment, we examined the timing of AML and MDS reporting after study registration. Finally, we examined the vital status and survival time from AML/MDS reporting until death for women developing these events.

We then performed a series of multivariable Cox regression models [14] and competing risk models [15] for the outcomes of developing an AML/MDS event, first adjusting for age (≥65 vs. <65 and separately for ≥70 vs. <70), race, ethnicity, insurance, and ECOG PS (base model). We then sequentially repeated models after including a variable for (a) anthracycline receipt (yes/no) and (b) an interaction term for age*anthracycline receipt. In a final model, because all patients receiving an anthracycline also received cyclophosphamide as ‘AC,’ we repeated models after inclusion of a categorical variable for receipt of CMF, paclitaxel, or

capecitabine, or AC in efforts to examine the independent effects of CMF on AML/MDS events.

Because this study utilized pre-existing data, Institutional Review Board exemption at Dana-Farber Cancer Institute's Office for Human Research Studies was granted for these analyses. Data collection and statistical analyses were conducted by the Alliance Statistics and Data Center. All analyses were based on the study databases as of December 10, 2015.

Results

Cohort characteristics

We included 9679 women enrolled on four adjuvant trials. Overall, 15% of enrolled patients were age ≥65 and 7% were age ≥70. Baseline characteristics for women by study and by age are shown in Tables 2 and 3, respectively. Overall, 7290 received anthracycline-based therapy on study (as part of AC, AC-paclitaxel [ACT], or sequential A-T-C), while 2374 received capecitabine, CMF, or paclitaxel. All patients receiving anthracycline also received cyclophosphamide. Overall, 69 patients enrolled to trials never initiated protocol therapy and no AML/MDS events occurred in these patients ($n = 51$ from CALGB 40101, $n = 10$ from CALGB 49907, and $n = 8$ from CALGB 9741).

Most patients were white and had an ECOG of 0–1 when reported; the median age on studies ranged from 48 to 72. In comparisons of characteristics for trial participants in the age ≥65 vs. <65 (Table 3), older women were primarily insured by Medicare, while younger women were mostly privately insured. Although there were also differences for ECOG PS by age, approximately 53.5% of patients had missing PS, limiting comparisons. Mean BSA was similar by age. Comparisons for age ≥70 and <70 were similar to those shown for the age cut-off of 65 (data not presented).

AML and MDS events

Overall, 30 cases of AML (0.3%) and 17 cases of MDS (0.2%) were reported across all four studies. Unadjusted results by patient characteristics and treatments received are shown in Table 4. Approximately, 0.2–0.4% of those receiving an anthracycline as part of their treatment regimen developed AML or MDS compared with 0–0.7% of those receiving non-anthracycline-based regimens (of note the 0.7% was based on 1 patient [of 134] who received CMF). All patients in this analysis who received anthracycline also received cyclophosphamide as 'AC' and 46 of 47 women who developed AML/MDS received cyclophosphamide.

In unadjusted comparisons by age, 0.4 and 0.4% of patients in the age ≥65 developed AML and MDS, respectively, compared with 0.3 and 0.1% of patients who aged <65. In comparisons using an age cut-off of 70 years old, 0.3 and 0.7% of those who aged ≥70 developed AML and MDS, respectively, compared with 0.3 and 0.1% of those who aged <70 (data not shown). Unadjusted comparisons by age were not significant for the development of AML for either age cut-off, but were significant for both age cut-offs for MDS ($p = 0.018$ for age ≥65 and $p = 0.0004$ for age ≥70, data not shown).

In the adjusted base model, age was the only variable significantly associated with AML/MDS (adjusted hazard ratio [HR] 2.86 for age ≥65 [vs. age <65], 95% CI 1.08–7.70). After anthracycline receipt was added to the model (Table 4, right column), the HR for age ≥65 [vs. <65] = 3.13, 95% CI 1.18–8.33, similar to the base model, and the HR for anthracycline receipt was 5.16 (95% CI 1.47–18.19). The interaction term for anthracycline*age was not significant ($p = 0.98$), and it was removed from the final model. No other variables were significantly associated with the combined event of AML/MDS.

