

Cytotoxic drugs for patients with breast cancer in the era of targeted treatment: back to the future?

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Background: Despite current trend of targeted therapy development, cytotoxic agents are a mainstay of treatment of patients with breast cancer. We reviewed recent advances in cytotoxic therapy for patients with metastatic breast cancer (MBC).

Materials and methods: Medline searches were conducted for English language studies using the term 'MBC' and 'cytotoxic drugs'. The data search was restricted to the period 2000–2011.

Results: Several novel cytotoxic compounds, all microtubule inhibitors, have been approved for clinical use in MBC: (i) nab-paclitaxel, reported to improve tumour response and decrease hypersensitivity reactions in comparison with other taxanes; (ii) ixabepilone, shown to have clinical benefit in taxane- and anthracycline-resistant disease and (iii) eribulin, shown to improve overall survival in heavily pre-treated patients, when compared with best available standard treatment. Agents, such as larotaxel, vinflunine, trabectedin and formulations, including cationic liposomal paclitaxel or paclitaxel poliglumex, are currently under evaluation in phase II/III trials.

Conclusion: Toxicity and chemotherapy resistance are still major limitations in the treatment of patients with MBC. Further research into new cytotoxic compounds is needed in order to maximise benefit, whilst minimising toxicity.

Key words: cytotoxic drugs, metastatic breast cancer, new drugs

Introduction

As the second most common cancer-related cause of death among females, breast cancer is considered a major public health concern [1]. Despite an improvement in overall survival (OS), with the use of anthracyclines and taxanes, resistance to therapy and subsequent progression of disease are still observed in metastatic patients [2]. Thus, it is clear that new agents and treatment strategies are needed.

This review aims to evaluate all available data regarding cytotoxic therapy for breast cancer.

Methods

Medline searches were conducted for English language studies in cancer patients using the terms 'breast cancer' and 'cytotoxic agents'. These searches were supplemented by reference list searches, the Cochrane database, American Society of Clinical Oncology and European Society for Medical Oncology abstracts and consultation with experts in the field.

Studies meeting the following criteria were selected: prospective phase I, II and III clinical trials of chemotherapy (weekly or daily schedules), including indicators of activity and toxicity, data on survival/mortality and at least one multivariate analysis examining survival.

Results

All results retrieved are classified by pharmacological type and further described with a focus on the mechanism of action, evidence of efficacy and the toxicity profile. Ongoing major trials are summarised in Table 1.

antimicrotubule agents

Microtubule inhibitors are among the most frequently used agents for breast cancer chemotherapy, with proven efficacy in both localised and metastatic disease [18]. However, the risk of hypersensitivity reactions and other severe adverse events impairing quality of life, together with susceptibility to resistance [19], are concerning limitations to their use. Another issue related to this class of agents is peripheral sensory neuropathy, in most of the cases dose-limiting toxicity for patients with metastatic breast cancer (MBC). For this reason, research into alternatives has intensified, thus resulting in the

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Table 1. Major clinical trials involving novel cytotoxic agents

