Peripheral Sensory Neuropathy Occurrence and Resolution: Results from the neoadjuvant randomized GeparSepto study (GBG 69)

Jenny Furlanetto[1], Gunter von Minckwitz[1], Christian Jackisch[2], Andreas Schneeweiss[3], Bahriye Aktas[4], Carsten Denkert[5], Hermann Wiebringhaus[6], Sherko Kümmel[7], Mathias Warm[8],Stefan Paepke[9], Marianne Just[10], Claus Hanusch[11], John Hackmann[12], Jens Uwe Blohmer[13], Michael Clemens[14], Serban Dan Costa[15], Bernd Gerber[16], Valentina Nekljudova[1], Michael Untch[17], Sibylle Loibl[1]

1German Breast Group, Neu-Isenburg; 2Sana Klinikum Offenbach; 3National Center for Tumor Disease, University Hospital Heidelberg; 4University Women´s Hospital Essen, Essen; 5Institute of Pathology and German Cancer Consortium (DKTK), Charité-University Hospital, Berlin; 6St. Barbara Klinik Heessen, Hamm; 7Interdisziplinäres Brustzentrum an den Kliniken Essen-Mitte; 8Brustzentrum in Krankenhaus Köln-Holweide, Köln; 9Klinikum rechts der Isar der TU München, Klinik und Poliklinik für Frauenheilkunde, München; 10Onkologische Schwerpunktpraxis, Bielefeld; 11Klinikum zum Roten Kreuz München; 12Marien Hospital Witten; 13Gynäkologie und Brustzentrum, Charité-University Hospital, Berlin; 14Klinik Mutterhaus der Borromäerinnen, Trier; 15Universitäts-Frauenklinik, Magdeburg; 16Universitäts-Frauenklinik, Rostock; 17Helios Clinics Berlin-Buch

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Background

The GeparSepto (NCT01583426), a phase 3 randomised neoadjuvant trial in patients with early breast cancer (BC), showed that nab-paclitaxel (nP) increases the pathological complete response (pCR) rate compared to paclitaxel (P) as part of a sequential taxane followed by epirubicin/cyclophosphamide (EC) neoadjuvant chemotherapy (pCR nP 38% vs. P 29%, p<0.001).[1] A safety interim analysis, conducted after 60 patients completed study treatment, indicated a higher rate of dose reductions, treatment discontinuations as well as peripheral sensory neuropathy (PSN) with nab-paclitaxel 150mg/m² weekly (nP150) compared to paclitaxel 80mg/m² weekly. Therefore the dose of nab-paclitaxel was reduced to 125mg/m² weekly (nP125) during the trial. The final safety results of GeparSepto showed that PSN grade 3–4 was significantly higher after nab-paclitaxel compared to solvent-based paclitaxel (10% vs. 3%, p<0.0001). A sub-analysis showed that the risk-benefit ratio of nP125 was improved over nP150 with better drug adherence and relative dose intensity, lower frequency of PSN and comparable pCR.[2] We report follow-up (FU) data on PSN occurrence and resolution.

Objectives

Primary objectives:

- Rate of PSN grade 2-4 and 3-4 in patients treated with nP150, nP125 and P
- Percentage of patients treated with nP150, nP125 and P with PSN grade 2-4 and 3-4 resolved to grade 1 at the end of treatment (EOT), i.e. 30 days after the last chemotherapy administration
- Percentage of patients treated with nP150, nP125 and P with PSN grade 2-4 and 3-4 resolved to grade 1 during FU
- Time to resolution (mTTR) of PSN grade 2-4 and 3-4 for P compared to nP and nP150 compared to nP125

Materials and Methods

Patients with untreated BC received paclitaxel 80mg/m² weekly or nab-paclitaxel 150/125mg/m² weekly followed by four cycles of epirubicin 90mg/m² plus cyclophosphamide 600mg/m² every three weeks. In patients with HER2+ tumors trastuzumab 6mg/kg (loading (LD) dose 8mg/kg) and pertuzumab 420mg (LD 840 mg) were administered every three weeks (Figure 1). In case of a PSN grade 2, nab-paclitaxel treatment was delayed by one week and subsequently continued at a lower dose (100mg/m² weekly). If symptoms did not resolved to grade 1 within 3 weeks, taxane treatment was stopped. In case of PSN grade 3-4 taxane treatment was discontinued. After the end of the study the protocol was amended in order to collect long-term data on PSN outcome as well as on treatment modalities. Since the data were retrospectively analyzed, time to PSN resolution could have been overestimated. PSN will be reported according treatment and dose received on day 1.