After addition of the categorical variable for CMF/AC/other to the base model, receiving 'other' chemotherapy (vs. AC) was significantly associated with a lower probability for AML/MDS (adjusted HR 0.07, 95% CI 0.01–0.55), but receipt of CMF was not significantly different from AC (adjusted HR 1.55, 95% CI 0.32–7.52).

The results for models using age 70 as a cut-off were similar to those reported for a threshold of age 65, with an adjusted HR for AML/MDS for age ≥70 [vs. age <70] = 3.44 (95% 1.18–10.0) in the models containing anthracycline (full model results not shown).

Time to AML and MDS events

The time-to-report of AML/MDS event rates by regimen is displayed in Table 5. Among those developing AML ($n = 30$), the median time-to-event was 1.65, 2.48, and 7.26 years after study registration for patients treated with AC, ACT, and CMF-treated patients, respectively (overall range 0.79–12.52 years). For MDS cases ($n = 17$), the median time-to-event was 2.74, 3.23, 2.22, and 5.87 years for those receiving AC, ACT, capecitabine, and CMF, respectively (overall range 0.29–7.84 years).

At last known follow-up, deaths had occurred in 33 of the 47 (70%) patients who developed AML or MDS (Supplemental Table). For those with AML specifically, deaths had occurred in 22 of 30 (73%) patients, with a median time-from-AML-report-to-death of 0.05 years (19 days) for the 11 women who received AC (range 0–3.68 years), 0.75 years for the 10 who received ACT (range 0.51–1.58 years), and 0.63 years for the 1 patient who received CMF. Among the 17 women who developed MDS, 11 (65%) deaths have been reported, with a median time-from-MDS report-to-death of 0.76 years for those receiving AC ($n = 5$) (range 0.20–3.67 years), 1.62 years for those who received ACT ($n = 4$) (range 0.39–2.71 years), 0.85 years for the patients who received capecitabine, and 1.28 years for the patients who received CMF.

Discussion

In this analysis of 9679 women with breast cancer receiving chemotherapy treatment on adjuvant Alliance protocols with over 90 months of follow-up, 30 cases of AML (0.3% patients) and 17 cases of MDS (0.2% of patients) have been reported to date. Among those who aged ≥65 and ≥70 who received chemotherapy on study, 0.8% (0.4% AML, 0.4% MDS) and 1.0% (0.3% AML, 1.7 % MDS) developed either AML or MDS, respectively, which is higher than what was observed in patients age<65 (0.3% developed AML, 0.1% developed MDS).

In adjusted models, older age and anthracyline were the only factors significantly associated with these events; however, there was no significant interaction for age and anthracycline use. All but 8 AML/MDS events (83%) occurred within 5 years of protocol registration, the time-frame that has typically been described for anthracycline-associated hematological malignant events, though a risk for later events has also been recognized [6, 7], and was also observed in our analysis for a small proportion of patients. Unfortunately, 70% of those developing AML/MDS died from these complications, often with a survival of less than one year, further emphasizing the seriousness of these events when they occur.

Reassuringly, our findings reflect the rarity of AML and MDS events for all women who were treated on study and who are typically expected to derive a 20–30% risk reduction for breast cancer mortality with adjuvant chemotherapy [16–18]. Our findings also suggest that age and anthracyclines may have independent effects on risk. Further, we would argue that the rates of AML observed in our study are not dissimilar from the incidence of AML [5] or MDS [2] observed in the general, aging population over a 5-year (60 months) time period (0.8% in those age ≥60 and higher risk with increasing age), where age itself is a dominant risk factor for hematologic malignancy. However, we acknowledge that isolating the impact of anthracycline receipt and its effect on age in studies such as ours is difficult because of the lack of a true ‘control’ group, the higher underlying risk for AML and MDS with increasing age as mentioned above, the fact that patients on study were likely healthier than the general population (because of eligibility requirements), and because of the co-administration of cyclophosphamide, which has also been shown to increase risk [19]. In our analysis, 46 of 47 patients who developed AML or MDS events had cyclophosphamide exposure, though it is important to note that the doses of cyclophosphamide typically used in adjuvant breast cancer have not traditionally been associated with higher hematologic malignancy risk [19, 20]. In attempts to explore the independent effect of cyclophosphamide further, we repeated analyses after including a variable for AC/CMF/other and found that receipt of paclitaxel or capecitabine was associated with lower risk of AML/MDS than AC, but results for CMF vs. AC had a wide confidence interval and have limited interpretability.

