Review Article

Drug-related toxicity in breast cancer patients: a new path towards tailored treatment?—a narrative review

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Background and Objective: Side effects of drugs administered for breast cancer (BC) according to cancer biology and patients' clinical features can limit patient's compliance and consequently the benefit. Precision medicine is a growing research field to improve the management of BC patient's care and evaluating toxicities profile could be an interesting feature in the choice a personalised treatment. This review aims to explore the implications of a tailored anti-cancer therapy knowing the safety profile and predisposing factors for potential specific drug-related toxicities. More specifically, this review aims to focus on personalised medicine and patients' selection according to clinical, laboratory and genetic features involved in adverse events (AEs) development.

Methods: We performed an extensive literature research on PubMed and available Medical Oncology Congresses resources regarding tailored anti-cancer therapy for BC, toxicity profile and predisposing factors for potential specific drug-related toxicities, selecting publications in English in a timeframe from January 1, 1997 to December 31, 2021. Furthermore, we provide a focus on personalised medicine with potential implications on patients' selection.

Key Contents and Findings: Literature review focused on the role of anti-cancer agents toxicity profile and AEs predisposing factors in the personalisation of BC patients treatment. For most anti-cancer agents, potential safety-related biomarkers and the implications of clinical features of BC patients for a tailored treatment were investigated.

Conclusions: A safety profile-tailored treatment combined with the clinical characteristics of BC patients and potential biomarkers predisposing to specific treatment-related toxicities might be particularly helpful in the therapeutic choice in the context of precision oncology. In this perspective, the knowledge and the application of these factors would be crucial for better choice and management of the best care for the right patient.

Keywords: Toxicity; precision oncology; breast cancer (BC); patient selection

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Introduction

Breast cancer (BC) is the most frequently diagnosed tumour and one of the leading causes of cancer death in women worldwide (1). Over the years, several agents have been introduced for the management of both early and advanced stage of BC, thus leading to a substantial improvement of survival outcomes. Indeed, the combination of conventional chemotherapy, endocrine therapy, target agents and immunotherapy are currently an integral part of clinical practice and have been validated in clinical trials (2). Treatment is tailored on the basis of tumour biologic profile and disease burden, patient's clinical features, comorbidities and preferences. Unfortunately, no drug is void of adverse events (AEs) and not all patients respond to treatment; moreover, some of them develop significant toxicities without obtaining clinical benefit. For these reasons, it crucial to identify factors which might improve the selection of patients who are candidate to a specific treatment.

Recently, the concept of "precision oncology", on the basis of which therapy is delivered to patients according to unique patient clinical and molecular features, has gained growing importance (3). The scientific rational is mainly represented by the identification of an oncogenic mutation in a patient's cancer genome that drives cancer growth, followed by treatment with target-selective drugs inhibiting that specific mutation product (4). Genomic sequencing results can be useful to classify cancer, predict prognosis and target therapies. Next-generation sequencing allows rapid and cost-effective sequencing of large portions of the genome, becoming crucial in the field of cancer genomics (5).

The identification of clinically useful gene expression signatures might be used to personalise treatment not only with the aim to improve survival, but also to reduce the risk of toxicity (6). However, not all Cancer Centres are provided with genomic testing that can be offered to BC patients in clinical practice. This leads to the need to identify further clinical and easy-to-use factors which might help improving patients' selection.

In this perspective, the toxicity profile is an interesting point to be investigated to personalise treatment. In this review, we aim to focus on personalised medicine and in particular to give an overview of the safety profile of the main anti-cancer agents for the treatment of BC patients with potential implications on patients' selection, taking into consideration their clinical characteristics. We present the following article in accordance with the Narrative Review reporting checklist (available at https://pcm.amegroups.com/article/view/10.21037/pcm-21-38/rc).

Methods

We performed an extended literature research on PubMed and available main Medical Oncology Congresses resources on tailored anti-cancer therapy for BC, toxicity profile and predisposing factors for potential specific drug-related toxicities. We selected papers published in a timeframe from January 1, 1997 to December 31, 2021. Our review was limited to manuscripts in the English language (*Table 1*). We provide a focus on personalised medicine with potential implications on patients' selection.

Anthracyclines

Anthracyclines represent a cornerstone of BC treatment (7). Cardiotoxicity, myelosuppression, nausea and vomiting are the main AEs, for which various studies assessed potential predisposing factors. An analysis by Chen *et al.* in 211 BC patients treated with epirubicin-cyclophosphamide-docetaxel chemotherapy reported a significant correlation between fibroblast growth factor receptor 2 (FGFR2) rs2420946 CC genotype and higher AEs occurrence *vs.* TT (P=0.038) and CT/TT genotypes (P=0.019); similar results were found for FGFR2 rs2981578 AG genotype *vs.* GG genotype (P<0.0001) (8).

Cardiotoxicity

Vaitiekus *et al.* identified a significant association between HFE gene H63D single nucleotide polymorphism (SNP) and subclinical cardiac damage in 81 BC patients treated with doxorubicin-based chemotherapy (P<0.005) (7). Eighteen SNPs of NFKBIL1, TNF-a, ATP6V1G2-DDX39B, MSH5, MICA, LTA, BAT1, and NOTCH4 were suggested as potentially related to doxorubicin-induced cardiotoxicity (9). A genome-wide association study in 3,431 patients of three phase III adjuvant BC trials found an association of rs28714259 SNP with congestive heart failure (CHF) induced by anthracyclines (10). Vulsteke *et al.* identified 6 cycles of 5-fluorouracil, epirubicin and cyclophosphamide *vs.* 3 cycles (OR 1.3, 95% CI: 1.1–1.4, P<0.001) and heterozygous status for ABCC1 rs246221 T-allele *vs.* homozygous (OR 1.6, 95% CI: 1.1–2.3, P=0.02) as significantly related to left ventricular ejection fraction (LVEF) reduction >10% in early BC (EBC) (11). Another

Table 1 The search strategy summary

Items	Specification
Date of search (specified to date, month and year)	15 February 2022
Databases and other sources searched	Extensive literature research on PubMed, Medical oncology congresses resources (ESMO, ASCO)
Search terms used (including MeSH and free text search terms and filters)	Breast cancer, toxicity profile, drug related-toxicities and predisposing factors
Timeframe	January 1, 1997 to December 31, 2021
Inclusion and exclusion criteria (study type, language restrictions, etc.)	English language
Selection process (who conducted the selection, whether it was conducted independently, how consensus was obtained, etc.)	The authors conducted independently the selection of articles. Consensus was not required

ESMO, European Society for Medical Oncology; ASCO, American Society of Clinical Oncology.

study detected UGT2B7-161 T allele as a potential independent biomarker of low occurrence of cardiotoxicity during adjuvant epirubicin-cyclophosphamide-docetaxel chemotherapy (P=0.004) (12).

