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Review

Adverse events of targeted therapies approved for women's cancers

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ABSTRACT

Breast cancer and gynecologic cancers affect >3 million women worldwide each year. With advances in precision medicine, a growing number of targeted therapies have been approved recently, and new therapeutic classes have emerged, including cell cycle inhibitors for hormone receptor positive breast cancer, antibody drug conjugate for human epidermal growth factor receptor 2 positive and triple negative breast cancer, and poly-ADP-ribose polymerase inhibitors for ovarian cancer. This article focuses first on the challenges for health care systems to address the specificities of each emerging targeted therapy and new issues raised by oral antitumor treatments, including individualization of prescriptions, drug–drug interaction assessment, pharmaceutical counseling, patient education, and outpatient management. Then, we provide an overview of the main adverse effects of targeted therapies approved for breast and gynecologic cancers, such as hematologic toxicity of cyclin-dependent kinase 4/6 inhibitors and poly-ADP-ribose polymerase inhibitors, metabolic disorders of phosphatidylinositol-3-kinase/Akt/mammalian target of rapamycin inhibitors, and cardiovascular toxicity of agents targeting human epidermal growth factor receptor 2.

Contents

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What is known about this subject in regard to women and their families?

- Women represent 9 million cancer cases worldwide each year and 4.4 million deaths.
- Breast cancer is the most common and most lethal cancer in women.
- Gynecologic cancers are the second most common cause of cancer in women.

What is new from this article as messages for women and their families?

- This article summarizes the toxicity profile of new targeted therapies approved recently for breast and gynecologic cancers.
- This article highlights new challenges for oral targeted therapies and outpatient care.

Introduction

Cancer is now the second leading cause of death worldwide and the first in developed countries. Cancer accounts for 20 million new cases and 10 million deaths per year. Of these cases, women represent 9 million cases and 4.4 million deaths annually worldwide. According to the World Health Organization, breast cancer is the most common and most lethal cancer in women with >2 million new cases and 685,000 deaths per year. Breast cancer can also affect men, but this situation is rarer. Together, gynecologic cancers are the second most common cause of cancer in women. Among these, cervical carcinoma is the more frequent and more lethal, with approximately 600,000 cases and 340,000 deaths per year. Uterine carcinoma is the second most frequent (>400,000 new cases each year and nearly 100,000 deaths), and ovarian cancer is the second most lethal (>200,000 deaths each year and 300,000 new cases; International Agency for Research on Cancer, 2021).

With advances in precision medicine, treatments have evolved considerably in recent years, particularly with approval of a growing number of targeted therapies. These treatments can be classified in two categories: monoclonal antibodies (and their new generation of antibody drug conjugate [ADC]) mainly administrated intravenously and oral enzymatic inhibitors. First approvals of molecular targeted therapies for solid tumors occurred in the 2000s. Trastuzumab was the first monoclonal antibody approved by the U.S. Food and Drug Administration in 1998, and imatinib was the first oral tyrosine kinase inhibitor approved in 2001. These targeted treatments now concern around 20 tumor types and 100 indications. Most are oral enzyme inhibitors with a lower proportion of monoclonal antibodies. They allow targeting of various oncogenic pathways, such as human epidermal growth factor receptor 2 (HER2) amplification, angiogenesis, or DNA repair defect.

The development of these treatments has led to new challenges. First, targeted therapies cause various adverse events that differ from chemotherapy. Their spectrum of toxicities is broad, but each class has a relatively typical adverse event profile. This requires identification and the development of new management protocols (Jackisch et al., 2021). Moreover, oral targeted therapy (OTT) treatments have raised new issues, such as ambulatory treatment management, including therapeutic patient education; consideration of drug interactions (Thomas-Schoemann et al., 2014); and patient adherence (Barillet et al., 2015; Greer et al., 2016).

In this article, we first focus on the challenges for health care systems to address the specificities of targeted therapies, especially oral treatments. Then, we provide an overview of the main nondermatologic toxicities of targeted therapies used for breast and gynecologic cancers.