Although older patients with breast cancer receiving adjuvant chemotherapy derive the same breast cancer mortality benefit as younger women [8, 17, 18, 21], concerns for treatment-related toxicity and functional decline likely result in under-treatment of many women. Prospective studies have identified predictors of acute chemotherapy-related toxicity among older adults such as hearing loss, fall risk, social activity, and functional limitations in addition to previously described clinical factors and laboratory abnormalities [22, 23]. These studies nicely provide information to help predict for acute toxicity and powerfully inform decisions about administering chemotherapy; however, they do not provide guidance regarding the risk for longer-term toxicity, particularly patients’ susceptibility to develop rare complications such as AML or MDS. Further insight into the genomic and clinical factors associated with these serious complications is challenging but worthwhile and will likely require pooled serum and/or tissue-based analyses within large cohorts of patients in order to better understand predisposition for these rare events.

Our data confirm prior reports [6, 7, 9–12, 19, 20] that hematologic malignancies are rare in older patients receiving standard chemotherapy regimens, including anthracyclines.

However, these serious complications do occur, should be included in discussions about the anticipated benefits and risks of treatment, and should be described in the context of the underlying risk of AML and MDS with increasing age. The likelihood of developing AML/MDS should not limit the use of adjuvant chemotherapy regimens that include anthracyclines where breast cancer recurrence and mortality benefits are expected to be substantial, but should provide pause when chemotherapy benefits are marginal or uncertain.

Using pooled data from modern adjuvant chemotherapy protocols with extended follow-up for nearly 10,000 patients provides a powerful resource to study outcomes in smaller subgroups (e.g., older patients), and our results meaningfully add to the limited availability of literature about the risks for AML and MDS in older patients receiving anthracycline-based chemotherapy regimens. However, we acknowledge several study limitations. First, these are secondary analyses of previously collected data with varying follow-up and treatments. Second, there is no 'control' arm of patients who did not receive chemotherapy and we did not have consistent information on radiation receipt, comorbidity, or growth factor use, precluding inclusion in models. Third, these patients represent a selected group of patients receiving chemotherapy on Alliance protocols and may not be generalizable to all older patients with breast cancer. However, the regimens administered on these trials are standard agents used frequently in clinical practice. Fourth, AML/MDS events were rare, possibly limiting our ability to detect associations with clinical and patient factors. Fifth, because the capture of AML/MDS events and time-to-events relied on the accuracy of data previously captured during long-term follow-up for individual trials, it is possible that some event dates were not accurate due to delays in adverse event reporting. Sixth, we did not have access to detailed medical records or cytogenetics of the AML/MDS cases that occurred, limiting some of the interpretability of what might have been treatment-related or not. Finally, we recognize that there were competing causes of death for women in this cohort and it is possible that some women died from breast cancer (or other causes) before their AML/MDS would have been diagnosed.

In summary, we demonstrated a small but increased risk for AML/MDS for older versus younger patients receiving chemotherapy *and* in those receiving anthracyclines but without a clear interaction of treatment and age. These data can be used in discussions with patients and can further inform decisions regarding anthracycline-based chemotherapy safety, particularly for older patients, where prospective data on serious toxicities are limited.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Included Alliance trials

