Higher Rate of Severe Toxicities in Obese Patients Receiving dose-dense Chemotherapy According to Unadjusted Body Mass Index – Results of the Prospectively Randomized GAIN study

Jenny Furlanetto[1], Wolfgang Eiermann[2], Frederik Marmé[3], Toralf Reimer[4], Mattea Reinisch[5], Sabine Schmatloch[6], Elmar Stickeler[7], Christoph Thomssen[8], Michael Untch[9], Carsten Denkert[10], Gunter von Minckwitz[1], Valentina Nekljudova[1], Sibylle Loibl[1], Volker Möbus[11]

[1]German Breast Group, Neu-Isenburg; [2]Inter-disciplinary Oncological Center, München; [3]University Clinic Heidelberg, Heidelberg; [4]Klinikum Südstadt Rostock, Rostock; [5]Kliniken Essen-Mitte, Essen; [6]Elisabeth-Krankenhaus Brustzentrum, Kassel; [7]University Clinic Freiburg, Freiburg; [8]Universitiy Clinic Halle, Saale; [9]Helios Klinikum Berlin Buch, Berlin; [10]Charite Berlin, Berlin; [11] Klinikum Frankfurt -Hoechst, Frankfurt

P1-13-04

Background

In routine clinical practice chemotherapy (CT) doses are frequently capped at a body surface area (BSA) of 2.0 m^2 or adjusted to an ideal weight (i.e. [body length in cm - 10%] + 40% [current weight-ideal weight]) for obese patients (BMI≥30 according to WHO) due to safety reasons.[1,2] There are no data on CT dosing within intense dose-dense regimen for obese patients. Therefore, a retrospective analysis of the GAIN study population has been conducted.

Objectives

Primary objectives:

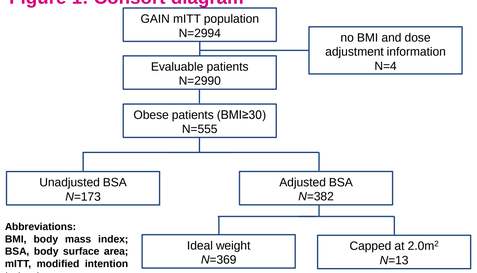
- Hematological and non-hematological toxicities in obese patients receiving full dose CT compared to patients receiving CT according to an adjusted body surface area.
- Disease-free survival (DFS) and overall survival (OS) in obese patients receiving full dose CT compared to patients receiving CT according to an adjusted body surface area.

Materials and Methods

Between August 2004 and July 2008 a total of 3023 patients were enrolled in the GAIN study, a randomized phase III adjuvant trial, comparing two types of dose-dense regimen. Patients were randomized to intense dose-dense ETC (Epirubicin 150 mg/m^2, Paclitaxel 225 mg/m^2, Cyclophosphamide 2500-2000 mg/m^2, i.v. q15 for 3 cycles) or EC followed by T plus capecitabine (X) (EC-TX) (E 112.5 mg/m^2 + C 600 mg/m^2, i.v. q15 for 4 cycles followed by T 67.5 mg/m^2 i.v. q8 for 10 weeks + X: 2000 mg/m^2 p. o. day 1-14, q22 for 4 cycles). An adjustment of CT dose to an ideal weight for obese patients was implemented by a protocol amendment. Yet some patients received a dose adjustment by capping at 2.0 m^2. We retrospectively evaluated a total of 555 patients with a BMI≥30 (Figure 1). Data on BSA and dose adjustment were collected from case report forms. Toxicities were compared between patients who received CT according to an unadjusted or adjusted BSA using the 2-sided exact test of Fisher. DFS and overall survival OS were calculated using the Kaplan-Meier method and the log-rank test.

Results

Figure 1: Consort diagram



Abbreviations:
BMI, body mass index; BSA, body surface area; mITT, modified intention to treat.