Haematological toxicity

In a study by Cui *et al.* CBR1 rs20572 (C>T), ABCG2 rs2231142 (G>T) SNPs involved in anthracyclines pharmacokinetics or the combination of two polymorphic alleles were significantly associated to reduced risk of leukopenia (OR 0.412, 95% CI: 0.187–0.905, P=0.025) and neutropenia (OR 0.354, 95% CI: 0.148–0.846, P=0.018) in 194 BC patients receiving adjuvant anthracyclines. Moreover, patients carrying polymorphic allele T of CBR1 rs20572, or polymorphic allele C of AKR1A1 rs2088102 combined with ABCG2 rs2231142 (G>T) plus SLC22A16 rs6907567 (A>G) mutations showed an extremely low risk of grade 3–4 anaemia (OR 0.058, 95% CI: 0.006–0.554, P=0.008; OR 0.065, 95% CI: 0.006–0.689, P=0.022; OR 0.037, 95% CI: 0.004–0.36, P=0.015, respectively). Thus, these SNPs might be useful to identify which patients who are less likely to develop haematological AEs (13).

Gastrointestinal toxicity: *nausea and vomiting*

A study conducted in 110 BC patients treated with epirubicin +/− cyclophosphamide exploring the role of 5-hydroxytryptamine receptor 3 (HTR3C) genes for chemotherapy-induced nausea and vomiting (CINV), the variant genotype of K163N (HTR3C) was associated with vomiting (P=0.009) (14). Tsuji *et al.* suggested that TACR1 1323TT SNP, involving the gene encoding the neurokinin 1 receptor, might be a genetic risk factor for the development of delayed CINV (OR, 2.57; P=0.014) (15).

Fluoropyrimidines

Over 30% of patients treated with fluoropyrimidines have severe treatment-related side effects, such as diarrhoea, hand-foot syndrome, myelosuppression and mucositis (16). Fluoropyrimidine-related toxicity is often due to the presence of genetic variants in the gene encoding the enzyme dihydropyrimidine dehydrogenase (DPYD), the leading enzyme involved in fluoropyrimidine degradation (17,18). A proportion of 3–5% of the European and North American have a DYPD deficient activity (~50% reduction), resulting in major risk of severe fluoropyrimidine-related AEs occurrence if treated with full dosage (19). Actually, four DPYD variants are considered most clinically relevant for their statistically significant association with severe toxicity: c.1905+1G>A, c.2846A>T, c.1679T>G, and c.1236G>A (20). For several years routine DPYD genotype screening prior to fluoropyrimidine administration has not been the standard of care for BC management. However, recent studies have shown significant clinical and financial benefits of routine DPYD genotype screening application also in this malignancy (21-25). Notably, this has increasing importance with the introduction of adjuvant capecitabine at similar doses as those for colorectal cancer in human epidermal growth factor receptor 2 (HER2)-negative, stage I–IIIB BC without complete pathologic response or with a complete response with positive lymph nodes after neoadjuvant chemotherapy and surgery (26).

For these reasons, EMA strongly recommends DYPD testing before starting treatment with infusional fluorouracil or with the related pro-drugs, capecitabine and tegafur (27). In case of DYPD variants, the dose of

fluoropyrimidines should be adapted according to guidelines and recommendations.

Anti-HER2 agents

Anti-HER2-targeted drugs in the last 20 years dramatically changed the clinical outcome of HER2 positive BC patients (28).

Cardiotoxicity

Cardiotoxicity is one of most concerning AE associated with the anti-HER2 therapy, both in terms of symptomatic events, such CHF, and asymptomatic, such the decrease of LVEF. Cardiac AEs have been extensively studied in both EBC and metastatic BC (MBC) (29).

In the pivotal phase III randomised clinical trial (RCT) that led to its approval as first line treatment in MBC, trastuzumab, an anti-HER2 monoclonal antibody (mAb), showed a higher incidence of cardiac dysfunction and CHF of New York Heart Association class III or IV (27% *vs.* 16%) when associated with anthracycline-based therapy, compared to anthracycline-based chemotherapy alone (8% *vs.* 3%); incidence of these AEs was lower in the trastuzumab plus paclitaxel arm (13% and 2%, respectively) (30). These data were re-dimensioned by a metanalysis that included this RCT and other six subsequent RCTs, counting a total of 1,497 HER2-positive women; a significant increased risk of CHF and decreased LVEF in patients receiving trastuzumab [risk ratio (RR) 3.49 and 2.65, respectively], with severe cardiac AE occurring in 4.7% of patients trastuzumab-treated patients (31) were reported. Another metanalysis comparing RCTs with cohort studies, found that cohort studies patients, who more closely reflected the real-life treated population, have a higher risk of severe cardiac AEs than RCTs ones (4.4% *vs.* 2.8%), although, overall, severe cardiotoxicity was observed in 4.28% of MBC patients. This study also confirmed that trastuzumab administrated with anthracycline-based regimens is associated with a higher proportion of severe cardiotoxicity than with taxane-based schedules alone (2.9% *vs.* 0.9%) (32).

In the adjuvant setting, a metanalysis of eight RCTs, involving a total of 11,991 women with HER2-positive EBC, showed a significant higher risk of CHF and LVEF decrease in patients treated with trastuzumab-containing regimens compared with control arm (RR =5.11, P<0.00001 and RR =1.83, P=0.0008, respectively). CHF and LVEF decrease occurred in 2.5% and 11.2%, respectively, in trastuzumab arm *vs.* 0.4% and 5.6% in control arm (33). In another metanalysis of 6 RCTs, the overall RR of NYHA III/IV CHF with trastuzumab was found to be 3.04-fold higher (P<0.00001) than in patients who did not receive trastuzumab (34). Long-term safety analysis of major RCTs found also that the cumulative incidence of cardiotoxicity and the overall risk of cardiac AEs was higher in trastuzumab-containing regimens (35-37). Results from a combined analysis of three clinical trials investigating safety and efficacy of trastuzumab plus anthracycline-based regimens in neoadjuvant setting did not differ from adjuvant and metastatic, confirming an increased risk of cardiotoxicity for combination therapy (38).

The risk of cardiac AEs seems to significantly increase with a longer exposure to trastuzumab (35) and with administration of higher doses (34). Age ≥60 years, basal LVEF between 50% and 54.9% and use of antihypertensive medications are also associated with a significant increased risk of cardiotoxicity, so this category of BC patients deserves a special attention (36). Cardiac AEs mostly occur during trastuzumab administration and many of them are reversible, with a complete or partial recovery observed in 86.1% of trastuzumab-treated patients with symptomatic heart failure events (35,39).

Pertuzumab (a humanised anti-HER2 mAb) administered together with trastuzumab does not increase the rate of cardiac dysfunction compared to trastuzumab plus standard chemotherapy in metastatic, adjuvant and neoadjuvant settings (40-44). Lapatinib, a dual tyrosine kinase inhibitor (TKI) of EGFR and HER2, was not associated with a greater risk of cardiac AEs in MBC, as showed in the pivotal phase III trial and confirmed by a metanalysis involving 3,689 patients treated with lapatinib from different clinical trials, in which the incidence of cardiac AE was 1.6% (45,46). Data from RCTs in EBC were also consistent (47,48). Trastuzumab-emtansine (T-DM1), an antibody drug conjugate composed of an anti-HER2 mAb connected to a cytotoxic antimicrotubule agent, showed a favourable cardiotoxicity profile (49,50), as well as trastuzumab-deruxtecan (antibody-drug conjugate composed of an anti-HER2 mAb, a cleavable tetrapeptide-based linker, and a cytotoxic topoisomerase I inhibitor) (51) and tucatinib, a highly selective TKI (52). There was also no evidence of cardiac toxicity with neratinib, a TKI targeting EGFR, HER2 and HER4 (53).