Adjuvant CALGB trial	Key eligibility	Treatments given	Years of accrual	Total study *N*	*N* (%) received anthracycline	*N* (%) age ≥65	*N*(%) age ≥70	Median follow-up time (mos.)
40101[15]	Up to 3 lymph nodes involved No locally advanced disease Performance status not specified	AC vs. T (4 vs. 6 cycles)	2002-2010	3871	1931 (50)	468 (12)	177 (5)	91.7
49907[2]	Age 65 and older Tumor >1 cm Life expectancy >5 years Performance status ≤2	AC/CMF vs. capecitabine	2002-2006	633	184 (29)	633 (100)	415 (66)	95.6
9344[16]	Node positive disease Performance status not specified	AC with 3 different doses of A (60, 75, 90 mg/m^2) × 4 cycles ± paclitaxel	1994-1997	3170	3170 (100)	182 (5)	55(2)	138.3
9741[17]	T1–T3, N1–N2 disease Performance status not specified	AC-T every two weeks vs. AC-T every 3 weeks vs. sequential A-T-C every 2 weeks	1997-1999	2005	2005 (100)	162 (8)	54(3)	99.6

CALGB is now part of the Alliance for Clinical Trials in Oncology

Eligibility criteria were collected from the primary publications of each trial

CALGB Cancer and Leukemia Group B, *Mos.* months, *AC* doxorubicin and cyclophosphamide, *CMF* cyclophosphamide, methotrexate, 5-fluorouracil, *T* paclitaxel, *ATC* doxorubicin, paclitaxel, cyclophosphamide

Table 2

Patient characteristics by trial (n = 9679)

Characteristic	Study					
	40101 (*N* = 3871)	**49907 (*N* = 633)**	**9344 (*N* = 3170)**	**9741 (*N* = 2005)**	**Total (*N* = 9679)**	***p* value**
Age at study entry (years)						<0.0001[a]
N	3871	633	3170	2005	9679	
Mean (standard deviation)	52.8 (9.6)	72.0 (4.8)	47.8 (9.8)	49.9 (9.8)	51.8 (11.1)	
Range	22.0–84.0	65.0–89.0	23.0–81.0	25.0–79.0	22.0–89.0	
Age group (years)						<0.0001[b]
<65	3403 (87.9%)	0 (0.0%)	2988 (94.3%)	1843 (91.9%)	8234 (85.1%)	
≥65	468 (12.1%)	633 (100.0%)	182 (5.7%)	162 (8.1%)	1445 (14.9%)	
Age group						<0.0001[b]
<70	3694 (95.4%)	218 (34.4%)	3115 (98.3%)	1951 (97.3%)	8978 (92.8%)	
≥70	177 (4.6%)	415 (65.6%)	55 (1.7%)	54 (2.7%)	701 (7.2%)	
Race						<0.0001[b]
White	3242 (83.8%)	538 (85.0%)	2653 (83.7%)	1652 (82.4%)	8085 (83.5%)	
Black	417 (10.8%)	72 (11.4%)	298 (9.4%)	218 (10.9%)	1005 (10.4%)	
Asian/Hawaiian/American Indian/ Indian Subcontinent	108 (2.8%)	10 (1.6%)	68 (2.1%)	39 (1.9%)	225 (2.3%)	
Other/missing/unknown/Hispanic American	104 (2.7%)	13 (2.1%)	151 (4.8%)	96 (4.8%)	364 (3.8%)	
Ethnicity						0.0619[b]
Hispanic/Latino	206 (5.3%)	30 (4.7%)	132 (4.2%)	81 (4.0%)	449 (4.6%)	
Non-Hispanic/not reported/unknown	3665 (94.7%)	603 (95.3%)	3038 (95.8%)	1924 (96.0%)	9230 (95.4%)	
ECOG performance status						<0.0001[b]
0	3441 (88.9%)	457 (72.2%)	0 (0.0%)	0 (0.0%)	3898 (40.3%)	
1	430 (11.1%)	161 (25.4%)	0 (0.0%)	0 (0.0%)	591 (6.1%)	
2	0 (0.0%)	15 (2.4%)	0 (0.0%)	0 (0.0%)	15 (0.2%)	
Missing	0 (0.0%)	0 (0.0%)	3170 (100.0%)	2005 (100.0%)	5175 (53.5%)	
Insurance						<0.0001[b]
Private	2684 (69.3%)	67 (10.6%)	2484 (78.4%)	1611 (80.3%)	6846 (70.7%)	
Medicaid based	366 (9.5%)	40 (6.3%)	195 (6.2%)	97 (4.8%)	698 (7.2%)	
Medicare/military/vet sponsored	572 (14.8%)	459 (72.5%)	209 (6.6%)	154 (7.7%)	1394 (14.4%)	
Other/missing	249 (6.4%)	67 (10.6%)	282 (8.9%)	143 (7.1%)	741 (7.7%)	
Body surface area[c]						<0.0001[a]
N	3832	632	3147	1948	9559	
Mean (standard deviation)	1.9 (0.2)	1.8 (0.2)	1.8 (0.2)	1.8 (0.2)	1.8 (0.2)	
Median	1.9	1.8	1.8	1.8	1.8	
*Q*1, *Q*3	1.7, 2.0	1.7, 2.0	1.7, 1.9	1.7, 1.9	1.7, 2.0	