Agents	Study	Reference	N	Phase/patients	Response	Grade 3/4 toxicity
Nab-P	Gradishar et al. [3]	-	460	III; metastatic, ABI-007 versus P	ORR: 33% versus 19% ($P = 0.001$); OS: 65.0 versus 55.7 weeks ($P = 0.374$)	Neutropaenia G4: 9 versus 22%; neuropathy G3: 10 versus 2%
	Gradishar et al. [4]	-	302	II; first line; ABI-007 versus docetaxel	PFS: 12.9 versus 7.5 m ($P = 0.0065$) for weekly ABI-007	Neutropaenia G4: 5 versus 75%; neuropathy G3: comparable (not stated)
	Ongoing trial	-	203	II; adjuvant; AC followed by P or ABI-007	Primary end points: safety	NCT ID number: NCT00394251
P-poliglumex	Lin [5]	-	18	II; metastatic, first or second lines	Trial suspended due to high rate of adverse events	Hypersensitivity: 22%; neuropathy: 22%
EndoTAG1	Awada [6]	-	143	II; metastatic, first or second lines, ET + P, ET or P	PFS at 16 weeks: 4.2, 3.4 and 3.7 m, respectively; OR: 25%, 5% and 38%	Neutropaenia G3/4: 20% (combination group); chills and fever related to ET
Larotaxel	Diéras et al. [7]	-	130	II; metastatic, first or second lines	Resistant to taxanes—ORR: 19%; TTP: 1.6 m; Non-resistant—ORR: 42%; TTP: 5.4 months	Neutropaenia: 82%; neuropathy: 7%; diarrhoea: 12%
	Ongoing trial	-	438	III; metastatic, late-line, larotaxel versus capecitabine	Primary end points: TTP; secondary end points: OS	NCT ID number: NCT00081796
Ixabepilone	Trial 009	[8]	49	II; metastatic, late-line ^a monotherapy	ORR: 12%; SD: 41%; DOR: 10.4 m; TTP 2.2 m; OS 7.9 m	Fatigue G3: 27%; neuropathy G3: 12%; myalgia G3: 10%; neutropaenia: 53%; febrile neutropaenia: 6%
	Trial 081	[9]	113	II; metastatic, late-line monotherapy	ORR: 11.5%; SD: 50%; DOR: 5.7 m; PFS 3.1 m; OS 8.6 m	Neutropaenia: 54%; febrile neutropaenia: 3%; neuropathy: 13%; fatigue/asthenia: 14%
	Trail 046	[10]	737	III; metastatic, late line; resistant A/T Ixa/Cap versus Cap	ORR: 34.7% versus 14.3%; DOR: 6.4 versus 5.6 m; PFS 5.8 versus 4.2 m; HR: 0.75	Neuropathy: 21%; hand-foot syndrome G3: 8%; neutropaenia: 68%; febrile neutropaenia: 5% ^a
	Trial 048	[11]	1221	III; metastatic; late-line pre-treated A/T; Ixa/Cap versus Cap	OS: 16.4 versus 15.6 m; PFS: 6.2 versus 4.2 m; RR: 43% versus 29%	Neuropathy: 24%; hand-foot syndrome: 21%; diarrhoea: 43%; neutropaenia: 73%
VFL	Campone et al. [12]	[12]	60	II; metastatic, late line;	ORR: 30%; SD: 35%; PFS: 3.7 m; OS: 14.3 m	Neutropaenia: 65%; Constipation G3: 11.7%
	Yardley et al. [13]	[13]	31	II; metastatic, first line, addition of trastuzumab according to HER2 status	VFL + trastuzumab—ORR: 48%; PFS: 6.6 m; OS not reached; VFL—PFS: 3.5 m; OS: 9 m	VFL + trastuzumab—neutropaenia G4: 24%; nausea/vomiting G3: 29%; VFL—neutropaenia G4: 9%; nausea/vomiting G3: 0%
	Ongoing trial	-	764 Plan	III; metastatic, late line	Primary end points: PFS; secondary end points: OS, ORR, safety, QoL	NCT ID number: NCT01095003
Eribulin	Cortes et al. [14]	[14]	299	II; metastatic, late line	ORR: 9.3%; SD: 46.5%; PFS: 2.6 m	Neutropaenia: 54%; febrile neutropaenia: 5.5%; neuropathy: 6.9%

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Table 1. (Continued)

Agents	Study	Reference	N	Phase/patients	Response	Grade 3/4 toxicity
	EMBRACE (2011)	[15]	762	III; metastatic, late line	OS: benefit of 2.5 m; HR: 0.81 ($P = 0.04$)	Neutropaenia: 44%; neuropathy: 8.4%
	Study 301	[16]	1102	III; metastatic, capecitabine versus E7389	Primary end points: OS and PFS	(Ongoing trial); NCT ID number: NCT00337103
Trabectedin	Zelek et al. [17]	-	27	II; metastatic, late line	ORR: 14%; TTP: 2.14 m; OS: 10 m	Neutropaenia G4: 33%; transaminitis: 75%

^aReported toxic effects occurring in the combination arm.