Results

- Overall 601 patients received P80, 220 patients nP150 and 385 patients nP125 on day 1. PSN grade 2-4 was observed in 19.0% of patients treated with P80 and in 41.8% with nP150 vs. 39.2% with nP125 (nP150 vs nP125: p=0.531). Grade 3-4 PSN was reported in 2.7% of patients in the P80 group, 14.5% in the nP150 and 8.1% in the nP125 group (nP150 vs nP125: p=0.019). PSN grade 2-4 did not resolve at EOT in 29.8% of P, 38.0% of nP150 and 29.8% of nP125; PSN grade 3-4 did not resolve at EOT in 31.3%, 62.5% and 58.1% of the patients respectively (Figure 2).
- After a median FU of 162 weeks after EOT, the remaining PSN grade 2-4 was resolved to grade 1 in 61.8% of patients with P, 45.7% with nP150 and 51.1% with nP125, whereas PSN grade 3-4 was resolved in 100.0%, 40.0% and 44.4% of patients respectively.
- The TTR of PSN grade 2-4 was significantly different between nP150 and nP125 (p=0.001); no significant difference was seen between P and nP125 (p=0.372) (Table 1; Figure 3A). Similarly, the TTR of PSN grade 3-4 was significantly different between nP150 and nP125 (p=0.043) but no significant difference was observed for P vs. nP125 (p=0.535) (Table 1; Figure 3B).

Figure 1: Study design

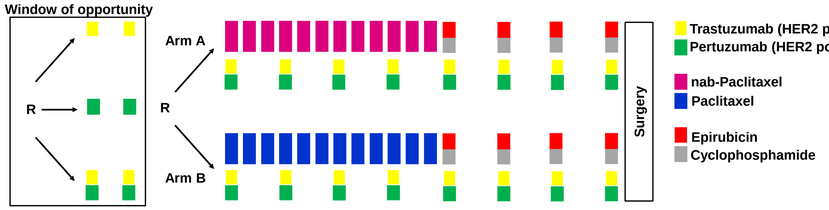

Figure 2: Consort diagram

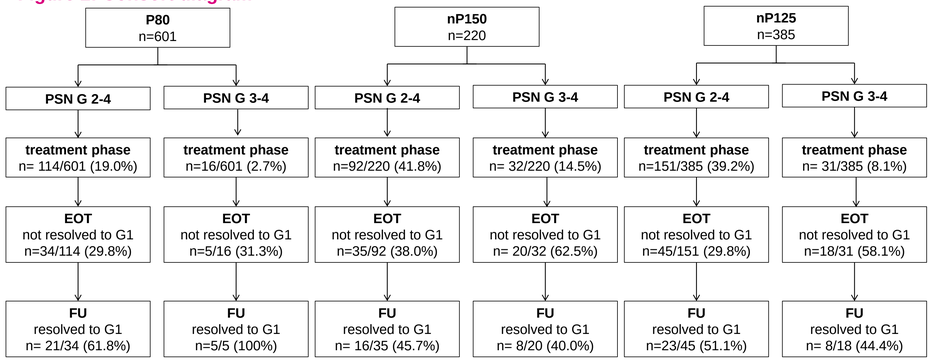

Figure 3: Time to resolve of PSN grade 2-4 (A) and grade 3-4 (B) to grade 1

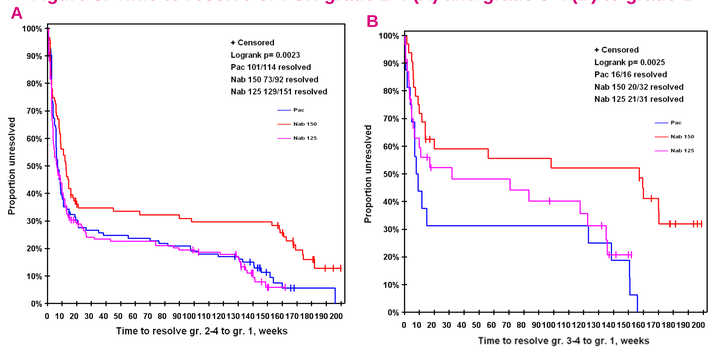

Table 1: Median time to resolution (TTR) of PSN to grade 1

comparison groups	Median TTR n (weeks); [95% CI]		
P vs nP	**P**	**nP150**	**nP125**
grade 2-4	7 [6.0-9.1]	9.0 [6.6-11.9]	
grade 3-4*	8.6 [4.0-123.3]	83.4 [11.6-157.3]	
nP150 vs nP125			
grade 2-4		12.7 [8.9-16.0]	6.4 [4.1-10.0]
grade 3-4*		157.3 [11.6-170.4]	32.0 [6.0-122.7]

*Probable overestimation due to the non continuous follow-up

Conclusions

nP125 is associated with a lower frequency of PSN compared to nP150 but higher frequency than P80.The PSN occurred after nP125 was associated with a more rapid resolution compared to nP150. Follow-up is continuing. Markers for selecting patients at risk are needed.

References

1.Untch M, Jackisch C, Schneeweiss A, et al. Nab-paclitaxel versus solvent-based paclitaxel in neoadjuvant chemotherapy for early breast cancer (GeparSepto-GBG 69): a randomised, phase 3 trial. Lancet Oncol. 2016;17:345-56.
2.von Minckwitz G, Untch M, Jackisch C et al. nab-Paclitaxel at a dose of 125 mg/m² weekly is more efficacious but less toxic than at 150 mg/m². Results from the neoadjuvant randomized GeparSepto study (GBG 69). Presented at SABCS 2015

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