Targeted therapies for women's carcinoma: Challenges for treatment management

Individualized prescription

OTTs are often characterized by a narrow therapeutic index, wide interindividual pharmacokinetic variability (de Wit et al., 2015), and dose–response relationship. Their clinical development is most of the time performed in trials conducted in very selected populations. As a result, prescribing them in daily clinical practice can be challenging to ensure their effectiveness while avoiding toxicities.

An accurate initial clinical assessment is necessary to allow a secure prescription. Indeed, an inadequate prescription may lead to insufficient exposure and loss of efficacy or increased exposure and toxicity. In both cases, there is a risk of premature treatment discontinuation. All clinical parameters of the patient must be considered before prescription, including age, sex, nutritional status (e.g., undernutrition, sarcopenia, obesity), genetic polymorphisms, kidney and liver function for treatment metabolism or elimination, and drug–drug interaction (with both conventional and complementary medicines). According to this baseline multidisciplinary evaluation, treatment adaptations should be considered. Most of the time, data are insufficient to recommend treatment dosage adjustment, but in daily clinical practice, treatment initiation at a reduced dose is sometimes considered for frail patients, although this is not usually included in the marketing authorization. Various supportive measures should be promoted to secure oral treatment: systematic medication reconciliation, enhanced outpatient care, suitable supportive care, or therapeutic drug monitoring that allows treatment dosages to be adjusted to plasmatic treatment exposure (Decosterd et al., 2015).

Assessing risk of drug interaction

Many OTTs are metabolized by cytochromes (mostly 3A4), which may cause drug interactions. One study of 898 patients with cancer identified 1359 potential interactions in 50% of patients, including 16% major interactions (van Leeuwen et al., 2013). Before OTT initiation, baseline evaluation should include medication reconciliation by a pharmacist to check the absence of drug interactions. In addition, the intake of complementary medicine, which involves a significant proportion of patients with cancer (40%–80%), should not be neglected (Saghatchian et al., 2014; Tagliaferri et al., 2001). Analyzing the risk of interaction with complementary therapies is time-consuming work, and declaring alternative or complementary treatment can be difficult during the medical consultation but could take plkace during pharmaceutical counseling (PC). In a study, drug–drug or herb–drug interactions were detected in >25% of all prescriptions through PC (Clairet et al., 2019), and 23 % of all cases resulted in pharmaceutical interventions (Babin et al., 2019).

Outpatient care including pharmaceutical counseling and patient education

Targeted therapies, especially oral ones, have contributed to the promotion of outpatient care. To ensure a favorable benefit–risk

balance for the treatment, it is necessary both to consider patient's frailty parameters and to organize counseling and patient education. In both cases, good cooperation between professionals (doctor, pharmacist, nurse) is essential.

The pharmacist could have a major role in supporting patients on OTT. Compared with injectable treatment, oral therapy has many advantages, but also the inconvenience of reducing patient contact with the treatment team. The pharmacist could thus become a new interlocutor to help manage adverse events, drug interactions, or treatment adherence. Thus, it is important to promote PC for any patient starting OTT.

Patients who were well informed about their OTT were less likely to experience dose-reducing or dose-interruption side effects (Simons et al., 2011), which also allowed for a reduction in severe side effects, hospitalization, and costs (Halpern et al., 2008). Clinical pharmacy services may improve the treatment knowledge of patients with cancer, as well as their quality of life (Wang et al., 2015).

For the first time, a randomized multicenter trial (AMBORA) has demonstrated a significant improvement of patient safety and outcomes during OTT by adding an intensified clinical pharmaceutical care program. Severe side effects (Common Terminology Criteria for Adverse Events grade $\geq$3) related to OTT were reduced by 45%. The hazard ratio for the composite endpoint (severe side effect, treatment discontinuation, hospitalization, and death) was 0.48 (95% confidence interval, 0.32–0.71; $p < .001$) with higher patient treatment satisfaction (Dürr et al., 2021). Another study had previously shown that a pharmaceutical program for OTT management led to a higher major molecular response rate (83%) in patients with leukemia compared with published clinical trials (Muluneh et al., 2018).

