Efficacy and safety of Darbepoetin alfa or Epoetin beta in 2994 high risk early breast cancer patients participating in the German Adjuvant Intergroup Node-positive Study (GAIN)

Marion van Mackelenbergh[1], Sibylle Loibl[1], Christian Jackisch[2], Hans-Joachim Lueck[3], Andreas Schneeweiss[4], Hans Tesch[5], Nadia Harbeck[6], Sabine Schmatloch[7], Tanja Fehm[8], Jens Huober[9], Volkmar Müller[10], Ingo Bauerfeind[11], Michael Untch[12], Gunter von Minckwitz[1], Valentina Nekljudova[1], Volker Möbus[13]

[1]German Breast Group Neu-Isenburg, [2]Sana Klinikum Offenbach, [3]Gynäkologisch-Onkologischen Schwerpunktpraxis Hannover, [4]Universitätsklinikum Heidelberg, [5]Praxis Bethanien, [6]Brustzentrum der Universität München, [7]Elisabethenkrankenhaus Kassel, [8]Universitätsklinikum Düsseldorf, [9]Universitätsklinikum Ulm, [10]Universitätsklinikum Hamburg, [11]Klinikum Landshut, [12]Helios Kliniken Berlin-Buch, [13]Klinikum Frankfurt-Höchst

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Background

Reduced quality of life during chemotherapy is often due to fatigue and dyspnea caused by chemotherapy-induced anemia. In breast cancer patients the incidence is estimated to be above 50% and rising during the course of treatment resulting as well in therapy delays. Despite red blood cell transfusion the administration of erythrocyte stimulating factors (ESF) serves as a treatment option. In comparison with conventional chemotherapy intense dose dense regimens have proven to be beneficial in high-risk breast cancer patients, but higher incidences of anemia have been reported. In the GAIN trial two dose dense regimens were evaluated and patients received either Darbepoetin alfa or Epoetin beta. The aim of this subanalysis was to analyse the efficacy and safety of the application of two different ESF during adjuvant chemotherapy for primary node positive breast cancer.

Materials and Methods

Patients were randomly assigned to receive three courses each of epirubicin (E), paclitaxel (T), cyclophosphamide (C) all given at 2-week intervals i.v. (idd ETC-regimen) or ddEC followed by paclitaxel weekly (Tw) plus capecitabine (X)(EC-TX-regimen). All patients received either primary prophylaxis with Epoetin beta (Epo) (450IE/kg weekly) or Darbepoetin alfa (D) (4,5µg/kg biweekly). Allocation to each ESF happened alternately by date of randomization. Patient outcome (rate of anemia and thromboembolic events, disease free survival (DFS), overall survival (OS)), overall and by regimen were compared according to ESF type applied and in subgroups defined by age.

Table 1: Baseline patient and tumor characteristics

Parameter	overall (N=2994) N (valid %)	Darbepoetin alfa (N=1482) N (valid %)	Epoetin beta (N=1512) N (valid %)
Age, years, median (range)	49.8 (20-72)	49.7 (20-71)	49.9 (23-72)
BMI, median (range)	26.04 (16.5-52.7)	26.1 (16.9-51.4)	26 (16.5-52.7)
pT1	955 (32.0)	490(33.2)	465 (30.9)
pT2	1669 (55.9)	823 (55.7)	846 (56.2)
pT3	305 (10.2)	136 (9.2)	169 (11.2)
pN1	1131 (37.8)	563 (38.0)	568 (37.6)
pN2	1058 (35.3)	520 (35.1)	538 (35.6)
pN3	805 (26.9)	399 (26.9)	406 (26.9)
ER and/or PgR positive	2301 (76.9)	1132 (76.4)	1169 (77.3)
HER2 positive	617 (22.0)	329 (23.7)	288 (20.3)
Tumor grade 3	1385 (46.4)	678 (45.8)	707 (46.9)
Ductal-invasive	2314 (77.3)	1152 (77.7)	1162 (76.9)

