Evidence-based approaches for the management of side-effects of adjuvant endocrine therapy in patients with breast cancer

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The growing availability of more effective therapies has contributed to an increased survival of patients with breast cancer. In hormone receptor-positive early disease, increased survival is strongly correlated with the use of adjuvant endocrine therapy, but this therapy can cause side-effects that have major consequences in terms of treatment adherence and patients' quality of life. In premenopausal breast cancer survivors, these side-effects might be even more prominent due to the abrupt suppression of oestrogen associated with the most intense endocrine therapies. An important ambition of cancer care in the 21st century is to recover pre-cancer quality of life and emotional and social functions, which is only possible through the mitigation of the side-effects of anticancer treatments. This Review presents a comprehensive summary of the efficacy and safety data of the available interventions (hormonal and non-hormonal pharmacological strategies, non-pharmacological approaches, and complementary and alternative medicine) to control selected side-effects associated with adjuvant endocrine therapy (hot flashes, sexual dysfunction, weight gain, musculoskeletal symptoms, and fatigue), providing updated, evidence-based approaches for their management.

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Introduction

Breast cancer mortality rates have been decreasing over the past 20 years, and patients with breast cancer now represent the largest group of cancer survivors.[1] About 70% of breast cancers are hormone receptor-positive, for which the mainstay of treatment is oestrogen deprivation (endocrine therapy).[2] Adjuvant therapy with either tamoxifen or aromatase inhibitors reduces breast cancer recurrence and improves overall survival in patients with hormone receptor-positive breast cancer.[3,4] However, the benefits achieved with adjuvant endocrine therapy come at a cost. Distressing side-effects associated with adjuvant endocrine therapy include hot flashes, sexual dysfunction, weight gain, musculoskeletal symptoms, bone density loss, depression, cognitive dysfunction, and fatigue.[5,6] There is solid evidence showing that these long-lasting side-effects substantially impair patients' quality of life and treatment adherence.[7]

In premenopausal patients with breast cancer, adjuvant endocrine therapy can be escalated with the addition of ovarian function suppression to tamoxifen or to an aromatase inhibitor.[8,9] Because of the abrupt decrease in oestrogen concentrations induced by ovarian function suppression, the side-effects of endocrine therapy can be even more prominent in premenopausal patients.[10] A recent study on premenopausal women with breast cancer found a rate of 16% non-adherence assessed through biochemical testing 1 year after prescription of tamoxifen, which was hypothesised to partly correlate with the presence of side-effects (fatigue and musculoskeletal symptoms). Importantly, non-adherence to tamoxifen resulted in impaired cancer-specific outcomes.[11] Ovarian function suppression increases the occurrence of side-effects of adjuvant endocrine therapy in premenopausal women; however, similar quality-of-life indicators have been reported for tamoxifen or aromatase inhibitors combined with ovarian function suppression. Patients treated with tamoxifen plus ovarian function suppression are more affected by hot flushes and night sweats, whereas patients treated with aromatase inhibitors plus ovarian function suppression report higher rates of sexual dysfunction and musculoskeletal symptoms.[12] Collectively, these side-effects can be severely bothersome and affect treatment adherence, as reflected in observed rates of early discontinuation: about 20% for both oral endocrine therapy (all types) and ovarian function suppression (regardless of the prescribed oral endocrine therapy).[8]

Although the rates of non-adherence are reported to be lower for postmenopausal patients, decreased quality of life[6] and treatment discontinuation[13] due to side-effects are also important issues for these patients.[14] In addition, treatment adherence appears to be different in clinical trials and in clinical practice, where discontinuation rates from oral adjuvant endocrine therapy are higher, varying from 31% to 73% after 5 years of treatment.[13,15,16]

Despite the high frequency of adverse events related to endocrine therapy, this topic is often underestimated and underaddressed during follow-up consultations, when the focus is usually on the risk of disease recurrence.[10,17] Chemotherapy-induced toxicities tend to be accepted by patients and physicians because the adjuvant or neoadjuvant treatment period is short and these toxicities are mostly reversible. By contrast, patients are asked to take adjuvant endocrine therapy for 5 years or 10 years, throughout which there is a continual potential to develop toxicities, even if such adverse events are of lower grade.[6] Proactive symptom management is an important element of survivorship care to ensure patients have the best possible treatment outcomes alongside the complex balance of tolerability, treatment adherence, and quality of life.

	Intervention	Control group	Study outcome	Results
HABITS[19] (2004), n=434	Oestrogen–progesterone combination	No hormone therapy	Risk of breast cancer recurrence	HR 3·50 (95% CI 1·50–8·10); p value not provided; trial stopped early due to increased risk of recurrence
Stockholm[20] (2005), n=378	Oestrogen–progesterone combination	No hormone therapy	Risk of breast cancer recurrence	HR 1·80 (95% CI 1·03–3·10); p value not provided; trial stopped after combined analysis with the HABITS trial
LIBERATE[21] (2009), n=3148	Tibolone	Placebo	Risk of breast cancer recurrence	HR 1·40 (95% CI 1·14–1·70); p=0·0009 for all patients; 1·25 (0·98–1·59); p=0·076 for patients taking tamoxifen; 2·40 (1·01- 5·00); p=0·047 for patients taking aromatase inhibitors; trial stopped early due to increased risk of recurrence

HR=hazard ratio.

Table: **Randomised controlled trials evaluating hormone-replacement therapy in patients with early breast cancer**

This work is a comprehensive overview that aimed to summarise the efficacy and safety data of the available interventions (hormonal and non-hormonal pharmacological strategies, non-pharmacological approaches, and complementary and alternative medicine) to control selected side-effects associated with adjuvant endocrine therapy (hot flashes, sexual dysfunction, weight gain, musculoskeletal symptoms, and fatigue) to provide updated evidence-based approaches for their management. These side-effects were chosen for their high prevalence and inconvenience to patients. Other important side-effects related to endocrine therapy (eg, cognitive dysfunction, depression, anxiety, distress about body image, insomnia, cardiovascular toxicity, and bone density loss) are not discussed in the present manuscript because of length constraints, but they warrant separate ad-hoc investigations.

See Online for appendix

Management of endocrine therapy-related side-effects

Previous data suggest that a comprehensive menopausal assessment intervention (including symptom assessment, education, counselling, and specific pharmacological and behavioural interventions according to the symptoms present) is associated with a substantial improvement in symptom control.[18]

Although the most effective therapy to treat symptoms related to oestrogen deficiency is hormonal replacement, this approach is contraindicated in breast cancer survivors because it increases the risk of recurrence (table).[19–21] Although safe and effective non-hormonal treatments are still needed, several therapeutic options have already shown benefits in randomised controlled trials for the management of side-effects of adjuvant endocrine therapy in breast cancer survivors (figure 1).

Hot flashes

Pharmacological strategies

For non-hormonal strategies, several studies have investigated the use of antidepressants (including selective serotonin reuptake inhibitors and serotonin–norepinephrine reuptake inhibitors) for the control of hot flashes in breast cancer survivors. The most studied agent is venlafaxine, which has been shown, in several randomised controlled trials, to reduce hot flashes by up to 60% (appendix p 3).[22–25] Different daily doses from 37·5 mg to 150 mg have been tested. Higher doses have shown a major reduction in hot flashes, but are also associated with important adverse events, such as mouth dryness, decreased appetite, nausea, and constipation.[26,27] Other serotonin reuptake inhibitors and serotonin–norepinephrine reuptake inhibitors, including duloxetine, escitalopram, paroxetine, and sertraline, have also shown positive results for the control of hot flashes in breast cancer survivors (appendix pp 3–4). Although controversial, selective serotonin reuptake inhibitors are potent inhibitors of CYP2D6 and could potentially reduce the bioavailability of tamoxifen.[28,29]

The anticonvulsants gabapentin and pregabalin are efficacious alternatives to treat hot flashes in breast cancer survivors. A crossover trial showed that gabapentin and venlafaxine have similar efficacy and cause similar reductions of hot flashes (66%), with patients preferring venlafaxine.[23] The α-adrenergic agonistic antihypertensive clonidine induces a 40% reduction in hot flashes (compared with placebo) in breast cancer survivors.[30] Because of the important side-effects related to the use of clonidine and of the results of a randomised trial showing the superiority of venlafaxine,[25] clonidine is generally not used as a first option for the treatment of hot flashes in breast cancer survivors.

A placebo-controlled trial showed positive results with lower doses of the anticholinergic oxybutynin (2·5 mg or 5 mg twice a day) for the treatment of hot flashes in patients with and without breast cancer.[31] A greater improvement in hot flashes and overall quality of life was observed when compared with placebo.[31] Treatment-related side-effects were mainly grade 1 or 2 and included dry mouth, difficulty urinating, and abdominal pain.[31] Importantly, although cognitive impairment was not evaluated in this trial, anticholinergic drugs can induce this potential adverse effect, of which physicians should be aware of.[31]

The choice of non-hormonal pharmacological therapy should be a shared decision between physician and patient. This discussion should also consider concomitant medications, comorbidities, and the safety profile of the proposed pharmacological strategies, including potential drug interactions. Considering that the efficacy of most of these therapies has also been shown with lower doses, starting with a low dose to evaluate response and tolerability is preferable.

For hormonal strategies, the progesterone analogues megestrol[32] and medroxyprogesterone[33,34] are highly efficacious for the treatment of hot flashes in women with breast cancer (appendix p 5). Although isolated progestogens have been used for the treatment of metastatic breast cancer in the past, their safety is not yet established in patients with early breast cancer. There are concerns associated with their use because the combination of oestrogen and progesterone has been shown to increase the risk of breast cancer recurrence.[19,21]

Non-pharmacological strategies

Weight control and dietary intervention might be an important strategy to reduce hot flashes in breast cancer survivors. As suggested by two cohort studies, weight gain was independently associated with the risk of developing hot flashes in women taking aromatase inhibitors or tamoxifen.[35,36] Although weight control can be achieved with a dietary intervention, a subgroup analysis of the WHEL study,[37] which investigated the effect of a high-vegetable, high-fibre, low-fat diet in breast cancer survivors, showed no decrease in vasomotor symptoms for patients receiving tamoxifen assigned to the intervention group.

A stellate ganglion block procedure is effective in the control of hot flashes in breast cancer survivors taking endocrine therapy, as initially shown in small single-arm studies with an improvement in the hot flash score of up to 60% (appendix p 6). Although one study showed a greater improvement in hot flash score with stellate ganglion block versus pregabalin,[38] a more recent study comparing this strategy to paroxetine showed similar results in both groups.[39] Therefore, considering the invasiveness of stellate ganglion block, the pharmacological approach might be preferred as a first strategy.

Cognitive behavioural therapy is another intervention that can help breast cancer survivors to manage vasomotor symptoms by affecting their perception and cognitive appraisal of hot flashes (appendix p 6). The randomised MENOS 1 trial[40] compared usual care versus usual care plus 6 weeks of group cognitive behavioural therapy (including psychoeducation, pace breathing, and relaxation). The intervention group reported a significant reduction of the perceived burden of hot flashes and night sweats, with a sustained effect after 26 weeks. However, there was no significant difference in the frequency of hot flashes between the two groups at either 9 weeks or 26 weeks. The dropout rates in this trial were low, suggesting that this intervention was highly acceptable.[40] The absence of adverse events and the additional benefits on mood and sleep[40] observed with this strategy call for additional studies comparing or adding this approach to non-hormonal active treatments.

Figure 1: **Interventions that showed positive results in randomised controlled trials for the management of adjuvant endocrine therapy side-effects in breast cancer survivors**
Compelling evidence refers to data from several randomised controlled clinical trials. Preliminary evidence refers to fewer or smaller randomised controlled clinical trials. SNRIs=serotonin–norepinephrine reuptake inhibitors. SSRIs=selective serotonin reuptake inhibitors. TCM=Traditional Chinese Medicine.

Complementary and alternative medicine

Data from randomised trials suggest that acupuncture might be an efficacious option for the treatment of hot flashes in breast cancer survivors receiving adjuvant endocrine therapy (appendix p 7). The efficacy of this intervention was initially reported as inconsistent, and data showed that sham acupuncture has also a positive effect on hot flash scores (placebo effect). Nevertheless, a more recent randomised trial suggested that patients treated with true acupuncture have a higher benefit in reduction of hot flashes composite score when compared with sham acupuncture, gabapentin, or placebo.[41,42] The durability of the therapeutic effects after treatment is an

interesting potential advantage of this therapy because the positive effect on hot flashes scores persisted in the acupuncture group for 4 months after treatment completion, which did not happen in the gabapentin group.[41] Whenever available, this intervention could be considered for breast cancer survivors because it has very few side-effects and is associated with additional benefits in other potential target symptoms, such as cancer-related fatigue[43] and joint pain.[44]

Two randomised trials showed that hypnosis can improve hot flashes in breast cancer survivors (appendix p 9). Elkins and colleagues[45] showed a significant benefit of hypnosis in hot flash score (68% reduction after five sessions), anxiety, depression, and sleep compared with a control group. A subsequent smaller study randomly assigned breast cancer survivors with hot flashes to hypnotherapy versus gabapentin and showed an improvement on the hot flash score in both groups, without significant differences.[46] Hypnosis might therefore be a useful intervention, and has fewer safety concerns than pharmacological approaches. However, the restricted availability of this intervention might be a challenge to a routine and widespread inclusion in patients' survivorship care.

