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Comprehensive Support Project

NSAS BC02 Substudy of Chemo-Induced Amenorrhea (CIA) in Premenopausal Women who received either taxane alone or AC followed by taxane as a Postoperative Chemotherapy

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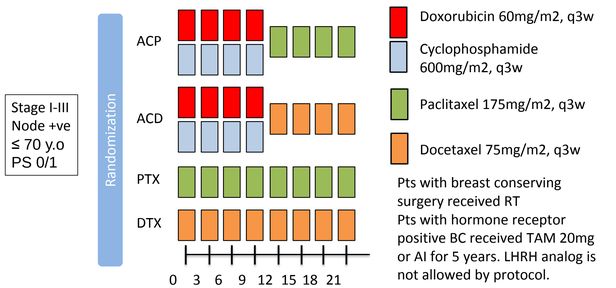
Background

- Chemotherapy has a direct cytotoxic effect to breast cancer cells as well as ovarian suppression. In NSABP-B30 study, Swain, et al demonstrated that CIA contributed to reduce recurrence and prolong overall survival in premenopausal women with ER positive breast cancer.
- Thus far, incidence of CIA by anthracycline and cyclophosphamide (AC) or CMF has been reported. However, there has been no report on CIA by taxane alone therapy.
- NSAS-BC02 (Watanabe T, ASCO2009) compared taxane alone (q3w Docetaxel 75mg/m2 x8: DTX:, q3w Paclitaxel 175mg/m2 x8: PTX) to AC -> taxane (q3wAC 60/600mg/m2 x4 -> DTX x4: ACD, q3wAC x4 -> PTX x4: ACP) in postoperative patients with node-positive breast cancer.
- We conducted post hoc retrospective study to examine the incidence of the CIA and the relationship between CIA and prognosis in NSAS-BC02 (CIA substudy) .

NSAS BC 02 study Schema



Pts with breast conserving surgery received RT
Pts with hormone receptor positive BC received TAM 20mg or AI for 5 years. LHRH analog is not allowed by protocol.

Objectives

- To examine the incidence of CIA after receiving chemotherapy in pre/perimenopausal women participating in NSAS BC02.
- To examined the relationship between CIA and prognosis in this substudy.

Methods

- Menstrual status of all women participating in NSAS BC02 was assessed at study entry, every cycle during chemotherapy, at 2 months after protocol treatment, and then at every 6 months until 5 years. After 5 years, menstrual status was assessed annually.
- Women with regular menstrual cycles (premenopause) or irregular menstrual cycle (perimenopause) at study entry were included in this CIA substudy.
- Definition of CIA is no menstrual cycle for at least 6 months after chemotherapy.
- Interactions between CIA incidence and risk factors were evaluated using logistic regression analysis.
- DFS and OS were estimated using the Kaplan-Meier method and was compared using the log-rank test. Hazard ratio (HR) and 95% confidence interval (CI) were calculated by Cox proportional hazards model. To reduce guarantee time bias (Giobbie-Hurder et al. JCO 2013), time-dependent Cox model was used.

Menstrual status by treatment group

	Menstrual status			Total
Treatment group	Regular	Irregular	Ceased	
ACP	71	20	166	257
ACD	87	18	152	257
PTX	79	15	163	257
DTX	78	27	149	254
Total	315	80	630	1025

Incidence of CIA by treatment group

	ACP (n=91)		ACD (n=105)		PTX (n=94)		DTX (n=105)	
	n	%	n	%	n	%	n	%
CIA (n=287)	70	76.9%	79	75.2%	59	62.8%	79	75.2%
NON-CIA (n=108)	21	23.1%	26	24.8%	35	37.2%	26	24.8%

	AC→Taxane (n=196)		Taxane (n=199)		P value
	n	%	n	%	
CIA (n=287)	149	76.0%	138	69.4%	0.14
NON-CIA (n=108)	47	24.0%	61	30.7%	

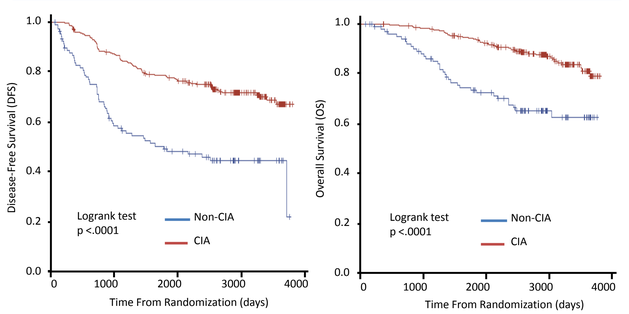
Interactions between CIA incidence and risk factors