Baseline ECG and baseline LVEF measurement through echocardiogram and/or multigated acquisition scan or magnetic resonance imaging are strongly recommended immediately prior to initiation of HER2-targeted

therapy to identify individuals at higher risk of future CV complications. Asymptomatic patients undergoing adjuvant trastuzumab treatment should repeat routine surveillance consisting of cardiac imaging every 3 months, for the early detection of cardiac toxicity during treatment, and every 6 months following discontinuation of treatment until 2 years from the last administration. Asymptomatic patients undergoing anti-HER2 treatment of MBC should also have general surveillance with cardiac imaging. If the anti-HER2-targeted therapy is withheld for symptomatic left ventricular cardiac dysfunction the LVEF measurement should be repeat after 4 weeks. Serial monitoring should be carried out preferably with the same imaging modality and at the same facility (54-58). Serum enzymes of cardiac damage have also been investigated as potential biomarkers of cardiotoxicity. Troponin I has been shown to predict LVEF reduction and cardiac AEs in trastuzumab-treated patients, especially those who have been exposed to anthracyclines. A higher risk for development of trastuzumab-induced cardiotoxicity was observed in patients with troponin I levels ≥0.08 ng/mL (HR =22.9, non-recovery HR =2.88) and with elevated high sensitivity troponin T levels>14 at the end of anthracycline therapy (59-64). The NeoALTTO sub-study BIG 1–06 showed that troponin T and proBNP were detected only in a few anthracycline-naïve patients receiving trastuzumab and/or lapatinib; so, they might not be effective early predictors of cardiotoxicity city in this patients' setting (65). Since most research on troponin focuses on anthracycline-pretreated patients, further studies are needed to explore the role of this biomarker and its application in clinical practice. As for the potential influence of FC gamma receptor (FCGR) polymorphisms, most studies focused on anti-HER2 efficacy and provided contrasting findings on FCGR2A and FCGR3A role (66,67). Limited data are available on FCGR SNP and toxicity. In a study by Cresti *et al.* in 101 HER2 positive EBC patients receiving trastuzumab every 3 weeks after adjuvant chemotherapy, FCGR2A His131Arg SNP was significantly related to trastuzumab-related cardiotoxicity occurrence (68). Roca *et al.* found a significant association between cardiotoxicity after trastuzumab and HER2–I655V genotype (P=0.025), but not with FCGR2A-H131R and FCGR3A–V158F SNPs (69). Though of interest, these findings require more extensive research to be confirmed.

Pulmonary toxicity

Trastuzumab-deruxtecan was associated with interstitial lung disease (ILD) incidence of 13.6% and four deaths were attributed to treatment-related ILD (51). Patients should be monitored for signs and symptoms of ILD/pneumonitis and suspected ILD/pneumonitis should be evaluated by computed tomography (CT) scan. In case of asymptomatic ILD/pneumonitis (grade 1), the administration should be withheld until recovery to grade 0 and it may be resumed, while for symptomatic ILD/pneumonitis (grade ≥2) it is recommended to permanently discontinued trastuzumab-deruxtecan, promptly administer corticosteroids for at least 14 days or until complete resolution of clinical and chest CT findings (51,70,71). In the KATHERINE trial, pneumonitis occurred in 2.6% of patients in the T-DM1 group compared to 0.8% in the trastuzumab group (50). ILD incidence is higher when trastuzumab is combined with mTOR inhibitors: in the BOLERO-3 trial, ILD incidence was 9.2% among patients who received trastuzumab with vinorelbine and everolimus compared with 3.9% of those who received trastuzumab vinorelbine and placebo, although the proportion of patients with grade 3–4 ILD was similar in the two arms (72).

Gastrointestinal and skin toxicity

HER2-targeted TKIs have a higher incidence of gastrointestinal and skin toxicity. In the lapatinib pivotal RCT for MBC, diarrhoea and cutaneous rash were the most common treatment-related AEs (any grade and grade ≥3) in lapatinib plus capecitabine arm (45). In neoadjuvant and adjuvant settings, lapatinib-containing regimens were associated most frequently with grade 3 diarrhoea and cutaneous rash compared to trastuzumab-containing regimens (47,48). Tucatinib and neratinib showed a higher incidence of gastrointestinal and skin toxicity compared to trastuzumab-containing regimens in MBC (52,73), as well as neratinib in adjuvant setting compared to placebo (37). Trastuzumab plus pertuzumab combination seems to be associated with higher number of any grade and grade ≥3 diarrhoea compared to trastuzumab in MBC and EBC (42,43,74).

Hepatotoxicity

Hepatotoxicity, predominantly in the form of asymptomatic increases in the concentrations of serum transaminases or bilirubin, has been observed during treatment with tucatinib (52), neratinib (53) and lapatinib. Serious hepatobiliary disorders, such as nodular

regenerative hyperplasia of the liver have been observed in patients treated with T-DM1 (49,50); in these cases, T-DM1 must be permanently discontinued (75).

Haematological toxicity

One of the most commonly reported grade 3–4 AEs with T-DM1 was thrombocytopenia (49-51). Routinely monitoring with haematological complete evaluation is recommended before each treatment cycle.

PIK3CA-AKT-mTOR pathway inhibitors

Everolimus

The phosphoinositide 3-kinase (PI3K) pathway plays a crucial role in the cells' growth, proliferation, migration, and death. PI3K mutations are frequently involved in BC development. Mammalian target of rapamycin (mTOR) is one of the PI3K-related kinase proteins. Everolimus is an oral mTOR inhibitor used in postmenopausal women with hormone receptor (HR) positive and HER2-negative BC, with recurrence during adjuvant non-steroidal aromatase inhibitor (AI) or disease progression in the pre-treated advanced setting (76).

Several studies evaluated the safety and feasibility of everolimus combined with other agents (72,77-86) (*Table 2*).

In the BOLERO-2 trial, 485 patients were randomized to receive everolimus plus exemestane. Everolimus discontinuation due to AEs occurred in 19% of the cases. Overall, 23% of patients referred to severe AEs. The most frequent grade 3 and grade 4 AEs were: stomatitis (8%), anaemia (6%), dyspnoea (4%), hyperglycaemia (4%), fatigue (4%), and pneumonitis (3%); seven treatment related-deaths occurred (77).

Likewise, various trials and a real-life retrospective study enrolling HR+ HER2- MBC patients treated with everolimus plus exemestane observed similar toxicities (84-86).

In clinical practice, toxicities are generally successfully managed with treatment interruption until symptoms improve to grade ≤1 and/or its dose reduction (87).