Characteristic	Study					
	40101 (*N* = 3871)	**49907 (*N* = 633)**	**9344 (*N* = 3170)**	**9741 (*N* = 2005)**	**Total (*N* = 9679)**	***p* value**
Range	1.0–3.1	1.3–2.7	1.1–2.8	1.2–5.0	1.0–5.0	
Estrogen receptor status						<0.0001[b]
Negative	1298 (33.5%)	214 (33.8%)	1276 (40.3%)	668 (33.3%)	3456 (35.7%)	
Positive	2564 (66.2%)	417 (65.9%)	1871 (59.0%)	1283 (64.0%)	6135 (63.4%)	
Missing	9 (0.2%)	2 (0.3%)	23 (0.7%)	54 (2.7%)	88 (0.9%)	
Progesterone receptor status						<0.0001[b]
Negative	1681 (43.4%)	296 (46.8%)	1364 (43.0%)	826 (41.2%)	4167 (43.1%)	
Positive	2175 (56.2%)	333 (52.6%)	1771 (55.9%)	1116 (55.7%)	5395 (55.7%)	
Missing	15 (0.4%)	4 (0.6%)	35 (1.1%)	63 (3.1%)	117 (1.2%)	
Human epidermal growth factor receptor 2 status						<0.0001[b]
Negative	3017 (77.9%)	528 (83.4%)	0 (0.0%)	0 (0.0%)	3545 (36.6%)	
Positive	719 (18.6%)	76 (12.0%)	0 (0.0%)	0 (0.0%)	795 (8.2%)	
Not done/unknown/missing	135 (3.5%)	29 (4.6%)	3170 (100.0%)	2005 (100.0%)	5339 (55.2%)	

Because of rounding, percentages may not total 100

ECOG Eastern Cooperative Oncology Group

[a] By Kruskal Wallis testing

[b] By Chi square testing

[c] Body surface area is reported for those with available data only (n = 9559) and 1 additional patient had a value of 5 which was counted as missing

Table 3

Baseline patient characteristics for all trials by age (n = 9679)