		Reference	Odds ratio	95% CI		P value
	taxane	AC→taxane	0.67	0.41	1.09	0.10
Age		5 years	1.50	1.23	1.83	<.0001
BMI		5kg/m^2	1.35	0.93	1.95	0.11
Stage	IIA	I	1.05	0.47	2.37	0.90
	IIB		1.22	0.51	2.91	0.65
	III		1.20	0.38	3.73	0.76
ER status	negative	positive	0.48	0.29	0.80	0.0051
T size	≥ 3cm	< 3cm	0.70	0.39	1.26	0.23
No. LN	4 - 9	1 - 3	1.58	0.85	2.96	0.15
	≥ 10		1.35	0.61	3.01	0.46
Surgery	mastectomy	Breast conserving	0.97	0.58	1.64	0.91

Patient characteristics by CIA

	Non-CIA	CIA	P value
Age	41.7 (27.0-54.0)	45.1 (24.0-62.0)	< .0001
BMI	22.1 (16.0-33.6)	22.8 (17.4-34.4)	0.0355
Stage I	13 (12.0%)	37 (12.9%)	0.9409
II	81 (75.0%)	219 (76.3%)	
III	14 (13.0%)	31 (10.8%)	
T size >3cm	60 (55.6%)	181 (63.1%)	0.1725
<3cm	48 (44.4%)	106 (36.9%)	
No. LN 1-3	71 (65.7%)	173 (60.3%)	0.484
4-9	23 (21.3%)	78 (27.2%)	
>10	14 (13.0%)	36 (12.5%)	
ER positive	43 (39.8%)	178 (62.0%)	0.0003
negative	65 (60.1%)	108 (37.6%)	
PgR positive	41 (38.0%)	174 (60.6%)	0.0001
negative	65 (60.2%)	112 (39.0%)	

DFS and OS by CIA in all substudy patients



DFS and OS by CIA according to ER status

	Hazard ratio	95% Confidence interval		p value
DFS all substudy patients	0.34	0.24	0.50	< 0.0001
ER positive	0.37	0.20	0.69	0.020
ER negative	0.28	0.17	0.48	< 0.0001

Prognostic factors in DFS by time-dependent Cox model

It must be considered that patients with short DFS times were disproportionately allocated to the no-amenorrhea group , because assignment into CIA group required a sufficiently long DFS interval before classification as having amenorrhea. To eliminate guarantee time bias (Giobbie-Hurder et al. JCO 2013), we used time-dependent Cox model.

DFS (All substudy patients)		Reference	HR	95% CI		P value
	CIA	non-CIA	0.77	0.52	1.16	0.21
Age		5 years	0.80	0.70	0.91	0.0009
BMI		5kg/m^2	0.88	0.68	1.14	0.33
Stage	IIA	I	1.11	0.56	2.17	0.77
	IIB		0.87	0.43	1.76	0.70
	III		1.02	0.45	2.32	0.96
ER status	negative	positive	1.90	1.32	2.74	0.0005
T size	≥ 3cm	< 3cm	1.91	1.28	2.85	0.0016
No. LN	4 - 9	1 - 3	2.29	1.51	3.48	<.0001
	≥ 10		3.57	2.19	5.80	<.0001
Surgery	mastectomy	Breast conserving	0.89	0.61	1.30	0.54

DFS by time-dependent Cox model according to ER status

Subjects	Hazard ratio	95% Confidence interval	p value
All substudy patients	0.77	0.52-1.16	0.21
ER positive	0.60	0.31-1.16	0.13
ER negative	0.82	0.47-1.43	0.49

Discussion

- To our knowledge, this is the first report that eight cycles of q3w docetaxel or paclitaxel alone resulted in high rate of CIA.
- This result is contrary to our expectation that AC containing regimen induced more amenorrhea, because it is believed cyclophosphamide plays major role to cause the CIA.
- Higher age and ER positivity are predictors of CIA, similar as previous reports. .
- In this study, CIA can predict good DFS regardless ER status. However after eliminating GTB, CIA is no longer predictive factor in both ER positive and ER negative patients, unlike NSABP-B30 and IBCSG 13-93 trial
- The reasons of discrepancy could be because sample size of subgroup in this study is small and analytical method to remove GTB in our study is different from other studies using landmark analysis.

Conclusion

- Eight cycles of taxane treatment caused a high frequency of CIA in premenopausal women with breast cancer (PTX62.8% and DTX75.2%) comparable to 4 cycles of AC followed by 4 cycles of taxane (no statistically significant difference: p=0.14).
- It would be cautious to conclude that CIA was statistically significant association with prognosis, because it might be due to GTB.

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