The American Society of Clinical Oncology has published recommendations about cancer treatment administration, including OTT (Neuss et al., 2017). OTT management can be optimized by specialized teams by including a complete baseline clinical assessment, multidisciplinary follow-up (with physicians, pharmacists and nurses), and improvement of patient education regarding side effects prevention and management.

Adverse events evaluation and management

Adverse events from targeted therapies are very different from those of conventional chemotherapy and differ from one class of targeted therapy to another. Thus, knowledge and management of adverse events is a major challenge for targeted therapies. This requires ongoing information and education for both caregivers and patients. Communication tools between patients and health care professionals (e.g., digital applications that allow fast interactions between patient and health care teams) have proven their utility (Duflot-Boukobza et al., 2020; Mir et al., 2020). Even with a mobile application, the involvement of nurses, in particular coordination nurses, is essential to help monitor side effects throughout treatment.

Nondermatologic adverse events of targeted therapies for breast and gynecologic cancers

Breast cancer treatments

For breast cancer treatment, targeted therapies differ according to histological subtype.

Hormone receptor-positive/human epidermal growth factor receptor 2-negative cancer

Cyclin-dependent kinase inhibitors

For hormone receptor (HR)-positive/HER2-negative cancer, targeted therapies are available only for metastatic disease with cyclin-dependent kinase 4/6 (CDK4/6) inhibitors as the main class. Among these cell-cycle inhibitors, three molecules have been approved combined with hormonotherapy and are now the gold standard for first-line treatment: abemaciclib (Goetz et al., 2017), palbociclib (Finn et al., 2016), and ribociclib (Hortobagyi et al., 2016). Although their mechanism of action is the same, there are some differences in their tolerance profile (Table 1). For palbociclib and ribociclib, the main limiting factor is neutropenia (79% and 74% of patients, respectively), even though few febrile neutropenias occur. With abemaciclib, the risk of neutropenia is divided by two (around 41%). The limiting toxicity of abemaciclib is diarrhea, which occurs in 81% of patients, usually during the first 2 months of treatment and then stops. Ribociclib requires monitoring of the electrocardiogram because of QT prolongation risk.

CDK4/6 inhibitors have few cutaneous side effects. The main one is alopecia, which is mostly grade 1 (32% for palbociclib; 33% for ribociclib; 26% for abemaciclib). Fifteen percent of stomatitis events have also been observed with palbociclib.

Phosphatidylinositol-3-kinase/Akt/mammalian target of rapamycin inhibitors

Everolimus and alpelisib are two other OTTs available for combination with hormonotherapy for subsequent treatment lines and targeting the phosphatidylinositol-3-kinase/Akt and mammalian target of rapamycin pathway. Everolimus has been approved since 2012 and is now used as second-line treatment after CDK4/6 inhibitors. Alpelisib can be proposed for the same indication, but only for patients with a phosphatidylinositol-3-kinase mutation (André et al., 2019). The main toxicities of everolimus are dermatologic. Stomatitis is the main limiting toxicity; it can be severe and require treatment interruptions (56% of patients; 8% with grade 3; Baselga et al., 2012a). Everolimus is responsible for xerosis and pruritus as well. We can also mention digestive toxicity, with diarrhea occurring in 30% of patients (3% with grades 3–4 diarrhea), hematologic toxicity (16% anemia; 12% thrombocytopenia), hyperglycemia (13% any grade; 5% grades 3–4), and interstitial lung disease that may require treatment discontinuation (12% all grades).

Targeting the same pathway, alpelisib also leads to metabolic disorders with hyperglycemia as the main limiting toxicity (64% any grade; 36% grade 3–4). Digestive adverse events are also reported (58% any grade diarrhea; 44% nausea; 35% anorexia; 24% stomatitis). Dermatologically, a maculopapular rash was described in 35% of patients. These last two treatments require good coordination with the diabetology team.

