Published online: 2020-04-21

Thieme

Use of Taxanes in Metastatic HER2-negative Breast Cancer – a Status Report

Einsatz von Taxanen beim metastasierten HER2-negativen Mammakarzinom – ein Statusreport

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Key words
breast cancer, metastatic, chemotherapy, taxanes

Schlüsselwörter
Mammakarzinom, metastasiert, Chemotherapie, Taxane

received 8.8.2019
revised 20.1.2020
accepted 21.2.2020

Bibliography
DOI https://doi.org/10.1055/a-1126-4247
Geburtsh Frauenheilk 2020; 80: 399–409 © Georg Thieme Verlag KG Stuttgart · New York | ISSN 0016-5751

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Deutsche Version unter:
https://doi.org/10.1055/a-1126-4247

ABSTRACT

The most important goal of treatment of patients with metastatic breast cancer is maintenance or even improvement of quality of life. In this setting, chemotherapy should be used with as much restraint as possible. If palliative chemotherapy is indicated, the taxane drug class is an established treatment option. The updated guidelines of the Gynaecological Oncology Working Group (AGO), Breast Committee, of the German Society for Gynaecology and Obstetrics (DGGG) and the German Cancer Society e.V. (DKG) provide recommendations with the greatest possible evidence on which of the licensed taxanes can be used in which treatment situation in the metastatic setting.

ZUSAMMENFASSUNG

Das wichtigste Therapieziel bei der Behandlung von Patientinnen mit metastasiertem Mammakarzinom ist die Erhaltung oder gar Verbesserung der Lebensqualität. Vor diesem Hintergrund sollte die Indikation zur Chemotherapie möglichst zurückhaltend gestellt werden. Falls die Indikation zur palliativen Chemotherapie besteht, ist die Wirkstoffklasse der Taxane als Therapieoption etabliert. Die aktualisierten Leitlinien der Arbeitsgemeinschaft Gynäkologische Onkologie (AGO), Kommission Mamma, der Deutschen Gesellschaft für Gynäkologie und Geburtshilfe (DGGG) und der Deutschen Krebsgesellschaft e.V. (DKG) geben Empfehlungen, in welcher Therapiesituation welches der zugelassenen Taxane im metastasierten Setting mit höchstmöglicher Evidenz eingesetzt werden kann.

Introduction

Drugs of the taxane group have been available since the mid-1990s for the treatment of breast cancer. Their broad clinical development and, in particular, their great efficacy, have led to taxanes becoming firmly established as the most important group of cytostatic agents in the treatment of breast cancer, alongside the anthracyclines, in all treatment lines (both curative and palliative) where chemotherapy is indicated [1, 2]. A consequence of this is that the disease is rarely taxane-naive in the event of recurrence. It is important to note at this point, however, that taxanes can be used both in the form of a re-challenge after previous taxane therapy and also in taxane-naïve patients. When it has been decided to use a taxane, the question arises as to which of the three licensed taxanes – paclitaxel, docetaxel or *nab*-(nanoparticle albumin-bound) paclitaxel – should be preferred in which treatment situation.

The object of this publication is to discuss the scenarios in which taxanes should or can be used in the metastatic situation also and which taxane should be recommended in which situation. Study data and publications on the three drugs were combined to provide a basis for an algorithm that might be helpful in making treatment decisions.

General Principles of Chemotherapy of Metastatic Breast Cancer

Palliative chemotherapy can be regarded as indicated in the following situations:

- Patients with metastatic hormone receptor (HR)-positive breast cancer who are considered unsuitable for endocrine intervention because of (repeated) resistance to endocrine therapy or with rapid (and therefore potentially life-threatening) disease progression with a pressing need to achieve disease remission,
- Patients with metastatic triple-negative breast cancer (TNBC) who can be treated with chemotherapy because of the absence of predictive factors for HER2-targeted or endocrine therapy,
- Patients with metastatic HER2-positive breast cancer who are to receive targeted therapy where chemotherapy forms part of the (licensed) treatment regimen.

It must be noted that hormone receptor status can change in the course of the disease [1]. Because of this, review of receptor status may be necessary (especially when the clinical course is unusual). Changes in the biology of the primary tumour (which can be due both to actual changes in receptor status and to clonal selection or to analytical factors) are described in up to 30 % of cases.

Monotherapy throughout all therapy lines is the treatment of first choice in patients with HR-negative or endocrine-insensitive and HER2-negative breast cancer, in whom chemotherapy is indicated but rapid remission is not required [1]. A range of drugs can be used:

- Taxanes (paclitaxel/docetaxel/*nab*-paclitaxel)
- Anthracyclines (epirubicin/doxorubicin/[PEG-] liposomal doxorubicin, mitoxantrone)
- Platinum (carboplatin/cisplatin)
- Vinorelbine
- Capecitabine
- Eribulin
- Gemcitabine

When rapid remission is required, it can be rational to use polychemotherapy (poly-CTX). In a Cochrane analysis that must be regarded as controversial [2], a significant benefit for overall response rate (ORR), time to progression (TTP) and survival is attested for polychemotherapy, but this benefit is obtained at the expense of sometimes markedly increased toxicity. In addition, it is important to recognise, firstly, that the use of polychemotherapy has not been studied systematically so that it is evidence-based and, secondly, that the "high" versus "low" need to obtain rapid remission has not been clearly defined, even though initial attempts were made at the 4th Advanced Breast Cancer Fourth International Consensus Conference in November 2019 in Lisbon. These describe a visceral crisis as severe organ dysfunction, as assessed from the symptoms, laboratory results and rapid disease progression. Combined chemotherapy should be offered especially to patients with rapid progression of the disease, life-threatening metastasis or need for very rapid disease control [3].