Willemsen *et al.* assessed the association of peripheral blood immunological cell subsets with antitumour response and pulmonary toxicity in 20 BC patients receiving everolimus plus exemestane. BC patients developing pulmonary toxicity compared to other patients had relatively more NKT cells (CD3+ CD56+) at baseline (6.0% versus 1.3%, P=0.0068, 59 k $\times 10^9$/L versus 12 k $\times 10^9$/L, P=0.0081) and at the moment of toxicity occurrence (5.2% versus 1.2%, P=0.0106 and 47 k $\times 10^9$/L versus 16 k $\times 10^9$/L, P=0.0466). Baseline percentage NKT cells predicted pulmonary toxicity with 0.78 sensitivity and 1.0 specificity, even if further validation is required to confirm these data (88).

Pascual *et al.* performed an exploratory analysis to assess the role of SNPs on AEs occurrence and outcomes by a pharmacogenetic study on 90 postmenopausal HR positive, HER2 negative MBC patients receiving exemestane-everolimus progressing after a non-steroidal AI. They conducted a genotyping analysis in 12 SNPs implicated in everolimus pharmacokinetics and pharmacodynamics and investigated the association with everolimus plasma concentrations, significant AEs and consequent drug schedule modifications, progression free survival and overall survival. Patients harbouring CYP3A4 rs35599367 SNP (CYP3A4*22 allele) showed increased drug plasma levels compared to other patients (P=0.019). ABCB1 rs1045642 carriers were exposed to increased risk of mucosal inflammation (P=0.031), whereas PIK3R1 rs10515074 and RAPTOR rs9906827 patients had an increased risk of hyperglycaemia (P=0.016) and non-infectious lung inflammation (P=0.024). These results show that SNPs might influence everolimus outcomes in MBC (89).

Paying attention to patients with comorbidity as diabetes or a history of lung disease is crucial. Nonetheless, these patients could benefit from treatment as well as those without these comorbidities.

Alpelisib

Alpelisib is an oral selective inhibitor of PI3K alpha (90). Alpelisib has been investigated in the SOLAR-1 phase III trial in postmenopausal women or men with HR positive, HER2 negative advanced chemo-naïve BC, pre-treated with an AI. Among 572 patients enrolled in SOLAR-1, 284 (169 PIK3CA-mutant and 115 wild type) received alpelisib combined with fulvestrant. The most common AEs of any grade were: hyperglycaemia (63.7%; 36.6% G3–4), diarrhoea (57.7%; 6.7% G3–4), nausea (44.7%), decreased appetite (35.6%), and rash (35.6%; 9.9% G3–4) or maculopapular rash (14.1%; 8.8% G3–4). AEs lead to permanent discontinuation in 25% of the cases. No treatment related deaths occurred (91).

The randomized, double-blind phase III NEO-ORB trial enrolled postmenopausal women with HR-positive HER2 negative resectable BC, including patients eligible for neoadjuvant therapy, and evaluated alpelisib combined with

Table 2 Main clinical trials on everolimus

Study	BOLERO-2 phase III	BOLERO-1 phase III	BOLERO-3 phase III	GINECO phase II	PrE0102 phase II	NCT00915603 phase II	MANTA phase II	VIcTORia phase II	EVEREXES phase III	EVA retrospective	Real world experience
Study details	HR+ HER2−	HR+/− HER2+	HR+/− HER2+	HR+ HER2−	HR+ HER2−	HR+ HER2−	HR+ HER2−	HR+ HER2−	HR+ HER2−	HR+ HER2−	HR+ HER2−
Treatment	EVE-EXE	EVE-TRAST-PCT	EVE-TRAST-VNR	EVE-TMX	EVE-FUL	EVE-BEV-PCT	EVE-FUL	EVE-VNR	EVE-EXE	EVE-EXE	EVE-EXE
Setting	UNR-MBC	UNR-MBC	MBC	UNR-MBC	UNR-MBC	UNR-MBC	UNR-MBC	UNR-MBC	UNR-MBC	UNR-MBC	UNR-MBC
Line of therapy	Post AI or 2nd line	Post AI or 1st line	2nd or more	Post AI or 1st line	Post AI or 2nd line	Post AI or 1st line	Post AI or 2nd line	Post AI or 2nd line	Post AI or 2nd line	1st or more	Post AI or 2nd line
n of patients	482	480	284	54	66	56	65	68	235	404	44
G3-G4 AEs											
Stomatitis (%)	8	13	13	11	11	15	12	7	10	11	11
Anemia (%)	6	30	19	2	3	11	NA	6	7	4	3
Fatigue (%)	4	35	13	6	6	15	NA	6	3	3	2
Dyspnea (%)	4	24	2	NA	3	2	0	NA	1	NA	NA
Hyperglicemia (%)	4	12	2	NA	2	NA	3	NA	7	1	0
Pneumonitis (%)	3	15	<2	2	6	NA	NA	NA	2	4	0
Treatment discontinuation (%)	19	50	10	17	NA	NA	NA	27	10	NA	18
Treatment related death (n)	7	17	2	NA	0	1	NA	NA	1	0	NA

AEs, adverse events; AI, aromatase inhibitor; BEV, bevacizumab; EVE, everolimus; EXE, exemestane; FUL, fulvestrant; MBC, metastatic breast cancer; PCT, paclitaxel; TMX, tamoxifen; TRAST, trastuzumab; UNR, unresectable; VNR, vinorelbine; NA, not available.

letrozole. No prior local or systemic treatment was allowed. AEs observed in the alpelisib plus letrozole arm were: hyperglycaemia (any grade 54%; G ≥3 27%), diarrhoea (any grade 52%), rash (any grade 45%; G ≥3 12%), nausea (any grade 44%), fatigue (any grade 41%), stomatitis (any grade 33%), decreased appetite (any grade 31%), alopecia (any grade 22%), headache (any grade 20%), and maculo-papular rash (G ≥3 8%). No treatment-related deaths occurred (92).

Recently, Rodon and colleagues reported the results of a pooled analysis of X2101 and SOLAR-1, a risk-analysis of alpelisib-induced hyperglycaemia according to baseline features of 505 solid cancers (including BC) patients. Risk modelling identified 5 baseline factors, namely fasting plasma glucose, body mass index, HbA1c, monocyte counts, and age which were associated with a higher probability of G3/4 hyperglycaemia. High risk patients showed higher rates of alpelisib modifications and anti-hyperglycaemic agents. This model might be useful to identify among BC patients candidate to alpelisib those who are at higher risk for alpelisib-induced hyperglycaemia (93).

Although the toxicities of grade 3/4 observed lead to discontinuation of treatment, they regress with the temporary suspension of treatment in the majority of cases. Thus, both alpelisib and everolimus appear safe.

Poly(ADP-ribose) polymerase inhibitors (PARPi)

PARPi represent one of the main innovative approaches in target therapy in BRCA-mutant BC patients. Several PARPi have been studied, including olaparib, talazoparib, niraparib, veliparib and rucaparib. Their mechanism of action is not univocal, so their efficacy is closely related to different pathways. In particular, their interaction with the PARP enzyme family is crucial (94).

Haematological toxicity

In clinical practice, haematological toxicities are very common during PARPi administration and they usually present in the early phases of treatment (95).

