Chemotherapy for Metastatic Breast Cancer – An Anachronism in the Era of Personalised and Targeted Oncological Therapy?

Chemotherapie des metastasierten Mammakarzinoms – ein Anachronismus in der Ära der personalisierten zielgerichteten onkologischen Therapie?

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Abstract

Based on the findings of modern molecular biology, breast cancer is nowadays considered to be a heterogeneous disease. This leads to the objective of an individualised, more patient-oriented therapy. A series of target molecules for this purpose has already been identified. The principle of targeted oncological therapy was realised decades ago with the introduction of endocrine therapy for patients with hormone receptor-positive tumours. The modern therapy for HER2-positive tumours is a further example for the translation of targeted therapy into clinical routine. For patients with HER2-negative metastatic breast cancer, to date two targeted drugs, bevacizumab and everolimus, are available for routine clinical use. Many other substances are still undergoing clinical development. However, validated predictive markers to aid in therapeutic decision-making and therapy control are still lacking. Chemotherapy constitutes an effective palliative therapy with proven efficacy for the patients. In this process strategies have also been realised for a targeted therapy against tumour cells with the help of chemotherapeutic agents such as, for example, the intracellular activation of the prodrug capecitabine or the active albumin-mediated transport of nab-paclitaxel which leads to higher peri- and intratumoural enrichments. The continuing unchanged relevance of chemotherapy is often underestimated in the current discussions and will be comprehensively evaluated in this review.

Zusammenfassung

Aufgrund der Erkenntnisse der modernen Molekularbiologie wird Brustkrebs heute als heterogene Erkrankung verstanden. Daraus ergibt sich das Ziel einer individualisierteren, mehr personalisierten Therapie. Hierfür sind schon eine Reihe von Zielmolekülen identifiziert worden. Mit der endokrinen Therapie von Patientinnen mit hormonrezeptorpositiven Tumoren wird der Grundsatz der zielgerichteten onkologischen Therapie bereits seit Jahrzehnten realisiert. Die moderne Therapie HER2-positiver Tumore ist ein weiteres Beispiel für die erfolgreiche Translation zielgerichteter Therapieprinzipien in den klinischen Alltag. Beim HER2-negativen metastasierten Mammakarzinom stehen Patientinnen in der klinischen Routine bisher mit Bevacizumab und Everolimus 2 zielgerichtete Medikamente zur Verfügung. Viele weitere neue Substanzen befinden sich noch in der klinischen Entwicklung. Es fehlen aber validierte prädiktive Marker zur Therapieentscheidung und -steuerung. Mit der Chemotherapie steht Patientinnen eine effektive palliative Therapie mit bewiesener Wirksamkeit zur Verfügung. Dabei wurden auch bei den Chemotherapeutika Ansätze für eine zielgerichtetere Therapie gegen Tumorzellen realisiert, so etwa mit der intrazellulären Aktivierung des Prodrugs Capecitabin oder mit dem aktiven albuminvermittelten Transports von nab-Paclitaxel, der zu einer höheren peri- und intratumoralen Anreicherung führt. Der unveränderte Stellenwert der Chemotherapie wird in den aktuellen Diskussionen jedoch häufig unterschätzt und soll in dieser Übersichtsarbeit umfassend beleuchtet werden.

Introduction

The advances in molecular biology have changed our opinions on an ideal oncological therapy. This is also true for breast cancer. The pioneering work of Perou and Sorlie on the intrinsic subtypes already published in 2000/2001 marks a turning point in our understanding of the disease [1,2]. Breast cancer is today considered to be a heterogeneous disease, the term is used as an umbrella for a multitude of molecularly defined tumour types. In addition, there is our knowledge of the intratumoural heterogeneity, since a tumour contains various molecular subpopulations including, most probably, also cells with stem cell properties [3,4]. Furthermore, the molecular properties of the primary tumour may differ from those of its metastases [5,6]. A further decisive factor in the development, maintenance and progression of malignant diseases is the interactions between tumour cells and their surroundings [3,7].

Ideally, modern oncological therapies should be directed at specific molecular biological properties of the tumour disease (in the sense of a targeted therapy). This may involve either properties of the tumour cells or properties of the surrounding tissue or of the microenvironment. A glance at the lists of the European Medicines Agency EMA on submitted pharmaceutical approvals in the period 2012–2014 shows that, among the antineoplastic substances listed there, almost all are target directed, i.e., are drugs acting on specific cell components. However, requests for authorisation of targeted therapies or drugs for breast cancer at all are only rarely found in these lists [8].