Yoga and relaxation training (appendix pp 9–10) sessions can help to reduce hot flashes in breast cancer survivors, according to the encouraging results of small randomised trials.[47,48] Additionally, the simple measure of using a cool pad pillow topper can bring comfort to patients having sleep disturbances due to hot flashes.[49]

Supplements (ie, black cohosh, soy phytoestrogens, magnesium, and vitamin E) and magnet therapy have been tested and found to have no effect on hot flashes compared with placebo. Although the results of some prospective single-arm studies and case-control studies suggested that homoeopathy could improve hot flashes, randomised, placebo-controlled trials of this approach yielded negative results (appendix p 8).

Sexual dysfunction

Sexual dysfunction in breast cancer survivors can have several manifestations, such as physical and vulvovaginal changes (eg, vaginal dryness and dyspareunia), and psychosocial effects (eg, decreased libido, changes in body image and self-esteem, and barriers to intimacy and partner communication). A comprehensive assessment and a multidisciplinary approach to this issue are needed.

Pharmacological strategies

Local hormone-based therapies include oestradiol-releasing intravaginal tablets, low-dose vaginal inserts, oestrogen-based vaginal creams, oestradiol-releasing vaginal rings, vaginal testosterone, and vaginal dehydroepiandrosterone. Each is systemically absorbed at different rates, and all of them have been shown to be effective in treating vaginal symptoms related to oestrogen deprivation. Oestrogen-based vaginal treatments, particularly, also result in improvements in the vaginal mucosa (appendix p 17). Currently, there is no formal evidence of increased risk of breast cancer recurrence with local vaginal oestrogen therapy, but several studies have shown that these agents can cause an elevation of serum oestradiol concentrations. This elevation in serum oestradiol could be of concern in premenopausal patients with breast cancer who are receiving ovarian suppression plus an aromatase inhibitor because achieving complete suppression of ovarian function is necessary for aromatase inhibitors to have an anticancer effect.[50] Short-term follow-up and small sample sizes are important limitations of the studies investigating these strategies.

Ospemifene is an oral selective oestrogen receptor modulator used for the treatment of moderate to severe dyspareunia associated with vaginal dryness related to menopause.[51] Although preclinical studies suggest that ospemifene might block oestrogen activity in breast cells,[52] there are no data yet supporting the safety of ospemifene in patients with breast cancer.

Until there is a clearer understanding of the potential effect of local hormone-based therapies on breast cancer recurrence, non-hormonal approaches should be the first-line choices for the management of genitourinary symptoms in breast cancer survivors. In case of severe refractory symptoms, temporary low-dose vaginal oestrogen therapy can be considered as a treatment option, after discussion of its potential risks and uncertainties with the patient.

The results of a small, randomised, placebo-controlled trial suggest that 4% aqueous lidocaine compresses applied to the vulvar vestibule before vaginal penetration can effectively improve dyspareunia and sexual distress in patients with breast cancer taking endocrine therapy. Lidocaine might, therefore, be a useful temporary strategy for patients reporting insertional pain.[53]

Randomised trials support the use of vaginal lubricants (water-based formulations, polycarbophil, and hyaluronic acid moisturisers) to treat genitourinary symptoms in breast cancer survivors receiving adjuvant endocrine therapy (appendix p 16). Placebo-controlled studies have shown that lubricants can moderately decrease dyspareunia, vaginal dryness,[54–56] and sexual distress.[56] Given their wide availability, low cost, and negligible side-effects, vaginal lubricants should be offered as a first approach to all breast cancer survivors reporting sexual dysfunction and vaginal symptoms. One study has also reported positive results with vitamin D or E vaginal suppositories, which resulted in a significant improvement in vaginal maturation index and vaginal symptoms compared with a placebo.[57]

Non-pharmacological strategies

Several studies have shown a benefit of cognitive behavioural therapy for breast cancer survivors facing sexual dysfunction (appendix p 15). In a Dutch trial, breast cancer survivors receiving adjuvant endocrine therapy

were randomly assigned to 24 weeks of internet-based cognitive behavioural therapy (done by a psychologist or sexologist specialised in the field) versus waitlist control.[58] Patients in the experimental group reported improvements in overall sexual function, sexual desire, arousal, and vaginal lubrication, as well as improvement in sexual pleasure, discomfort during sex, and sexual distress.[58] A telephone counselling intervention has also shown a positive effect on sexual dysfunction.[59] An in-person 6 week sexual life reframing programme (including interventions on psychological but also physical aspects of sexual health) delivered to breast cancer survivors has also shown a significant improvement in sexual satisfaction.[60] A small single-arm study tested a brief psychosexual intervention targeted to manage sexual dysfunction and psychological distress in young breast cancer survivors treated with ovarian function suppression.[61] In this study, participants received a 4 h group intervention that included sexual health rehabilitation, body awareness exercises, and mindfulness-based cognitive therapy skills followed by a telephone call 1 month later. Female sexual health and anxiety improved significantly from baseline to 2 months.[61] Based on the available evidence, cognitive behavioural therapy should be highly encouraged for breast cancer survivors facing sexual dysfunction. Dedicated and experienced counselling in this regard should be made available to all patients facing these side-effects.

Several retrospective and single-arm prospective studies have shown a positive effect of vaginal (CO_2 or erbium) laser for genitourinary symptoms related to sexual dysfunction, such as vaginal dryness, dyspareunia, vaginal itching, and burning in breast cancer survivors (appendix pp 15–16). A significant improvement of vaginal atrophy (vaginal health index) was reported with this intervention.[62,63] However, despite promising initial results, the absence of well designed randomised trials and of long-term safety follow-up and the high costs of this treatment option limit a broader recommendation.

In a small single-arm study, local intramucosal injections of autologous platelet-rich plasma combined with hyaluronic acid was been reported to improve vaginal atrophy and sexual distress in breast cancer survivors (appendix p 17). However, additional evidence is needed before this approach can be considered in clinical practice.

Weight gain

Weight management has an important role in breast cancer survivorship care because obesity or weight gain might lead to poorer breast cancer prognosis, as well as serious comorbidities, fatigue, functional decline, and poorer health and overall quality of life.[64] Furthermore, fat tissue is an additional source of serum oestrogen precursors that are metabolised to oestrogen by the enzyme aromatase.[64] Therefore, weight gain could affect the efficacy of adjuvant endocrine therapy. In premenopausal patients with breast cancer receiving ovarian function suppression plus aromatase inhibitors, higher body-mass index was shown to be a risk factor for incomplete ovarian function suppression.[50,65]

Randomised trials have shown that weight loss is feasible in patients receiving adjuvant endocrine therapy,[66–70] and it should be recommended for breast cancer survivors with overweight or obesity. The most efficient interventions include a multidisciplinary approach with regular physical exercise, diet, and cognitive behavioural therapy. Ongoing studies are addressing how to support breast cancer survivors in losing weight and the potential effect of diet and weight loss on breast cancer outcomes (NCT02750826 and NCT04304924).

Both in-person or remote interventions have proven efficacy and are superior to standard medical care (where oncologists encourage patients to keep a healthy diet and achieve or maintain an ideal body-mass index). Several studies have investigated interventions targeting weight loss in breast cancer survivors taking adjuvant endocrine therapy (appendix pp 21–24). There is a growing number of smaller pilot studies investigating the use of eHealth tools, such as mobile apps and self-monitoring devices, with promising results. These interventions, if proven to be efficacious in subsequent properly powered and designed studies, might help physicians to assist breast cancer survivors at a low cost and with relatively easy implementation.

Musculoskeletal symptoms

Pharmacological strategies

Some patients with aromatase inhibitor-induced musculoskeletal symptoms might benefit from the strategy of switching to a different aromatase inhibitor, allowing them to continue therapy (appendix p 27). A multicentre study showed that, after switching to a different aromatase inhibitor, 39% of the patients were able to continue the second aromatase inhibitors for a median of 13·7 months.[14] The ATOLL study,[71] evaluating the switch from anastrozole to letrozole, both non-steroidal aromatase inhibitors, reported that 72% of patients continued therapy after 6 months. However, a considerable proportion of patients continued to have musculoskeletal symptoms, including 74% of patients complaining of arthralgia, 21% of myalgia, 16% of arthritis, 14% of tendinitis, and 13% of polyalgic syndrome, after taking letrozole for 6 months.[71] A crossover trial of a switch from exemestane (a steroidal aromatase inhibitor) to letrozole or vice versa showed less worsening of the functional status after 3 months with the second aromatase inhibitor when compared with the first one.[72]

The use of duloxetine for 13 weeks can reduce aromatase inhibitor-induced joint pain in breast cancer survivors. In a randomised trial,[73] after 12 weeks of treatment, the average joint pain score was 0·82 points lower for patients who received duloxetine than for patients who received placebo (95% CI –1·24 to –0·40; p=0·0002). Grade 3 adverse events were rare, but low-grade toxicities,

including fatigue, nausea, dry mouth, and headache, were significantly more frequent in the duloxetine group.[73] Of note, patients taking duloxetine reported additional substantial improvements in quality of life that could be multifactorial, rather than exclusively the result of improved pain control. Duloxetine is also an effective hot flashes treatment, and this potential positive effect in multiple symptoms (including depression) should be considered together with its safety profile when prescribing this therapy.

Although one randomised trial suggested a benefit of high-dose vitamin D in reducing musculoskeletal symptoms in breast cancer survivors taking endocrine therapy, all other trials reported negative results (appendix p 27). Therefore, vitamin D is not generally recommended for this purpose, but should be used for the prevention of bone density loss during therapy with aromatase inhibitors. Other medications investigated for the control of aromatase inhibitor-induced joint pain include furosemide, glucosamine plus chondroitin, calcitonin, and a short course of low-dose oral prednisolone with positive results. However, the evidence for the use of these therapies derives from small single-arm studies and, therefore, is insufficient to support a formal recommendation (appendix p 27).

Non-pharmacological strategies

Control of musculoskeletal symptoms is one of the potential benefits of physical exercise in breast cancer survivors (appendix p 28). In the phase 3 HOPE trial,[74] patients with breast cancer with joint pain during therapy with aromatase inhibitors were randomly assigned to 150 min per week of aerobic exercise and supervised strength training twice per week, or usual care. At 12 months, worst joint pain scores decreased by 29% in the exercise group and increased by 3% in the usual care group ($p<0·001$). Additionally, pain severity, pain interference, and other pain scores decreased significantly for women assigned to the exercise group and increased in the usual care group.[74] Other exercise options (eg, Nordic walking, home-based walking, and aquatic exercises) were also evaluated in smaller trials with shorter follow-up periods and reported a positive effect on joint pain (appendix p 28).

Complementary and alternative medicine

Acupuncture can be a complementary therapy for the control of musculoskeletal symptoms (appendix pp 28–29). Similarly to its effect on hot flashes control, sham acupuncture also produces a placebo effect when used for joint pain. In a multicentre randomised trial, true acupuncture compared with sham acupuncture or with waitlist control in patients with breast cancer receiving an aromatase inhibitor resulted in a significant reduction in joint pain at 6 weeks.[44] In this study, the maintenance of true acupuncture once a week for an additional 6 weeks, compared with sham acupuncture, was associated with significant improvements in average pain, but no significant improvement in worst pain, pain interference, pain severity, or worst stiffness at 12 weeks.[44]

Several reports from single-arm trials and qualitative research showed the benefit of yoga in improving musculoskeletal symptoms (appendix p 29). In a post-hoc analysis of a randomised trial, a 4 week standardised yoga intervention (YOCAS) in breast cancer survivors taking endocrine therapy showed greater reductions in musculoskeletal symptoms such as general pain, muscle aches, and total physical discomfort from pre-intervention to post-intervention than the control group.[75] However, the primary endpoint of this trial was sleep quality, and questionnaires designed to specifically measure musculoskeletal symptoms were not used. Additional studies to better elucidate the true effect of yoga on musculoskeletal symptoms are needed.

The use of omega-3 supplementation was compared with placebo in a randomised phase 3 trial, and no difference in joint pain was found across groups.[76] Therefore, omega-3 supplementation should not be recommended for the treatment of musculoskeletal symptoms, although it can be considered for patients with obesity, for whom it has been shown to have benefits in a subsequent post-hoc analysis. Neuromuscular tapping and the traditional Chinese medicine Yi Shen Jian Gu granules have shown positive preliminary results in reducing joint pain induced by aromatase inhibitors, warranting further investigation in properly designed clinical trials (appendix p 29).