Cap, capecitabine; DOR, Duration of response; ET, EndoTAG1; HR, hazard ratio; m, months; Ixa, ixabepilone; NCT ID, tracking identification number from clinicaltrials.gov; ORR, overall response rate; OR, objective response; OS, overall survival; PFS, progression-free survival; P, paclitaxel; QoL, quality of life; RR, response rate; SD, stable disease; TTP, time to progression; VFL, vinflunine.

discovery of the following new compounds and more tolerable formulations of paclitaxel.

new taxane formulations

nab-paclitaxel. mechanism of action. Agents, such as nab-paclitaxel (ABI-007 or Abraxane™), were developed in an attempt to avoid the hypersensitivity reactions associated with taxanes, which are related to the solvent suspension in polyoxyethylated castor oil (cremophor). ABI-007 consists of a colloidal formulation, prepared by homogenisation of paclitaxel in human serum albumin at a concentration of 3%–4% [20]. The resulting nanoparticles form systemic albumin-bound complexes, which potentially deliver higher intracellular concentrations of taxane [20].

activity. In phase I studies, the maximum dose of nab-paclitaxel is reported as 300 mg/m² every 3 weeks; thus, there is delivery of a higher dosage than by cremophor paclitaxel [20]. The USA FDA (Food and Drug Administration) granted approval for the use of ABI-007 in clinical practice following a phase III multicentre, open-labelled trial, involving 460 patients with MBC. ABI-007 (dose of 260 mg/m² at 21-day intervals) was compared with 175 mg/m² paclitaxel every 3 weeks [3]. The primary outcome measurements demonstrated a benefit with nab-paclitaxel, which was statistically significant in all patients, in terms of overall response rate (ORR) (33% versus 19%; $P = 0.001$) and time to progression (TTP) [23.0 versus 16.9 weeks; hazard ratio (HR) = 0.75; $P = 0.006$]. A small improvement was suggested in median survival, though this was not significant (65.0 versus 55.7 weeks; $P = 0.374$). A phase II trial compared nab-paclitaxel as first-line therapy in three distinct regimens (300 mg/m² 3 weekly, weekly 100 or 150 mg/m²), with docetaxel (100 mg/m² 3 weekly). Authors reported an improvement in progression-free survival (PFS) of 12.9 versus 7.5 months ($P = 0.0065$) with the weekly regimen of ABI-007 [4]. In our opinion, the right dose and the right schedule is still not determined and this is a potential limitation for clinical development of this drug in the early, neoadjuvant setting.

toxicity. Relative to cremophor paclitaxel, ABI-007 is reportedly associated with reduced myelotoxicity and with

5%–9% grade 4 neutropaenia, but with a greater incidence of grade 3 neuropathy (10% versus 2% for paclitaxel) [3, 4]. However, there are fewer reported instances of hypersensitivity reactions. Gradishar et al. [3] described the use of corticosteroid and anti-histamine premedication (for emesis, myalgia/arthralgia or anorexia) in 99% of patients administered paclitaxel, in comparison with 8% from the nab-paclitaxel group.

paclitaxel poliglumex. mechanism of action: Paclitaxel poliglumex (CT-2103) is also a conjugate compound, in this case with paclitaxel bound to α -poly-L-glutamic acid. This formulation was developed with the aim of improving selective delivery of the drug to neoplastic tissue, thus increasing efficacy.

activity: This compound is more extensively studied in non-small-cell-lung cancer [21], with little research conducted for breast cancer. A phase II trial of 18 patients with HER2-negative MBC was suspended as rates of neurotoxicity and late hypersensitivity reactions were much higher than expected [5].

toxicity: As stated above, hypersensitivity reactions and neuropathy were common, occurring in 4 of 18 patients [5]. However, this same schedule has been widely studied for other tumours and been found to have an acceptable tolerability profile [22].

cationic liposomal paclitaxel. mechanism of action: With a similar concept to liposomal anthracyclines, in which the cytotoxic agent is encapsulated by a phospholipid membrane, liposomal formulations containing paclitaxel were created with the aim of minimising toxicity. In preclinical studies, liposomal taxanes modify pharmacodynamics but maintain similar antitumoural activity [23]. Moreover, in animal models, cationic liposomes were targeted to negatively charged activated endothelial cells of tumour vessels, thus altering drug delivery [24].