The choice of specific systemic therapy can depend on various factors [1]. These include:

- ER/PR, HER2, PD-L1 and gBRCA status,
- previous treatments (and their side effects),
- recurrence-free interval after (neo-) adjuvant therapy,
- aggressiveness of the disease,
- location of the metastases,
- estimated survival time,
- comorbidities and organ function,
- patient's expectations and preferences.

Relevant Cytostatic Drugs in the Metastatic Situation

The following selected cytotoxic drugs are recommended for use in metastatic breast cancer [4].

Taxane Rechallenge

Taxanes (e.g. *nab*-paclitaxel or paclitaxel q1w or docetaxel q3w) can be used again in patients previously treated adjuvantly with anthracyclines and/or taxanes [4, 6], especially when the treatment-free interval lasts longer than 12 months. If the treatment-free interval is less than 12 months, apart from the aforementioned options, capecitabine, vinorelbine and eribulin as well as a taxane can be used as first-line therapy in the metastatic situation, when there is an increased need to achieve rapid remission [7].

Taxanes in Combination with Bevacizumab

Both capecitabine and paclitaxel can be combined with the angiogenesis inhibitor bevacizumab; this is approved in the first-line situation and can improve response rates and prolong progression-free survival (PFS) in the treatment of HER2-negative, metastatic breast cancer [7, 8]. Moreover, a slight improvement in the 1-year OS rates was observed in a combined analysis of phase III first-line studies, especially in patients with TNBC [8]. The combination of taxane and bevacizumab can also be used when the treatment-free interval is more than 12 months [9].

Taxane Plus Immunotherapy

The phase III IMpassion130 study investigated the anti-PD-L1 antibody atezolizumab + *nab*-paclitaxel compared with placebo + *nab*-paclitaxel as first-line therapy in patients with previously untreated, inoperable, locally advanced or metastatic TNBC [10]. In the ITT population a significant advantage with regard to median PFS was seen for the addition of atezolizumab at 7.2 vs. 5.5 months with *nab*-paclitaxel only (HR 0.8; 95% CI: 0.69–0.92; p = 0.002). The median OS also was longer with the combination at 21.3 months than with chemotherapy alone at 17.6 months (HR 0.84; 95% CI: 0.69–1.02; p = 0.08). The advantage was more pronounced in patients with PD-L1 expression, where the risk reduction for disease progression or death was 38%. The final OS analysis shows an overall survival advantage in the cohort of patients with PD-L1 expression of 25 vs. 18 months in favour of the combination [11]. In an analysis of the effectiveness in immune biomarker subgroups, presented at SABCS 2018, it was shown that patients with PD-L1 expression on the tumour-infiltrating immune cells (PD-L1 IC +) benefited in particular from the addition of the immune checkpoint inhibitor [12]. PD-L1 IC status was highly predictive for the efficacy of combined atezolizumab + nab-paclitaxel therapy. Based on these results, the combination atezolizumab + nab-paclitaxel was licensed in August 2019 by the EMA, the European Medicines Agency, as first-line therapy of PD-L1 positive metastatic TNBC.

At ESMO 2019 Schmid et al. presented promising data on the combination of paclitaxel + carboplatin followed by EC with the PD-1 antibody pembrolizumab in the neoadjuvant situation. In addition to the higher pCR rate, this even showed an early survival signal in favour of the treatment that included immunotherapy [13]. Interestingly, a predictive effect of PD-L1 expression as regards pCR was not observed. Very recent data from SABCS 2019 in the neoadjuvant situation surprisingly did not confirm these data in patients with markedly advanced tumours. In the much smaller NeoTRIP study, patients received 8 cycles of anthracycline-free chemotherapy consisting of nab-paclitaxel/carboplatin on days 1 and 8 with/without atezolizumab [14]. Interestingly, this did not show any increase in pCR (secondary end point) with the addition of the PD-L1 antibody so that further data must be awaited before final conclusions can be drawn regarding the best combination strategy. This should be noted especially because of the sometimes severe side effects of the treatment [15].

Taxane As Part of Polychemotherapy

If polychemotherapy is regarded as necessary, the data after previous anthracycline and taxane treatment are limited. It is not possible to finally assess how much the combinations of anthracycline/cyclophosphamide and anthracycline/taxane differ in efficacy [1]. A further alternative available for patients previously treated with anthracycline and taxane is the combination of vinorelbine and capecitabine [16]. In taxane-naive patients, the combinations gemcitabine/paclitaxel [17], docetaxel/capecitabine [18] or gemcitabine/carboplatin [19] have proved effective. Promising results were recently published for the combination of *nab*-paclitaxel and carboplatin in patients some of whom had had prior treatment with anthracycline and taxane [20]. There are no data on a direct comparison of polychemotherapy with combinations of chemotherapy and bevacizumab.