A tumour exhibits two to eight gene mutations that are relevant for the development and maintenance of malignant growth and which can be assigned to 12 signal transduction pathways [9]. Hereby basic research has in the meantime identified a series of promising targets, also for breast cancer, as can be seen in **Table 1**, however, due to the dynamics of basic research, this table does not claim to be complete. A detailed description of all target structures and processes is beyond the scope of this review. For more details we refer the reader to other review articles [3,9–11]. Our intention is to illustrate the position that chemotherapy still occupies in modern oncological therapy but without completely omitting a presentation of targeted therapies that are often the focal point of current discussions.

Targeted Therapy for HER2-Positive Breast Cancer

The modern therapy for HER2-positive tumours is an impressive example for the successful translation of a targeted therapeutic principle into clinical routine. HER2 was initially identified as an unfavourable prognostic parameter, then as a target and finally as a predictive marker for an anti-HER2 therapy. The targeted therapy against HER2 results in a significantly prolonged survival for both early and advanced breast cancer and this is a significant clinical benefit for the patients [12–15]. The additional administration of the monoclonal antibody trastuzumab directed against HER2 to a first-line chemotherapy in combination with paclitaxel lengthens the median overall survival of patients with metastatic HER2-positive breast cancer from 18.4 to 22.1 months and in combination with docetaxel from 22.7 to 31.2 months [16,17]. In the second line after pre-treatment with trastuzumab and chemotherapy, the combination of the tyrosine kinase inhibitor lapatinib with capecitabine significantly improves the time to progression in comparison to capecitabine alone (hazard ratio [HR] 0.57, $p < 0.001$) but does not show any difference in overall survival (HR 0.87, $p = 0.206$). The median overall survival of patients in the combination arm amounted to 75 weeks (corresponding to about 16.7 months) [18,19]. Trastuzumab emtansine, an antibody-active substance conjugate of trastuzumab and the cytotoxin DM1, achieved for patients pre-treated with trastuzumab and taxane a significant prolongation of overall survival from 25.1 to 30.9 months in comparison to lapatinib and capecitabine [20]. In the meantime a median overall survival of 56.5 months has been realised with the first-line combination of docetaxel, trastuzumab and pertuzumab, a monoclonal antibody against HER2 and a HER2/HER3 dimerisation inhibitor [21]. Thus, due to the excellent results from the dual blockade alone, the necessity for chemotherapy was called into question and it was investigated whether the combination of two therapies targeted against HER2 offers an equivalent clinical benefit together with a better tolerability [22,23], as is being examined, for example, in the PERNETTA trial [24]. In the case of HER2-positive, hormone receptor-positive breast cancer, a “dual attack” with endocrine therapy and a targeted therapy against HER2 can be employed. Three trials have investigated the combination of trastuzumab or lapatinib with aromatase inhibitors [25–27]. In two studies an improvement of the progression-free survival in comparison to the aromatase inhibitor alone was demonstrated [26,27]. A benefit with regard to overall survival was not seen in any of the three trials [25–27].

Targeted Therapy for HER2-Negative Breast Cancer

For patients with HER2-negative metastatic breast cancer, besides the classical endocrine therapy for hormone receptor-positive disease, two targeted drugs are at present approved for use in clinical routine.

Everolimus

Everolimus is a selective inhibitor of the mammalian target of rapamycin (mTOR), a serine threonine kinase that participates in regulation of the cell cycle, angiogenesis and glycolysis, the activities of which are up-regulated in many human tumours [28,29]. In the BOLERO-2 trial, patients with hormone receptor-positive, advanced breast cancer who had experienced progression under a prior therapy with a non-steroidal aromatase inhibitor achieved a significant prolongation of progression-free survival (PFS) with a combination of everolimus and exemestane in comparison to exemestane alone (median PFS according to the evaluation of the study physician: 6.9 vs. 2.8 months, HR 0.43, $p < 0.001$) [30]. This was not accompanied by a prolongation of overall survival (HR 0.89, $p = 0.14$) [31]. On the basis of the BOLERO-2 trial, everolimus in combination with exemestane was approved as therapy for hormone receptor-positive, HER2-negative, advanced breast cancer in postmenopausal women without symptomatic visceral metastases, when progression had occurred under treatment with a non-steroidal aromatase inhibitor [29].

Bevacizumab

Bevacizumab is a recombinant humanised monoclonal IgG-antibody against the vascular endothelial growth factor (VEGF) A. The docking of VEGF on the VEGF receptors of endothelial cells of blood vessels is prevented. In this way endothelial proliferation and angiogenesis are inhibited. Accordingly, the mechanism of

Table 1 Survey of targeted, effective therapies undergoing clinical testing for metastatic breast cancer (modified from [3]).