Table 1: Baseline characteristics

characteristics at baseline	non obese patients N=2435		obese N=555		P-value*	unadjusted BSA N=173		adjusted BSA N=382		P-value**
	N	valid %	N	valid %		N	valid %	N	valid %	
Age (years)					**<0.001**					**0.456**
<40	387	15.9	50	9.0		19	11.0	31	8.1	
40-49	892	36.6	163	29.8		54	31.2	109	28.5	
50-59	763	31.3	204	36.1		63	36.4	141	36.9	
>60	393	16.1	138	25.0		37	21.4	101	26.4	
Median age (range)	49 (21-72)		50 (27-70)			52 (27-69)		53 (29-70)		
ECOG PS					**0.290**					**0.053**
0	2310	95.0	513	92.6		165	95.9	348	91.1	
1	122	5.0	41	7.4		7	4.1	34	8.9	
Tumor stage					**<0.001**					**0.989**
pT1	817	33.7	137	24.8		43	24.9	94	24.7	
pT2	1326	54.6	340	61.5		105	60.7	235	61.8	
pT3	238	9.8	67	12.1		22	12.7	45	11.8	
pT4	46	1.9	9	1.6		3	1.7	6	1.6	
Nodal status					**0.022**					**0.497**
pN0	0	0.0	0	0		0	0.0	0	0.0	
pN1	937	38.5	193	34.8		59	34.1	134	35.1	
pN2	869	35.7	187	33.7		64	37.0	123	32.2	
pN3	629	25.8	175	31.5		50	28.9	125	32.7	
Histo type					**0.362**					**0.119**
ductal	1876	77.0	434	78.2		142	82.1	292	76.4	
lobular	314	12.9	60	10.8		19	11.0	41	10.7	
other	245	10.1	61	11.0		12	6.9	49	12.8	
Surgery					**0.052**					**0.264**
BCS	1339	55.0	330	59.6		97	56.1	233	61.2	
mastectomy	1095	45.0	224	40.4		76	43.9	148	38.8	
Tumor grade					**0.815**					**0.098**
1	79	3.2	17	1		2	1.2	15	3.9	
2	1221	50.2	286	51.7		84	48.8	202	53.0	
3	1131	46.5	250	45.2		86	50.0	164	43.0	
HR status					**0.434**					**0.286**
Negative	554	22.8	135	24.4		47	27.3	88	23.0	
Positive	1881	77.2	419	75.6		125	72.7	294	77.0	
HER2 status					**0.266**					**1.000**
Negative	1770	77.6	418	79.9		128	80.0	290	79.9	
Positive	511	22.4	105	20.1		32	20.0	73	20.1	

Overall, 18.6% (n=555) of patients were obese: 31.2% (n=173) of them received CT according to an unadjusted BSA. For the remainder BSA was adjusted to ideal weight or was capped at 2.0 m^2 (68.8%; n=382) (Table 1). A total of 14.7% (n=25) of obese patients receiving full dose of chemotherapy vs 6.3% (n=24) of obese patients with an adjusted BSA experienced febrile neutropenia (p=0.003) and 9.4% (n=16) vs 2.9% (n=11) high grade thrombopenia (p=0.002) (Table 2). Overall, 17.3% (n=30) vs 9.9% (n=38) had a thromboembolic event (p=0.017), which was high grade in 12.7% (n=22) vs 6.3% (n=24), respectively (p=0.019) and 2.9% (n=5) vs 0.3% (n=1) experienced high grade hot flushes (p=0.013). The only significant differences in favor of the non-adjusted group were for dizziness (4.6% [n=8] vs 11.0% [n=42]; p=0.016), diarrhea (18.5% [n=32] vs 27.2% [n=104]; p=0.033) and an increase in serum creatinine (6.6% [n=11] vs 13.8% [n=52]; p=0.019) (Table 3).

No differences in DFS and OS were observed between the two groups (Figure 2): 5year DFS 81.9% [95% CI 74.9%-87.2%] vs 80.8% [95% CI 76.3%-84.6%]; p=0.850; 5year OS 86.4% [95% CI 79.9%-90.9%] vs 88.3% [95% CI 84.4%-91.3%]; p=0.491.