Human epidermal growth factor receptor 2-positive breast cancer

Breast cancer with HER2 protein overexpression can benefit from various treatments targeting this pathway. These treatments include monoclonal antibodies and oral tyrosine kinase inhibitors, and are characterized by a common cardiac toxicity (Table 2). This toxicity is related to HER2 receptor expression on cardiomyocytes and its role for oxidative stress resistance. Cardiac toxicity of anti-HER2 agents is usually an asymptomatic decrease in the left ventricular ejection fraction and is mostly observed with trastuzumab in both metastatic and adjuvant settings (Moja et al., 2012). With early management, this toxicity is reversible most of the time, justifying regular cardiac function assessments during treatment.

Other anti-HER2 treatments cause cardiac dysfunction in 2% to 4% of patients in clinical trials despite cardiac monitoring. In the

Table 1
Summary of adverse events observed with cyclin-dependent kinase inhibitors in clinical trials for first-line treatment of metastatic breast cancer

	Palbociclib(Finn et al., 2016)		Ribociclib (Hortobagyi et al., 2016)		Abemaciclib(Goetz et al., 2017)	
	Any grade, %	Grades 3–4, %	Any grade, %	Grades 3–4, %	Any grade, %	Grades 3–4, %
Neutropenia	79.5	**66.4**	74.3	**59.3**	41.3	21.1
Febrile neutropenia		**1.8**		**1.5**		**<0.1**
Anemia	24.1	**5.4**	18.6	**1.2**	28.4	**5.8**
Infection	39.2	***1.1***	50.3	**4.2**	39.1	**4.9**
Fatigue	37.4	**1.8**	36.5	**2.4**	40.1	**1.8**
Nausea	35.1	**0.2**	51.5	**2.4**	38.5	**0.9**
Diarrhea	26.1	**1.4**	35	**1.2**	**81.3**	**9.5**
Stomatitis	15.3	**0.2**				
Alopecia	32.9		33.2		26.6	
Rash	17.8	0.9	17.1	**0.6**		
Increased liver enzymes			15	**9.3**	15.6	**6.2**
Others			QTc prolongation (3.3/2.7)		Increased creatinine (19/2.1)	

neoadjuvant/adjuvant setting, anti-HER2 treatments include pertuzumab (another monoclonal antibody used in combination with trastuzumab) and ado-trastuzumab emtansine (an ADC composed of trastuzumab and maytansine, which is an antimitotic agent). The main adverse events are diarrhea for pertuzumab (Baselga et al., 2012b) and thrombopenia and increased liver enzymes for ado-trastuzumab emtansine (Verma et al., 2012). Pertuzumab can cause grade 1–2 maculopapular rash in 36% of patients. Several others anti-HER2 agents are available for the metastatic setting: three tyrosine kinase inhibitors (lapatinib, tucatinib, and neratinib), one monoclonal antibody (margetuximab), and one ADC (trastuzumab deruxtecan).

Oral tyrosine kinase inhibitors raise adherence and interaction issues (especially tucatinib, which is at very high risk of drug interaction). Their main toxicity is diarrhea. For trastuzumab deruxtecan, attention should be given to hematologic and pulmonary toxicities (Modi et al., 2020), whereas margetuximab is mainly responsible for infusion-related reactions. Regarding dermatologic toxicities, trastuzumab deruxtecan and margetuximab mainly cause grade 1–2 alopecia in 48% and 17% of patients, respectively, whereas tyrosine kinase inhibitors, which are prescribed in association with capecitabine, are mostly associated with palmar–plantar erythrodysesthesia.

Triple-negative breast cancer

Apart from immunotherapy, only one targeted therapy has been approved recently for triple-negative breast cancer. Sacituzumab govitecan is an ADC composed with an anti-Trop2 antibody loaded with SN38 (a topoisomerase inhibitor). This ADC may cause severe neutropenia (51% grade 3–4) and diarrhea (10% grade 3–4), including febrile neutropenia and neutropenic colitis (Bardia et al., 2021). The main dermatologic adverse event is alopecia (grade 1–2), which occurs in 48% of patients.