activity: The first phase II randomised trial involving the use of cationic liposomal paclitaxel (EndoTAG™-1) enrolled 143 patients with triple-negative (TN) MBC in first- or second-line

therapy to a three-arm 2:2:1 study of EndoTAG™-1 plus paclitaxel, isolated EndoTAG™-1 or paclitaxel [6]. Preliminary analysis showed a PFS of 4.2, 3.2 and 3.7 months and objective response of 25%, 5% and 38%, respectively. Longer follow-up is needed to better define whether such a combination offers advantage in terms of efficacy, as well as toxicity.

toxicity: EndoTAG™-1 has been associated with fever and chills, although a tolerable toxicity profile is reported on phase II studies [6, 25]. The ongoing trial, above described, observed 20% grade 3/4 neutropaenia with the cremophor paclitaxel preparation.

new taxanes: larotaxel.

mechanism of action: Larotaxel (XRP 9881) is a semisynthetic taxoid derived from the natural compound 10-deacetyl baccatin III, extracted from the tree *Taxus baccata*. Its mechanism of action is similar to that of other taxanes: it aggregates tubulin and inhibits microtubule dynamics. Additionally, evidence supports its action in taxane-resistant cells [26] and its ability to cross the blood–brain barrier in animal experiments [27].

activity: In phase I preclinical studies, the most well-tolerated dosage regimen was 90 mg/m² every 3 weeks [28]. Other schedules evaluated were the same dose on days 1 and 8 of each 21-day cycle [29], in which the main limiting toxicity was diarrhoea [30]. The largest phase II trial (*n* = 130) studied the use of 1-h infusions of 90 mg/m² larotaxel every 3 weeks. All patients had previously been treated with taxane as adjuvant, neoadjuvant or first-line therapy and were stratified as resistant or non-resistant in accordance with their response. The ORR was 42% and the TTP 5.4 months in the non-resistant group; while in the resistant group, the ORR was 19% and the TTP 1.6 months, thus showing that larotaxel retained minimal benefit in patients previously exposed to taxanes [7].

toxicity: Myelotoxicity is the major side-effect with the use of this agent. The most common grade 3/4 adverse events, documented by Diéras et al. [7], were neutropaenia (82%), febrile neutropaenia (9%) and sensory neuropathy (7%). Grade 3/4 diarrhoea was reported in 12% of patients. Seventeen patients discontinued larotaxel due to side-effects.

epothilones

Originally isolated from myxobacterium *Sorangium cellulosum* [31], the epothilones are macrolide compounds with strong antitumour activity against several human cancer cell types [32]. Currently, there are five epothilones undergoing investigation in clinical trials: ixabepilone, patupilone, BMS-310705, KOS-852 and ZK-EPO [33]. One of the most active epothilone analogues is ixabepilone, which has been evaluated in combination or monotherapy for MBC.

ixabepilone. mechanism of action: Epothilones are strong promoters of tubulin polymerisation *in vitro* [34], enhancing microtubule stability and the formation of abnormal mitotic spindles, which induce G₂–M cell cycle arrest and apoptosis. Structural analysis indicates that epothilones may bind at or near the paclitaxel binding site on the β-tubulin protein [35]

having, however, different characteristics for microtubule binding interaction [36].

activity: ixabepilone monotherapy. The best tolerated regimen in phase I preclinical studies was 40 mg/m² every 21 days [37]. A phase II randomised trial, comparing a weekly schedule with a 3-weekly schedule, demonstrated a trend towards a longer PFS for the 3-week regimen, although weekly ixabepilone was better tolerated [38]. Two key phase II clinical trials evaluated ixabepilone in a highly refractory population, showing significant activity. The 009-phase II trial enrolled 49 patients with MBC [8] receiving 40 mg/m² ixabepilone, infused over 3 h, every 21 days. Efficacy analysis reported an ORR of 12% with a median duration of response of 10.4 months and stable disease (SD) in 41%. Median TTP was 2.2 months [95% confidence intervals (CI): 1.4–3.2 months]. Another phase II trial assessed ixabepilone in 126 patients, using the same treatment schedule [9]. In the 113 assessable patients, the ORR was 11.5%. The median duration of response was 5.7 months (95% CI: 4.4–7.3 months) and the median PFS 3.1 months (95% CI: 6.9–11.1 months).