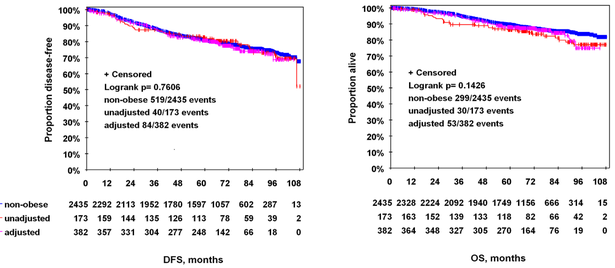
Table 3: Non-hematological toxicities

Non-hematological adverse events	grade	non-obese N=2435 N	non-obese N=2435 valid %	obese unadjusted BSA N=173 N	obese unadjusted BSA N=173 valid %	obese adjusted BSA N=382 N	obese adjusted BSA N=382 valid %	P-value non-obese vs obese unadjusted	P-value obese unadjusted vs adjusted
Infection	**1-4**	768	31.5	52	30.1	133	34.8	0.735	0.286
	3-4	203	8.4	16	9.2	37	9.8	0.670	0.878
Mucositis	**1-4**	1162	47.7	85	49.1	164	42.9	0.753	0.197
	3-4	108	4.4	7	4.0	23	6.0	1.000	0.420
Thromboembolic event	**1-4**	226	9.3	30	17.3	38	9.9	**0.001**	**0.017**
	3-4	145	6.0	22	12.7	24	6.3	**0.002**	**0.019**
Cardiac Disorder	**1-4**	179	7.4	11	6.4	29	7.6	0.762	0.724
	3-4	28	1.2	4	2.3	7	1.8	0.159	0.746
Nausea	**1-4**	1371	56.3	92	53.2	216	56.5	0.429	0.463
	3-4	127	5.2	6	3.5	19	5.0	0.375	0.513
Vomiting	**1-4**	811	33.3	53	30.6	113	29.6	0.504	0.841
	3-4	127	5.2	9	5.2	11	2.9	1.000	0.218
Diarrhea	**1-4**	601	24.7	32	18.5	104	27.2	0.067	**0.033**
	3-4	65	2.7	6	3.5	12	3.2	0.470	0.802
Hepatobiliary disorder	**1-4**	2066	84.8	138	79.8	319	83.5	0.082	0.282
	3-4	190	7.8	7	4.0	29	7.6	0.074	0.138
Increased serum creatinine	**1-4**	233	9.8	11	6.6	52	13.8	0.220	**0.019**
	3-4	8	0.3	0	0.0	3	0.8	1.000	0.557
Renal and urinary disorder	**1-4**	332	13.6	18	10.4	67	17.5	0.250	**0.031**
	3-4	15	0.6	2	1.2	7	1.8	0.313	0.727
Sensory neuropathy	**1-4**	1183	48.6	79	45.7	169	44.2	0.479	0.783
	3-4	93	3.8	10	5.8	10	2.6	0.221	0.084
Dizziness	**1-4**	188	7.7	8	4.6	42	11.0	0.177	**0.016**
	3-4	8	0.3	2	1.2	2	0.5	0.139	0.592
Hand-foot syndrome	**1-4**	697	28.6	44	25.4	99	25.9	0.385	1.000
	3-4	143	5.9	4	2.3	17	4.5	0.058	0.336
Hot flushes	**1-4**	381	15.6	22	12.7	49	12.8	0.329	1.000
	3-4	17	0.7	5	2.9	1	0.3	**0.013**	**0.013**
Fatigue	**1-4**	1212	49.8	76	43.9	202	52.9	0.157	0.055
	3-4	131	5.4	8	4.6	29	7.6	0.861	0.270

Table 2: Hematological toxicities

Hematological adverse events	grade	non-obese N=2435 N	non-obese N=2435 valid %	obese unadjusted BSA N=173 N	obese unadjusted BSA N=173 valid %	obese adjusted BSA N=382 N	obese adjusted BSA N=382 valid %	P-value non-obese vs obese unadjusted	P-value obese unadjusted vs adjusted
Leucopenia	**1-4**	2192	91.2	150	87.7	334	87.9	0.129	1.000
	3-4	1513	63.0	105	61.4	210	55.3	0.683	0.193
Neutropenia	**1-4**	1626	68.8	101	61.2	245	65.9	**0.046**	0.329
	3-4	1080	45.8	71	43.3	155	42.1	0.571	0.849
Febrile neutropenia	**3-4**	201	8.4	25	14.7	24	6.3	**0.008**	**0.003**
Anemia	**1-4**	2047	85.3	141	82.5	312	82.1	0.318	1.000
	3-4	77	3.2	9	5.3	13	3.4	0.180	0.348
Thrombopenia	**1-4**	1056	44.0	77	45.0	154	40.5	0.811	0.351
	3-4	125	5.2	16	9.4	11	2.9	**0.034**	**0.002**

Figure 2: Disease-free-survival and overall survival



Conclusions

This analysis of patients treated with a dose-dense regimen showed that obese patients who received CT according to their real BSA have a higher risk of severe toxicities, in particular of febrile neutropenia, high grade thrombopenia and high grade thromboembolic events. Therefore, a dose adjustment of intense dose-dense CT should be performed for obese patients to avoid life-threatening complications.

References

1. Griggs JJ, Mangu PB, Anderson H et al. American Society of Clinical Oncology. Appropriate chemotherapy dosing for obese adult patients with cancer: American Society of Clinical Oncology clinical practice guideline. J Clin Oncol. 2012;30:1553-61.
2. Hourdequin KC, Schpero WL, McKenna DR et al. Toxic effect of chemotherapy dosing using actual body weight in obese versus normal-weight patients: a systematic review and meta-analysis. Ann Oncol. 2013;24:2952-62.

Presented at: San Antonio Breast Cancer Symposium - December 8-12, 2015