Germline BRCA-mutated breast cancer

HER2-negative breast cancers with germline BRCA mutation are eligible for poly-ADP-ribose polymerase inhibitor (PARPi) treatments. Olaparib is available for metastatic and adjuvant settings, whereas talazoparib concerns only metastatic disease. Their main adverse events are hematologic toxicities, especially anemia (talazoparib: 52% any grade and 39% grade 3–4; olaparib: 40% any grade 16% grade 3–4), and nausea (talazoparib: 48% any grade; olaparib: 58% any grade; Litton et al., 2018; Robson et al., 2017).

Gynecologic cancer treatments

Targeted therapies for gynecologic cancers include antiangiogenic treatments with indications in each type of cancer (endometrial, cervical, and ovarian) and PARPi that are specific to ovarian cancer treatment.

Antiangiogenic treatments

Antiangiogenic treatments have long been the only class of targeted therapy approved for gynecologic cancers. The main antiangiogenic treatment used is bevacizumab with approval for cervical and ovarian cancer treatment. Recently, lenvatinib, an oral antiangiogenic agent, has also been approved for metastatic endometrial cancer treatment in combination with immunotherapy. Antiangiogenic agents are used in many types of cancers; thus, their toxicities are now well described. Cardiovascular toxicities (hypertension, arterial and veinous thromboembolism, left ventricular dysfunction, and myocardial ischemia) and noncardiovascular effects including proteinuria and nephrotic syndromes, intestinal perforation and fistula, and reversible posterior leukoencephalopathy have been combined. Their main dermatologic toxicity is delayed wound healing.

For example, in ovarian cancer, bevacizumab proved its efficacy in combination with first-line platinum-based chemotherapy, followed by maintenance treatment in two trials (ICON7 and GOG-0218; Burger et al., 2011; Perren et al., 2011). The main toxicities in both bevacizumab groups were vascular complications. Grade $\geq$2 hypertension was found in 18% and 22.9% of cases in the ICON7 and GOG-0218 studies, respectively. There was 1% of grade 3 proteinuria and around 7% of grade 3 embolism (venous or arterial) in both trials. Bowel perforation happened in 1% of patients in both bevacizumab groups.

PAOLA-1, a phase 3 study, has since evaluated bevacizumab in association with olaparib (PARPi) as first-line maintenance therapy for ovarian cancer. The safety profile was not modified by the combination of targeted therapies. This trial found 19% of grade 3–4 hypertension in olaparib + bevacizumab patients versus 30% for the placebo + bevacizumab treatment arm (Ray-Coquard et al., 2019). Almost the same safety profile was observed in patients with metastatic cervical cancer who were treated with bevacizumab, but fistula risk was higher (6%; Penson et al., 2015), which could be related to previous pelvic radiotherapy.

Lenvatinib has recently been approved for metastatic endometrial cancer treatment in combination with immunotherapy. In addition to typical adverse events of antiangiogenic treatments, this tyrosine kinase inhibitor leads to diarrhea (52% any grade) and palmar–plantar erythrodysesthesia (26% any grade; Makker et al., 2020).

Poly-ADP-ribose polymerase inhibitors

PARPi have become a major maintenance treatment for ovarian cancer after platinum-based chemotherapy. They first proved their efficacy for BRCA-mutated ovarian cancer, then for homolo-

Table 2
Summary of anti-human epidermal growth factor receptor 2 treatments toxicities