First Generation Taxanes: Paclitaxel and Docetaxel

Taxanes are cytotoxic substances that bind to tubulin and help to stabilise microtubules [21]. Their efficacy in early and advanced breast cancer has been confirmed with a high level of evidence. Taxane-based treatment regimens have proved significantly more effective in the treatment of early and metastatic breast cancer than taxane-free regimens according to meta-analyses [7, 22–24].

Paclitaxel

The taxane paclitaxel was first licensed in 1995 for the treatment of patients with breast cancer [25]. Paclitaxel is poorly water-soluble and requires cremophor and ethanol as solubilisers. Cremophor is held responsible on the one hand for the non-linear pharmacokinetics of conventional paclitaxel [26, 27]. On the other hand, the solubiliser causes severe hypersensitivity reactions [25, 26, 28, 29] and possibly contributes to the neutropenia and peripheral neuropathy that occur on paclitaxel therapy [30]. Premedication with corticosteroids and H1 and H2 antagonists is necessary to avoid hypersensitivity reactions [28, 29]. Paclitaxel is today used preferably in treatment schedules that include weekly paclitaxel [4, 31] as the weekly schedule has proved significantly superior to the licensed three-weekly dosage as regards ORR and OS in patients with metastatic breast cancer [32].

The recently published 10-year update of the adjuvant study E1199 defined a new treatment standard specially for patients with TNBC [33]. The study investigated the efficacy of different taxane regimens in about 5000 node-positive or node-negative high-risk patients with breast cancer, including about 1000 patients with TNBC. The women had received 4 cycles adjuvantly of doxorubicin and cyclophosphamide (AC) q3w, followed by either paclitaxel or docetaxel, each q1w or q3w. In the overall population the regimens containing paclitaxel q1w and docetaxel q3w (see below), compared with paclitaxel q3w, were associated with a significant improvement in disease-free survival and docetaxel with marginally improved overall survival. There was no significant dif-

ference in disease-free survival or overall survival between the combined paclitaxel arms and the combined docetaxel arms. Significant differences were not recorded between the combined arms q1w and q3w either. The 1025 patients with TNBC who received paclitaxel q1w, however, showed a survival advantage of about 10% compared with the women treated otherwise (overall survival probability 75.1 vs. 65.6% [paclitaxel q3w] and 68.6% [docetaxel q1w] and 68.7% [docetaxel q3w]). Paclitaxel given weekly thus proved to be the most effective regimen investigated in the study in women with TNBC [34].

Docetaxel

The taxane docetaxel, which likewise obtained EU approval in 1995 for the treatment of patients with breast cancer, requires the solubilisers ethanol and polysorbate 80 to achieve adequate solubility [34]. Pretreatment for 3 days with dexamethasone is recommended to avoid fluid retention and hypersensitivity reactions. The infusion is delivered over 1 hour every 3 weeks. Weekly administration of docetaxel does not offer any advantages with regard to efficacy and toxicity compared with three-weekly administration [35–38].

In the analysis of the long-term data from the aforementioned E1199 study, the regimen of 4× AC followed by 4× docetaxel showed the greatest efficacy especially in patients with HR-positive breast cancer [33].

In a direct comparison, the two first-generation taxanes proved similarly effective but with different toxicity profiles [33, 39]. Typical serious side effects, which occurred equally with paclitaxel and docetaxel, were alopecia, stomatitis, haematological toxicity with febrile neutropenia and peripheral polyneuropathy, with the latter occurring more often with paclitaxel q1w than with paclitaxel q3w [32]. Overall, grade 3/4 haematological toxicity, mucositis, diarrhoea and fatigue were more common with docetaxel than with paclitaxel [39].

Second Generation Taxane: *nab*-Paclitaxel

Besides the conventional taxanes docetaxel and paclitaxel, *nab*-paclitaxel – a solvent-free colloidal suspension of paclitaxel and human serum albumin – has been licensed in Europe since 2008 as monotherapy for the treatment of metastatic breast cancer in which first-line therapy for metastatic disease has failed and for which standard anthracycline-containing therapy is not indicated [4]. Because of its patented nanoparticle formulation, *nab*-paclitaxel does not need any solubiliser. Premedication for prophylaxis of severe hypersensitivity reactions is therefore not necessary. The infusion is given over 30 minutes [40].

Compared with conventional paclitaxel, absorption of *nab*-paclitaxel from the intravascular space is significantly improved by the use of albumin as transport protein [41], which leads to linear pharmacokinetics and dose-dependent anti-tumour activity. *Nab*-paclitaxel is distributed 4 times faster and 10 times more in peripheral tissue than conventional paclitaxel [42]. In addition, the paclitaxel-albumin complex shows particularly high affinity for secreted protein, acidic and rich in cysteine (SPARC), expression of which is increased on the surface of breast cancer cells [43], so that a targeted mechanism for accumulation in tumour tissue is ascribed to *nab*-paclitaxel.