Anaemia is the most frequent, followed by thrombocytopenia and neutropenia. In the three phase 3 maintenance trials, all-grade anaemia was reported in 44% of patients receiving olaparib, 50% of patients receiving niraparib and in 37% of patients receiving rucaparib. Grade 3 and 4 AEs were more frequent with niraparib (25%), followed by rucaparib (19%) and olaparib (19%). Thrombocytopenia of any grade is more common with niraparib (61% *vs.* 28% with rucaparib and 14% with olaparib). All-grade neutropenia occurred in 18–30% of subjects, with grade 3–4 AEs higher with niraparib (20%) (96-98).

For all patients starting a PARPi or those requiring dose changes, a complete blood count once a month is recommended to assess haematological AEs. The FDA niraparib label recommends testing once per week in the first month to check haematological toxicity and especially platelet concentrations (99-101). Actually, no validated predictive biomarkers for this AEs are available. A retrospective analysis of the ENGOT-OV16/NOVA trial of maintenance niraparib in patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer in complete or partial response to platinum-based chemotherapy was performed to assess clinical parameters predicting dose reductions. Baseline platelet count <150,000/μL and baseline body weight <77 kg were identified as risk factors for increased incidence of grade 3 thrombocytopenia and dose reduction to 200 or 100 mg. PFS was not influenced by dose changes in these patients, suggesting that they may benefit from a starting dose of 200 mg/day. Although retrospective, these data might be a starting point for further research on this topic in BC patients (102).

Gastrointestinal toxicity

Gastrointestinal AEs are quite common, the most frequent being nausea, followed by constipation, vomiting, and diarrhoea (99-101). Their management is similar to that of chemotherapy-induced gastrointestinal toxicities, using prokinetics and antiemetic drugs like metoclopramide, dexamethasone (103,104). Aprepitant, neurokinin-1 receptor antagonist, should not be administered with olaparib as it is a potent CYP3A4 inhibitor and may influence olaparib plasma concentrations (105).

Renal toxicity

The administration of rucaparib in ARIEL3 led to an increase of creatinine (any grade) levels in 15% of patients *vs.* 2% in the placebo group in the first weeks of treatment. Rucaparib inhibits the renal transporter proteins MATE1 and MATE2-K, that are involved in creatinine secretion (96). In study SOL0218, 21/195 olaparib-treated patients had a grade 1–2 increase in creatinine (no grade 3–4) *vs.* 1% in the placebo arm while niraparib did not induce an increase in serum creatinine (98). This alteration may not reflect a true decline in glomerular filtration rate (GFR). If GFR is

appropriate (i.e., GFR is typical or inconsistent with elevated creatinine), dose reductions or interruptions are not strictly necessary (95).

Fatigue

A proportion of 59–69% of patients assuming PARPi had fatigue of any grade (96-98). Experts recommend non-pharmacological approach, namely exercise, massage therapy, and cognitive behavioural therapy (95).

Clinical laboratory abnormalities

The most common laboratory abnormalities are hypercholesterolemia and increased serum levels of alanine aminotransferase and aspartate aminotransferase. These effects are generally transient (98). Particular caution should be taken in patients with pre-existing liver dysfunctions and of lipid profile. In the case of persistent hypercholesterolemia, a statin-based treatment is indicated (95).

Other toxicities

Less frequent AEs include neurological symptoms which may comprise headaches and insomnia. The underlying mechanism is not yet fully understood but some preclinical studies have identified a role of PARP1 in maintaining the transcription of circadian genes, with PARP1 inhibition leading to a disconnect in key circadian rhythm transcriptional components (106).

For mild symptoms symptomatic therapy may be sufficient, while for more severe symptoms a dose reduction may be required, on the basis of the FDA label of each PARPi (99-101).

Reported respiratory symptoms include dyspnoea, cough, nasopharyngitis and more rarely pneumonia (96-98). The mechanism causing these symptoms has not been understood. Preclinical data only showed that PARP activation is related with bronchial hyper-reactivity and airway remodelling (107). The management of suspected or confirmed pneumonitis should be performed according accepted guidelines for drug-induced pneumonitis (108).

Other rarer side effects include musculoskeletal toxicities (arthralgia, back pain), skin toxicities (photosensitivity reactions, pruritis, rash, peripheral edema) and cardiovascular toxicities (hypertension, tachycardia, palpitations) (96-98). For the last mentioned, patients on niraparib should undergo blood pressure and heart rate monitoring once a month for the first year and regularly afterwards, especially in case of cardiovascular comorbidities (101).

Secondary malignancies

Since the primary mechanism of PARP inhibition involves interference with DNA repair pathways, myelodysplastic syndrome and acute myeloid leukaemia, are serious AEs requiring treatment discontinuation. Incidence is rare (0.5–1.4%) and after long-term treatment. In all clinical trials, all patients developing these AEs had been previously treated with platinum-based chemotherapy or other DNA-damaging drugs, making it difficult to define PARPi as responsible (96-98).

Immunotherapy

The clinical activity of programmed cell death-1/programmed death ligand-1 (PD-1/PD-L1) antagonists was demonstrated in the treatment of triple negative BC (TNBC) (109).

In the IMpassion 130 trial, the association of the anti-PD-L1 atezolizumab and nab-paclitaxel, showed an acceptable safety profile and it was approved as first-line treatment for patients with unresectable locally advanced or metastatic TNBC whose tumours have a PD-L1 >1% expression. In the atezolizumab group, 49% of patients had grade 3–4 AEs. Peripheral neuropathy occurred in 6% of patients in the atezolizumab arm and it was the leading cause for treatment discontinuation due to toxicity (4%), but it was also deemed to be taxane-related, which is known to be cumulative. The AEs of special interest that differed substantially between atezolizumab group and placebo group were any-grade rash, hypothyroidism, hyperthyroidism, pneumonitis, and adrenal insufficiency. Treatment-related deaths occurred in <1% patients in the atezolizumab group (one due to autoimmune hepatitis and one due to septic shock related to nab-paclitaxel only) and <1% patient in the placebo group (hepatic failure) (110,111).

In the neoadjuvant setting, atezolizumab showed a safety profile consistent with MBC. In the IMpassion031 trial, hypothyroidism occurred in 7% of patients in the atezolizumab arm versus 1% control arm. The number of patients who discontinued atezolizumab or placebo due to AEs was 13% versus 11% (112).

Data from the KEYNOTE-522 trials evaluating pembrolizumab plus chemotherapy, reported an incidence of immune-related AEs in 38.9% of patients

and included hypothyroidism (any grade: 14.9%; grade >3: 0.4%), hyperthyroidism (any grade: 5.1%; grade >3: 0.3%), severe skin reaction (any grade: 4.4%; grade >3: 3.8%) and adrenal insufficiency (any grade: 2.3%; grade >3: 1.3%). Even if manageable, immune checkpoint inhibitors-related AEs might lead to persistent alterations, including thyroid disorders and adrenal failure, for which hormone replacement treatment might become necessary for undefined time (113,114). In GeparNuevo trial, the addition of durvalumab to standard neoadjuvant chemotherapy did not lead to more frequent incidence of AEs, with the exception of thyroid dysfunction (any grade), which was more frequently reported on durvalumab (47%). Seven patients had hypothyroidism and 9 patients hyperthyroidism; one patient had a hypophysitis (115).

