Malignant Hematologic Complications Among Older Patients Receiving Adjuvant Anthracycline-Based Chemotherapy on Modern Cooperative Group Trials

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Outcomes of Interest

PRIMARY:

- MDS/AML events for included trials an time during follow-up period
  - By age 65+ and 70+ separately

SECONDARY:

- Compare event rates in those receiving anthracyclines (vs. non-anthracylines)
- Examine other factors that may be associated with MDS/AML in an adjusted model

Alliance Trials Included in our Analysis *

Trial	Treatments Given	Follow-up (median yrs)
~~**Z1041**~~	~~Neoadjuvant FEC->paclitaxel+trastuzumab vs. P+T->FEC+T~~	~~4.5~~
CALGB 40101**	AC vs. T (4 vs. 6 cycles)	7.5
CALGB 49907**	AC/CMF vs. capecitabine	8.6
CALGB 9344	AC (60, 75, 90 mg/m2 of A) x 4 cycles +/- paclitaxel	11.9
CALGB 9741	ACT on q2 vs. q3 week vs. sequential ATC	7.9

Total N	**12,883**
Age <65	**11,175 (87%)**
Age >/=65	**1,708 (13%)**
Age >/= 70	**810 (6%)**

*Cardiotoxicity not consistently reported in long term follow-up and not examined
**40101 and 49907 were only trials with non-anthracycline arms
***Z1041 had no long term AE data

Selected Baseline Demographics By Age Across Trials (n=9,679)

Variable	Age <65 (%)	Age 65+ (%)	Age 70+	P-value** (for <65 vs. 65+)
Race				<0.0001
White	83	86	87	
Black	10	8	10	
Asian	2	2	2	
Ethnicity				<0.0001
Hispanic	5	4	4	
Performance status				<0.0001
Missing	67	34	16	
0	27	50	61	
1	5	15	22	
2	0.2	1	2	
Insurance				<0.0001
Private	61	13	10	
Medicare and private	1	48	80	
Medicaid	5	1	5	
Missing	25	15	6	
Mean BSA (Q1, Q3)	1.8 (1.7-2.0)	1.8 (1.7, 1.9)	1.8 (1.3, 2.6)	0.09

AML and MDS Raw Frequencies by Trial (0.1-0.5%)

AML & MDS rates By Study

	40101 (N=3871)	49907 (N=633)	9344 (N=3170)	9741 (N=2005)	Total (N=9679)	p value
Acute myeloid leukemia						0.5059[1]
No	3863 (99.8%)	631 (99.7%)	3158 (99.6%)	1997 (99.6%)	9649 (99.7%)	
Yes	8 (0.2%)	2 (0.3%)	12 (0.4%)	8 (0.4%)	30 (0.3%)	
Myelodysplastic syndrome						0.2154[1]
No	3867 (99.9%)	630 (99.5%)	3164 (99.8%)	2001 (99.8%)	9662 (99.8%)	
Yes	4 (0.1%)	3 (0.5%)	6 (0.2%)	4 (0.2%)	17 (0.2%)	

[1]Chi-Square

AML/MDS Frequencies by Age, Agents, ECOG PS

AML and MDS Raw Frequencies by Age <65 and ≥65

AML & MDS rates By Age Group

	< 65 (N=8234)	>= 65 (N=1445)	Total (N=9679)	p value
Acute myeloid leukemia				0.4351[1]
No	8210 (99.7%)	1439 (99.6%)	9649 (99.7%)	
Yes	24 (0.3%)	6 (0.4%)	30 (0.3%)	
Myelodysplastic syndrome				0.0184[1]
No	8223 (99.9%)	1439 (99.6%)	9662 (99.8%)	
Yes	11 (0.1%)	6 (0.4%)	17 (0.2%)	

[1]Chi-Square

Overall MDS + AML = 0.4% in age <65 and 0.8% for age ≥65

AML and MDS Raw Frequencies by Age <70 and ≥70

AML & MDS rates By Age Group

	< 70 (N=8978)	>= 70 (N=701)	Total (N=9679)	p value
Acute myeloid leukemia				0.9030[1]
No	8950 (99.7%)	699 (99.7%)	9649 (99.7%)	
Yes	28 (0.3%)	2 (0.3%)	30 (0.3%)	
Myelodysplastic syndrome				0.0004[1]
No	8966 (99.9%)	696 (99.3%)	9662 (99.8%)	
Yes	12 (0.1%)	5 (0.7%)	17 (0.2%)	

[1]Chi-Square

MDS + AML = 0.4% in age <70 and 1.0% for age ≥70

AML and MDS Raw Frequencies by Agents Received

	AC (n=3695)	ACT (n=6514)	Cape (n=300)	CMF/CF (n=134)	Paclitaxel (n=1940)	Total (9,664)	P-value (chi-square)
AML	16 (0.4)	13 (0.4)	0 (0)	1 (1)	0 (0)	30 (0.3)	0.078
MDS	7 (0.2)	8 (0.2)	1 (0.3)	1 (1)	0 (0)	17 (0.2)	0.233

Note: Some interesting findings for ECOG PS as well (higher rates of AML for ECOG PS=2 (vs. 0,1) but numbers very small (data not shown here)

Adjusted Cox models for AML/MDS Combined

ONLY AGE and ANTHRACYCLINE RECEIPT WERE SIGNIFICANT

Age <65 vs. 65+

Variable	HR (95%CI)	P-value
Age <65 vs. 65+	0.29 (0.11-0.77)	0.013
Anthracycline no vs. yes	0.26 (0.09-0.78)	0.016

Age <70 vs. 70+

Variable	HR (95%CI)	P-value
Age <70 vs. 70+	0.25 (0.08-0.75)	0.013
Anthracycline no vs. yes	0.25 (0.08-0.75)	0.08363

**[adjusting for race/ethnicity, ECOG PS (incl those with missing), insurance, anthracycline yes/no]:

Limitations

- These are secondary analyses of previously collected data with varying follow-up and treatments administered
- No ‘control’ arm of patients
- Patients represent a selected group of patients receiving chemotherapy on Alliance protocols and may not be generalizeable to all older patients receiving treatment
- MDS/AML events are rare

Summary, Conclusions, and Implications

- Context: 0.5-1% risk of developing AML in U.S. population at baseline
  - Risk increases with age and MDS incidence harder to define
- Past studies examining AML for those receiving anthracyclines report overall rates of 1% but with possible 2-fold increase for older patients
- Our findings show 0.8-1.0% of those age 65+ and 70+ developed AML or MDS after receipt of chemotherapy on study
- In adjusted models, age and anthracycline were significantly associated with these events
- Overall, events are very rare and not that increased over general population risk, though higher than younger patients and in those receiving anthracyclines
- Results are reassuring and reflect safety of these drugs but with rare, serious complications
  - Pooled, long term data using modern regimens are powerful and add to the body of literature

Next Steps

- Completing statistical analyses and write-up
- Draft to co-authors soon

Thank you!!

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