ixabepilone combination regimens. capecitabine: The biological rationale behind this combination is a synergistic interaction as a consequence of enhanced expression of thymidine phosphorylase [39, 40]. The activity of this association was shown in a phase II trial assessing 62 patients previously treated with anthracycline and taxane (Table 2). The preliminary results were encouraging, hence prompting phase III trials [40]. The CA163-046 study enrolled 752 patients with MBC resistant to anthracyclines and taxane [10], randomised to receive either the combination treatment (40 mg/m² ixabepilone, infused over 3 h on day 1 plus 2000 mg/m² capecitabine on days 1–14 of a 21-day cycle) or the capecitabine monotherapy (2500 mg/m² on days 1–14 of a 21-day cycle). A significant increase in PFS (5.8 versus 4.2 months; HR = 0.75; *P* = 0.0003) and ORR (35% versus 14%; *P* < 0.0001) was seen in the combination arm compared with the monotherapy arm. Furthermore, SD was recorded in 41% versus 46% of patients. A second phase III (CA163-048) trial with the same design was conducted with 1221 patients with MBC, who were anthracycline and taxane pre-treated, but not necessarily chemotherapy resistant [11]. No significant difference in OS was observed (16.4 versus 15.6 months; HR = 0.9; 95% CI, 0.75–1.03; *P* = 0.1162). PFS (6.2 versus 4.2 months; HR = 0.79; *P* = 0.0005) and response rate (RR) (43% versus 29%; *P* < 0.0001) were improved. Other combinations are being tested in phase I/II trials, namely, with epirubicin, and to date demonstrate an acceptable safety profile [41]. A randomised clinical trial (PAC 8) in the neoadjuvant setting comparing ixabepilone to weekly paclitaxel was recently prematurely closed due to futility.

bevacizumab: A phase II, randomised study in 123 HER2-negative MBC patients compared weekly versus 3-weekly ixabepilone plus bevacizumab (ixa/bev), versus paclitaxel plus bevacizumab (pac/bev) as first-line therapy [42]. The ORR was 48% (95% CI: 32.9% to 63.1%) in the weekly ixa/

Table 2. Summarised data for cytotoxic agents: mechanism, Supporting evidence, status and disadvantages

Class	Agents	Mechanism	Supporting evidence	Developmental status	Main side-effects
Antimicrotubules					
Taxanes	<i>New formulations</i>				
	Nab-paclitaxel	Paclitaxel in albumin-bound complexes	Better response rates Less need to premedicate Less neutropaenia	FDA and EMA approval for metastatic setting Ongoing trials on adjuvant and neoadjuvant treatment	Increased neurotoxicity Related reports of cystoid macular oedema Alopecia: 33%
	Paclitaxel poliglumex	Paclitaxel conjugated to α -poly-L-glutamic acid	Lacking evidence for breast cancer	New ongoing phase II trials	Higher neurotoxicity and hypersensitivity in a small phase II study Hair thinning: 7%
	Cationic liposomal paclitaxel	Paclitaxel in positively charged liposomes	Lacking evidence of benefit Possible superiority when combined with classical paclitaxel	Need to evaluate this drug in other breast cancer subtypes	Fever and chills (reported tolerability) Association to classical paclitaxel: increased neutropaenia (20%)
	<i>New agents</i>				
	Larotaxel	Similar to other taxanes	Activity observed in taxane resistance	Ongoing phase III trial to compare with capecitabine	Increased frequency of neutropaenia (82%) High rates of grade 3/4 diarrhoea Alopecia: 84%
Distinct agents	Eribulin	Tubulin destabilisation: unknown site of action	Survival benefit in late-line regimen Activity observed in taxane resistance	Ongoing phase III trial to compare with capecitabine FDA and EMA approval for metastatic setting	Increased frequency of neutropaenia (44%–54%) Alopecia: 60%
Vinca alkaloids	Vinflunine	Similar to other vinca alkaloids	Activity observed in taxane resistance Less neurotoxicity	Ongoing phase III trial testing combination treatment with capecitabine, another comparing paclitaxel/gemcitabine versus gemcitabine/vinflunine	Increased frequency of neutropaenia (up to 65%) Alopecia: 55%
Epothilones	Ixabepilone	Promoters of tubulin polymerisation, enhancing microtubule stability	Activity observed in taxane resistance	FDA approval for metastatic setting Ongoing trials on neoadjuvant and metastatic setting with epirubicin, bevacizumab, trastuzumab	Toxicity profile similar to other taxanes Alopecia: 84%
Alkylating agents					
	Trabectedin	DNA-interacting agent and transcription inhibitor	Activity in phase II trial	Ongoing phase II trial testing trabectedin in HER2-positive and BRCA1/BRCA2 mutation carriers	Grade 4 neutropaenia (33%) and hepatitis (44%)