Results

2994 patients were randomized to receive one of the dose dense chemotherapies and of these 1482 patients were given Darbepoetin alfa and 1512 received Epoetin beta. In the trial 84.7% of patients suffered from anemia in the Darbepoetin as well as in the Epoetin group and grade 3/4 anemia was observed in 3.6% vs 3.1% of patients, respectively. In the ETC arm anemia rates, especially grade 3/4 were slightly higher, but there was no significant difference within the treatment arms according to ESF applied (anemia any grade: D 86.1% vs. Epo 87.2%; EC-TX: D 83.2% vs. Epo 82.3%). In the ETC arm anemia was most frequently observed in patients aged 60+ years, but there was no significant difference between the ESF (D 90.5% vs. Epo 89.8%). No significant differences in the incidence of anemia by ESF treatment were observed in various age groups of the EC-TX arm.
Thromboembolic events occurred in 9.1% in the Darbepoetin group and in 10.1% of patients treated with Epoetin (p=0.355). Interestingly there were more thromboembolic events in the EC-TX arm compared to the ETC arm (p<0.001), but irrespective of the ESF type (EPC: D 7.0% vs. Epo 7.7%; EC-PX: D 11.3% vs. Epo 12.5%). OS and DFS analyses showed no difference between ESF treatment overall as well as stratified by chemotherapy regimen.

Table 2: Anemia according to chemotherapy and ESF

	CTC Grade	Darbepoetin alfa N (valid %)	Epoetin beta N (valid %)	p-value
ETC	any	644 (86.1)	635 (87.2)	n.s.
	3-4	37 (4.9)	29 (4.0)	n.s.
EC-TX	any	593 (83.2)	629 (82.3)	n.s.
	3-4	16 (2.2)	17 (2.2)	n.s.
overall	any	1237 (84.7)	1264 (84.7)	n.s.
	3-4	53 (3.6)	46 (3.1)	n.s.

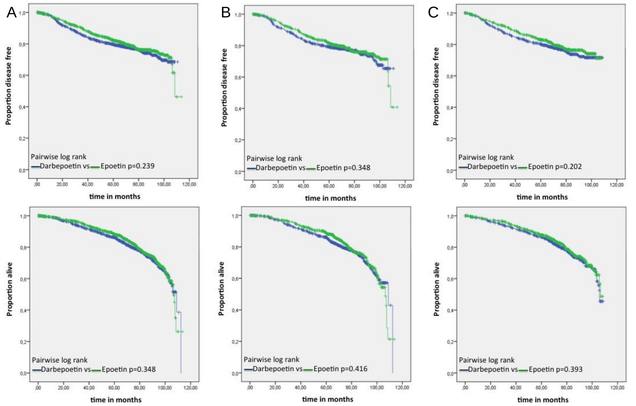
Table 4: Thromboembolic events according to chemotherapy and ESF

	CTC Grade	Darbepoetin alfa N (valid %)	Epoetin beta N (valid %)	p-value
ETC	any	53 (7.0)	57 (7.7)	n.s.
	3-4	38 (5.0)	34 (4.6)	n.s.
EC-TX	any	82 (11.3)	96 (12.5)	n.s.
	3-4	58 (8.0)	61 (7.9)	n.s.
overall	any	135 (9.1)	153 (10.1)	n.s.
	3-4	96 (6.5)	95 (6.3)	n.s.

Table 3: Anemia acccording to chemotherapy and ESF in various age groups

		ETC (N=1498)			EC-TX (N=1496)		
		Darbepoetin alfa	Epoetin beta		Darbepoetin alfa	Epoetin beta	
Age group	**CTC Grade**	**N (valid %)**	**N (valid %)**	**p-value**	**N (valid %)**	**N (valid %)**	**p-value**
<40	any	101 (88.6)	91 (88.3)	n.s.	86 (88.7)	96 (81.4)	n.s.
	3-4	4 (3.5)	4 (3.9)	n.s.	1 (1.0)	4 (3.4)	n.s.
40-49	any	213 (85.2)	224 (83.0)	n.s.	221 (81.5)	200 (79.4)	n.s.
	3-4	10 (4.0)	10 (3.7)	n.s.	4 (1.5)	5 (2.0)	n.s.
50-59	any	206 (83.4)	205 (90.3)	0.027	190 (82.6)	205 (82.3)	n.s.
	3-4	13 (5.3)	5 (2.2)	0.014	9 (3.9)	3 (1.2)	n.s.
>60	any	124 (90.5)	115 (89.8)	n.s.	96 (83.5)	128 (88.3)	n.s.
	3-4	10 (7.3)	10 (7.8)	n.s.	2 (1.7)	5 (3.4)	n.s.

Figure 1: Disease free (DFS) and overall survival (OS) in patients according to ESF. A: overall, B: ETC, C: EC-TX



Conclusions

High risk breast cancer patients treated with two different dose dense chemotherapy schedules have comparable incidences of anemia, thromboembolic events and a similar long term outcome if they receive a preventive treatment with either Darbepoetin alfa or Epoetin beta. However, the number of thromboembolic events is high and a careful risk benefit analysis is warranted prior to application of an ESF, especially as other options to treat/prevent anemia are at hand.

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