Fatigue

Non-pharmacological strategies

Physical exercise is the most studied intervention targeting fatigue in breast cancer survivors taking endocrine therapy and should be recommended for the management of this side-effect. Several randomised trials have shown a positive effect of physical exercise in reducing fatigue scores and improving quality of life, anxiety, and depression. Various types of exercise seem effective, with more evidence available for regular aerobic and muscle strength training.[77,78] Home-based and outdoor walking have also shown benefit and should be encouraged (appendix pp 35–37).

Cognitive behavioural therapy is another non-pharmacological intervention that effectively helps women to face fatigue related to adjuvant endocrine therapy and potentially reduces its intensity and interference with daily life. Cognitive behavioural therapy can also help patients to engage in healthy habits that additionally reduce fatigue. Several randomised trials have tested the efficacy of this intervention with positive results (appendix pp 37–38). Because cognitive behavioural therapy can be costly and time-consuming, the CHANGE study[79] evaluated the effect of an internet-based cognitive behavioural therapy compared with usual care, and showed that significantly less fatigue and clinically significant, self-rated improvement

can be achieved with the intervention. Additional benefits included significant less functional impairment and psychological distress, and better quality of life compared with usual care. This internet-based intervention was based on a previous face-to-face cognitive behavioural therapy protocol that was shown to be effective for severe fatigue in cancer survivors. An ongoing non-inferiority trial (NTR5179) is comparing internet-based cognitive behavioural therapy versus a face-to-face approach. Results of this study and future cost-effectiveness analyses will be important for a broader dissemination of this strategy.

Complementary and alternative medicine

Several small studies have investigated the effect of acupuncture for fatigue control in patients with breast cancer taking adjuvant endocrine therapy (appendix p 33). A randomised trial of an 8 week course of acupuncture compared with waitlist control and sham acupuncture showed a significant improvement in fatigue, anxiety, and depression during the 12 week intervention and follow-up period for the acupuncture group.[43] By contrast, sham acupuncture did not produce a significant reduction in fatigue and anxiety symptoms.[43] This study is consistent with the growing body of literature suggesting that acupuncture might be effective for fatigue, anxiety, and depression in breast cancer survivors.

Two forms of self-administered acupressure (relaxing or stimulating acupressure) were compared with usual care in a randomised trial for breast cancer survivors with fatigue.[80] At 6 weeks, the percentages of patients achieving normal fatigue levels (Brief Fatigue Inventory score <4) were higher for patients assigned to relaxing acupressure (66%) or stimulating acupressure (60%) interventions compared with control (31%; p=0·01), with sustained results at 10 weeks.[80] Although the results appear interesting, the placebo effect was not examined in this study.

A number of pilot studies investigating yoga and mindfulness interventions compared with waitlist control or usual care have shown positive effects in lowering fatigue scores and improving overall quality of life and mood distress in the intervention group (appendix pp 33–34). Compared with usual care, a 12 week intervention of yoga and meditation was shown to improve menopausal symptoms, quality of life, and fatigue scores immediately after the end of the intervention and at a 3 month follow-up.[81] A 6 week programme of mindfulness-based stress reduction compared with usual care was also shown to be effective on immediately improving psychological symptoms and fatigue, with a sustained effect up to 12 weeks.[82] Yoga and mindfulness interventions can, therefore, be an important treatment option for breast cancer survivors taking endocrine therapy, and efforts should be made to increase their availability.

Other interventions such as martial arts (eg, qigong or Tai Chi Easy) and ginseng supplements might help to decrease fatigue scores, as suggested by randomised trials (appendix pp 34–35). Studies to further increase the knowledge on these interventions are needed. Melatonin might help to control insomnia, but appears to have no effect on improving fatigue (appendix p 35).

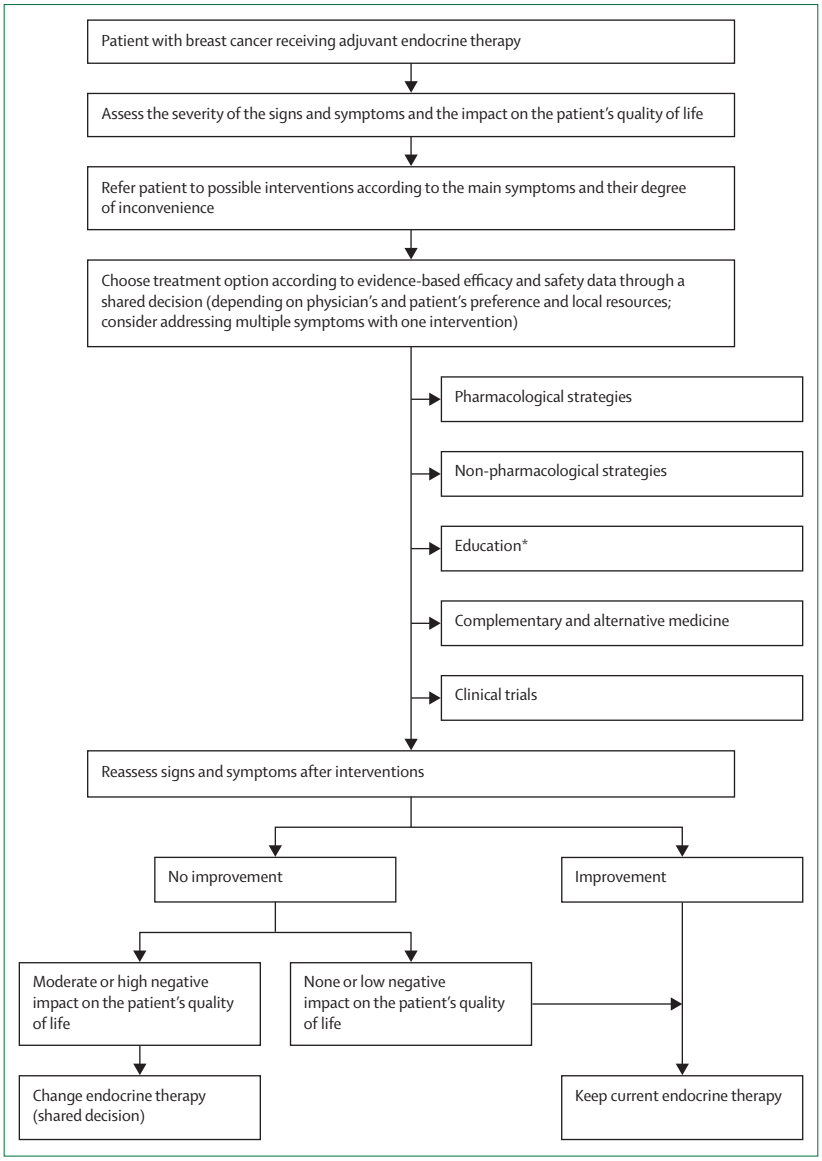

Figure 2: **Workflow to assess side-effects of endocrine therapy in breast cancer survivors**
*Internet-based and technology devices can be a good vehicle for this approach.

Conclusion

Hot flashes, sexual dysfunction, weight gain, musculoskeletal symptoms, and fatigue are prevalent side-effects in patients with breast cancer undergoing adjuvant endocrine therapy. The burden of these unaddressed symptoms (often for several years) on patients should not be underestimated.

Endocrine therapy side-effects must be routinely assessed during consultations because several

√√√ Probably efficacious (data from RCTs) √√ Might be efficacious (data from RCTs with smaller samples)
√ Could be effective (single-arm studies) .. No sufficient data for breast cancer survivors

	Hot flashes	Sexual dysfunction	Weight gain	Musculo-skeletal symptoms	Fatigue
SSRIs and SNRIs	√√√	..	..	√√√	..
Anticonvulsants	√√√	..	..	..	..
Oxybutynin	√√√	..	..	..	..
Aromatase inhibitor switch	..	..	..	√√	..
Vaginal lubricants or moisturisers	..	√√√	..	..	..
Vaginal CO_2 laser	..	√	..	..	..
Stellate ganglion block	√√	..	..	..	..
Cognitive behavioural therapy	√√√	√√√	√√√	√√√	√√√
Physical exercise	..	..	√√√	√√√	√√√
Acupuncture	√√	..	..	√√√	√√
Hypnosis	√√	..	..	..	..
Yoga and mindfulness	√√	..	√	√√	√√

Figure 3: **Efficacy of selected non-hormonal interventions to control endocrine therapy side-effects in breast cancer survivors**
RCTs=randomised controlled trials. SNRIs=serotonin–norepinephrine reuptake inhibitors. SSRIs=selective serotonin reuptake inhibitors.

Search strategy and selection criteria

We searched PubMed for publications from inception to Aug 10, 2020, using the search terms "breast cancer" OR "breast neoplasm" OR "breast tumor" OR "breast tumors" OR "breast tumour" OR "breast tumours" OR "breast neoplasms" [Medical Subject Headings]) AND "endocrine therapy side-effects" OR ''endocrine therapy toxicity" OR "early menopause" OR "sexual dysfunction" OR "genitourinary syndrome" OR "vaginal dryness" OR "dyspareunia" OR "vaginal atrophy" OR "Hot flashes" OR "vasomotor symptoms" OR "weight gain" OR ''weight loss" "asthenia" OR "arthralgia" OR ''fatigue" OR ''quality of life" OR ''QoL" NOT (animals [Medical Subject Headings] NOT humans [Medical Subject Headings]) with no time restriction. We reviewed only papers in English investigating an intervention in breast cancer survivors treated with adjuvant endocrine therapy. The full list of assessed articles and their main findings are available in the appendix. The final references included in this manuscript were selected on the basis of their relevance to the scope of this Review.

interventions are available to control or reverse them. This is crucial to increase treatment adherence and quality of life during adjuvant endocrine therapy. An individualised approach when choosing an intervention to control these symptoms is likely to have better chances of achieving a positive effect. The presence and degree of severity of the specific side-effects and their impact on everyday life should be assessed during consultations, and balanced with the expectations of the patient with the intervention. Notably, the instruments for outcome measures frequently differ among the studies, making it difficult to aggregate and pool the data to give clear treatment recommendations. Additionally, the duration of the supportive intervention is an important knowledge gap, considering the indication of endocrine therapy for up to 5–10 years after diagnosis.

After careful consideration of the efficacy, safety, and adverse event profile of the treatment options, a decision should be made taking into account the resources available, reimbursement by private and or public health care systems, consequences on patients' financial resources, and patients' preference (figure 2). Some interventions might be effective for different symptoms (figure 3), which should be taken into consideration during the decision process, as the ability to address multiple symptoms with one intervention could, ultimately, be the key to improving the patient's quality of life. We acknowledge that complementary and alternative medicine strategies are not completely unified procedures and that, consequently, the results of the intervention might vary according to the protocol used, training of the health-care professional, and the patient's characteristics. In addition, few studies compared complementary and alternative medicine strategies with traditional interventions.

A multidisciplinary, certified, and dedicated team facilitating patient access to effective interventions should be pursued. Remote interventions (internet, telephone, and home-based) could also be effective and might be a good vehicle for disseminating these important interventions at a lower cost and time with a greater reach, including breast cancer survivors living in remote areas. Considering the potential upcoming availability of escalated adjuvant strategies,[83] including combinations with targeted agents characterised by a peculiar safety profile,[84] the burden of endocrine therapy-related side-effects is expected to become even more relevant in the near future and a growing attention to their proper management is likely to become essential.

Contributors
MAF and ML conceptualised the manuscript and wrote the original draft. MAF did the search, data collection, data analysis, figures, and revision of the manuscript. EA did the data collection, data analysis, and revision of the manuscript. MP did the data collection and revision of the manuscript. LDM, EdA, IL-V, AHP, and ML did the data analysis and revision of the manuscript. ML supervised the project.