460 women with metastatic breast cancer were included in the phase III licensing study. About 80% of them had been pretreated with anthracycline in the adjuvant or metastatic situation. In this study, an improvement in the response rate (33 vs. 19%; $p = 0.001$, primary end point) and the time to progression (TTP: 23.0 vs. 16.9 weeks; $p = 0.006$) was shown with treatment with *nab*-paclitaxel (260 mg/m^2, d1, q3w, without premedication), compared with conventional paclitaxel containing solubiliser (175 mg/m^2, d1, q3w) and the usual standard premedication with antihistamines and dexamethasone. A survival advantage (56.4 vs. 46.7 weeks; $p = 0.024$) was even evident in patients on their 2nd or 3rd treatment line [44].

Nab-paclitaxel proved well tolerated overall. Grade 3–4 neutropenia occurred more seldom than with conventional paclitaxel (grade 4: 9 vs. 22% $p < 0.001$), but patients in the *nab*-paclitaxel arm developed sensory neuropathy more often (incidence of grade 3 was 10% with paclitaxel vs. 2% in the control arm [$p < 0.001$]; no grade 4 neuropathy was observed). Unlike in the paclitaxel arm, the neurotoxicity with *nab*-paclitaxel was readily controllable with dose reductions and interruptions in treatment and also resolved faster (median time to improvement to ≤ grade 2: 22 vs. 79 days for paclitaxel) [45].

A phase II study demonstrated the best therapeutic index – optimal overall survival with minimised side effects – for *nab*-paclitaxel (150 mg/m^2; d 1/8/15, q4w) compared with docetaxel q3w [46]. In patients with metastatic breast cancer, who had received *nab*-paclitaxel in a dosage of 300 mg/m^2 (d1 q3w) or 100 mg/m^2 or 150 mg/m^2 weekly (d 1/8/15, q4w) or docetaxel in a dosage of 100 mg/m^2 (d1 q3w), the safety profile of weekly and three-weekly administration of *nab*-paclitaxel was found to be similar [46, 47]. With regard to effectiveness (overall response rate), *nab*-paclitaxel in a weekly dosage of 100 and 150 mg/m^2 showed a higher overall response rate compared with docetaxel (45% and 49 vs. 35% [$p = 0.224$]). With regard to PFS also, *nab*-paclitaxel in the weekly dosage of 150 mg/m^2 showed advantages compared with docetaxel (assessment by independent radiologists, median PFS 12.9 vs. 7.5 months, HR 0.495, $p = 0.0065$) [46, 47]. All patients with prior anthracycline therapy benefited from treatment with *nab*-paclitaxel as regards overall survival, regardless of whether the pretreatment had been in the metastatic or adjuvant situation [44, 48].

Another randomised phase III study in 799 patients investigated how far *nab*-paclitaxel 150 mg/m^2 vs. paclitaxel 90 mg/m^2 q3/4 w should be combined with bevacizumab in first-line therapy of HER2-negative breast cancer [49]. The final analysis of the study, presented at SABCS 2017, did not show any significant difference with regard to PFS or overall survival between the two study arms, with, as expected, greater dose-dependent toxicity in the *nab*-paclitaxel arm. Interestingly, however, the overall survival (as secondary end point of the study) tended to be better in favour of the *nab*-paclitaxel arm (21 vs. 15 months, HR = 0.74, 95% CI: 0.51–1.07) in the triple-negative subgroup, which is clinically particularly problematic. The effect was rather the opposite in HR+/HER2− breast cancer. The assuredly too high dosage of *nab*-paclitaxel and the high rate of early treatment discontinua-

tions due to toxicity might be regarded as a possible explanation for these results, particularly given the more favourable course of HR+/HER2− disease [50].

The GeparSepto study, a prospective randomised phase III study in about 1200 women with early breast cancer, compared weekly neoadjuvant administration of conventional paclitaxel (80 mg/m^2) with *nab*-paclitaxel (150 mg/m^2 at first, then reduced to 125 mg/m^2 after an interim analysis) over 12 weeks. After conclusion of the study, it was shown that the rate of pathologic complete remission (pCR, ypT0 ypN0) with *nab*-paclitaxel in the overall population was 9% better absolutely than with conventional paclitaxel (38.4 vs. 29%, odds ratio 1.53; $p < 0.001$). The two study arms were very largely comparable with regard to the incidence of higher-grade haemotoxicity. On *nab*-paclitaxel 10% of the patients developed peripheral sensory neuropathy ≥ grade 3 compared with 3% in the paclitaxel arm [51].

A subgroup analysis also showed that the benefit was particularly pronounced for women with TNBC: the rate of pathologic complete remission increased in these patients from 26 to 48% ($p = 0.00027$), and thus nearly doubled [51]. Despite the dose reduction from 150 mg/m^2 (nP150) to 125 mg/m^2 (nP125) of *nab*-paclitaxel, no worsening in pCR was found (46.9% for nP150 vs. 49.3% for nP125 in the TNBC patients). The dose reduction to nP125 reduced the incidence of sensory neuropathy grade 3/4 to 8% for nP125 (vs. 15% für nP150). Grade 4 sensory neuropathy did not occur with nP125 [52, 53].