Site of action	Targeted structure/process	Drugs
Breast cancer cells	human epidermal growth factor (HER) 2 receptor	anti-HER2 monoclonal antibodies
		HER2-tyrosine kinase inhibitor
		anti-HER2-antibody-active substance conjugate
	poly-(ADP-ribose-)polymerase (PARP)	PARP inhibitors
	phosphoinositide 3-kinase (PI3K)/serine-threonine-kinase (AKT)/ mammalian target of rapamycin (mTOR) signal pathway	mTORC1/2 inhibitors
		dual PI3K-mTOR inhibitors
		pan-PI3K inhibitors
		PI3Kα inhibitors
		PI3Kβ inhibitors
		AKT inhibitors
	insulin-like growth factor (IGF) and receptor (R)	IGF-1R inhibitors
		dual IGF-1R insulin receptor inhibitors
		anti-IGF monoclonal antibodies
	fibroblast growth factor (FGF)	multi-targeted FGFR inhibitors
		highly selective FGFR inhibitors
	methionine (MET) signal pathway	MET signal pathway inhibitors
	cyclin-dependent kinases (CDK)	CDK inhibitors
	mitogen-activated protein kinase (MAPK) signal pathway	MAPK signal pathway inhibitors
	epigenetic regulation	histone deacetylation (HDAC) inhibitors
		histone methyltransferase (HMT) inhibitors
	SRC protooncogene, non-receptor tyrosine protein kinase (SRC)	SRC inhibitors
	human epidermal growth factor (HER) 3 receptor	HER3 inhibitors
	aurora kinase inhibitors	aurora kinase inhibitors
	androgen receptor	androgen receptor inhibitors
	prolactin receptor	prolactin receptor inhibitor
Breast cancer stem cells	notch signal pathway	γ-secretase inhibitors
		delta-like ligand-4 inhibitors
	hedgehog signal pathway	receptor-smoothened homologue (SMO) inhibitors
	wingless-Int1 (WNT) signal pathway	frizzled receptor inhibitors
		β-catenin inhibitor
		porcupine inhibitor
Tumour microenvironment	angiogenesis	anti-VEGF monoclonal antibodies
		tyrosine kinase inhibitor
	programmed cell death protein (PD-1) and ligand (PD-L-1)	PD-1 inhibitors
		PD-L-1 inhibitors
	lysis oxidase (LOX)	LOX inhibitors
	chemokines and receptors	chemokine receptor inhibitor
	integrins	integrin inhibitors
	hypoxia	hypoxia-induced factor (HIF) 1α inhibitor
		hypoxia-activated prodrugs

action is assumed to involve a deficient supply of nutrients and oxygen to the tumour with a subsequent inhibition of growth [32, 33].

Data from three phase III trials on the first-line therapy for HER2-negative breast cancer that have tested the additional administration of bevacizumab to chemotherapy are available. In all three studies a significant benefit in PFS was demonstrated for the therapy with bevacizumab: in the E2100 trial for the combination of bevacizumab with weekly paclitaxel compared with paclitaxel monotherapy (median PFS 11.8 vs. 5.9 months, HR 0.60, $p < 0.001$) [34], in the RIBBON-1 trial for the combination of bevacizumab and capecitabine vs. capecitabine (median PFS 8.6 vs. 5.7 months, HR 0.69, $p < 0.001$) and for bevacizumab in combination with taxane or anthracycline vs. only chemotherapy (median PFS 9.2 vs. 8.0 months, HR 0.64, $p < 0.001$) [35] as well as in the AVADO trial for the combination of bevacizumab with docetaxel vs. docetaxel alone (median PFS 10.0 vs. 8.1 months, HR 0.67, $p < 0.001$) [36]. In none of the three studies did the significant PFS prolongation translate into an advantage with respect to survival. A meta-analysis of all three studies confirmed the PFS benefit (HR 0.70, 95% CI 0.57–0.86), but could not identify any advantage in overall survival for the combination of bevacizumab with chemotherapy as compared to chemotherapy alone (HR 0.95, 95% CI 0.85–1.06) [37]. In the phase III TURANDOT trial in the first line, the combination of paclitaxel and bevacizumab was tested against the combination of capecitabine and bevacizumab. The required non-inferiority of capecitabine and bevacizumab for the primary end point PFS was not achieved in the planned interim analysis. The PFS for the combination of paclitaxel and bevacizumab amounted to 11.0 months and that for capecitabine with bevacizumab to 8.1 months; simultaneously the total response rate of 44% for the taxane-containing combination was significantly higher than that of 27% for the capecitabine-containing combination [38].

Also in the second line, the additional administration of bevacizumab to chemotherapy achieved a significant improvement in PFS (median PFS 7.2 vs. 5.1 months, HR 0.78, $p = 0.0072$) but no

improvement in overall survival when compared to chemotherapy alone [39].

In November 2011 the American FDA withdrew the approval provisionally granted in 2008 for bevacizumab as treatment for metastatic breast cancer [40]. According to estimations of the European Medicines Agency, there is in the first line a positive benefit-risk balance. Therefore bevacizumab in combination with paclitaxel or capecitabine is approved in the EU for the first-line treatment of patients with metastatic breast cancer [33].