Age at study entry (years)				
Characteristic	**<65 (*N* = 8234)**	**≥65 (*N* = 1445)**	**Total (*N* = 9679)**	***p* value**
Race				0.0234[b]
White	6838 (83.0%)	1247 (86.3%)	8085 (83.5%)	
Black	879 (10.7%)	126 (8.7%)	1005 (10.4%)	
Asian/Hawaiian/American Indian/Indian Subcontinent	198 (2.4%)	27 (1.9%)	225 (2.3%)	
Other/missing/unknown/Hispanic American	319 (3.9%)	45 (3.1%)	364 (3.8%)	
Ethnicity				0.5845[b]
Hispanic/Latino	386 (4.7%)	63 (4.4%)	449 (4.6%)	
Non-Hispanic/not reported/unknown	7848 (95.3%)	1382 (95.6%)	9230 (95.4%)	
ECOG performance status				<0.0001[b]
0	3047 (37.0%)	851 (58.9%)	3898 (40.3%)	
1	356 (4.3%)	235 (16.3%)	591 (6.1%)	
2	0 (0.0%)	15 (1.0%)	15 (0.2%)	
Missing	4831 (58.7%)	344 (23.8%)	5175 (53.5%)	
Insurance				<0.0001[b]
Private	6630 (80.5%)	216 (14.9%)	6846 (70.7%)	
Medicaid based	615 (7.5%)	83 (5.7%)	698 (7.2%)	
Medicare/military/vet sponsored	331 (4.0%)	1063 (73.6%)	1394 (14.4%)	
Other/missing	658 (8.0%)	83 (5.7%)	741 (7.7%)	
Body surface area[a]				0.3748[c]
N	8122	1437	9559	
Mean (standard deviation)	1.8 (0.2)	1.8 (0.2)	1.8 (0.2)	
Median	1.8	1.8	1.8	
*Q*1, *Q*3	1.7, 2.0	1.7, 2.0	1.7, 2.0	
Range	1.0–5.0	1.3–2.7	1.0–5.0	
Estrogen receptor status				0.0177[b]
Negative	2949 (35.8%)	507 (35.1%)	3456 (35.7%)	
Positive	5201 (63.2%)	934 (64.6%)	6135 (63.4%)	
Missing	84 (1.0%)	4 (0.3%)	88 (0.9%)	
Progesterone receptor status				0.0004[b]
Negative	3487 (42.3%)	680 (47.1%)	4167 (43.1%)	
Positive	4638 (56.3%)	757 (52.4%)	5395 (55.7%)	
Missing	109 (1.3%)	8 (0.6%)	117 (1.2%)	
Human epidermal growth factor 2 status				<0.0001[b]
Negative	2662 (32.3%)	883 (61.1%)	3545 (36.6%)	
Not done/unknown/missing	4952 (60.1%)	387 (26.8%)	5339 (55.2%)	

Age at study entry (years)				
Characteristic	**<65 (*N* = 8234)**	**≥65 (*N* = 1445)**	**Total (*N* = 9679)**	***p* value**
Positive	620 (7.5%)	175 (12.1%)	795 (8.2%)	
Anthracycline received				<0.0001[b]
No	1705 (20.7%)	669 (46.3%)	2374 (24.5%)	
Yes	6529 (79.3%)	761 (52.7%)	7290 (75.3%)	
Missing	0 (0.0%)	15 (1.0%)	15 (0.2%)	
Cyclophosphamide received				<0.0001[b]
No	1705 (20.7%)	535 (37.0%)	2240 (23.1%)	
Yes	6529 (79.3%)	895 (61.9%)	7424 (76.7%)	
Missing	0 (0.0%)	15 (1.0%)	15 (0.2%)	
CMF received				
No	8234 (100%)	1311 (90.7%)	9545 (98.6%)	
Yes	0 (0%)	134 (9.3%)	134 (1.4%)	
Paclitaxel or capecitabine only received				
No	6529 (79.3%)	910 (63.0%)	7439 (76.9%)	<0.0001
Yes	1705 (20.7%)	535 (37.0%)	2240 (23.1%)	

Because of rounding, percentages may not total 100

ECOG Eastern Cooperative Oncology Group

[a] Body surface area is reported for those with available data only ($n = 9559$)

[b] By Chi Square testing

[c] By Kruskal Wallis testing

Table 4

Unadjusted proportions of acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS) by relevant patient characteristics (left columns) and the adjusted hazard ratio (HR) of AML and MDS as a combined endpoint (right column)