The first survival data have now been published as the study's secondary end point. Significantly longer disease-free survival was found after a median follow-up period of 49 months (HR = 0.66, 95% CI: 0.51–0.89). The advantage due to *nab*-paclitaxel was observed in all studied subgroups. No significant difference in overall survival was observed, probably because of the short follow-up period [54].

In a further large neoadjuvant study by Gianni et al. (ETNA), different scheduling of the taxane-containing chemotherapy was chosen in patients with "luminal-B-like" or TN tumours. Patients were given either paclitaxel 90 mg/m^2 or *nab*-paclitaxel 125 mg/m^2 on days 1.8.15 q4w followed by 4 cycles of EC (epirubicin, cyclophosphamide) or FEC (5-fluorouracil, epirubicin, cyclophosphamide) every 3 weeks preoperatively. Only a trend to greater effectiveness of the *nab*-paclitaxel-containing chemotherapy was shown. The pCR (no invasive tumour in the breast and lymph nodes) was 22.5% in the *nab*-paclitaxel arm and 18.6% in the paclitaxel arm. In TNBC also, only a trend to higher pCR was observed (41.3 vs. 37.3%) [55]. Whether different scheduling of the taxane therapy and therefore a lower cumulative dose and dose intensity of the two taxanes provides the sole explanation for the results cannot be conclusively judged as the pCR in the standard arm was markedly above that in the GeparSepto study in TN patients also. The survival data of the study were first presented at ASCO 2019. Only a non-significant positive trend in favour of the *nab*-paclitaxel-containing arm was demonstrated in the 5-year event-free (EFS) and overall survival (OS) [56].

Carboplatin has proved to be a suitable combination partner for *nab*-paclitaxel in women with TNBC. An analysis of the prospective phase II ADAPT-TN study showed that 4× *nab*-paclitaxel 125 mg/m^2 in combination with carboplatin AUC2 d1.8 q3w in patients with TNBC led to a nearly doubled rate of pathologic complete remission with better tolerability than when combined with gemcitabine (29 vs. 46%) [57]. Further (neo-)adjuvant anthracycline-containing chemotherapy was obligatory in the case of non-pCR. Even if no significant difference was observed in 3-year event-free survival, exploratory analysis showed that women with pCR had not benefited from further anthracycline-containing chemotherapy especially after chemotherapy containing *nab*-paclitaxel/carboplatin and/or high PD-L1 expression [58]. These results should be validated in further prospective studies.

Analysis of the neoadjuvant GeparSixto study of survival of patients with high-risk breast cancer showed that the addition of a platinum compound to chemotherapy containing anthracycline/taxane in patients with TNBC resulted in benefit. The pCR was markedly increased by the addition of carboplatin in these patients so that a survival advantage resulted [59].

In view of the very interesting results of GeparSepto and also of the ADAPT-TN study, the question of the optimal schedule and dosage of *nab*-paclitaxel has remained unclear to date. In this respect, the results of the neoadjuvant phase II GeparX study were recently published by Blohmer et al. at SACS 2019. They showed significantly greater pCR (39 vs. 44.9%), but also greater toxicity in favour of the *nab*-paclitaxel 125 mg/m^2 d 1.8.15 q3w regimen vs. the *nab*-paclitaxel 125 mg/m^2 d1.8 q3w arm (with TNBC in both arms in combination with carboplatin AUC2). This difference was attributable particularly to the TNBC cohort with pCR of 60 vs. 50% [60]. In the light of the 3 studies, GeparSepto, ADAPT-TN and GeparX, it is apparent that the pCR rate with neoadjuvant therapy with *nab*-paclitaxel/carboplatin can be increased by about 5% by the addition of anthracyclines and by about 10% by the addition of platinum to *nab*-paclitaxel-EC. These results certainly raise some questions regarding patient selection for the 4-fold combinations, which should be investigated as part of further prospective studies.

The phase II tnAcity study found that the combination of *nab*-paclitaxel and carboplatin (compared with other polychemotherapy options, such as gemcitabine/carboplatin or *nab*-paclitaxel/gemcitabine, which are discussed for TNBC) had a positive effect in the first-line treatment of metastatic TNBC. In this study, the combination of *nab*-paclitaxel and carboplatin (125 mg/m^2/carbo AUC2 d1.8 q3w) showed both the highest response rate (72 vs. 39/44% in the other two arms) and also the longest median PFS of 7.4 months (vs. 5.4 and 6 months respectively) and OS of 16.4 months (vs. approximately 12 months in the other two study arms). These figures appear quite promising in view of the taxane-containing pretreatment of the patients in the adjuvant setting (56% in the *nab*-pac/carbo arm) and indirectly comparable as regards effectiveness with the option of weekly paclitaxel plus bevacizumab in TNBC if the need to achieve rapid remission is high. If the toxicities are compared, rather less grade 3–4 peripheral neuropathy would be expected with the combination therapy in the aforementioned scheduling than with weekly paclitaxel plus bevacizumab (5 vs. 18%), but (as also to be expected) with greater haemotoxicity (42% neutropenia [NP] and 5% febrile neutropenia [FN] vs. 18% NP and 2% FN). How acceptable these toxicity data are in the metastatic situation should probably be decided individually from patient to patient.

