Development of brain metastases in breast cancer patients treated in the neoadjuvant trials Geparquinto and Geparsixto

Witzel I[1], Laakmann E[1], Fasching PA[3], Rezai M[4], Schem C[5], Solbach C[6], Tesch H[7], Klare P[8], Schneeweiss A[9], Salat C[10], Zahm D[11], Blohmer J[12], Ingold-Heppner B[13], Huober J[14], Hanusch C [15], Jackisch C[16], Reinisch M[17], Untch M[18], von Minckwitz G [2], Nekljudova V[2], Müller V[1], Loibl S[2]

[1]University Medical Center, Department of Gynecology, Hamburg, Germany, 20246; [2]German Breast Group, Neu Isenburg, Germany; [3]University Medical Center, Department of Obstetrics and Gynecology, Erlangen, Germany; [4]Medical Center Luisenkrankenhaus, Düsseldorf, Germany; [5]University Medical Center, Department of Obstetrics and Gynecology, Kiel, Germany; [6]University Medical Center, Department of Obstetrics and Gynecology, Frankfurt, Germany; [7]Center for Hematology und Oncology Bethanien, Frankfurt, Germany; [8]Praxisklinik, Standort Lichtenberg, Berlin, Germany; [9]University Medical Center National Center for Tumor Diseases, University Hospital Heidelberg, Germany; [10]Medical Center for Hematology and Oncology, Munich, Germany [11]Breast Center Ostthüringen, Gera, Germany; [12]University Medical Center, Charité-Campus Mitte, Department of Gynecology, Berlin, Germany; [13]University Medical Center, Institute for Pathology, Charité, Berlin, Germany; [14]University Medical Center,Department of Gynecology and Obstetrics, Ulm, Germany; [15]Department of Gynecology, Rotkreuzklinikum, Munich, Germany; [16]Department of Gynecology and Obstetrics, Hospital Offenbach, Offenbach, Germany; [17]Department of Senology, Kliniken Essen-Mitte, Essen, Germany and [18]Klinikum Berlin-Buch, Department of Gynecology and Obstetrics, Berlin, Germany.

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Background

The incidence of central nervous system (CNS) metastases in breast cancer patients is rising and has become a major clinical challenge. So far, the incidence of CNS metastases after modern neoadjuvant treatment is not clear. Only few data is published concerning risk factors for the development of CNS metastases as first site of distant relapse in breast cancer patients.

Materials and Methods

- In Geparquinto (Fig. 1a), patients with primary HER2-positive breast cancer (n=615) received either lapatinib or trastuzumab, patients with HER2 negative breast cancer (n=1925) received an anthracycline and taxane-containing regimen and 956 patients received bevacizumab and those not responding after four cycles of anthracyclines (n=395) received paclitaxel (n=198) or paclitaxel and everolimus (n=197).
- In Geparsixto (Fig 1 b), patients with HER2-positive tumors (n=273) received trastuzumab and lapatinib and patients with triple-negative tumors (n=315) received bevacizumab in addition to chemotherapy.
- We analyzed clinical factors associated with the occurrence of CNS metastases as first site of metastatic relapse after neoadjuvant treatment in both trials.
- A total of 3160 patients treated in Geparquinto and Geparsixto trials were available for the analysis (Table 1). 2572 of the patients were treated within the Geparquinto, 588 within the Geparsixto trial. 73% (n=2306) of the patients had a cT1 tumor stage before the neoadjuvant chemotherapy. 51% (n= 1581) had node-negative and 49% (n=1533) node-positive (cN1-3) initial breast cancer. Concerning the tumor subtype, 32% of patients (n= 1008) had triple-negative tumors, 30% (n=954) luminal A, 12% (n=381) luminal B, and 26% (n=809) HER2-positive tumors. pCR after neoadjuvant treatment could be observed in 23% (n= 738) of patients.
- Time (in months, from randomization in the study) to the occurrence of CNS metastases as first site of relapse was analyzed according to the competing risk model of Fine, Gray (1999); other distant metastases, contralateral breast cancer, secondary malignancies occurred as first site of relapse or death before any event were considered competing events; multivariate analysis was also adjusted for study.