Finally, it should be noted that the above-reported results were all obtained in unselected patient populations since there are as yet no established predictive markers for a response to bevacizumab. It is possible that patients with higher VEGFR-2 or VEGF-A plasma levels benefit more from therapy with bevacizumab [41, 42]. A further possibility could be circulating endothelial cells [43]. However, prospective evidence is still lacking.

For patients with early breast cancer, the combination of bevacizumab with adjuvant chemotherapy did not show an advantage in invasive event-free survival or in overall survival in two large randomised trials [41,44].

Deficits in the Targeted Therapy for HER2-Negative Metastatic Breast Cancer

In the SAFIR01 trial between June 2011 and July 2012, 423 patients with metastatic breast cancer and a maximum of two previous chemotherapies were enrolled and the genomic profiles of their metastatic tissue were determined. In 48 of 407 patients with evaluable biopsy samples, targeted therapy could be initiated on the basis of the detection of specific genomic changes. 16 different regimes were employed. 28 patients were treated in the framework of phase I or phase II trials. For 43 patients it was possible to evaluate the response to therapy, 4 showed a partial response and 9 exhibited stable disease over > 16 weeks [45]. This study exemplarily illustrates the problems which a personalised therapy has to face today. The feasibility of taking biopsies from metastases was an enrollment and thus a selection criterion. For these patients it was possible to obtain a comprehensive individual profile of at least the biopsied metastatic tissue. However, only for a small portion of these patients it was possible to initiate a targeted therapy based on the results of this analysis. The efficacy of this targeted therapy selected with the help of the most up to date methods was circumscribed, referred to the initially enrolled 423 patients, the rate of clinical benefits (partial remission or stable disease for > 16 weeks) amounted to 3%. Just the validation of the necessary predictive biomarkers in prospective studies represents an enormous challenge.

Chemotherapy for Metastatic Breast Cancer

Chemotherapy targets rapidly proliferating cells and thus is rather an unspecific therapy. However, it remains an indispensable pillar of therapy for the treatment of patients with metastatic breast cancer, especially those with HER2-negative disease. At this point a short summary is called for on what we know and what we can expect from chemotherapy for HER2-negative breast cancer. The summary is limited to a presentation of results from randomised studies and meta-analyses.

Chemotherapy for HER2-negative breast cancer is indicated for hormone-receptor negative, i.e., triple-negative, disease or when for hormone receptor-positive patients an endocrine therapy is not possible, e.g., in the case of acute life-threatening disease or in cases with endocrine resistance. Even though a polychemotherapy leads to a better response and a longer progression-free survival compared with a monochemotherapy, it is however associated with a higher rate of toxicity [46–48]. Polychemotherapy should thus only be used in cases with a high pressure for remission, i.e., in cases with pronounced symptoms or a rapid progression of disease. The highest remission rates were achieved with a taxane in combination with an anthracycline or antimetabolites. Otherwise the progression-guided sequential administration of different monochemotherapies should be preferred over polychemotherapy [46,49].

In cases of hypercalcaemia, bone pain due to metastases, osteolytic metastases or manifest osteoporosis induced by the tumour therapy there is in addition an indication for osteoprotective therapy with a bisphosphonate or the RANKL inhibitor denosumab. In this way the occurrence of skeletal complications can be delayed [46,50–54]. With regard to the efficiency in preventing skeletal events, a large phase III trial revealed a significant advantage of denosumab as compared to zoledronate. Neither of the two substances led to an improvement in survival [54]. Both substances constitute valid therapeutic options with different side effect profiles.

In principle, a wide spectrum of cytostatic agents is available. The decision for a specific regime depends on the previous adjuvant and palliative treatments, the response to a neoadjuvant therapy, symptoms and aggressiveness of the disease as well as toxicity to be expected in combination with the patient's general condition, previous diseases, comorbidity and the patient's expectations [49]. Recommendations of the AGO on palliative chemotherapy for breast cancer provide a useful aid in this respect (**Tables 2** to **4**) [49]. Anthracyclines and taxanes are considered to be the most effective substances [46,49]. In a recent meta-analysis it was also shown that a longer duration of therapy is associated with a better overall survival for the patient [55]. Whether or not this applies to all subtypes such as, e.g., ER-positive diseases with the possibility for endocrine maintenance therapy or the HER2-positive subtype with the possibility for an anti-HER2 maintenance therapy is a still open question. Thus, in general and especially for the palliative situation, it holds that therapy should be continued for as long as the therapeutic index remains positive, i.e., the metastatic disease is kept under control by the therapy and at the same time the toxicity of the therapy does not severely impair the patient's quality of life.