As mentioned above, according to the results of the IMpassion130 study, patients with advanced or metastatic TNBC and PD-L1 expression on tumour-infiltrating immune cells (PD-L1 IC +) can benefit from the addition of the anti-PD-L1 antibody atezolizumab to *nab*-paclitaxel [10, 12].

Use of *nab*-Paclitaxel

There is no doubt that taxanes, which have been developed steadily over the years, now form part of state-of-the-art chemotherapy in early and metastatic breast cancer [4, 31, 61]. Which taxanes are used in the metastatic situation under which conditions are the object of current discussions.

Since first-generation taxanes have now been on the market for about 20 years, there is intensive clinical experience for the use of these drugs, which is not available to the same extent for *nab*-paclitaxel. *Nab*-paclitaxel has nevertheless become undoubtedly established in the treatment of breast cancer since it was licensed in 2008. Since it was licensed in Germany, about 15 600 patients with breast cancer and about 8600 patients with metastatic pancreatic cancer and non-small cell lung cancer have now been treated with *nab*-paclitaxel [62]. In the case of breast cancer, apart from 3-weekly administration in a dosage of 260 mg/m^2, in practice it is now given preferably in a dosage of 125 mg/m^2 weekly for 3 weeks with a one-week break in treatment (qw3/4) [63]. As regards use and the dosage of *nab*-paclitaxel to be chosen in the metastatic situation in women with HER2-negative and endocrine-insensitive breast cancer, we follow the recommendations formulated in 2012 by a panel of experts [63] and refer to the guidelines published by the AGO, breast committee, in March 2019.

In non-pretreated patients for whom combined treatment with chemotherapy and bevacizumab is not desired, anthracycline monotherapy should be used initially, followed, for example, by *nab*-paclitaxel. In patients who have already had previous treatment with an anthracycline, *nab*-paclitaxel can be used subsequently, regardless of whether the setting is (neo-)adjuvant or metastatic. The dosage to be selected is guided by the patient's performance status.

Patients who have previously received (neo-)adjuvant anthracycline and/or taxane therapy and have good performance status and a disease-free interval of over 12 months can be given *nab*-paclitaxel as re-induction in a dosage of 150 mg/m^2 (d1, 8, 15, q28d), while the dose should be reduced to 125 mg/m^2 (d1, 8, 15, q28d) in adjuvantly pretreated women with impaired performance status.

For patients who received anthracycline and/or taxane-based therapy as first line and have good performance status, *nab*-paclitaxel is recommended in the reduced dosage of 125 mg/m^2 (d1, 8, 15, q28d) and in the further reduced dosage of 100 mg/m^2 (d1, 8, 15, q28d) in the case of impaired performance status. Alternatively, a combination of taxane or capecitabine plus bevacizumab can be given [4]. If *nab*-paclitaxel is the taxane chosen as part of combined therapy, the reduced dosage of 125 mg/m^2 (d1, 8, 15, q28d) should be used.

In general, *nab*-paclitaxel should be used after failure of first-line therapy. The dosage recommendations given above apply. When used in later treatment lines, a reduced dosage of 100 or 125 mg/m^2 should be chosen.

Nab-paclitaxel with its special formulation shows a better therapeutic profile than the solvent-based first-generation taxanes. For this reason, the second-generation taxane is also a component of modern neoadjuvant and biomarker-aided study designs.

First-generation taxanes have the disadvantage that solubilisers are necessary to obtain adequate solubility of the cytostatic agents. The solubilising agents are often the cause of hypersensitivity reactions and other undesirable effects and necessitate premedication [34]. If dexamethasone is used, there is a further risk of a rise in glucose tolerance and suppression of the adrenal cortex [64 – 66]. Moreover, dexamethasone probably induces CYP3A, thus influencing taxane metabolism [67].

The second-generation taxane – *nab*-paclitaxel – does not require any solubiliser because of its special formulation, which uses the transport protein albumin. Negative effects of corticosteroid premedication therefore do not arise. This could also prove to be an advantage for this modern taxane in the long term, particularly as a possible combination partner for future immuno-oncological treatment concepts. On the other hand, it must be pointed out that clinical experience with the first-generation taxanes is very extensive (for both breast cancer and other oncological diseases). The drug costs associated with *nab*-paclitaxel are higher at first glance than with the generic first-generation taxanes, but this is relative as the costs for co-medication are cancelled [68].

Neuropathy

Peripheral sensory and motor neuropathies are probably the most frequently discussed side effects of taxane-containing chemotherapy protocols. The frequency of grade 3–4 neuropathy (severe limitation of self-sufficiency) is reported especially for weekly (*nab*-)paclitaxel in higher dosage and paclitaxel given weekly with an incidence of 10–30 % (▶ **Table 1**). Most cases are reversible but in a few cases they become chronic. In up to 80 % of cases, mild symptoms are still reported up to 2 years after conclusion of the taxane-containing chemotherapy [69]. Prompt identification of the risk factors (such as poorly controlled diabetes mellitus, alcohol consumption, immune diseases) is the best strategy for avoiding these complications.