FDA, Food and Drug Administration.

bev arm, 71% (95% CI: 55.7% to 83.6%) in the 3-weekly ixa/bev arm and 63% (95% CI: 43.7% to 78.9%) in the pac/bev arm. In terms of toxicity, a higher frequency of grade 3/4 neutropaenia was observed with the 3-weekly ixa/bev regimen (60% versus 22% for pac/bev and 16% for weekly ixa/bev); however, rates of peripheral neuropathy were similar.

trastuzumab: The efficacy of ixabepilone with trastuzumab was investigated in a non-randomised, phase II study conducted in 39 patients with HER2-positive MBC. The patients enrolled received this combination as first-line therapy or following one or two trastuzumab-containing regimens [43]. The RR was 51%. Neuropathy was the major toxicity (grade 2 \geq 55%). There were no cardiac toxicity episodes of grade 2 or greater. In another phase II trial of trastuzumab, weekly ixabepilone and carboplatin were administered in first-line setting to 59 patients with HER2-positive MBC [44]. The ORR was 42%, with median PFS of 8 months, and one death related to therapeutic complications.

toxicity: The most common toxicity with ixabepilone monotherapy is myelosuppression, primarily neutropaenia, although peripheral sensory neuropathy is also reported (grade 3/4: 7%–20%), and, rarely, febrile neutropaenia [45]. Combination regimens with capecitabine were well tolerated with minimal overlapping toxic effects. The most frequently reported grade 3/4 non-haematological adverse events were peripheral sensory neuropathy (21%–23%), hand–foot syndrome (18%–21%), fatigue (9%–12%) and diarrhoea (6%–7%). Myelosuppression was common and consisted primarily of leucopaenia and neutropaenia, with a low incidence of febrile neutropaenia (5%–7%) [10, 11].

Sensory neuropathy is a major issue for this class of agents. A major adverse effect of treatment with microtubule-stabilising agents, such as epothilones, is peripheral neuropathy, which is probably caused by the interruption of axonal transport induced by microtubule-stabilising agents. The development of neuropathy can be dose or treatment limiting for many cancer patients, and neuropathy can lead to permanent neuronal dysfunction in a minority of patients. Identification of clinical tools to predict and intervention trial to prevent neurotoxicity are key areas of research.

new vinca alkaloids

vinflunine. mechanism of action: Synthesised in 1997, vinflunine is one of the newest vinca alkaloids in this review. The chemotoxicity of this agent is primarily through the depolymerisation of tubulin compounds leading to formation of tubulin paracrystals, although additional anti-angiogenic properties have been observed *in vitro* [46].

activity: Phase II studies of other neoplasms have demonstrated an optimum starting dose of 320 mg/m² vinflunine every 3 weeks [47], although the maximum dose is reported as 400 mg/m² [48]. The first phase II trial in breast cancer evaluated vinflunine at a dose of 320 mg/m² every 21 days in 60 patients, with metastatic disease, who had progressed following taxane and anthracycline therapy [12]. This study indicated benefit in this particular group, with an