In The TONIC trial, after a 2-week induction with chemotherapy or irradiation in metastatic TNBC patients, nivolumab was not associated with any previously unreported toxicity. Induction treatment-related AEs of any grade occurred in 28% of patients (3% grade 3) and immune-related AEs of grade 3–5 occurred in 19% of patients (116).

Moat available data on potential predictive factors for toxicities that might help the selection of patients derive from studies in melanoma and non-small-cell lung cancer. In a retrospective analysis by Krishnan *et al.*, patients who developed eosinophilia during treatment were more likely to have toxicity (P=0.042), thus suggesting further prospective investigation (117). Increased white blood cells count and decreased relative lymphocyte count have been reported to be independently associated with lung/gastrointestinal toxicities from nivolumab (118). Baseline anti-thyroglobulin antibodies and anti-thyroid peroxidase antibodies levels and their early increase during treatment with anti-PD-1 were associated with the development of thyroiditis and thyroid dysfunction (119-121). Additionally, cutaneous toxicity was observed more frequently among patients with pre-existing rheumatoid factor (120,122). Further larger studies with prospective design are needed to confirm these findings and to assess their potential application in clinical practice.

Endocrine treatment

Tamoxifen acts as Selective Estrogen Receptor Modulator (123). In breast tissue, it exerts an anti-estrogenic effect by competitive binding to estrogen receptors. In other tissues, tamoxifen has an estrogen agonistic effect, e.g., by stimulating endometrium proliferation with subsequent higher risk of endometrial malignancy. Other reported side effects are: dizziness, headache, depression, confusion, fatigue and muscle cramps (124). The increased thromboembolic risk might be related to the tamoxifen-induced altered circulating coagulation inhibitors, namely reduced antithrombin III, protein C and protein S levels (125,126). Scientific evidence shows that long-term use of tamoxifen is related to secondary endometrial cancer in women. Based on the available results, the risk of endometrial cancer increases from 2 to 4 times with longer therapy duration with tamoxifen (127). In the ATLAS study, which evaluated continuation of adjuvant tamoxifen therapy for a total of 10 years, the cumulative risk of endometrial cancer during years 5–14 was 3.1% (mortality 0.4%) in patients who continued treatment and 1.6% (0.2% mortality) for patients who stopped treatment at 5 years (128).

The CYP2D6 enzyme is essential to convert tamoxifen into endoxifen, the main active metabolite. CYP2D6 gene alterations might be responsible for abnormal enzyme activity, thus configuring the profile of ultrarapid metabolizer (increased activity), intermediate metabolizer (decreased activity), poor metabolizer (absent activity). These two last conditions may result in reduced endoxifen blood levelsand consequently in decreased tamoxifen efficacy (129).

Third-generation AI—anastrozole, letrozole and exemestane are an effective endocrine treatment for HR positive EBC and MBC patients (130,131).

Estrogens exert their physiologic action on several tissues including bone, immune system, central nervous system and cardiovascular system (132). They may induce a protective cardiovascular effect, as suggested by lower incidence of coronary heart disease by older age at the first cardiovascular event compared with men (133,134). The protective action of tamoxifen on cardiovascular system is related to estrogen-like activity (agonist on alfa receptor) leading to decreased low-density lipoprotein (LDL) cholesterol and homocysteine serum levels. In fact, a meta-analysis of 12 studies comparing tamoxifen with placebo, revealed a lower incidence of heart attack (HR =0.62, 95% CI: 0.41–0.93) with tamoxifen (135). In a combined analysis of two trials evaluating up-front AI versus up-front tamoxifen, AI were significantly associated with cardiovascular disease (OR =1.30, 95% CI: 1.06–1.61, P=0.01) (135-137). Consistent findings were reported in the study comparing switching from tamoxifen to AI versus up-front AI (OR =1.37, 95% CI: 1.05–1.79, P=0.02) (138). The biologic rationale for a potential negative effect of AI on cardiovascular system is mainly related to their action on lipid metabolism. Contrary to tamoxifen, AI raise the serum cholesterol levels and this may lead to higher cardiovascular

risk, especially in case of pre-existing arterial hypertension, diabetes and obesity (139).

Extended adjuvant endocrine therapy with either tamoxifen or AI after 5 years of initial tamoxifen treatment has been shown to improve the disease-free survival in EBC (108,140-142). The EBCTCG meta-analysis has shown that administration of AI in the first 5 years of adjuvant therapy was superior to tamoxifen monotherapy (143). In a literature-based meta-analysis published in 2019, comprising eight trials, longer treatment with AI was related to higher RR of bone pain (RR =1.26, RD =0.04, P=0.003), bone fractures (RR =1.59, RD =0.02, P=0.002), osteoporosis (RR =1.53, RD =0.07, P=0.005), myalgia (RR =1.26, RD =0.04, P=0.02), and therapy discontinuation for AEs (RR =1.51, RD =0.06, P=0.0009) (144).

AI administration might be associated with hot flushes and musculoskeletal AEs affecting quality of life. rs10046 variant T/T of CYP19A1 seemed to be associated to lower occurrence of hot flashes/sweating with exemestane and ovarian function suppression in premenopausal patients enrolled in the TEXT trial, thus improving patients' compliance to AI treatment (145). Borrie *et al.* found that BC patients with higher body mass index (P=0.001) and those receiving letrozole *vs.* anastrozole (P=0.018) were more likely to develop arthralgia and subsequently discontinue AI. Moreover, the Authors found that CYP19A1 rs4775936 and ESR1 rs9322336, rs2234693, rs9340799 SNPs were associated with occurrence of arthralgia (P=0.016, 0.018, 0.017, 0.047) and that CYP19A1 rs4775936 SNP was related to AI discontinuation for intolerable arthralgia (146). rs2073618 SNP in osteoprotegerin gene was found to be related with higher risk of muscoloskeletal symptoms and pain in 254 AI-treated (147). In a nested case-control correlative study by Niravath *et al.* in BC patients enrolled in the MA.27 trial, VDR Fok-I variant genotype was associated to lower incidence of arthralgia after 6 months of AI *vs.* wild type VDR (P<0.0001) (148).

Fulvestrant is the first pure anti-estrogen approved to treat MBC postmenopausal patients. Fulvestrant acts as both a competitive antagonist and a Selective Estrogen Receptor Degrader (149). The acute toxicity of fulvestrant is low. Some reported AEs include injection site reactions, nausea, pain, headaches, asthenia, and increased liver enzymes. A review analysed data from the main available studies to assess the efficacy and safety of fulvestrant for postmenopausal hormone-sensitive locally advanced or MBC patients versus other standard endocrine agents. There was no significant difference in vasomotor toxicity (RR =1.02, 95% CI: 0.89–1.18, 3,544 women, 8 studies), arthralgia (RR =0.96, 95% CI: 0.86–1.09, 3,244 women, 7 studies), and gynaecological toxicities (RR =1.22, 95% CI: 0.94–1.57, 2,848 women, 6 studies) (150).

CDK4/6 inhibitors

Currently, three cyclin-dependent kinase (CDK) 4 and 6 inhibitors (CDK4/6) inhibitors are approved for HR positive MBC patients in combination with AI and fulvestrant: palbociclib, ribociclib and abemaciclib (128,151).