Anthracyclines

Anthracyclines were originally isolated from bacteria or produced semi-synthetically, they are antibiotics with cytostatic activity. They lead to inhibition of DNA replication and transcription. The cell cycle is blocked, above all during the S-phase and mitosis, as a result of an inhibition of the topoisomerase II enzyme and an intercalation in DNA [56].

A Cochrane meta-analysis of 33 studies with 5284 randomised patients showed a significant advantage of antibiotics-based anti-tumour regime with regard to the time to progression as compared to regimes without antibiotics (HR 0.84, 95% CI 0.77–0.91) and tumour response (odds ratio [OR] 1.34, 95% CI 1.21–1.48). This was also true when only the 29 trials with anthracycline-based regimes were considered [57].

In phase III trials for doxorubicin, first-line remission rates of 36%, median time to therapy failure of 5.8 months, median pro-

Table 2 AGO recommendations on palliative chemotherapy for HER2-negative, HR-positive MBC, first-line treatment.

	Oxford/AGO LoE/GR		
Monotherapy:			
▶ paclitaxel (q1w) (T), docetaxel (q3w)	1b	A	++
▶ doxorubicin, erirubicin, mitoxanthrone (A), PEG-liposomal doxorubicin (A_{lip})	1b	A	++
▶ vinorelbine	3b	B	+
▶ capecitabine	2b	B	+
▶ nab-paclitaxel	2b	B	+
Polychemotherapy:			
▶ A + T	1b	A	++
▶ paclitaxel + capecitabine	2 b	B	+
▶ docetaxel + capecitabine after adj. A	1b	A	+
▶ T + gemcitabine after adj. A	2b	B	++
▶ A + C or A_{lip} + C	1b	B	++

AGO: Arbeitsgemeinschaft Gynäkologische Onkologie (working group for gynaecological oncology); HR: hormone receptor; MBC: metastatic breast cancer [49].

Table 3 AGO recommendations on palliative chemotherapy for HER2-negative, HR-positive MBC after a previous anthracycline treatment.

	Oxford/AGO LoE/GR		
▶ paclitaxel q1w	1a	A	++
▶ docetaxel q3w	1a	A	++
▶ capecitabine	2b	B	++
▶ nab-paclitaxel	2b	B	++
▶ PEG-liposomal doxorubicin	2b	B	+
▶ eribulin	1b	B	+
▶ vinorelbine	2b	B	+
▶ docetaxel + PEG-liposomal doxorubicin	1b	B	±

AGO: Arbeitsgemeinschaft Gynäkologische Onkologie (working group for gynaecological oncology); HR: hormone receptor; MBC: metastatic breast cancer [49].

Table 4 AGO recommendations on palliative chemotherapy for HER2-negative, HR-positive MBC after previous treatment with taxanes and anthracyclines.

	Oxford/AGO LoE/GR		
▶ experimental therapies in trials			++
▶ capecitabine	2b	B	++
▶ eribulin	1b	B	++
▶ vinorelbine	2b	B	++
▶ (PEG-)liposomal doxorubicin	2b	B	+
▶ gemcitabine + cisplatin/carboplatin	2b	B	±
▶ gemcitabine + capecitabine	2b	B	±
▶ gemcitabine + vinorelbine*	1b	B	–

* NB: neutropenia/therapeutic index!

AGO: Arbeitsgemeinschaft Gynäkologische Onkologie (working group for gynaecological oncology); HR: hormone receptor; MBC: metastatic breast cancer [49].

gression-free survival of 7.8 months and median time for overall survival (OS) of 18.9, 20 and 22 months were reported [58–60].

Alopecia, mucositis, haematological toxicity (neutropenia, thrombocytopenia, anaemia) and cardiotoxicity are typical severe side effects of anthracyclines [52,53]. For liposomal formulations of doxorubicin similar efficacy data with reduced cardiotoxicity have been published [59–61].

Taxanes

Taxanes are cytostatic agents that occur in nature in certain types of yew tree and are now prepared semi-synthetically. Their mechanism of action is based on an attack on the cytoskeleton. They lead to an enhanced polymerisation of microtubules and then prevent disaggregation of the spindle apparatus through binding to a tubulin subunit. Thus the cell cycle is blocked in the G2 phase or, respectively, the M phase [62,63].

Taxanes vs. anthracyclines

Several studies have compared the efficacy of anthracyclines and taxanes in metastatic breast cancer. A meta-analysis of 11 randomised trials that compared first-line taxanes in mono- or combination therapies with anthracycline-based therapy displayed a mixed picture. Therapy with taxanes exhibited a significantly reduced progression-free survival compared with anthracycline monotherapy (HR 1.19, $p = 0.011$), but no significant differences with regard to response rate (38 vs. 33 %, $p = 0.08$) and overall survival (HR 1.01, $p = 0.90$). Taxane-based combinations achieved significantly better results for response rate (57 vs. 46 %, $p < 0.001$) and progression-free survival (HR 0.92, $p = 0.031$), but not overall survival (HR 0.95, $p = 0.24$). On the whole, the median overall survival for all 3953 patients under anthracycline- or taxane-based therapies amounted to 19.3 months in the first line [64].