Unfortunately, there are no confirmed targeted prophylactic strategies. The most effective therapeutic measure is prompt interruption of treatment or dose modification. Several studies and meta-analyses have investigated the most varied prevention strategies in recent times (both pharmacological and with various vitamins, Ca/Mg etc.). Because of the very heterogeneous results of these studies, to date there is no generally accepted prophylaxis and treatment strategy.

Drugs such as gabapentin, pregabalin, duloxetine and tricyclic antidepressants have been shown to be possible treatments for neuropathic pain. Current recommendations for the management of polyneuropathy should be followed [15, 70]. Several studies are currently ongoing to identify the genetic risk factors for polyneuropathy.

▶ **Table 1** Selection of cytostatic agents for use in metastatic breast cancer (licensing status in August 2019).

Drug	Area of use	Toxicity spectrum	Comment
Doxorubicin	I. v. therapy, 3-weekly or weekly Especially first line in HER2-neg., HR-pos. and triple-negative (ER/PR/HER2- breast Ca.) (TNBC)	Alopecia, cardiotoxicity, myelosuppression, mucositis, nausea and vomiting	LVEF due to adjuvant anthracycline therapy reduced Note cumulative A dose
Epirubicin	I. v. therapy, 3-weekly or weekly Especially first line in HER2-neg., HR-pos. and in TNBC	Alopecia, myelosuppression, cardiomyopathy, but less cardiotoxicity than doxorubicin, nausea and vomiting	LVEF due to adjuvant anthracycline therapy reduced Note cumulative A dose
Mitoxantrone	I. v. therapy Especially later lines in HER2-neg., HR-pos. and in TNBC	Alopecia, nausea and vomiting	
Docetaxel	I. v. therapy, 3-weekly Especially first line in HER2-neg., HR-pos. and in TNBC, in HER2-pos. in combination with anti-HER2 therapy	Alopecia, diarrhoea, mucositis, dose-limiting myelosuppression, nausea and vomiting, dose-dependent peripheral neuropathy (at the dosage 100 mg/m^2 as monotherapy in 2–30 % of cases [grade 3–4])	Hypersensitivity reactions more seldom than with paclitaxel
Paclitaxel	I. v. therapy, preferably weekly Especially first line in HER2-neg., HR-pos. and in TNBC, in HER2-pos. in combination with anti-HER2 therapy	Dose-limiting myelosuppression, dose-dependent and dose-limiting cumulative peripheral polyneuropathies (3-weekly dosage 175 mg/m^2: 2–13 %, weekly dosage 80 mg/m^2: 17–30 % grade 3–4) Allergic reactions because of cremophor	Anti-allergic premedication required. No direct correlation between dose and anti-tumour effect. Combination with bevacizumab possible.
nab-Paclitaxel	I. v. therapy, 3-weekly or weekly in adult patients in whom the first-line treatment of metastatic disease has failed and for whom standard anthracycline-containing therapy is not indicated (in HER2-pos in combination with anti-HER2 therapy)	Alopecia, myelosuppression, peripheral polyneuropathy in 9–22 % of cases (grade 3–4) [5]	No premedication required after anthracycline pretreatment, also after taxane pretreatment and treatment-free interval of more than 12 months
Pegylated liposomal doxorubicin	I. v. therapy, 3-weekly or weekly as first-line in patients with increased cardiac risk and after A pretreatment and after A and T pretreatment	Alopecia, myelosuppression, PPE	Lower cardiotoxicity than with non-liposome encapsulated doxorubicin
Liposomal doxorubicin	I. v. therapy, 3-weekly or weekly after anthracycline pretreatment, with increased cardiac risk	Alopecia, nausea and vomiting	Lower cardiotoxicity than with non-liposome encapsulated doxorubicin
Capecitabine	P. o. first-line and after A pretreatment and after A and T pretreatment	PPE, nausea and vomiting	After A pretreatment and after A and T pretreatment. Combination with bevacizumab possible
Vinorelbine	I. v. or p. o. therapy after A and T pretreatment	Myelosuppression, dose-dependent neurotoxicity	After A and T pretreatment
Eribulin	I. v. therapy after A and T pretreatment	Alopecia, myelosuppression, peripheral neuropathy, nausea and vomiting	After A and T pretreatment
Carboplatin	I. v. therapy, weekly or 3/4-weekly TNBC with BRCA mutation TNBC with BRCA mutation Possibly in combination with gemcitabine (warning: off label use)	Nausea and vomiting	

Continued next page

▶ **Table 1** Selection of cytostatic agents for use in metastatic breast cancer (licensing status in August 2019). *(Continued)*

Drug	Area of use	Toxicity spectrum	Comment
Cisplatin	I. v. therapy, 3-weekly in TNBC in combination with gemcitabine (warning: off label use)	Alopecia, myelosuppression, nephrotoxicity, neurotoxicity, ototoxicity, nausea and vomiting	
Gemcitabine	I. v. therapy, 3/4-weekly in combination with a taxane after adjuvant A therapy in TNBC in combination with cisplatin or carboplatin	Flu-like symptoms and peripheral oedema, myelosuppression	

A = anthracyclines, T = taxanes

Predictive factors for taxane use

To date there are no validated predictive markers for the use of taxanes in the early and late situation. Several studies in the adjuvant situation have focused on Ki-67, SPARC and tau protein as markers, and most actually show greater effectiveness of anthracycline/taxane-based chemotherapy compared to use of anthracycline alone (e.g. CEF) in patients with HR+/HER2− and higher Ki-67 (or HER2-positive breast cancer) [71, 72]. However, how far these results should apply especially for taxanes or generally for the generally higher chemosensitivity of these tumours remains unclear. Unfortunately, there are no reliable data for predictive factors for use in the metastatic situation.