The enzymes primarily involved in the metabolism of CDK4/6 inhibitors, which are in turn time-dependent CYP3A-inhibitors, are represented by CYP3A and SULT2A1 (152-154). Administration with strong CYP3A inhibitors (e.g., itraconazole) and with strong (e.g., phenytoin, clarithromycin) or moderate (e.g., modafinil, diltiazem) CYP3A inducers (152-154) is strongly discouraged. Thus, it is crucial to investigate on eventual concomitant medications in BC patients who are candidate to these agents, especially elderly patients with multiple comorbidities and polipharmacy. The safety profile is similar for all CDK4/6 inhibitors, except for some aspects (155-158). In general, the most frequent AE (all grades) in the group treated with the combination of CDK4/6 inhibitor plus endocrine therapy was neutropenia (65%) followed by diarrhoea (49%), infections (44%), nausea (40%), fatigue (39%), and leukopenia (35%) (159). Other safety issues reported in clinical trials include hepatobiliary toxicity (ribociclib, abemaciclib), prolongation of the QT interval on ECG (ribociclib), and venous thromboembolism (160,161). To date, no prospective factors predicting toxicity have been validated and can be used in clinical practice to identify which patients are more likely to develop AEs. However, some available data discussed afterwards might deserve further investigation.

Haematological toxicity

Neutropenia and leukopenia represent the most common grade 3/4 CDK4/6-related AEs. Anaemia or thrombocytopenia are less frequent (155-158,162,163). The rate of all-grade neutropenia with abemaciclib is 50% lower than palbociclib and ribociclib due to the greater CDK4 selectivity (164). CDK4/6 inhibitors cause cell-cycle stop by reducing hematopoietic stem cells division, which is regained after reducing or interrupting the dose;

for this reason, neutropenia has a quick recover, as opposed to the same AE induced by chemotherapy (165). In the PALOMA-3 trial with palbociclib and fulvestrant, grade 3/4 neutropenia generally recovered in a week timeframe (166). granulocyte-colony stimulating factor is not required and febrile neutropenia reported in CDK4/6 inhibitors studies is significantly lower than chemotherapy (156-158,162,164,167,168). Timing for neutropenia occurrence is usually 15 days after the first dose for palbociclib and ribociclib and within the first two cycles (155,164,166,169) with abemaciclib. A complete blood count is recommended prior to treatment start, at the beginning of each further cycle and on day 14 of cycle 1 and 2 (170). In palbociclib-treated patients from PALOMA-2 (n=584) and PALOMA-3 (n=442), low baseline absolute neutrophil count was a strong independent risk factor for C1D15 grade 3/4 neutropenia. ABCB1_rs1128503 (C/C *vs.* T/T: OR =0.57, 95% CI: 0.311–1.047, P=0.070) and ERCC1_rs11615 (A/A *vs.* G/G: OR =1.75, 95% CI: 0.901–3.397, P=0.098) SNPs were identified as potential independent risk factors for C1D15 grade 3/4 neutropenia in non-Asian patients; therefore, pharmacogenetic testing might be informative on potentially increased risk of developing severe neutropenia (171). A study by Modi *et al.* pooling the data from MONARCH-1, 2 and 3 demonstrated the ability of a clinical prediction tool including ethnicity, Eastern Cooperative Oncology Group Performance Status and pre-treatment white blood cell count, in identifying subgroups with significantly different risks of grade ≥3 neutropenia after abemaciclib initiation. This tool might be useful to assess personalised risks and the risk-benefit ratio of abemaciclib (172).

Gastrointestinal toxicity

Abemaciclib has a higher rate of grade 3 diarrhoea compared to palbociclib and ribociclib. In the MONARCH-1 trial, 90% of the patients receiving abemaciclib monotherapy had diarrhoea, (generally within 1 week of treatment initiation), that required to dose reductions in 21% of the patients. The vast majority of episodes had a short duration (median: 7.5 days for grade 2 and 4.5 days for grade 3) (173). In the MONARCH-2 grade 1 and 2 diarrhoea was reported in 73% and grade 3 in 13.4% and, occurred, consistently with MONARCH-1, in the first treatment cycle, with a median duration of 6 days, without requiring treatment modifications in 70.1% of the patients (168). Advanced age has been identified as significantly correlated to an increased risk of grade ≥3 diarrhoea [HR for age >70: 1.72 (95% CI: 1.14–2.58); P=0.009] (172). Particular caution is required also for patients with inflammatory bowel disease (e.g., ulcerative colitis and Chron).

QTc prolongation

Treatment with ribociclib is strongly discouraged in patients at risk of developing QTc prolongation, since this drug may induce prolonged QT interval according to its concentration. In the MONALEESA-2 trial, 3.3% of patients treated with ribociclib plus letrozole experienced QTc prolongation to >480 ms, mostly in the first cycle and limited by proactive dose interruption or reduction (162). Caution should be taken when prescribing symptomatic therapies because of potential drug interactions. In clinical practice, it is recommended to check patients eligible for ribociclib on the basis of their cardiac status and their potentially QTc-prolonging concomitant medication. Electrocardiograms at baseline, day 14 in cycle 1 and day 1 in cycle 2, and careful monitoring should be performed to limit the incidence of this AE (174). Particular caution should be kept when ribociclib is administered with antiemetics (e.g., intravenous ondansetron, dolasetron, metoclopramide, diphenhydramine, haloperidol) because of the risk of QT interval prolongation (175,176).

Conclusions

Several advances have been introduced in the recent years for the management of BC in the perspective of personalised treatment, on the basis of tumour biology, genetics and patients' clinical features (2). Despite intensive research, no validated prospective factors able to identify the best treatment for each category of BC patients to guide the therapeutic choice are available yet.

In the era of precision medicine and tailored therapy, genomic testing and the identification of potential biomarkers are a growing field of research in BC patients. In that regard, the exploration of drugs' toxicity profile is increasingly appealing, due to the potential application in everyday clinical practice (5,6). Indeed, a safety profile-tailored treatment combined with the clinical characteristics of BC patients might be particularly helpful in the therapeutic choice (*Table 3*). Therefore, the awareness of the patients' comorbidities and potential biomarkers predisposing to specific treatment-related toxicities could be crucial for better choice and management of the best care