A meta-analysis from the Cochrane Institute of 21 trials with altogether 3643 patients suffering from metastatic breast cancer revealed significant advantages with regard to overall survival (HR 0.93, $p = 0.05$), time to progression (HR 0.92, $p = 0.02$) and response rate (OR 1.34, $p < 0.00001$) for the taxane-based regime compared to regimes without a taxane. This was not the case for a comparison between taxane monotherapy vs. anthracycline monotherapy, which demonstrated comparable efficacies in three trials [65,66].

Taxanes after anthracycline pre-treatment

After anthracycline pre-treatment a median overall survival of up to 15.4 months was achieved with docetaxel. In a direct comparison this was significantly lower with paclitaxel, namely 12.7 months ($p = 0.03$) [67]. However, this was valid for a once every three weeks dosage which was later proved to be significantly inferior to a once weekly scheme in a phase III trial on patients with metastatic breast cancer with regard to response rate (29 vs. 42 %, $p = 0.0004$), time to progression (HR 1.43, $p < 0.0001$) and overall survival (HR 1.28, $p = 0.0092$) [68].

Docetaxel vs. paclitaxel

A meta-analysis of 7 trials involving 1694 patients with metastatic breast cancer that directly compared the two taxanes paclitaxel and docetaxel with each other showed comparable efficacies with regard to overall response rates (RR 1.01, 95 % CI 0.88–1.15, $p = 0.92$), time to progression (HR 1.13, 95 % CI 0.81–1.58, $p = 0.46$), progression-free survival (HR 0.76, 95 % CI 0.58–1.00, $p = 0.052$), and overall survival (HR 0.87, 95 % CI 0.60–1.27,

p = 0.48) albeit with different toxicity profiles [64]. Typical severe side effects of both taxanes were alopecia, stomatitis, haematological toxicity with febrile neutropenia as well as peripheral polyneuropathy [62,63,69]. In this context the incidence of severe peripheral polyneuropathy was significantly higher under the once weekly dosage of paclitaxel when compared to the once every three weeks dosage [68].

nab-Paclitaxel

nab-Paclitaxel, available in USA since 2005 and in Europe since 2008, is a further taxane for the treatment of patients with breast cancer. As opposed to the other conventional taxanes paclitaxel and docetaxel, nab-paclitaxel does not need a solubilising agent and thus also no pre-medication as prophylaxis against severe hypersensitivity reactions [70]. Albumin serves as a physiological carrier molecule in the body for hydrophobic substances. nab-Paclitaxel is a suspension of nanoparticles from human serum albumin to which the paclitaxel molecules are bound. A peri- and intratumoural enrichment of the active substance is achieved by means of an improved active transport via vascular endothelium by active receptor-mediated transcytosis [70–72]. There is as yet no confirmation from prospective data for the role attributed to the albumin-binding protein SPARC as a predictive biomarker in the therapy with nab-paclitaxel for metastatic breast cancer [73]. In three randomised studies nab-paclitaxel was compared with conventional taxanes. In a phase III trial nab-paclitaxel administered once every three weeks to patients with metastatic breast cancer, in comparison to conventional solvent-based paclitaxel administered once every three weeks, exhibited a significantly higher overall response rate (33 vs. 19%, p = 0.001) and a significant prolongation of the time to disease progression (median TTP 23.0 vs. 16.9 weeks, HR 0.75, p = 0.006). 42% of the patients were treated first line. A significant survival benefit of therapy with nab-paclitaxel was not seen for the entire collective but was observed for patients from the second line onwards (median OS 56.4 vs. 46.7 weeks, HR 0.73, p = 0.024) [74]. In the phase III GeparSepto trial 12 weekly doses of nab-paclitaxel (125 mg/m^2) or conventional paclitaxel (80 mg/m^2) were compared, both followed by 4 cycles of epirubicin and cyclophosphamide, as neoadjuvant therapy in patients with early breast cancer. Under neoadjuvant nab-paclitaxel the pathological complete remission rate (pCR) compared to conventional solvent-based paclitaxel could be increased significantly (pCR 38 vs. 29%, odds ratio 1.53, p < 0.001) [75].