Use of Taxanes in Metastatic Breast Cancer According to AGO 2019 Recommendations

In March 2019 the AGO, Breast Committee, presented its updated recommendations on the use of chemotherapy in patients with metastatic breast cancer [4]. The following recommendations apply especially for the use of taxanes:

For first-line treatment of HER2-negative/HR-positive metastatic breast cancer, monotherapy with the taxanes paclitaxel (q1w) or docetaxel (q3w) should be given (AGO ++ recommendation). Monotherapy with nab-paclitaxel can be given (+ recommendation). If polychemotherapy is used in the patients, for instance because of a need to achieve rapid remission, a combination of anthracycline plus taxane or taxane + gemcitabine (after adjuvant anthracycline) should be used (AGO ++ recommendation). Paclitaxel + capecitabine and docetaxel + capecitabine can be used after adjuvant anthracycline treatment (+ recommendation).

If bevacizumab is to be used in first-line treatment, paclitaxel (q1w) is recommended from the taxane group as combination partner (+ recommendation). For docetaxel (q3q) and *nab*-paclitaxel, the Breast Committee of the AGO has issued only a +/− recommendation. The combination bevacizumab plus taxane also receives a +/− recommendation as second line.

If patients have already been pretreated with an anthracycline, paclitaxel (q1w), docetaxel (q3w) and *nab*-paclitaxel as well as capecitabine are likewise recommended by the AGO for palliative chemotherapy in HER2-negative/HR-positive metastatic breast cancer (++ recommendation). This is somewhat irritating in the case of both *nab*-paclitaxel and capecitabine as, unlike the first-generation taxanes now used for over 25 years clinically and in corresponding studies, the evidence is lower because of the smaller patient numbers with LoE 2b and B instead of LoE 1a and A in the case of paclitaxel and docetaxel. After anthracycline and taxane pretreatment, a taxane re-challenge can be given (AGO + recommendation), though it is not specified which taxane should preferably be used. A precondition is that the patient was recurrence-free for at least 1 year after adjuvant treatment.

In women with metastatic TNBC, independent of BRCA1/2 germ line mutation, *nab*-paclitaxel plus carboplatin (vs. gemcitabine/carboplatin) and gemcitabine/cisplatin (vs. paclitaxel/gemcitabine) is recommended with "+" if polychemotherapy is indicated. The + recommendation to add the anti-PD-L1 antibody atezolizumab to *nab*-paclitaxel in the first line in the event of PD-L1-IC positivity (PD-L1 IC +) is new. For this, patients' PD-L1 expression on tumour-infiltrating immune cells must be measured.

Summary

Palliative chemotherapy is indicated in the metastatic situation in patients with HR-positive, HER2-negative breast cancer if endocrine therapy is not or is no longer possible, in women with TNBC [73] and in patients with HER2-positive breast cancer who are to receive targeted treatment in which chemotherapy is part of the treatment regimen. All three taxanes licensed for the treatment of breast cancer, paclitaxel, docetaxel and *nab*-paclitaxel, can be used in the metastatic setting. The AGO, Breast Committee guidelines, updated in March 2019, have assigned a different degree of recommendation to the individual taxanes for different treatment situations, which appreciably facilitates routine clinical decision-making.

Acknowledgements

We thank Petra Ortner (POMME-med GmbH) for her assistance in producing the manuscript.

Conflict of Interest

Oleg Gluz: lecture/consultancy fees: Celgene, Roche, Genomic Health, Amgen, Pfizer, Novartis, Lilly, Nanostring, Eisai, MSD; assistance with travel costs: Celgene, Roche, Daiichi Sankyo.
Cornelia Liedtke: lecture/consultancy fees: Phaon Scientific, Novartis, Pfizer, Celgene, Roche, AstraZeneca, Lilly, Hexal, Amgen, Eisai, SonoScape; research sponsorship: Roche, Novartis, Pfizer; travel costs: Roche, Novartis.
Marc Thil: lecture/consultancy fees: Amgen, AstraZeneca, Aurikamed, Biom'Up, Celgene, Daiichi Sankyo, Eisai, Genomic Health, Hexal, Lilly, MCI, Medtronic, MSD, Myriad, Neodynamics, Norgine, Novartis, OnkoLive, OmniaMed, pfmMedical, Pfizer, Roche, Tesaro, Teva, RTI Surgical and research support by Genomic Health.
Frederik Marme: lecture/consultancy fees: AstraZeneca, Tesaro, Roche, Novartis, Pfizer, PharmaMar, GenomicHealth, CureVac, Amgen, Eisai, MSD, Celgene, Clovis, Vaccibody, Immunomedics, Janssen-Cilag.

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