Characteristic	Unadjusted incidence of AML (*n*, %)	*p* value[a]	Unadjusted incidence of MDS (*n*, %)	*p*-value[a]	Adjusted HR for AML/MDS (95% CI)[b]
Age (years)		0.435		**0.018**	
≥65	6 (0.4)		6 (0.4)		Reference
<65	24 (0.3)		11 (0.1)		**3.13 (1.18–8.33)**
Anthracycline received		**0.025**		0.464	
No	1 (0.0)		2 (0.1)		Reference
Yes	29 (0.4)		15 (0.2)		**5.16 (1.47–18.19)**
Type of chemotherapy received		0.078		0.233	–
AC	16 (0.4)		7 (0.2)		
ACT	13 (0.4)		8 (0.2)		
Capecitabine	0 (0)		1 (0.3)		
CMF[c]	1 (0.7)		1 (0.7)		
Paclitaxel	0 (0)		0 (0)		
CALGB protocol		0.506		0.215	–
40101	8 (0.2)		4 (0.1)		
49907	2 (0.3)		3 (0.5)		
9344	12 (0.4)		6 (0.2)		
9741	8 (0.4)		4 (0.2)		
Baseline ECOG PS		**<0.0001**		0.974	
0	9 (0.2)		6 (0.2)		Reference
1	0 (0)		1 (0.2)		0.73 (0.16–3.28)[d]
2	1 (6.7)		0 (0)		–
Missing	20 (0.4)		10 (0.2)		1.23 (0.60–2.53)
Race		0.475		0.400	
White	28 (0.3)		15 (0.2)		Reference
Other/missing/unknown/Hispanic	1 (0.3)		1 (0.3)		0.34 (0.05–2.24)
American	0 (0.0)		1 (0.4)		0.84 (0.11–6.18)
Asian/Hawaiian/American Indian/ Indian subcontinent	1 (0.1)		0 (0.0)		0.20 (0.03–1.44)
Black					
Ethnicity		0.162		0.807	
Non-Hispanic	27 (0.3)		16 (0.2)		Reference
Hispanic	3 (0.7)		1 (0.2)		2.92 (0.68–12.56)
Insurance		0.889		0.263	
Private	20 (0.3)		9 (0.1)		Reference
Medicaid	3 (0.4)		2 (0.3)		2.08 (0.74–5.90)
Medicare/military/vet sponsor	4 (0.3)		5 (0.4)		1.00 (0.34–2.98)

Characteristic	Unadjusted incidence of AML (*n*, %)	*p* value[a]	Unadjusted incidence of MDS (*n*, %)	*p*-value[a]	Adjusted HR for AML/MDS (95% CI)[b]
Other/missing	3 (0.4)		1 (0.1)		1.47 (0.49–4.42)

CALGB Cancer and Leukemia Group B, *ECOG PS* Eastern Cooperative Oncology Group Performance Status, *AC* doxorubicin and cyclophosphamide, *CMF* cyclophosphamide, methotrexate, 5-fluorouracil, *T* paclitaxel

[a] Unadjusted comparisons using Chi square testing; bolded results have $p < 0.05$

[b] Adjusted Cox proportional hazards model results, adjusting for age <65 versus ≥65, anthracycline received (yes/no), ECOG PS, race, ethnicity, and insurance. Bolded results are significant

[c] One patient received CM only and was categorized as CMF

[d] ECOG PS 1 and 2 were combined into one category for the model due to low numbers of patients with ECOG PS = 2

Table 5

Time from study registration to report of acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS) by chemotherapy regimen received

Chemotherapy regimen	*n*	Median (mean) Years to AML[a]	Min	Max	Standard deviation
AML events ($n = 30$)					
AC	16	1.65 (2.67)	0.79	12.52	0.74
ACT[b]	13	2.48 (2.78)	0.88	6.98	0.44
CMF	1	7.26 (7.26)	7.26	7.26	–
MDS events ($n = 17$)					
AC	7	2.74 (3.95)	2.03	7.84	0.83
ACT[b]	8	3.23 (3.47)	0.29	7.16	0.82
Capecitabine	1	2.22 (2.22)	2.22	2.22	–
CMF	1	5.87 (5.87)	5.87	5.87	–

AC doxorubicin and cyclophosphamide, *ACT* AC-paclitaxel, *CMF* cyclophosphamide, methotrexate, 5-fluorouracil

[a] From study registration

[b] Including all schedules of administration