One once every three weeks and two once weekly regimes with nab-paclitaxel were compared in a randomised phase II study with docetaxel in a once every three weeks dosage as first-line therapy for patients with metastatic breast cancer. Here nab-paclitaxel in the once weekly dose of 150 mg/m^2 in comparison with docetaxel achieved a significant prolongation of the median progression-free survival (assessed by independent radiologists, median PFS 12.9 vs. 7.5 months, HR 0.495, p = 0.0065) [76]. In the final analysis of overall survival the median overall survival with nab-paclitaxel in the once weekly dose of 150 mg/m^2 amounted to 33.8 months, that with nab-paclitaxel in the once weekly dose of 100 mg/m^2 to 22.2 months, to 27.7 months for nab-paclitaxel in the once every three weeks dose of 300 mg/m^2 and to 26.6 months for the once every three weeks dose of 100 mg/m^2 docetaxel. Merely the difference between nab-paclitaxel 150 mg/m^2 vs. nab-paclitaxel 100 mg/m^2 reached statistical significance (HR 0.575, p = 0.008) [77]. The toxicity profile of nab-paclitaxel differed from those of the conventional taxanes. Third and fourth degree neutropenias occurred significantly less often under nab-paclitaxel [62,64]. With nab-paclitaxel patients developed a peripheral sensory neuropathy more often than those under conventional paclitaxel administered once every three weeks, however this regressed more rapidly in the former patients. Thus, the median time to improvement of 2nd degree disease and less was 22 days under nab-Paclitaxel compared to 79 days under solvent-based paclitaxel [74].

Vinorelbine

The vinca alkaloid vinorelbine is also a spindle inhibitor. In contrast to the taxanes it inhibits the polymerisation of tubulin and so blocks mitosis in the G2-M phase [78].

After pre-treatment with anthracycline a vinorelbine monotherapy in contrast to monotherapy with melphalan achieves significant improvements with regard to time to progression and time to therapy failure (both 12 vs. 8 weeks, p < 0.001) as well as overall survival (35 vs. 31 weeks, p = 0.034) [79]. Patients who received vinorelbine as a monotherapy after pre-treatment with anthracycline and taxane (15% as first line, 54% as second line, and 31% as third line) achieved an overall response rate of 26%, a median PFS of 4 months and a median OS of 16.4 months [80].

In the first line the additional administration of vinorelbine to epirubicin therapy resulted in a significant lengthening of the PFS compared to epirubicin monotherapy (median PFS 10.1 vs. 8.2 months, p = 0.019). However, there was neither a significant improvement in overall response rate (50 vs. 42%, p = 0.15) nor in overall survival (median OS 19.1 vs. 18.0 months, p = 0.50) [81].

Neutropenia and anaemia are the typical severe side effects of vinorelbine [78–80].

Capecitabine

Capecitabine is a cytostatic agent from the group of antimetabolites. It is a prodrug that is transformed in the cell to the actual active substance, 5-fluorouracil (5-FU). 5-FU possesses a structural similarity with uracil and is incorporated into the RNA in place of uracil. In addition, it inhibits thymidylate synthetase, a key enzyme of pyrimidine synthesis that occurs both in healthy tissue and in higher concentrations in tumour tissue. Capecitabine thus leads to an inhibition of cell growth especially in cells with higher replication rates [82].

After anthracycline pre-treatment the combination of docetaxel and capecitabine in comparison to monotherapy with docetaxel achieves significant improvements in overall response rate (42 vs. 30%, p = 0.006), prolongation of the time to progression (median TTP 6.1 vs. 4.2 months, HR 0.652, p = 0.0001) and overall survival (median OS 14.5 vs. 11.5 months, HR 0.775, p = 0.0126) [83].

After therapy with anthracycline and taxane monotherapy with capecitabine results in an overall response rate of up to 24.3%, a median PFS of up to 5.2 months and a median OS of 22.4 months [84].

Typical severe side effects of capecitabine are stomatitis, diarrhoea and hand-foot syndrome [82–84].

Eribulin

Since 2011 eribulin has been available for the treatment of patients with local advanced or metastatic breast cancer after pretreatment with anthracycline and taxane and since 2014 for progression after at least one palliative chemotherapy line [85]. Eribulin belongs to the class of halichondrines that has been isolated from a marine sponge. It realises its antineoplastic activity in the

same way as the taxanes and the vinca alkaloids by way of attack at the spindle apparatus of the cells. Eribulin inhibits the growth of microtubules but does not inhibit their polymerisation. Non-functional tubulin aggregates are formed. The cell cycle is blocked in the G2-M phase [85,86].

For patients with metastatic breast cancer and pre-treatment with two to five chemotherapeutic regimes including one with an anthracycline and one with a taxane, a monotherapy with eribulin in comparison with the therapy of choice of the testing physician (up to 96% a chemotherapy) achieved a significant improvement in overall survival (median OS 13.1 vs. 10.6 months, HR 0.81, p = 0.041) [87].