Declaration of interests
LDM reports an advisory role for Roche, Novartis, Merck Sharp and Dohme, Pfizer, Ipsen, AstraZeneca, Genomic Health, Lilly, Seattle Genetics, Eisai, Pierre Fabre, and Daiichi Sankyo; honoraria from Roche, Novartis, Lilly, and Merck Sharp and Dohme; and travel grants from Roche, Pfizer, and Celgene. IV-L reports honoraria paid to institution from AstraZeneca, Amgen, and Pfizer. EdA reports honoraria from and an advisory board for Roche; and travel grants from Roche, and Novartis; research grants from Roche, Radius, AstraZeneca, Lilly, Merck Sharp and Dohme, Novartis, Synthon, Servier, and Pfizer paid to Institut Jules Bordet. AHP reports royalty payments for coauthoring the breast cancer survivorship section of UpToDate. ML reports an advisory role for

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New Drugs, New Toxicities: Side Effects of New and Emerging Breast Cancer Therapies

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OVERVIEW

With the rapid introduction of novel breast cancer therapies, recognizing and managing side effects is essential to maintain adherence and improve outcomes. As novel oral endocrine therapies and combination strategies including targeted agents have prolonged progression and in some cases disease-free survival, early recognition and appropriate management of these toxicities is critical to optimize quality of life. Dermatologic adverse events are frequently associated with novel breast cancer therapies including immune checkpoint inhibitors (ICIs), targeted therapies, and antibody-drug conjugates (ADCs). These include various rashes, stomatitis, and alopecia, necessitating multidisciplinary dermatologic intervention to allow for prompt management of cutaneous toxicities and continuation of oncologic therapy. Targeted breast cancer therapies, including ADCs, can also induce ocular adverse events (OAEs), such as corneal pseudomicrocysts which lead to blurry vision and eye pain. Current preventative therapies have had limited success for these OAEs, necessitating dose interruptions. Although anthracycline-based chemotherapy and human epidermal growth factor receptor 2 (HER2)–targeted therapy are associated with an increased risk of heart failure and left ventricular (LV) dysfunction, novel breast cancer therapies including ADCs, HER2 tyrosine kinase inhibitors, cyclin-dependent kinase 4 and 6 inhibitors, ICIs, and oral selective estrogen receptor degrader are also associated with an increased risk of LV dysfunction, heart failure, corrected QT prolongation, myocarditis, and bradycardia. This review provides a comprehensive overview of novel and emerging breast cancer therapy toxicities, with suggested management strategies to prevent and mitigate these adverse events. Through a multidisciplinary approach involving preventative strategies, monitoring, proactive interventions, providers can minimize symptom burden and improve patient adherence, ultimately improving breast cancer outcomes.

INTRODUCTION

With the rapid evolution of breast cancer treatment including targeted agents, next-generation endocrine therapies, immunotherapy, and antibody-drug conjugates (ADCs), it is important for providers to be aware of and recognize their associated toxicities. These agents are now being incorporated into clinical trials and treatment paradigms for early-stage breast cancer and into earlier lines of treatment in the metastatic setting, as both monotherapy and in combination. The goal is to continue to improve invasive disease-free survival, progression-free survival (PFS), and overall survival (OS) for high-risk cancers. Therefore, heightened awareness, application of preventive strategies, and prompt management of toxicities is necessary to minimize side effects, achieve improved outcome, and improve/maintain health-related quality of life.

From endocrine-related symptoms and dermatologic reactions to ocular complications and cardiotoxicity, these novel breast cancer therapies present with a wide range of shared and unique toxicities. A multidisciplinary approach incorporating patient education, close monitoring, and tailored pharmacologic and nonpharmacologic strategies is critical to mitigate these adverse events. By managing side effects early and proactively, providers can decrease symptom burden and improve patient adherence to these novel breast cancer therapies, which ultimately leads to improved treatment outcomes. This review provides a comprehensive description of the toxicities of these novel and emerging breast cancer therapies and outlines effective management strategies to improve treatment outcomes.

AN ONCOLOGIST'S APPROACH TO MANAGING ENDOCRINE TOXICITIES

Appropriate management of endocrine toxicities in hormone receptor–positive (HR+) breast cancer is essential to improve patient adherence to endocrine therapy and their combination partners. With the emergence of novel targeted

PRACTICAL APPLICATIONS

- With expanding oral endocrine therapies and combination strategies involving targeted agents in hormone receptor–positive breast cancer, early recognition and appropriate management of these toxicities is critical to maintain patient adherence, optimize quality of life, and ultimately improve treatment outcomes.
- Dermatologic adverse events are frequently associated with emerging treatments for breast cancer including immunotherapy, targeted therapy, and antibody-drug conjugate (ADC) therapy and in severe cases affect patients' quality of life and disrupt oncologic therapy. Multidisciplinary care improves clinical outcomes and allows for continuation of oncologic therapy.
- Cardiovascular toxicity, including left ventricular dysfunction, heart failure, corrected QT prolongation, myocarditis, and bradycardia, is an important consideration with novel breast cancer therapies, necessitating a multidisciplinary approach to patient care.
- Ocular adverse events (OAEs) are associated with ADCs, such as corneal pseudomicrocysts which lead to blurry vision and eye pain in patients with breast cancer. Current preventative therapies have limited success for these OAEs, necessitating ADC dose interruptions.

agents and next-generation endocrine therapies, patients can remain on endocrine therapy for longer duration, and targeted agents are now used in the early-stage setting with next-generation therapies in multiple clinical trials. As a result, early recognition of endocrine-related symptoms and effective management of these side effects are necessary to mitigate long-term toxicity and improve treatment outcomes.

Common Toxicities and Management Considerations for Endocrine Therapy

Proactive management of endocrine-related toxicities is key to promote long-term adherence and improve tolerability of endocrine therapies. Tamoxifen, a selective estrogen receptor modulator (SERM), has been a standard treatment for HR+ breast cancer for over 30 years.[1,2] Common side effects include vasomotor symptoms (VMS), which generally improve over time, irregular menses, and vaginal discharge or dryness.[3,4] Other common and related toxicities include sexual dysfunction, fatigue, difficulty sleeping, weight gain, joint stiffness, cataract development, and mood changes including depression and irritability. Venous thromboembolism (VTE) and endometrial cancer are rare side effects, occurring in <5% and 1% of patients, respectively.[3,4]

Aromatase inhibitors (AIs), which block the aromatase enzyme, have largely replaced tamoxifen as a treatment option for postmenopausal women and premenopausal women receiving ovarian function suppression for higher-risk disease. Like tamoxifen, AIs can cause VMS and sexual dysfunction including vaginal dryness, dyspareunia, and decreased libido. Additionally, AI-induced musculoskeletal symptoms (AIMSS), characterized by arthralgias, myalgias, and/or tendonitis, are common; musculoskeletal symptoms are seen less frequently with tamoxifen.[5] AIs can also accelerate bone loss leading to osteopenia and osteoporosis.[6] Chemotherapy-induced ovarian failure leads to greater bone loss in premenopausal women, and having osteopenia or osteoporosis at baseline before starting AIs is a strong risk factor of fractures.[6] AIs may also slightly increase cardiovascular (CV) risk when compared with tamoxifen.[7,8]

Management of VMS includes lifestyle changes, such as avoidance of triggers and implementing cooling strategies (Table 1).[40] Nonhormonal options include selective serotonin reuptake inhibitors, selective serotonin-norepinephrine reuptake inhibitors, and gabapentin.[40] One study also evaluated oxybutynin at two doses (2.5 mg twice daily or 5 mg twice daily) and both were effective at reducing hot flashes but were associated with some anticholinergic effects including dry mouth, difficulty urinating, and abdominal pain.[41] Fezolinetant, a neurokinin three receptor antagonist with recent regulatory approval, is effective for moderate-to-severe VMS.[42]

For sexual side effects, improving vaginal symptoms is key. Nonhormonal options, such as vaginal moisturizers, lubricants, and gels, can improve vaginal dryness (Table 1).[43] For more severe symptoms associated with vulvovaginal atrophy, use of vaginal hormonal therapy including twice weekly low-dose estradiol-releasing intravaginal tablets, every 3 months use of an estradiol-releasing vaginal ring, and short-term use of minimal estrogen-based creams can improve the integrity of the vaginal mucosa.[43] Vaginal testosterone and dehydroepiandrosterone (also known as prasterone) can also be effective.[44-47] Although concerns related to increased estrogen exposure exist, the majority of studies indicate minimal to no increases in serum estradiol levels with low-dose vaginal estrogen therapy.[48] Discussion of the existing safety data is necessary, with a recent meta-analysis demonstrating a potential increased risk of recurrence with vaginal estrogen therapy and AI use but no difference in mortality. However, significant limitations were noted, including the lack of clinical characteristics, length of follow-up, and treatment variables such as dose and duration of use.[49]

Management of low sexual desire and sexual dysfunction associated with endocrine therapy is challenging, but can

TABLE 1. Side Effects and Management Considerations of US Food and Drug Administration–Approved Endocrine Therapies and Targeted Agents

Class of Drug	Drug Name	Common Side Effects (≥15% of patients)	Serious (≥5% of patients) and Clinically Important Side Effects	Key Management Considerations
Endocrine therapies				
SERM	Tamoxifen[3,4,9]	Hot flashes, irregular menses, vaginal discharge, mood changes	VTE (1%-5%), endometrial carcinoma (<1%). Sexual dysfunction can occur	Vasomotor symptoms: Lifestyle changes are recommended, including avoidance of triggers and the implementation of cooling strategies For severe symptoms, nonhormonal options include SSRIs, SNRIs, gabapentin (starting dose 100 mg nightly, uptitrate as needed), oxybutynin (2.5 mg or 5 mg twice daily), and fezolinetant (45 mg daily) Sexual symptoms: Nonhormonal options for vaginal symptoms include vaginal moisturizers, lubricants, and gels. For severe symptoms, vaginal hormonal therapy including estradiol-releasing intravaginal tablets, low-dose estrogen vaginal inserts, estradiol-releasing vaginal rings, and estrogen-based creams can be considered Consider referral to individual and couples counseling, cognitive behavioral therapy, and/or sex therapy to improve sexual desire and dysfunction Consider referral to pelvic physical therapy to provide pelvic floor muscle relaxation techniques Medications such as bupropion (150 mg daily), flibanserin (100 mg nightly), and bremelanotide (1.75 mg subcutaneously, at least 45 minutes before sexual activity) can improve low libido Musculoskeletal symptoms: Exercise, including aerobics, strength training, and yoga, and acupuncture are helpful Referral to physical or occupational therapy can be helpful to improve physical activity Pain medications such as acetaminophen (325-600 mg every 4-6 hours), NSAIDs, (eg, ibuprofen 200-400 mg every 4-6 hours) and COX-2 inhibitors (eg, celecoxib 200 mg once daily or 100 mg twice daily) are helpful for short-term pain relief Consider duloxetine (30 mg once daily for 1-2 weeks, then increase to 60 mg once daily as tolerated) to improve joint pain Low bone mineral density: Screening for low bone mineral density is recommended for all patients on an AI. Adequate intake of calcium (1,200 mg/day) and vitamin D (800-100 IU/day) decreases bone loss and prevents hypocalcemia induced by bone-modifying agents Exercise and weight training are recommended Treatment of osteoporosis includes bisphosphonates and denosumab For postmenopausal women with early breast cancer, intravenous bisphosphonates is the preferred agent To prevent osteonecrosis of the jaw, dental clearance before initiation of a bone-modifying agent and regular dental care during treatment is recommended Patients with significant bone loss should be managed in conjunction with endocrinology
AIs	Letrozole, anastrozole, exemestane[10-14]	Hot flashes, arthralgias/arthritis, mood changes	Grade ≥3: Arthralgia (3%-4%); Osteoporosis/fractures (3%-11%), cardiovascular events (1%-7%), and sexual dysfunction can occur	
SERDs	Fulvestrant[15,16]	Hot flashes, arthralgias/arthritis	Injection site reactions (<1%). Sexual dysfunction can occur	
	Elacestrant[17,18]	Arthralgias/arthritis, nausea, vomiting	Grade ≥3: Arthralgias/arthritis (7%), nausea (3%)	

(continued on following page)

TABLE 1. Side Effects and Management Considerations of US Food and Drug Administration–Approved Endocrine Therapies and Targeted Agents (continued)