Treatment	Trastuzumab (Moja et al., 2012)	Pertuzumab (Baselga et al., 2012b)	Trastuzumab emtansine (Verma et al., 2012)	Trastuzumab deruxtecan (Modi et al., 2020)	Lapatinib (Geyer et al., 2009)	Tucatinib (Murthy et al., 2020)	Neratinib (Saura et al., 2020)	Margetuximab (Rugo et al., 2021)
Approval	Adjuvant metastatic	Adjuvant metastatic	Adjuvant metastatic	Metastatic	Metastatic	Metastatic	Adjuvant metastatic (FDA)	Metastatic (FDA)
Cardiac toxicity (decline in LVEF)	11% (and CHF 2.5%)	2%	2%	1.6%	2%	NA	4%	3%
Other toxicity (any grade)								
Administration disorders	IRR 30%							IRR 13%
Respiratory disorders	Pulmonary events 10%			ILD 13%				Cough 14%; dyspnea 13%
Gastrointestinal disorders		Diarrhea 67%	Diarrhea 23%; nausea 40%	Nausea 77%; constipation 35%; diarrhea 29%	Diarrhea 65%	Diarrhea 80%; nausea 58%	Diarrhea 83%; nausea 53%	Nausea 32%; diarrhea 25%
Hematologic disorders		Neutropenia 53% (including febrile neutropenia)	Thrombopenia 13%; neutropenia 5%	Neutropenia 35%; anemia 30%		Anemia 19%		Neutropenia 28%
Dermatologic disorders		Rash 36%; stomatitis 27%; pruritus 16%; dry skin 10%	Stomatitis 6%	Alopecia 48%	PPE 54%; rash 27%	PPE 63%; stomatitis 25%	PPE 45%; stomatitis 20%; rash 9%	Alopecia 17%; PPE 12%; stomatitis 10%
Hepatobiliary disorders			Increased liver enzymes 7%			Increased liver enzymes 21%		
General disorders			Asthenia 35%	Asthenia 49%	Asthenia 24%	Asthenia 45%	Asthenia 34%	Asthenia 42%

CHF = congestive heart failure; FDA = U.S. Food and Drug Administration; ILD = interstitial lung disease; IRR = infusion-related reaction; LVEF = left ventricular ejection fraction; NA = not available; PPE = palmar–plantar erythrodysesthesia

Table 3
Summary of adverse events observed with poly-ADP-ribose polymerase inhibitor maintenance therapy for relapsed ovarian cancer

	Olaparib (SOLO-2 study; Pujade-Lauraine et al., 2017)		Niraparib (NOVA study; Mirza et al., 2016b)		Rucaparib (Ariel-3 study; Coleman et al., 2017)	
	All grades, %	**Grade 3–4, %**	All grades, %	**Grade 3–4, %**	All grades, %	**Grade 3–4, %**
Hematologic toxicities						
Anemia	43	**19**	50.1	**25.3**	37	**19**
Neutropenia	19	**5**	30.2	**19.6**	18	**7**
Thrombopenia	14	**1**	61.3	**33.8**	28	**5**
Digestive toxicities						
Nausea	76	**3**	73.6	**3**	75	**2**
Diarrhea	33	**1**	19.1	**0.3**	32	**1**
Vomiting	37	**3**	34.3	**1.9**	37	**4**
Constipation	21	**0**	39.8	**0.5**	37	**2**
Abdominal pain	25	**3**	22.6	**1.1**	30	**2**
Elevated liver enzymes	Unknown	**Unknown**	Unknown	**Unknown**	34	**10**
Other toxicities						
Fatigue	66	**4**	59.4	**8.2**	69	**7**
Headache	25	**1**	25.6	**0.3**	18	**<1**
Insomnia	Unknown	**Unknown**	24.3	**0.3**	14	**0**
Hypertension	Unknown	**Unknown**	19.3%	**8.2%**	Unknown	**Unknown**
Elevated creatinine	11	**0**	Unknown	**Unknown**	15	**<1**

Table 4
Summary of main toxicities observed with targeted therapies approved for breast and gynecologic cancers

Targeted therapies		Common toxicities		Specific toxicities
CDK4/6 inhibitors: Abemaciclib, palbociclib, ribociclib		Hematologic toxicity		Ribociclib: QT prolongation Abemaciclib: Diarrhea
Phosphatidylinositol-3-kinase/Akt/mammalian target of rapamycin inhibitors: Everolimus, alpelisib		Metabolic disorders (hyperglycemia), digestive toxicities (diarrhea, stomatitis)		Everolimus: Stomatitis, ILD
Anti-human epidermal growth factor receptor 2 treatments	**Monoclonal antibodies: Trastuzumab, pertuzumab, margetuximab**	Cardiac toxicity (decreased LVEF)	IRR	Pertuzumab: Diarrhea Margetuximab: Nausea
	ADC: TDM-1, T-Dxd			TDM-1: Thrombopenia, hepatic cytolysis T-Dxd: Nausea, hematologic toxicity, ILD, alopecia
	TKI: Lapatinib, tucatinib, neratinib		Diarrhea, nausea	
Sacituzumab govitecan				Neutropenia; diarrhea; alopecia
Poly-ADP-ribose polymerase inhibitors: Olaparib, niraparib, rucaparib, talazoparib		Hematologic toxicities, nausea, myelodysplastic syndrome, photosensibility		Niraparib: Hypertension Rucaparib: Hepatic cytolysis
Angiogenesis inhibitors: Bevacizumab, lenvatinib		HTA, arterial and veinous thromboembolism, proteinuria, delayed wound healing, intestinal perforation/fistula		Lenvatinib: Diarrhea