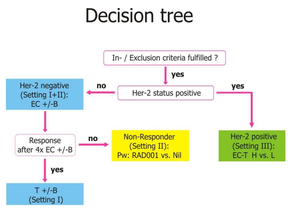
Results

Table 1. Patients`characteristics

Parameter	CNS metastases as first site of distant relapse, N=108	Non-CNS metastases as first site of distant relapse, N=411	Patients without distant relapse, N=2642	Overall, N=3160
Age, median (years)	48.5	48.0	49.0	48.0
cT (n, %)				
- cT1-2	61 (57.0)	259 (63.2)	1986 (75.5)	2306 (73.3)
- cT3	15 (14.0)	77 (18.8)	366 (13.9)	458 (14.5)
- cT4a-c	5 (4.7)	26 (6.3)	118 (4.5)	149 (4.7)
- cT4d	26 (24.3)	48 (11.7)	161 (6.1)	235 (7.5)
missing	1	1	10	12
cN (n, %)				
- cN0	28 (26.2)	159 (39.5)	1394 (53.5)	1581 (50.8)
- cN1	68 (63.6)	209 (51.9)	1100 (42.2)	1377 (44.2)
- cN2	9 (8.4)	23 (5.7)	90 (3.5)	122 (3.9)
- cN3	2 (1.9)	12 (3.0)	20 (0.8)	34 (1.1)
- missing	1	8	37	46
Breast cancer subtype				
- Luminal A (grade 1-2)	11 (10.2)	107 (26.2)	836 (31.7)	954 (30.3)
- Luminal B (grade 3)	7 (6.5)	61 (14.9)	313 (11.9)	381 (12.1)
- HER2+	34 (31.5)	76 (18.6)	699 (265	809 (25.7)
- TNBC	56 (51.9)	165 (40.3)	787 (29.9)	1008 (32.0)
- missing	0	2	6	8
Ki67-Index (n, %)				
≤20%	10 (18.5)	58 (28.9)	438 (33.0)	506 (32.0)
>20%	44 (81.5)	143 (71.1)	888 (67.0)	1075 (68.0)
missing	54	210	1315	1579
Grading (n, %)				
- G1	0 (0.0)	10 (2.4)	88 (3.3)	98 (3.1)
- G2	41 (38.0)	186 (45.5)	1305 (49.6)	1532 (48.7)
- G3	67 (62.0)	213 (52.1)	1236 (47.0)	1516 (48.2)
- missing	0	2	12	14
pCR				
- no	91 (85.0)	370 (91.4)	1915 (73.6)	2376 (76.3)
- yes	16 (15.0)	35 (8.6)	688 (26.4)	738 (23.7)

Figure 1. Study design of the trials Geparquinto and Geparsixto

a) Geparquinto



b) Geparsixto

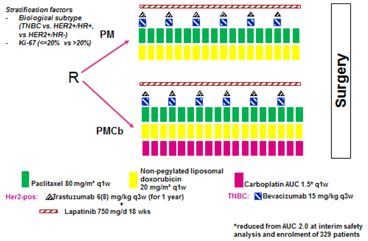


Figure 2. Cumulative incidence of metastases

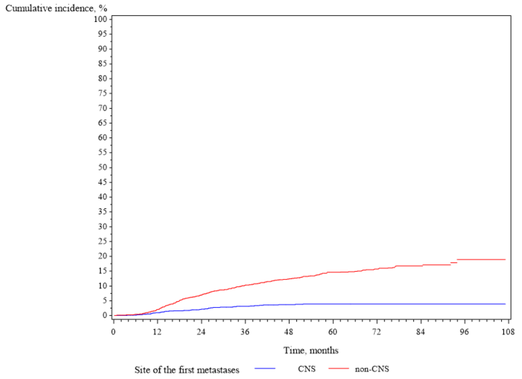
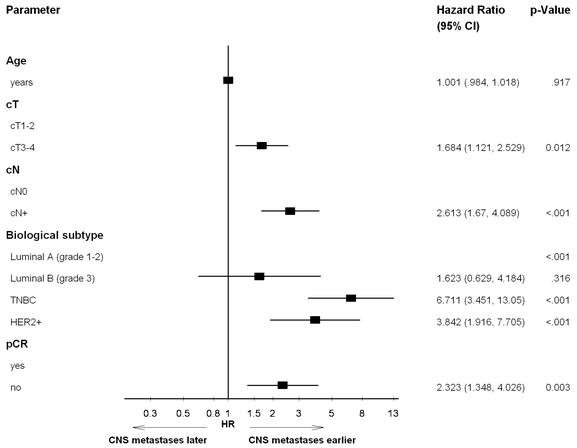


Figure 3: Factors associated with the occurrence of central nervous system metastases as first site of metastatic relapse (multivariate analysis)



- After a median follow-up of 61 months, 108 (3%) of the total 3160 patients developed CNS metastases as first site of recurrence and 411 (13%) patients had distant metastases outside the brain.
- CNS metastases as first site of recurrence occurred less frequently than other metastases (5-year cumulative incidence of CNS metastases was 3.8% and cumulative incidence of the metastases outside the brain was 14.6% according to the Fine-Gray competing risk model, Fig.2).
- Regarding subtypes of the primary tumor, 1% of luminal A (11/954), 2% of luminal B (7/381), 4% of HER2 positive (34/809) and 6% of triple-negative patients (56/1008) developed CNS metastases as first site of recurrence.
- In multivariate analysis, risk factors for the development of CNS metastases were larger tumor size (cT3-4; HR 1.7, 95%-CI 1.1-2.5, p=0.012), node positive disease (HR 2.6, 95% CI 1.7-4.1, p<0.001), no pCR after neoadjuvant chemotherapy (HR 2.3, 95% CI 1.3-4.1, p=0.003) and HER2 positive (HR 3.8, 95% CI 1.9-7.7, p<0.001) or triple-negative subtype (HR 6.7, 95% CI 3.5 – 13.1, p< 0.001) (Fig. 3).
- Breast cancer subtype remained the most relevant risk factor for CNS metastases. Patients who developed CNS metastases had more often HER2 positive or triple-negative breast tumors compared with patients who developed metastases outside the brain (HER2 positive subtype 32 vs. 19%, triple-negative subtype 52 vs. 40%, p< 0.001).

Conclusions

Especially patients with HER2-positive and triple negative tumors are at risk of developing CNS metastases despite active systemic treatment. A better understanding of the underlying mechanisms is required in order to develop potential preventive strategies.

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