Class of Drug	Drug Name	Common Side Effects (≥15% of patients)	Serious (≥5% of patients) and Clinically Important Side Effects	Key Management Considerations
Targeted agents				
CDK4/6 inhibitor	Palbociclib + endocrine therapy[19-22]	Cytopenias, infections, rash, nausea, vomiting, diarrhea, stomatitis, alopecia, fatigue	Grade ≥3: Neutropenia (67%-70%), infections (5%-7%); ILD/pneumonitis (any-grade: 1%; grade ≥3: <1%)	Hematologic toxicity (*all CDK4/6 inhibitors*): Frequent monitoring of blood counts at baseline, every 2 weeks for the first 2 cycles, and prior to each cycle are indicated Withhold treatment for grade 3 hematologic toxicity until improvement, then resume at the same dose Withhold treatment and reduce dose for prolonged or recurrent grade 3 toxicity, grade 3 neutropenia with fever, and for grade 4 toxicity Hepatotoxicity (*ribociclib and abemaciclib*): Frequent monitoring of LFTs at baseline, every 2 weeks for the first 2 cycles, and prior to each cycle are indicated For grade 3 ALT/AST elevations, withhold treatment until recovery to grade ≤1, then resume at some dose For recurrent grade 3 ALT/AST elevations, withhold treatment until recovery to grade ≤1, then resume at a lower dose Discontinue treatment for grade 4 ALT/AST elevations Consider corticosteroids (starting dose 1 mg/kg) for grade 3 or 4 ALT/AST elevations and for Hy's law For persistent or severe hepatotoxicity, changing treatment to a different CDK4/6 inhibitor is an option QTc prolongation (*ribociclib only*): Avoid use of concomitant tamoxifen with ribociclib due to higher rates of QTc prolongation observed Obtain ECGs at baseline, on cycle 1 day 14, and as clinically indicated For QTc >480-500 ms: Withhold treatment until QTc resolves to ≤480 ms and resume at the same dose For QTc >500 ms: Withhold treatment until QTc resolves to ≤480 ms and resume at next lower dose. If QTc >500 ms recurs, discontinue treatment Permanently discontinue therapy for symptomatic or life-threatening arrhythmias Diarrhea (*abemaciclib only*): Start antidiarrheal agents (eg, loperamide) with first sign of loose stool For grade 2 diarrhea, withhold treatment and resume at the same dose For recurrent grade 2 or grade ≥3 diarrhea, withhold treatment and reduce dose Permanently discontinue treatment for grade 4 diarrhea ILD/pneumonitis (*all CDK4/6 inhibitors*): For asymptomatic grade 1 ILD/pneumonitis, no dose adjustment is necessary. Consider starting corticosteroids (e.g. at least 0.5 mg/kg/day prednisone equivalent until improvement, followed by gradual taper) as appropriate For grade 2 symptomatic ILD/pneumonitis, withhold treatment until recover to grade 1, initiate corticosteroids (eg, at least 1 mg/kg/day for ≥14 days or until complete resolution of clinical and chest CT findings, followed by gradual taper), and consider resuming at reduced dose For grade ≥3 ILD/pneumonitis, permanently discontinue treatment. Initiate high-dose methylprednisolone IV treatment (eg, 500-1,000 mg/day for 3 d), followed by at least 1.0 mg/kg/day of prednisone (or equivalent) for ≥14 days or until complete resolution of clinical and chest CT findings, then followed by a gradual taper Alopecia (*all CDK4/6 inhibitors)*: Initiate oral minoxidil (1.25-2.5 mg per day). Can consider topical minoxidil although may be less effective VTE: Treat with appropriate anticoagulation as needed. Continue therapy
	Ribociclib + endocrine therapy[23-27]	Cytopenias, infections, nausea, vomiting, diarrhea, constipation, rash, fatigue, stomatitis, alopecia increased ALT/AST	Grade ≥3: Neutropenia (62%), ALT/AST elevations (8%-11%; Hy's law 1%); QTc prolongation (any-grade: 7%); ILD/pneumonitis (any-grade: 1%-2%; grade ≥3: <1%) Note: Adverse reactions reflect the starting dose approved for advanced/metastatic breast cancer (600 mg). In patients with early breast cancer who receive ribociclib 400 mg plus a nonsteroidal aromatase inhibitor, a lower incidence of dose-dependent toxicity (eg, neutropenia and QT prolongation) is observed	
	Abemaciclib + endocrine therapy[28-31]	Diarrhea, nausea, vomiting cytopenias, infections, fatigue, alopecia, stomatitis, increased ALT/AST, increased creatinine	Grade ≥3: Neutropenia (20%-30%), diarrhea (8%-20%), infections (5%), ALT/AST elevations (2%-6%); ILD/pneumonitis (any-grade: 3%; grade ≥3: <1%); VTE (any-grade: 2%-5%; approx. 2%-3% with AIs and 4%-5% with tamoxifen)	

(continued on following page)

TABLE 1. Side Effects and Management Considerations of US Food and Drug Administration–Approved Endocrine Therapies and Targeted Agents (continued)

Class of Drug	Drug Name	Common Side Effects (≥15% of patients)	Serious (≥5% of patients) and Clinically Important Side Effects	Key Management Considerations
mTOR inhibitor	Everolimus + endocrine therapy[32,33]	Stomatitis, cytopenias, infections, hyperlipidemia, hyperglycemia, rash, fatigue, diarrhea, nausea, vomiting	Grade ≥3: Hyperglycemia (9%), stomatitis (8% without prophylaxis), anemia (6%), infections (6%), ILD/pneumonitis (4%)	Stomatitis: *For everolimus only:* Initiate prophylactic mouthwash with dexamethasone (0.5 mg/5 mL oral solution, swish and spit four times daily) at the start of therapy to prevent stomatitis For developing mouth sores, oral dexamethasone mouthwash can be used along with spot application of a steroid dental paste For grade 2 stomatitis, withhold treatment until improvement to ≤grade 1 For recurrent grade 2 and grade 3 stomatitis, withhold treatment until improvement to ≤ grade 1, then resume at a lower dose Permanently discontinue treatment for grade 4 stomatitis Hyperglycemia: *For alpelisib and inavolisib:* Consider initiation of metformin 500 mg twice daily and uptitrate as tolerated to prevent hyperglycemia Frequent of monitoring of blood glucose is needed, particularly in patients at high risk of hyperglycemia and with abnormal baseline values. *For everolimus*: Monitor blood glucose as needed. *For alpelisib*: After initiating treatment, monitor fasting glucose least once every week for the first 2 weeks, then at least once every 4 weeks, and as clinically indicated. Monitor HbA1c every 3 months and as clinically indicated *For capivasertib:* After initiating treatment, monitor or self-monitor fasting glucose levels on day 3 or 4 of the dosing week during weeks 1, 2, 4, 6, and 8; then monthly, and as clinically indicated. Monitor HbA1c every 3 months and as clinically indicated *For inavolisib*: After initiating treatment, or in patients who experience hyperglycemia after initiating treatment, monitor or self-monitor fasting glucose levels once every 3 days for the first week (day 1 to 7), then once every week for the next 3 weeks (day 8 to 28), then once every 2 weeks for the next 8 weeks, then once every 4 weeks thereafter, and as clinically indicated. Monitor HbA1C every 3 months and as clinically indicated For grade 1 hyperglycemia, initiate metformin 500 mg daily and uptitrate as needed For grade 2 hyperglycemia, increase metformin as able and/or initiate additional oral hypoglycemic agents. If fasting glucose does not resolve to ≤ grade 1, reduce dose For grade 3 hyperglycemia, withhold treatment and consider initiation of additional hypoglycemic agents. Permanently discontinue treatment if fasting glucose does not decrease to grade 1 within 21 days following appropriate hypoglycemic therapy For grade 4 hyperglycemia, administer IV hydration and insulin and correct electrolyte abnormalities. Permanently discontinue treatment if no improvement of fasting glucose to <500 mg/dL Consider endocrinology referral as needed Rash: *For alpelisib (and consider for capivasertib)*: Initiate daily oral nonsedating antihistamines (cetirizine 10 mg, levocetirizine 5 mg, loratidine 10 mg, or fexofenadine 180 mg once daily) at the start of therapy for prevention of rash For grade 1 rash (BSA <10%), topical corticosteroids (eg, triamcinolone 0.1%, betamethasone dipropionate 0.05%, fluocinonide 0.05% BID) are recommended For grade 2 rash (BSA 10%-30%), topical corticosteroids are recommended. Can consider low-dose systemic corticosteroids (e.g. prednisone 0.5-1 mg/kg/daily) For grade 3 and 4 rash (BSA > 30%), withhold treatment and initiate systemic corticosteroids (eg, prednisone 0.5-1 mg/kg/daily for 10-14 days followed by a taper). Resume at a lower dose Permanently discontinue therapy for severe bullous, blistering, or exfoliating skin conditions Diarrhea: See management considerations as above Hematologic toxicity: See management considerations as above ILD/pneumonitis: See management considerations as above
PI3K Inhibitor	Alpelisib + fulvestrant[34,35]	Hyperglycemia, diarrhea, nausea, vomiting, cytopenias, rash, weight loss, stomatitis, fatigue, alopecia	Grade ≥3: Hyperglycemia (39%), rash (20%), increased GGT (11%), diarrhea (7%), increased lipase (7%), fatigue (5%), ILD/pneumonitis (any-grade: 2%)	
AKT inhibitor	Capivasertib + fulvestrant[36,37]	Diarrhea, nausea, vomiting, stomatitis, rash, fatigue, hyperglycemia, cytopenias	Grade ≥3: Rash (15%), diarrhea (12%), hyperglycemia (9%)	
PI3K Inhibitor	Inavolisib + palbociclib + fulvestrant[38,39]	Cytopenias, hyperglycemia, stomatitis, diarrhea, nausea, rash, fatigue	Grade ≥3: Neutropenia (82%), thrombocytopenia (16%), hyperglycemia (12%), anemia (8%) stomatitis (6%), hypokalemia (6%)	

Abbreviations: AIs, aromatase inhibitors; BSA, body surface area; CDK4/6, cyclin-dependent kinase 4 and 6; COX-2, cyclooxygenase-2; ECGs, electrocardiograms; GGT, gamma glutamyl transferase; ILD, interstitial lung disease; LFTs, liver function tests; mTOR, mammalian target of the rapamycin; NSAIDs, nonsteroidal anti-inflammatory drugs; PI3K, phosphoinositide 3-kinase; QTc, corrected QT; SERD, selective estrogen receptor degrader; SERM, selective estrogen receptor modulator; SNRIs, selective serotonin-norepinephrine reuptake inhibitors; SSRIs, selective serotonin reuptake inhibitors; VTE, venous thromboembolism.

improve with individual and couples counseling, cognitive behavioral therapy, and/or sex therapy.[50-54] Pelvic physical therapy can improve pelvic floor muscle dysfunction associated with vaginal atrophy and strictures.[53,54] Medications such as bupropion, flibanserin, and bremelanotide may also improve low libido.[55-57]

To improve AIMSS, regular exercise, including aerobics, strength training, and yoga, and acupuncture have been shown to improve symptoms (Table 1).[58-65] Pain medications such as acetaminophen, nonsteroidal anti-inflammatory drugs, and cyclooxygenase-2 inhibitors (eg, celecoxib) are helpful for short-term pain control.[66] In addition, duloxetine has been shown to reduce AI-associated joint pain.[67]

For intolerable symptoms, switching to a different AI is an option, as symptoms may improve for unclear reasons with switching to a different AI, or changing to tamoxifen.[68,69] Managing endocrine symptoms and supporting adherence is essential, as endocrine treatment of any type is still better than none.

For the long-term impact of AIs on bone loss, regular monitoring of bone mineral density is recommended. The bone density at initiation of AI therapy may trigger the frequency of bone density scans, which should occur no less than every 2 years. All patients treated with an AI should be advised adequate intake of calcium and vitamin D, along with exercise and weight training. Treatment of osteoporosis includes bone-strengthening agents such as bisphosphonates and denosumab. For postmenopausal women with early breast cancer, intravenous bisphosphonates is the preferred agent because of its reduced rate of breast cancer recurrence in the bone and improved breast cancer survival.[70] To prevent the rare effect of osteonecrosis of the jaw, dental clearance before initiation of a bone-modifying agent and regular dental care during treatment is recommended. Patients with significant bone loss should be managed in conjunction with endocrinology.

Common Toxicities and Management Considerations of CDK4/6 Inhibitors Plus Endocrine Therapy

Three oral cyclin-dependent kinase 4 and 6 (CDK4/6) inhibitors—palbociclib (given on a 3 week on, one week off schedule), ribociclib (given on the same schedule as palbociclib), and abemaciclib (given continuously)—are approved in combination with endocrine therapy in HR+ metastatic breast cancer (MBC).[19,23,71] Ribociclib and abemaciclib are also indicated for the treatment of high-risk, early HR+ breast cancer to reduce recurrence.[24,72] CDK4/6 inhibitors are generally well-tolerated, with most toxicities managed with dose modifications and supportive measures. The most common toxicities across palbociclib and riboclib include cytopenias (particularly neutropenia), and for abemaciclib diarrhea. All three agents are associated with fatigue, nausea, and hair loss.

Palbociclib is considered the most well-tolerated of the three CDK4/6 inhibitors, with common toxicities including neutropenia, fatigue, and, nausea.[19-22] Serious symptomatic toxicities are rare, with grade ≥3 toxicities primarily consisting of neutropenia. Management involves delaying the start of the next cycle for grade ≥3 neutropenia and reducing the dose for prolonged/recurrent grade ≥3 neutropenia and febrile neutropenia (Table 1).

Similar to palbociclib, the most common toxicities of ribociclib are neutropenia, fatigue, and nausea. Unique toxicities of ribociclib include reversible prolongation of the QT interval in 7% of patients (Cardiovascular Toxicity section; Table 1).[73] The risk of QT prolongation is increased when ribociclib is given in combination with tamoxifen; higher-grade toxicity is rare. In the early-stage setting, ribociclib is given at a dose of 400 mg daily (3 weeks on, 1 week off), contrasting with the 600 mg daily (3 weeks on, 1 week off) dose approved for metastatic disease, resulting in a lower incidence of both higher grade neutropenia and QT prolongation.[24]

Abemaciclib is unique in that it is given continuously and although neutropenia is seen, it is much less frequent that the other two CDK4/6 inhibitors. By contrast, the most common toxicity associated with abemaciclib is diarrhea, with grade ≥3 diarrhea occurring in up to 20% of patients (Table 1).[28-31] Management includes antidiarrheals (eg, loperamide) and dose holding and reductions as needed. Abemaciclib can also increase VTE risk, particularly when combined with tamoxifen as compared with AIs (4.3% *v* 1.8%)[74]; therefore, heightened monitoring for VTE symptoms are needed with this combination.