ADC = antibody drug-conjugate; CDK = cyclin-dependent kinase; ILD = interstitial lung disease; IRR = infusion-related reaction; LVEF = left ventricular ejection fraction; TDM-1 = trastuzumab emtansine; T-Dxd = trastuzumab deruxtecan; TKI = tyrosine kinase inhibitor

gous recombination deficient cancer, and finally niraparib demonstrated a benefit even for nonhomologous recombination deficient cancer. The three major drugs prescribed are olaparib (Moore et al., 2018; Pujade-Lauraine et al., 2017), niraparib (González-Martín et al., 2019; Mirza et al., 2016), and rucaparib (Coleman et al., 2017).

The main PARPi adverse events are hematologic, with both acute and long-term effects (Table 3). Among these adverse events, anemia is the most frequent. In relapsed disease, grade 3–4 anemia was observed in 19% of patients with olaparib monotherapy (SOLO-2 trial) and 19% of patients with rucaparib (ARIEL-3 trial). The highest rate was observed with niraparib treatment, ranging from 25% of grade 3–4 anemia in second-line treatment (NOVA trial) to 31% in first-line treatment (PRIMA trial). Interestingly, there was no increase with olaparib and bevacizumab combination (17% grade 3–4 anemia; PAOLA-1 trial).

With regard to neutropenia, grade 3–4 toxicity occurred in approximately 5% of patients with olaparib and rucaparib but 20% of patients with niraparib. Grade 3–4 thrombopenia ranged from <5% with olaparib and rucaparib to 38% with niraparib. Due to hematologic toxicity, niraparib must be prescribed at 200 mg once daily for patients weighing <77 kg. Hematologic toxicity of PARPi is often a limiting factor and justifies a strict blood monitoring during the first weeks of treatment.

Long-term toxicities involve myelodysplastic syndrome and acute myeloid leukemia and vary from 1% in PAOLA-1 to 8% in SOLO-2. Meta-analyses of randomized trials have confirmed an increased risk of myelodysplastic syndrome and acute myeloid leukemia with an odds ratio of 2•63 (95% confidence interval, 1.13–6.14; $p = .026$; Morice et al., 2021).

Other toxicities are mainly gastrointestinal with nausea and abdominal pain. Rucaparib has a specific hepatic toxicity with 10% of

grade 3–4 cytolysis, occurring during the first week of treatment and normalizing with treatment interruption (Oza et al., 2020). In the PRIMA study, grade 3–4 hypertension was described in 6% of patients treated with niraparib (González-Martín et al., 2019). With regard to cutaneous toxicity, PARPi can cause photosensitivity reactions, and require specific patient education about sun protection.

Conclusion

Several new targeted therapies, including monoclonal antibodies and oral enzymes inhibitors, have been approved for women with breast and gynecologic cancers in the last few years. New therapeutic classes have emerged (cell cycle inhibitors, PARPi, antibody drug-conjugate targeting HER2 or Trop2) with new toxicity profiles to consider (Table 4). Descriptions and knowledge of these toxicities are essential to define management rules. Multidisciplinary cooperation, including dermatology to manage cutaneous adverse effects as well as pharmacy and nursing coordination, is crucial for adequate outpatient care, especially for oral treatments that raise new issues, such as drug interaction, adverse effects, compliance, or patient education.

Declaration of Competing Interest

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