ORR of 30% and SD achieved in 35% of patients, as well as PFS of 3.7 months and an OS of 14.3 months. Two recent trials analysed a combination of vinflunine and trastuzumab therapy in a metastatic setting: the first, a phase I study of 30 HER2-positive patients, assessed the dosage and safety of vinflunine (280 or 320 mg/m² every 3 weeks) with trastuzumab (loading dose of 4 mg/kg and subsequently 2 mg/kg/week) [49]. Interim analysis showed RRs of 62.5% and 73.7% in patients receiving vinflunine at 280 and 320 mg/m², respectively, with adequate safety. A subsequent phase II, non-randomised, open-labelled trial of 31 HER2-positive patients evaluated combination (280 mg/m² vinflunine plus 6 mg/kg trastuzumab 3 weekly) or monotherapy (320 mg/m² vinflunine) [13]. For those 20 patients receiving combination therapy, there was a partial response (PR) in 48%, with PFS of 6.6 months. All these results are in line with other data showing the potential benefit of giving trastuzumab beyond progression, even if available data in this field are limited. In primary analysis for monotherapy patients, there was median PFS of 3.5 months and OS of 9 months.

toxicity: The main toxicity noted during monotherapy with 320 mg/m² vinflunine was grade 3/4 neutropaenia, observed in 65% [12]. Grade 3 constipation in 11% of patients was also reported by Campone et al. [12]. The addition of trastuzumab resulted in a significant increase in grade 4 neutropaenia (24% versus 9%) and grade 3 nausea and vomiting (29% versus 0%) [13].

Eribulin. mechanism of action: Eribulin mesylate (E7389) is a synthetic analogue of halichondrin B, a polyether macrolide originally extracted from the marine sponge *Halichondria okadaica* [50, 51]. Polymerisation is inhibited by eribulin, causing aggregation of tubulin into non-functional units, hence leading to destabilisation of microtubules; in contrast, classical compounds act to stabilise tubulin.

activity: Phase I and II trials have demonstrated a maximum dose of 1.4 mg/m², initially administered at days 1, 8 and 15 of a 28-day cycle [52] but later used in 21-day regimens to decrease myelotoxicity [53]. A recent phase II trial administered eribulin at days 1 and 8 of a 21-day cycle to 299 patients, with manageable toxicity, and primary end points reported as an ORR of 9.3% and SD rates of 46.5% [14]. The first study to analyse OS was the recent phase III trial EMBRACE of 762 patients with MBC previously exposed to anthracycline and taxanes, comparing eribulin (regimen as above) to treatment of physician's choice (TPC) (either monotherapy or supportive care). In primary analysis, there was a statistically significant benefit conferred by the use of eribulin, with an absolute gain of 2.5 months in survival (HR = 0.81; 95% CI: 0.66–0.99; *P* = 0.04) [15]. OS was significantly improved in women assigned to eribulin (median 13.1 months, 95% CI: 11.8–14.3) compared with (TPC) (10.6 months, 9.3–12.5; HR = 0.81, 95% CI: 0.66–0.99; *P* = 0.041).

toxicity: The most common adverse events in both groups were asthenia or fatigue [270 (54%) of 503 patients on eribulin

and 98 (40%) of 247 patients on TPC at all grades] and neutropaenia [260 (52%) patients receiving eribulin and 73 (30%) of those on TPC at all grades]. Peripheral neuropathy was the most common adverse event leading to discontinuation from eribulin, occurring in 24 (5%) of 503 patients. [15].

alkylating agents

Trabectedin (ET-743). mechanism of action: Trabectedin is a marine-derived DNA-interacting agent and transcription inhibitor found in the ascidian *Ecteinascidia turbinata* [17]. Evidence supports ET-743 as an effective agent, acting by down-regulation of P-glycoprotein/MDR1 and by immunomodulation (having an inhibitory effect on macrophage viability, differentiation and cytokine production) [54].

activity: Following promising findings in phase I studies [55], a multicentre, open-labelled, phase II non-randomised trial assessed the activity of trabectedin and the feasibility of its use in 27 women with advanced breast cancer previously treated with anthracyclines and/or taxanes [17]. Trabectedin, as a 24-h infusion of 1.5 mg/m², was administered at 3-week intervals. Twenty-two patients (81.5%) were assessable for response. The ORR was 14% (95% CI: 3.5% to 32%), with a median survival of 10 months (95% CI: 4.88–15.18 months). Six patients had SD. Preclinical and clinical data reporting a better outcome in sarcoma patients with low levels of BRCA1 [56] prompted a phase II trial of trabectedin in 95 patients with TN (group A), HER2-positive (group B) and BRCA1/2 germ line (group C) mutated MBC. Trabectedin was given at a dose of 1.3 mg/m², as a 3-h i.v. infusion every 2 weeks. Data were available for 72 patients. Trial accrual was closed due to no activity in TN MBC [57]. A total of 55 patients were enrolled in groups B (*n* = 31) and C (*n* = 24) with a PR in 10% and 14% and disease remaining stable in 58.6% and 38.1%, respectively. Median PFS was 3.9 months in each arm [58].