Management of fatigue across the CDK4/6 inhibitor class includes dose reduction and delay and is more common in older patients.[75] Additional toxicities which impact quality of life include grade 1 alopecia, which can be managed by low-dose minoxidil. Oral minoxidil is supported by prospective data and is generally well-tolerated and effective, although can cause hair growth in other areas including the face.[76] Topical minoxidil can also be considered but is less effective and may be challenging in application. Low-grade stomatitis can also occur from these agents, which responds nicely to steroid dental paste and steroid mouthwash (see below, everolimus stomatitis).

Ribociclib and abemaciclib are associated with grade ≥3 elevations in ALT or AST in up to 11% and 6% of patients, respectively.[25,31] Liver toxicity was the most common reason for ribociclib discontinuation, with 9% of patients discontinuing treatment because of liver abnormalities in the NATALEE trial.[24] Hy's Law, which indicates drug-induced liver injury defined by concurrent AST or ALT elevations >3 times the upper limit of normal (ULN), total bilirubin >2 times the ULN, normal alkaline phosphatase, and the absence of cholestasis, has been observed but is uncommon.[25]

Management of grade 3 hepatotoxicity involves holding treatment until improvement and resuming at a lower dose (Table 1). For more severe cases, systemic corticosteroids (starting at 1 mg/kg) have also demonstrated efficacy in case reports.[77-81] For recurrent, or resolved severe hepatotoxicity, changing to a different CDK4/6 inhibitors appears safe, with one study reporting minimal reoccurrence of hepatotoxicity after switching.[82]

Each of the 3 CDK4/6 inhibitors can rarely cause interstitial pneumonitis/interstitial lung disease (ILD), with grade 3 or higher toxicity occurring in <1% of patients.[22,25,31] Unlike the management of ADC-associated ILD, grade 1 asymptomatic ground glass opacities are monitored without holding the targeted agent. Symptomatic grade 2 or high ILD should be treated with steroids, with dose hold and consideration for dose reduction when symptoms have resolved. For more symptomatic ILD, treatment should be discontinued.

Common Toxicities and Management Considerations Associated With PI3K/Akt/mTOR Signaling Pathway

Several targeted agents inhibiting the phosphoinositide 3-kinase (PI3K)/protein kinase B (Akt)/mammalian target of the rapamycin (mTOR) signaling pathway are approved in HR+ MBC. Four agents are approved in combination with endocrine therapy for endocrine-resistant disease, the MTOR inhibitor everolimus,[80,81] the alpha-specific PI3K inhibitors alpelisib[34,35] and inavolisib,[38,39] and the AKT inhibitor capivasertib,[36,37] with multiple agents in clinical trials. Although toxicities vary in incidence between the specific target within the PI3K pathway and between agents, PI3K/Akt/mTOR inhibitors share several common on-target effects including hyperglycemia, rash, and diarrhea.[83,84] Toxicities with these targeted agents, similar to the CDK4/6i, appear to be largely unaffected by the endocrine partner. Novel oral endocrine agents (see below) are being studied in combination to evaluate efficacy and potential drug-drug interactions (DDIs).[85,86] Several preventative strategies are recommended to reduce the onset of toxicities (Table 1).

Common toxicities associated with everolimus include stomatitis, which can be markedly reduced in both incidence and severity by use of a preventive steroid mouthwash.[87] Developing mouth sores can also be treated with the steroid mouthwash and spot application of a steroid dental paste. Management of symptomatic stomatitis despite preventive strategies includes withholding treatment and dose reduction (Table 1). Additional adverse events of the pathway toxicities include rash, hyperglycemia and diarrhea.[32,33] Some data suggest that use of prophylactic nonsedating antihistamines can reduce both severity and incidence of rash (see alpelisib below). Hyperglycemia management is covered below, and diarrhea is managed by antipropulsive agents, starting with loperamide, dose interruption, and dose reduction when poorly controlled.

Finally, interstitial pneumonitis/ILD is a rare but well-documented late toxicity, which can occur with any of these agents.[88] Similar to CDK4/6 inhibitor-associated ILD, management of grade 1 ILD involves monitoring, whereas grade 2 or higher ILD involves dose holding and initiation of steroids. For more symptomatic ILD, treatment should be discontinued.

The toxicities from PI3Kα-specific inhibitors are quite variable, with differences between the two approved agents alpelisib[34,35] and the recently approved agent inavolisib.[38,39] Alpelisib, given in combination with fulvestrant, causes hyperglycemia in 79% of patients, with half of these patients experiencing grade 3 to 4 hyperglycemia.[35] Other common toxicities include rash, diarrhea, and nausea. By contrast, inavolisib, a PI3Kα-specific inhibitor and mutant PI3Kα degrader, is approved in combination with palbociclib and fulvestrant for PIK3CA-mutated HR+/human epidermal growth factor receptor 2 (HER2−) MBC following recurrence on or within one year after adjuvant endocrine therapy. Common toxicities of the combination include cytopenias (because of palbociclib), with all-grade toxicities including neutropenia (95%), hyperglycemia (85%), stomatitis (51%), and diarrhea (48%).[39] When separating out the effects of palbociclib (on the basis of monotherapy data from the phase Ia dose escalation study), inavolisib appears to cause minimal rash compared with alpelisib (inavolisib monotherapy any-grade rash: 15%; grade ≥3: 0% *vs.* alpelisib any-grade rash: 52%; grade ≥3: 20%).[35,89] The incidence of hyperglycemia in the overall population is not well understood, as patients enrolled in the triplet trial noted above were required to have normal or minimally altered glucose metabolism. Neither of the agents have been studied in patients with insulin-dependent diabetes mellitus.

The AKT inhibitor, capivasertib, is approved in combination with fulvestrant for patients with HR+/HER2− MBC with *PIK3CA*, *AKT1* or *PTEN* mutations.[36,37] Common toxicities include diarrhea (77%), rash (56%), fatigue (38%), and nausea (35%).[37] Although hyperglycemia occurs in approximately one third of patients, serious hyperglycemia is less common than that seen with alpelisib despite the inclusion of patients with HgbA1c up to 7.9% in the registration trial.[37] Capivasertib is given on a 4 day on, 3 day off schedule, which helps with management of toxicity. Delaying the start of the next cycle, symptomatic management (loperamide, antihistamines, and topical steroids), and dose reduction are effective strategies for diarrhea and rash.

Patients starting agents targeting the PI3K pathway should have a baseline HgbA1c and fasting glucose (Table 1). Glucose must be monitored closely during therapy, as reports of postmarketing diabetic ketoacidosis have emerged and are increased in patients with other risk factors such as systemic infection. Those with abnormal starting values should be managed in collaboration with endocrinology, and every effort should be made to obtain optimal glucose control before starting the targeted agent.

Prophylactic initiation of metformin at the start of alpelisib treatment has been shown to decrease the incidence and severity of hyperglycemia[90]; this approach could be used across the pathway-specific agents. Management of developing hyperglycemia also depends on its severity, with incorporation of hypoglycemic agents and multidisciplinary team management with an endocrinologist. Metformin is the recommended initial oral hypoglycemic agent, with the addition of other oral hypoglycemics and insulin, as necessary.

Prophylactic initiation of nonsedating antihistamines can reduce the incidence and severity of the rash associated with alpelisib[91] and may also be applied to the use of capivasertib. Management of rash varies depending on the extent of body surface area involved, with topical corticosteroids recommended for mild rash and systemic corticosteroids for more severe symptoms along with dose interruption and consideration for dose reduction when rash has improved (Skin Toxicities section; Tables 1 and 2).

Other common side effects of these agents include GI symptoms and cytopenias, which are generally effectively managed with symptomatic and supportive care, including dietary recommendations, and/or dose modifications.[92] It is important to be aware of the timeline of adverse events, to allow optimal monitoring and intervention. Hyperglycemia, stomatitis, rash, and diarrhea generally occur within the first 8 weeks of therapy, with most occurring in the first 1-2 cycles although certainly later events have been described. For everolimus, diarrhea is a later event, often occurring after months of therapy. Notably, ILD is a late event, with approximately three quarters of events occurring after the first 12 weeks.[88]

Common Toxicities and Management Considerations of SERDs and Other Emerging Endocrine Therapies

Selective estrogen receptor degraders (SERDs) are pure estrogen receptor (ER) antagonists that block ER through proteasome-dependent degradation.[93] The first-generation SERD, fulvestrant, is given as a monthly intramuscular injection with a day 15 loading dose during the first month of therapy.[15] Overall, symptoms are fairly similar to AIs; however, higher rates of GI symptoms, less joint symptoms, and injection site reactions are observed with fulvestrant.[15]

Elacestrant, an oral SERD, is currently the only approved for HR+ MBC with an ESR1 mutation after at least one prior line of endocrine therapy.[17,18] Elacestrant is generally well-tolerated, although associated with more GI toxicity than fulvestrant. Any-grade nausea, vomiting, and diarrhea occurred in the phase III registration trial in 35%, 19%, and 14% of patients, respectively.[17] Elacestrant is being studied in combination with multiple targeted agents in the ELEVATE trial, with encouraging efficacy and no drug interactions noted.[85,86]

Multiple oral SERDs and other ER targeted agents are being investigated in phase II and III clinical trials. Phase III trials are ongoing with many having completed accrual. Imlunestrant is a novel oral SERD and pure ER antagonist, with phase III data from the EMBER-4 trial demonstrating improved PFS with imlunestrant compared with endocrine therapy in patients with ESR1 mutations and in combination with abemaciclib irrespective of ESR1 status.[94] Overall, side effects of imlunestrant appear to be relatively similar to other oral SERDs (predominantly GI symptoms), whereas the combination with abemaciclib led to additional toxicities consistent with abemaciclib's known safety profile.[28,95]

The phase II multidose SERENA-2 trial demonstrated a PFS benefit of camizestrant, with side effects generally similar to other oral SERDs.[96] Visual effects (photopsia or flashing lights) were observed in 12% of patients receiving the 75 mg dose. Giredestrant is another oral SERD which showed a trend toward benefit among patients with ESR1 mutations in the phase II acelERA trial, with ongoing phase III studies including both agents.[97] The toxicity profile of giredestrant is similar to other oral SERDs, although slightly higher rates of hepatotoxicity and less GI toxicity were observed in the trial. Bradycardia was reported with camizestrant doses >75 mg and in 3% of patients treated with giredestrant 30 mg (Cardiovascular Toxicity section).

Additional ER-targeting agents in development include proteolysis-targeting chimeras (PROTACs), complete ER antagonists (CERANs), novel SERMs, and selective ER covalent antagonists. Vepdegestrant, a PROTAC, recently reported improved PFS in patients with pretreated ESR1-mutated ER+/HER2− MBC in the phase III VERITAC-2 trial with data to be reported at ASCO 2025.[98,99] Palazestrant, an oral CERAN and SERD, has also displayed promising results in a phase I/II study, leading to an ongoing phase III trial.[100] The novel SERM, lasofoxifene, has also shown activity in early-phase studies, and is being evaluated in combination with abemaciclib in patients with ESR1-mutated MBC.[101,102] These emerging oral endocrine therapies exhibit relatively similar toxicity profiles to other endocrine agents and have the potential to improve efficacy in resistant ESR1-mutated disease.

Through successful management of endocrine toxicities and novel targeted agents, efficacy can be maintained with optimal symptom control. Both prophylactic strategies to minimize toxicities, as well as proactive management strategies including both pharmacologic and nonpharmacologic interventions, are necessary to improve treatment outcomes.

Table 1 summarizes common and serious side effects and key management strategies for US Food and Drug Administration (FDA)–approved endocrine therapies and targeted agents. Figure 1 illustrates shared and unique toxicities of these agents.

SKIN TOXICITIES, STEROIDS, AND SALVES: DERMATOLOGY FOR TODAY'S BREAST CANCER ONCOLOGIST

Dermatologic toxicities are among the most frequently reported adverse events in women with breast cancer on oncologic therapies. These dermatologic adverse events (dAEs) have substantial impact on physical, psychological, and financial well-being, which has been directly associated with treatment outcomes.[103,104] Here, we review the cutaneous toxicity profiles of emerging breast cancer therapies, including immunotherapy, targeted therapy, and ADCs along with management strategies (Table 2).