Table 3 Main drug-related adverse events and application in patients' selection

Treatment	Drug	Main AEs	Risk factors	Management	References
Anthracyclines	Doxorubicin and epirubicin	Cardiotoxicity; myelosuppression; nausea and vomiting	Longer treatment duration, FGFR2 rs2420946 CC genotype, FGFR2 rs2981578 AG genotype, HFE H63D SNP, NFKBIL1, TNF-a, ATP6V1G2-DDX39B, MSH5, MICA, LTA, BAT1, and NOTCH4 SNPs, rs28714259 SNP, heterozygous status for ABCC1 rs246221 T-allele, UGT2B7-161 T allele for cardiotoxicity	Baseline and routine monitoring with ECG and Echocardiogram and/or MUGA for LVEF evaluation; baseline and routine monitoring of complete blood count; prophylaxis and monitoring of nausea and vomiting	(7-15)
Fluoropyrimidines	Capecitabine and 5-fluorouracil	Diarrhoea; HFS; myelosuppression; mucositis	DYPD variants c.1905+1G>A, c.2846A>T, c.1679T>G, and c.1236G>A	DYPD testing before treatment start; identification of variants associated with severe toxicity: dose adaptation according to guidelines	(10-27)
Anti-HER2	Trastuzumab	Cardiotoxicity	Longer exposure; high doses; age ≥60 years; baseline LVEF 50–54.9%; anti-hypertensive drugs	Baseline ECG and Echocardiogram and/or MUGA or MRI for LVEF evaluation immediately prior to initiation; asymptomatic patients: routine surveillance with cardiac imaging every 3 months during treatment and every 6 months following discontinuation of treatment until 2 years from the last administration	Overview (30,31,33,42,43,45,47-55), cardiotoxicity specific references (29,32,34-41,44,46,56-58)
	Neratinib, lapatinib and tucatinib	Diarrhoea; cutaneous rash	–	Monitoring for gastrointestinal symptoms	(45,47,48,53)
	T-DM1	Thrombocytopenia	–	Baseline and routine monitoring of complete blood count	(49-51,74)
	Trastuzumab deruxtecan	ILD-pneumonitis	–	Chest CT scan at baseline and strict monitoring for signs and symptoms of ILD during treatment	(51,70,71)
PIK3CA-AKT-mTOR inhibitors	Everolimus	Stomatitis; anaemia; dyspnoea; hyperglycaemia; fatigue; pneumonitis	High number of NKT cells: pulmonary toxicity; ABCB1 rs1045642: risk of mucositis; PIK3R1 rs10515074 and RAPTOR rs9906827: hyperglycaemia and non-infectious pneumonitis	Caution in case of comorbidities as diabetes or history of lung disease; monitoring for signs and symptoms of toxicity	(72,77,89)
	Alpelisib	Hyperglycaemia; diarrhoea; nausea; decreased appetite; maculopapular rash	Fasting plasma glucose, body mass index, HbA1c, monocyte counts and age: hyperglycaemia	Caution in patients with diabetes mellitus; monitoring for signs and symptoms of toxicity	(91-93)

Table 3 (*continued*)

Table 3 (*continued*)

Treatment	Drug	Main AEs	Risk factors	Management	References
PARP-inhibitors	Olaparib, niraparib, rucaparib, talazoparib, veliparib	Anaemia; thrombocytopenia; neutropenia; nausea; constipation; vomiting; diarrhoea; fatigue; hypercholesterolemia; AST/ALT increased serum levels	Baseline platelet count <150,000/mL and baseline body weight <77 kg: grade 3 thrombocytopenia with niraparib	Complete blood count to monitor haematological toxicity; caution in patients with pre-existing liver disfunction and dyslipidemia	(94-101)
Immunotherapy	Atezolizumab nivolumab, pembrolizumab	Rash; hypothyroidism; hyperthyroidism; pneumonitis; adrenal insufficiency; diarrhoea; skin toxicity	Eosinophilia development during treatment; increased WBC count and decreased relative lymphocyte count: lung/ gastrointestinal toxicities with nivolumab; baseline and early increase of anti-Tg Ab and anti-TPO Ab: thyroiditis and thyroid dysfunction with anti-PD-1; pre-existing rheumatoid factor: cutaneous toxicity	Clinical monitoring for toxicities; laboratory assessments including thyroid function; caution in patients with pre-existing autoimmune disorders	(109-122)
Endocrine therapy	Tamoxifen	Dizziness; headache; depression; confusion; fatigue; muscle cramps; thromboembolic events; endometrial cancer	Longer duration for endometrial cancer	Regular gynecological visits and monitoring for signs and symptoms of toxicity	(124-128)
	AI	Bone pain; bone fracture; osteoporosis; myalgia; hypercholesterolemia; cardiovascular disease	Longer treatment duration; higher body mass index; letrozole *vs.* anastrozole; CYP19A1 rs4775936 and ESR1 rs9322336, rs2234693, rs9340799 SNPs, osteoprotegerin gene SNP	Caution in patients with severe osteoporosis; vitamin D and calcium supplementation; caution in patients with arterial hypertension, diabetes, obesity, dyslipidemia	(128,130,131,135-142,146,147)

Table 3 (*continued*)

Table 3 (*continued*)

Treatment	Drug	Main AEs	Risk factors	Management	References
CDK4/6 inhibitors	Palbociclib	Neutropenia; diarrhoea; infections; nausea; fatigue	Low baseline absolute neutrophil count: cycle 1 day 15 grade 3/4 neutropenia; ABCB1_rs1128503 and ERCC1_rs11615 SNPs: cycle 1 day 15 grade 3/4 neutropenia in non-Asian patients	Complete blood count prior to the start of treatment, at the beginning of each new treatment cycle and on day 14 of cycle 1 and 2	(156-158,165-171)
	Ribociclib	Neutropenia; Tc prolongation; diarrhoea; infections; nausea; fatigue; hepatobiliary toxicity	Concomitant administration of intravenous ondansetron, dolasetron, metoclopramide, diphenhydramine, haloperidol and other known QTc potentially prolonging drugs: QTc prolongation	Complete blood count prior to the start of treatment, at the beginning of each new treatment cycle and on day 14 of cycle 1 and 2; ECG at baseline, day 14 in cycle 1 and day 1 in cycle 2 and careful monitoring; caution in patients with polipharmacy for potential interactions with QTc potentially prolonging agents	(159,162,174-176)
	Abemaciclib	Diarrhoea; neutropenia; infections; nausea; fatigue; hepatobiliary toxicity	Advanced age, inflammatory bowel disease: grade ≥3 diarrhoea; ethnicity, ECOG PS and pre-treatment WBC count	Particular caution in patients with inflammatory bowel disease (e.g., ulcerative colitis and Chron); complete blood count prior to the start of treatment, at the beginning of each new treatment cycle and on day 14 of cycle 1 and 2	(159,168,172,173)

AEs, adverse events; ALT, alanine aminotransferase; anti-Tg Ab, anti-thyroglobulin antibodies; anti-TPO Ab, anti-thyroid peroxidase antibodies, AST, aspartate aminotransferase; CT, computed tomography; DYPD, dihydropyrimidine dehydrogenase; ECG, electrocardiogram; ECOG PS, Eastern Cooperative Oncology Group Performance Status; HER2, human epidermal growth factor receptor 2; HFS, hand-foot syndrome; ILD, interstitial lung disease; LVEF, left ventricular ejection fraction, MRI, magnetic resonance imaging; MUGA, multigated acquisition; PD-1, programmed cell death-1; SNPs, single nucleotide polymorphisms; WBC, white blood cells.

for the right patient. Currently, the upcoming application of these findings in clinical practice is urgently needed to reach this objective, but further research is needed. We believe that these factors, if confirmed in the near future and in further studies, might be helpful in the individualisation of treatment; on one hand, they would allow a better selection of patients; on the other hand, they will permit to tailor the patients' monitoring for toxicities in the perspective of an individualised I and improvement of clinical outcome.

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