toxicity: The most common observed toxic effects with trabectedin use were grade 3 neutropaenia (33%) and transaminitis (44%) [17]. Neutropaenic fever did not arise and although transaminitis occurred in the majority of patients, it led to no serious clinical events. It is worth mentioning that the absence of other severe toxic effects, namely, grades 3–4 alopecia, and the lack of cumulative toxic effects make trabectedin attractive for long-term palliative use.

discussion

In attempt to overcome chemotherapy resistance, new agents have been developed for therapy in patients with MBC. Two novel cytotoxic compounds are currently approved by USA FDA, both with antimicrotubule activity. The first, ixabepilone, either in monotherapy after previous exposure to anthracycline, taxane and capecitabine (ORR 11.5% and PFS 3.1 months) [9] or in combination with capecitabine, was accepted based on benefit observed in PFS (relative increment

of 25%) and ORR (35% versus 14%) in patients resistant to anthracycline and taxane [10]. The European Medicine Agency (EMA) Committee for Medicinal Products for Human Use (CHMP) adopted a negative opinion of the marketing authorisation for ixabepilone (2 mg/ml powder and solvent for concentrate for solution for infusion) intended to treat locally advanced or MBC and recommended that it be refused. The CHMP recommended that ixabepilone be refused marketing authorisation because it was concerned that ixabepilone's benefits in terms of increasing TTP and the very small increase in survival rates did not outweigh concerns over the medicine's safety. In particular, the Committee was concerned over neuropathy, which was a severe and common side-effect in patients taking the medicine. The second agent is eribulin, recently approved in taxane- and anthracycline-resistant disease, after primary outcome measures from the EMBRACE trial, in which a statistically significant improvement in OS of 2.5 months was observed [15]. Neutropaenia was the most frequent adverse grade 3/4 event (54%) recorded for either drug, together with sensory neuropathy (21%–24% in ixabepilone and 8.4% in eribulin) [8, 15]. Following phase II studies demonstrating activity on refractory disease, other agents deemed to hold promise were larotaxel and vinflunine. Approved by FDA and EMA for clinical application in anthracycline-resistant disease since 2005, nab-paclitaxel, an alternative taxane formulation, is associated with fewer hypersensitivity reactions and significantly less myelotoxicity, in comparison to castor oil paclitaxel (9 versus 22%), however greater grade 3 neuropathy (10% versus 2%) [6]. In contrast to standard paclitaxel, nab-paclitaxel was characterised by a greater ORR (33% versus 19%) and TTP (HR = 0.75), though benefit on OS cannot be yet proven statistically. Such favourable results led to the initiation of a study, not yet completed, of nab-paclitaxel in localised breast cancer. A disadvantage of nab-paclitaxel is cost, which is up to five times higher than the standard formulation, and reported to be comparable to docetaxel in overall cost analysis [59, 60].

Summary of supporting evidence and disadvantages of cytotoxic agents are presented in Table 2.

conclusion

Most of the recent developments in breast cancer therapy, some of which have already been included into clinical practice, have been shown to improve PFS and RR allowing the possibility of achieving chronic status in metastatic disease. Unfortunately, as treatment duration increases, toxicity and resistance to therapy become more evident, hence justifying the continued quest for new cytotoxic agents with greater efficacy and tolerability. The main issue is still toxicity, as most of the compounds tested have displayed, at best, a distinct adverse event profile. Overcoming chemotherapy resistance and identifying predictive markers or subgroups most likely to respond to these agents should also be better investigated. As it is already clear that an integrative approach is often the most effective, the future holds the challenge of best combining cytotoxic and targeted therapy.

disclosure

The authors have declared no conflict of interest

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