Immunotherapy

Cutaneous adverse events of immune checkpoint inhibitors (ICIs) including PD-1 and PD-L1 inhibitors are well-established given their historic use for melanoma and numerous solid organ and hematologic malignancies. These agents have now been applied to the treatment of triple-negative breast cancer (TNBC) in combination with cytotoxic chemotherapy. In addition to the dAEs of chemotherapy, namely taxanes, which commonly includes alopecia, toxic erythema of chemotherapy (hand-foot syndrome or palmoplantar erythrodysesthesia), hyperpigmentation, and nail changes (paronychia, brittle nails, onycholysis),[105,106] up to 22% of patients on therapeutic regimens that include ICIs experienced cutaneous immune-related adverse events (irAEs).[107,108] These irAEs include pruritus as well as maculopapular, eczematous, psoriasiform, lichenoid, and bullous eruptions.

On the basis of Common Terminology Criteria for Adverse Events (CTCAE) criteria, grade 1 and 2 rashes are mild or localized and can typically be managed with topical corticosteroids in addition to oral antihistamines without interruption of therapy. Recalcitrant grade 2 and 3 rashes affect quality of life and generally require medical intervention with systemic corticosteroids.[107,109] Importantly, targeted or steroid-sparing immunomodulating agents may be required such as oral retinoids (eg, acitretin) for psoriasiform and lichenoid rashes and biologic agents (eg, etanercept) for life-threatening toxic epidermal necrolysis.[110] Generally, these dAEs respond to treatment and ICI therapy may be readministered. For any severe cutaneous adverse reactions, reintroduction should be avoided if alternative treatment is available.

Targeted Therapy

Targeted therapies harness unique molecular signatures of malignancy to interfere with pathways responsible for tumor proliferation and survival. These drugs have been long used in breast cancer management including inhibitors of HER2 and CDK4/6. The predominant dAEs associated with HER2 inhibitors include acneiform rash, which can be managed with topical steroids and antibiotics as well as oral tetracyclines and short courses of oral steroids for severe presentations. CDK4/6 inhibitors may be associated with xerosis

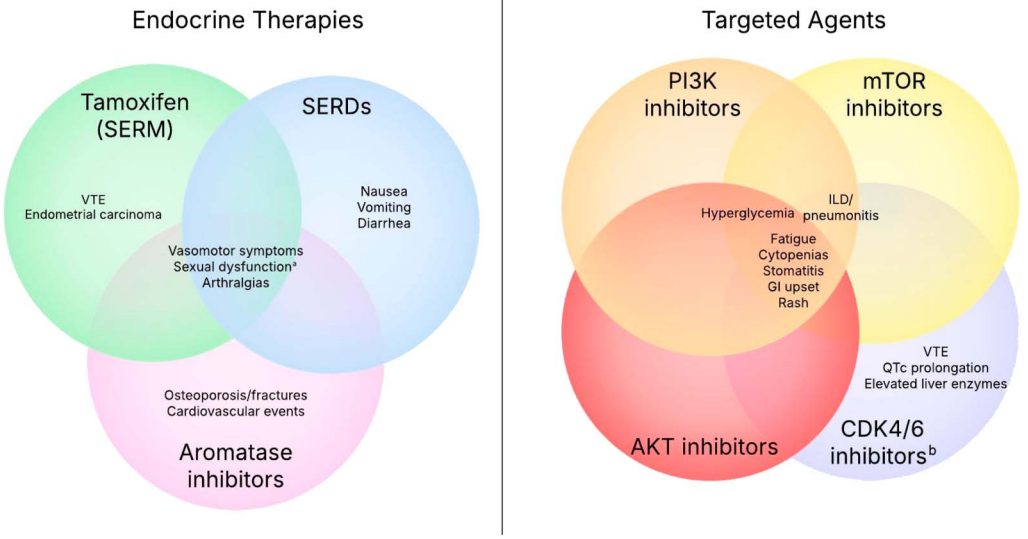

FIG 1. Shared and unique toxicities among the FDA-approved endocrine therapies and targeted agents. [a]Sexual dysfunction has not been reported with oral SERDs, although this may be due to underreporting. [b]Of the CDK4/6 inhibitors, abemaciclib is associated with an increased risk of VTE and elevated liver enzymes; ribociclib is associated with corrected QT prolongation and elevated liver enzymes. CDK4/6, cyclin-dependent kinase 4 and 6; FDA, US Food and Drug Administration; ILD, interstitial lung disease; mTOR, mammalian target of the rapamycin; PI3K; phosphoinositide 3-kinase; SERD, selective estrogen receptor degraders; SERM, selective estrogen receptor modulator; VTE, venous thromboembolism.

TABLE 2. Dermatologic Adverse Events of Emerging Breast Cancer Therapies and Their Management

Drug Class	Dermatologic Adverse Event	Management
Immunotherapy		
PD-1 (pembrolizumab) PD-L1 (durvalumab, atezolizumab)	Pruritus Rash—maculopapular, eczematous, psoriasiform, lichenoid, bullous	*Grade 1 and 2* Topical corticosteroids Oral antihistamines *Grade 3 or refractory grade 2* Hold immunotherapy Urgent dermatology consult Oral corticosteroids (0.5-1 mg/kg/daily) *Rash-specific immunomodulators:* Oral retinoids (lichenoid, psoriatic rash), Dupilumab (pruritus, eczematous, bullous pemphigoid) IL-12/23 or IL-23 inhibitor (psoriasis) TNF-alpha inhibitor (SJS/TEN) Reintroduction of immunotherapy after rash response to grade 1 (or doses of prednisone <10 mg daily) *Grade 4* Discontinue immunotherapy Hospitalization Urgent dermatology consult Follow grade 3 recommendations
Targeted therapy		
PI3K Inhibitor (alpelisib)	Rash—maculopapular, eczematous, DRESS	*Grade 1 and 2* Topical corticosteroids Oral antihistamines *Grade 3 or refractory* Hold targeted therapy Systemic corticosteroids Reintroduction with or without dose reduction when grade 1
PARP inhibitor (olaparib)	Palmoplantar erythrodysesthesia	Topical corticosteroids, NSAIDs
	Erythema nodosum	NSAIDs, topical corticosteroids
	Urticaria	Oral antihistamines
	Photosensitivity	Photoprotection, topical corticosteroids
	Maculopapular eruption	Topical corticosteroids (grade 1 and 2); systemic corticosteroids (grade 3 and 4)
AKT inhibitor (capivasertib)	Rash—maculopapular	Topical corticosteroids (grade 1 and 2); systemic corticosteroids (grade 3 and 4)
ADC		
TROP2 (SG, Dato-DXd)	Rash—maculopapular, bullous, acneiform, lichenoid	Topical corticosteroids (grade 1 and 2); systemic corticosteroids (grade 3 and 4) Oral tetracyclines and topical clindamycin/corticosteroids (acneiform)
	Alopecia	Topical or oral minoxidil may speed recovery after conclusion of treatment
	Stomatitis	Corticosteroid/lidocaine mouthwash, gentle oral care
HER2 (T-DXd)	Alopecia	Topical or oral minoxidil may speed recovery after conclusion of treatment
	Stomatitis	Corticosteroid/lidocaine mouthwash, gentle oral care
	Rash—morbilliform, acneiform	Topical corticosteroids (grade 1 and 2); systemic corticosteroids (grade 3 and 4) Oral tetracyclines and topical clindamycin/corticosteroids (acneiform)
	Pruritus	Oral antihistamines, emollients
	Hyperpigmentation	Photoprotection

Abbreviations: ADC, antibody-drug conjugate; AKT, protein kinase B; Dato-Dxd, datopotamab deruxtecan; DRESS, drug reaction with eosinophilia and systemic symptoms; HER2, human epidermal growth factor receptor 2; NSAIDs, nonsteroidal anti-inflammatory drugs; PARP, poly ADP-ribose polymerase; PI3K, phosphoinositide 3-kinase; SG, sacituzumab govitectan; SJS/TEN, Stevens-Johnson syndrome/toxic epidermal necrolysis; T-Dxd, trastuzumab deruxtecan; TROP2, humanized trophoblast cell-surface antigen 2.

and pruritus of the skin, as well as androgenetic pattern of alopecia in combination with endocrine (hormonal) therapy. Emerging classes of targeted therapies for breast cancer with dAEs include inhibitors of PI3K, poly ADP-ribose polymerase (PARP), and AKT.

PI3K inhibitors, such as alpelisib, are correlated with maculopapular, also known as, morbilliform eruptions. Safety data from the SOLAR-1 trial documented rash in 35.6% of patients,[34] which was reflected by a retrospective analysis of more than 100 patients on alpelisib in clinical trials with 40%

of patients developing a morbilliform rash (~half were at least grade 3).[111] Other PI3K inhibitors for breast cancer have demonstrated similar dAEs with predominately maculopapular or eczematous rashes,[112] as well periorbital edema,[113] and drug reaction with eosinophilia and systemic symptoms.[114] Management of grade 1 and 2 morbilliform and eczematous eruptions includes moderate to high potency topical corticosteroids and systemic antihistamines. Grade 3 and 4 reactions require interruption of therapy along with systemic corticosteroids (0.5-1 mg/kg/day for 10-14 days followed by a taper) with drug reintroduction once the rash is reduced to grade 1. In most cases, there was no rash recurrence following reintroduction even without dose reduction.[111]

PARP inhibitors have few reported dAEs. In the OlympiAD trial, olaparib monotherapy was associated with palmoplantar erythrodysesthesia, an acral variant of toxic erythema of chemotherapy, which occurred in < 5% of patients.[115] Supplemental reports have additionally included two cases of erythema nodosum,[115,116] pseudoporphyria,[117] dermatitis,[118] urticaria,[119] sweet syndrome,[120] photosensitivity, pruritus, and maculopapular eruptions,[121] with < 1% categorized as grade 3 reactions.[122]

Most recently, the AKT inhibitor capivasertib has been approved in combination with fulvestrant for treatment of HR+ advanced breast cancer. In the CAPItello-291 trial, rash was reported in 38% of patients (12% grade 3).[36] The morphology of these rashes was predominantly maculopapular; however, some patients also developed targetoid lesions reminiscent of erythema multiforme. Patients improved with systemic corticosteroids while capivasertib was held, and one tolerated reintroduction without rash recurrence while the other did not.[123]

Antibody-Drug Conjugate Therapy

Humanized trophoblast cell-surface antigen 2 (TROP2) antibody and topoisomerase I inhibitor drug conjugates, including sacituzumab govitecan (SG) and datopotamab deruxtecan (Dato-DXd), are used in the treatment of pretreated HER2− MBC. In clinical trials of SG, rash was reported in 12%-32% of patients and morphologies included maculopapular (morbilliform), bullous, acneiform, and lichenoid, with only 1%-2% being grade 3 or higher.[124] About half of patients experienced alopecia, typically reported as mild hair thinning, and up to 17% experienced low-grade stomatitis.[124] In the I-SPY2.2 trial, rash was reported in 75% of patients treated with Dato-DXd monotherapy (1% grade 3) along with stomatitis (69%) and alopecia (65%). Further characterization of these rash morphologies by dermatologists is required.[125] Approaches for prophylaxis of ADC-induced stomatitis have been outlined recommending gentle oral care and use of a corticosteroid-containing mouthwash as a swish and spit four times daily before and throughout drug initiation along with cryotherapy (ice chips or water held in mouth) during infusions.[126]

Fam-trastuzumab deruxtecan (T-DXd) was recently approved for HER2+, HER2-low, and HER2-ultralow breast cancer, with associated dAEs including most commonly stomatitis (20%) and alopecia (37%).[127-129] In addition, less common dAEs include rash (1%), with morbilliform and acneiform morphologies, as well as pruritus (8%) and hyperpigmentation (6%).[130,131]

It is important for oncologists to be aware of the variety of dAEs associated with emerging breast cancer therapies, including immunotherapy, targeted therapy, and ADC therapy. Increased use of these agents will aid in more specific characterization of dAEs and their multidisciplinary management with dermatologists. In general, rashes may be graded adapting the principles of CTCAE, with supportive topical agents and antihistamines for low-grade rashes and more aggressive approaches with systemic steroids and drug holiday in severe presentations. Prompt multidisciplinary dermatologic management allow for amelioration of symptoms, improvement of patient's quality of life, and continuation of potentially life-saving cancer therapy when possible.