In a randomised comparison with capecitabine monotherapy for patients with local advanced or metastatic breast cancer and previous treatments with anthracyclines and taxanes, eribulin therapy did not demonstrate a significant difference in progression-free survival (median PFS 4.1 vs. 4.2 months, HR 1.079, p = 0.305) or in overall survival (median OS 15.9 vs. 14.5 months, HR 0.879, p = 0.056) [83]. In the trials neutropenia, fatigue and peripheral neuropathy constituted the typical side effects [85,87,88].

Platinum salts

The platinum salts cisplatin and carboplatin act via an interlinking of DNA single and double strands [89]. A specific status has been postulated for them in the therapy for patients with triple-negative and BRCA-positive breast cancer. In the CALGB 40603 phase III trial involving patients with triple-negative early breast cancer, the additional administration of carboplatin to taxane- and anthracycline-based neoadjuvant chemotherapy resulted in a significant increase in the pCR rate (pCR in breast and axilla [54 vs. 41%, p = 0.0029]) [90]. This had also been shown in the GeparSixto randomised phase II trial whereby the additional administration of carboplatin to a taxane- and anthracycline-based neoadjuvant chemotherapy led to a significant increase in the pCR rate for patients with triple-negative breast cancer (53.2 vs. 36.9%, p = 0.005). In a retrospective subgroup analysis, the benefit from the additional administration of carboplatin was most apparent for patients with a BRCA mutation or a family history thereof [91,92].

In the British TNT phase III trial involving patients with metastatic triple-negative or BRCA1/2-positive breast cancer, a monochemotherapy with carboplatin (AUC6 q3w) was compared with a monochemotherapy of docetaxel (100 mg/m^2 q3w). Here in the entire population of triple-negative patients carboplatin was not superior to docetaxel. In a small subgroup of 43 patients with proven BRCA1/2 mutations, on the other hand, a significantly higher overall response rate was seen for therapy with carboplatin in comparison to that with docetaxel (ORR 68.0 vs. 33.3%, p = 0.03) [93].

Conclusions

Our knowledge about breast cancer has increased at a rapid pace. Accordingly the opportunities for more intelligent, more individualised therapies have grown too.

However, for patients with HER2-negative metastatic breast cancer, a molecular biological, personalised therapy is still not a clinical reality. Most of the candidate drugs still have a long way to go before they can be approved. In the final analysis the relevant targets can be assigned to 12 signal transduction pathways [9]. Even today, and this is also true for the two already available drugs, there are (still) no validated predictive markers on the basis of which one can deduce a therapeutic response and thus selectively treat individual patients. Data from randomised trials that would be necessary for a prospective assessment are still lacking. After the disappointing results of the non-randomised preliminary trials, patients with HER2-negative, metastatic breast cancer received in one arm of the SAFIR02 trial targeted therapies according to individual genomic analyses and in the other arm maintenance chemotherapy [94].

However, in the light of the numerous targeted and effective therapies currently undergoing clinical development, the conventional practices for gaining scientific evidence must also be subject to scrutiny. Alternative concepts for intelligent approval studies need to be found. Also the call for biopsy samples of metastases is gaining in importance in combination with targeted therapies. In consideration of the evolution of the tumour genome, repeated rebiopsies and reanalyses appear to be meaningful prior to every new therapy line. A less invasive and more comprehensive alternative in future could be the sequencing of tumour DNA from plasma samples [95]. The creation of an effective and country-wide infrastructure to enable a rapid and reliable testing is one of the basic prerequisites for the successful integration of targeted therapies into clinical reality.

In spite of all the understandable enthusiasm for specific, targeted and effective therapies, it is often forgotten in the general discussion that for the patients chemotherapy still represents an effective, albeit unspecific, palliative therapy for which the efficacy has been unequivocally confirmed. In addition, options for a targeted therapy against tumour cells have also been realised with chemotherapeutic agents, examples for this include the intracellular activation of the prodrug capecitabine or the peri- and intratumoural enrichment of nab-paclitaxel on account of its improved, active albumin-mediated transport via vascular endothelium.

Finally, if we consider the targeted concepts for not only HER2-positive but also for HER2-negative breast cancer more exactly, we can see that, alongside endocrine therapy, chemotherapy as a combination partner in targeted therapy continues to serve as the backbone not only for palliative but also for personalised systemic treatments. Chemotherapy is thus not an anachronism but rather is still an elemental building block in the systemic therapy for metastatic breast cancer.

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Conflict of Interest

The authors declare that, within the past three years, they have received support for the following activities: AS: consulting fees from Roche, Celgene, Eisai, Novartis; fees for lectures from Roche, Celgene, AstraZeneca, Amgen, GSK, Novartis. ER: fees for lectures from Amgen, AstraZeneca, Celgene, GSK, Janssen Cilag, Novartis, Pierre Fabre, Roche, Teva. JH: consulting fees from Roche, Novartis, Amgen, Eisei, GSK; fees for lectures from Roche, Novartis, Celgene, AstraZeneca.

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