EYES WIDE OPEN: ADDRESSING OCULAR TOXICITIES OF BREAST CANCER THERAPIES

ADC-Induced Ocular Adverse Events

A rising unmet need associated with breast cancer therapies is off-target ocular adverse events (OAEs) that reduce patient quality of life.[132] Chemotherapies for breast cancer, such as taxanes (eg, docetaxel and paclitaxel), are associated with an increased risk for several OAEs, including optic neuropathy, cystoid macular edema (fluid in the retina), and epiphora (excessive tearing).[133] ADCs are an emerging class of targeted therapies with a particularly high propensity to induce OAEs.[134] These drugs act as biological missiles to leverage the potent killing effect of cytotoxic drugs with the tumor-targeting specificity of a monoclonal antibody (mAb).[135] Following the success of HER2-targeted antibodies, ADCs have further improved the outcomes for patients with HER2+ breast cancer.[127,136-139] Other ADCs, including SG and the recently approved Dato-DXd, target TROP2, an epithelial antigen highly expressed in HER2− and TNBC.[140-143]

Currently, there are 12 FDA-approved ADCs, four of which are used for breast cancer, with more than 160 currently in clinical development (Table 3). Nearly 50% of FDA-approved ADCs induce OAEs termed corneal pseudomicrocysts, which are microcystic-like structures located in the basal layer of the corneal epithelium (Fig 2).[134,148,149] As their name implies, corneal pseudomicrocysts are not actual cysts but rather apoptotic epithelial cells located in the basal layer of the corneal epithelium.[149,150] They appear as tiny hyperreflective circles that are best visualized with in vivo confocal microscopy. Pseudomicrocysts begin to develop as early as 3 weeks after ADC infusion in the periphery of the cornea

TABLE 3. ADCs for Breast Cancer With Reported OAEs

Phase of Development	ADC	Company	Breast Cancer Indication	Antibody	Linker	Payload	DAR	OAE (%)	References
FDA-approved	Datopotamab deruxtecan	AstraZeneca, Daiichi Sankyo	HR-positive, HER2-negative unresectable or MBC (received prior endocrine-based therapy and chemotherapy)	TROP2	Cleavable	TOP1i	4	51	[142]
	Trastuzumab deruxtecan	AstraZeneca, Daiichi Sankyo	HER2-positive unresectable or MBC (received prior anti-HER2–based regimens) or HER2-low and HER2-ultra-low MBC (received prior systemic therapy or endocrine therapy in the metastatic setting)	HER2	Enzyme-cleavable	TOP1i	8	11	[127-129]
	Trastuzumab emtansine	Genentech	HER2-positive MBC (received trastuzumab and/or a taxane)	HER2	Noncleavable	DM1	3.5	6	[144]
	Sacituzumab govitecan	Gilead	HER2-negative MBC (received prior systemic therapy)	TROP2	Cleavable	TOP1i	7.6	5	[140,141]
Phase III	Trastuzumab duocarmazine	Byondis	HER2-positive unresectable, locally advanced, or MBC (progressed after prior anti-HER2 therapy)	HER2	Cleavable	DNA alkylating	2.8	78	[145]
	Anvatabart opadotin	Johnson & Johnson	HER2-positive MBC (resistant or refractory to prior anti-HER2 therapy)	HER2	Noncleavable	PEG4-aminooxy-MMAF	2	75	[146]
Phase I/II	SYS6002	Corbus Pharmaceuticals	MTNBC	Nectin-4	Cleavable	MMAE	2	66	[147]

Abbreviations: ADCs, antibody-drug conjugates; DAR, drug to antibody ratio; FDA, US Food and Drug Administration; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; MBC, metastatic breast cancer; MMAE, monomethyl auristatin E; MMAF, monomethyl auristatin F; MTNBC, metastatic triple-negative breast cancer; OAE, ocular adverse events; TROP2, humanized trophoblast cell-surface antigen 2.

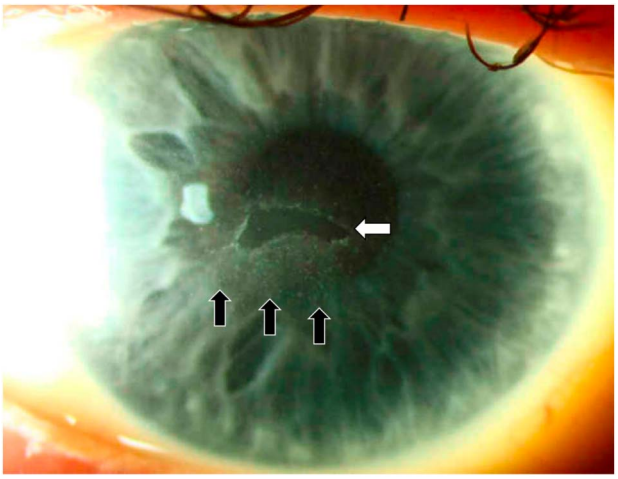

FIG 2. Slit-lamp photograph of the right eye of a patient on CRB-701, an ADC targeting nectin-4 that is currently in phase I clinical trial, with OAEs including numerous paracentral corneal pseudomicrocysts (black arrows) and a central corneal epithelial defect (white arrow). ADC, antibody-drug conjugate; OAEs, ocular adverse events.

then migrate centrally causing a refractive shift leading to blurry vision.[151] Corneal changes are reversible and typically resolve within weeks to months (2-32 weeks) after the cessation of treatment.[151-156] However, corneal pseudomicrocysts may quickly reappear if ADC treatment resumes.[157] Currently, the only effective strategy for mitigating corneal pseudomicrocysts are delays, reductions, or discontinuations of ADC therapy.[149,158-161] One study found that 72% of patients taking belantamab mafodotin (Blenrep), an ADC for multiple myeloma which was withdrawn from the market in 2022, developed corneal pseudomicrocysts, necessitating dose delays, reductions, and discontinuations in 47%, 27%, and 3% of patients, respectively.[148,152]

Current Strategies for Mitigating ADC-Induced OAEs

The current standard for the mitigation and prevention of ADC-associated OAEs include preservative-free artificial tears (PFATs), vasoconstrictors, and topical steroid eye drops.[134] However, the success of each intervention varies and needs further investigation. Matulonis et al[162] found that the rate of OAEs in patients receiving mirvetuximab soravtansine, an ADC used for ovarian cancer, reduced from 41% to 30% in patients receiving topical steroid eye drops (4-6×/daily for 10 days after infusion). Another study from Corbelli et al[163] found that a group of patients receiving mirvetuximab soravtansine had complete clearance of corneal pseudomicrocysts after 4-6 weeks of topical steroid eye drops and PFATs. Studies of belantamab mafodotin found that a combination of topical steroid eye drops and PFATs administered 4×/daily for 4-7 days starting the day before infusions had no preventative effect on OAEs.[152,161,164] An ocular substudy of tisotumab vedotin, an ADC used for cervical cancer, found that topical steroid eye drops (1 day before infusion and 3×/daily for 3 days after infusion), vasoconstrictor eye drops (brimonidine 0.2% 3 × 10 minutes before infusion), PFATs (as needed), and cold eye masks during infusions reduced the rate of OAEs from 80% to 60%.[165] Further research on the prophylactic capacity of PFATs, vasoconstrictors, and topical steroid eye drops with other ADCs is needed.

Alternative prophylactic therapies have been implemented in various case reports, animal studies, and cell lines. In one case report, a patient with breast cancer who developed corneal pseudomicrocysts while on trastuzumab emtansine (T-DM1) showed no progression in corneal pseudomicrocysts over 14 months of ADC treatment after initiating 20% autologous serum tears.[166] Loberg et al[167] investigated the efficacy of administering the mAb component of an ADC topically or systemically before ADC treatment in nonhuman primates along with the preventative efficacy of topical antioxidants, anti-inflammatories, and vasoconstrictors. Neither the mAb nor the preventative therapies successfully mitigated OAEs. Warbington et al[168] found that topical vasoconstrictor eye drops (brimonidine 0.2% 3×/daily) delayed the onset and severity of corneal pseudomicrocysts in rabbits treated with mirvetuximab soravtansine. In human corneal epithelial cells (HCECs), Klienman et al[169] reported that a positively charged polymer, poly(l-lysine)-graft-poly(ethylene glycol) (PLL-g-PEG), successfully inhibited ADC uptake. PLL-g-PEG is hypothesized to prevent the ADC internalization via electrostatic interference. Several studies have investigated inhibiting macropinocytosis, a type of nonspecific endocytosis known as cell drinking, as a potential mechanism for ADC-induced corneal pseudomicrocysts. The gold-standard pharmaceutical macropinocytosis inhibitor, 5-(N-ethyl-N-isopropyl) amiloride, reduced ADC uptake and increased cell viability after ADC administration in HCECs.[169-171] Additionally, Zhao et al[170] found that decreasing positively charged residues, conjugating negatively charged residues, or conjugating PEG (decreasing hydrophobicity) to ADCs reduced macropinocytosis and cytotoxicity in HCECs.

Future Directions for ADC-Induced OAEs

The screening, classification, and prevention of ADC-induced OAEs are areas ripe for innovation. Current screening eye examinations are performed in the eye clinic, which may take significant time to schedule and cause delays in cancer therapy. Portable screening eye examinations in the oncology clinic may reduce wait times and improve accessibility to care for patients with cancer. Currently, the only effective treatment for ADC-induced OAEs is dose modification. Thus, effective communication between eye care providers and oncologists is crucial to safely administer ADCs. However, the ocular CTCAE has major limitations, including ambiguous terms, mixed signs and symptoms, no representative clinical images, and no oncology drug dose modification recommendations. New consensus OAE grading scales have been developed that use clear anatomic

terms, separate signs and symptoms, include representative clinical images, and provide oncology drug dose modification recommendations. Further investigation into macropinocytosis inhibition and ADC structural changes, including altering the charge and hydrophobicity, are under investigation for preventing ADC-induced OAEs.

CV TOXICITY OF NOVEL BREAST CANCER THERAPIES

Anthracycline-based chemotherapy has been an essential component of breast cancer therapy for several decades but is associated with an increased risk of cardiotoxicity, which manifests clinically as heart failure or drops in left ventricular (LV) ejection fraction (LVEF) with a reported incidence of 4%-36%.[172] Although the use of anthracyclines in North America has diminished over the last several years, they still play an important role in the treatment of high-risk triple-negative and HR+, lymph node–positive breast cancer. HER2-targeted therapies have led to improvements in clinical outcomes in patients with early and advanced HER2+ disease but are associated with an increased risk of cardiotoxicity (heart failure in up to 3.9%).[173,174] Dual HER2-targeted therapy (pertuzumab/trastuzumab) is now standard of care for patients with high-risk HER2+ early and advanced disease. Although there does not appear to be an increased risk of cardiotoxicity with dual HER2 blockade, a recent meta-analysis reported an almost 2-fold increased risk of cardiotoxicity in individuals treated with this approach.[175,176]

Antibody-Drug Conjugates

ADCs are now being incorporated into the breast oncology treatment paradigm regardless of subtype. With high drug-to-antibody ratios, novel targets, and bystander effect, the possible impact of these drugs on CV toxicity is unclear. Within landmark DESTINY-Breast studies (01, 03, 04, 06, 12), the incidence of T-DXd–associated LVEF decrease was reported between 1.6% and 11.8% (DB-01, 1.6%; DB-03, 2.3%; DB-04, 4.6%; DB-06, 8.1%; DB-12, 10.8%-11.8%).[127-129,177,178] T-DM1 demonstrated a low incidence of grade 3 or worse cardiac dysfunction (< 1%) when compared with lapatinib/capecitabine in the EMILIA trial.[179] For patients with HR+, HER2− MBC, Dato-DXd may be a reasonable option when patients are otherwise limited by cardiotoxicity. Understanding the impact of sequencing of ADCs on CV toxicity will be better elucidated in the ongoing TRADE-DXd study. ASCENT, TROPICS-02, and TROPION-Breast01, which demonstrated the benefit of SG and Dato-DXd, did not report any associated cardiac events, although patients with significant CV disease were excluded.[140-142] Lack of data in the real-world setting may underestimate the incidence of CV toxicity in patients with comorbidities and underlying cardiac disease. The evolution of ADCs will continue to include varying chemotherapy payloads, linkers, and targets. It will be essential to understand the CV toxicity of these drugs because they are adopted into clinical practice.

HER-2 Tyrosine Kinase Inhibitors

Several oral HER2-targeted tyrosine kinase inhibitors (TKIs) are approved for patients with HER2+ breast cancer including lapatinib, neratinib, and tucatinib. Neratinib is a pan-inhibitor, lapatinib targets HER1 and HER2, and tucatinib, the most selective, targets HER2 specifically. Lapatinib has been associated with an increased risk of cardiac events including decreased LVEF and corrected QT (QTc) prolongation requiring cardiac monitoring and dose modifications. The proposed mechanism may be secondary to AMPK pathway activation, which inhibits TNF-alpha–induced cardiomyocyte cell death.[180]

The use of adjuvant neratinib on the basis of the EXTENET study has not been associated with an increase in CV toxicity, although patients with clinically significant cardiac morbidities were excluded.[181] Similarly in the NALA trial, neratinib was compared with lapatinib, both in combination with capecitabine, and no significant cardiotoxicity concerns were noted.[182] Neratinib targets an additional receptor, HER4, and both HER2 and HER4 are expressed on cardiomyocytes. The activation of HER2/HER4 heterodimers may be essential in maintaining ventricular structure, function, and overall cell survival.

In the HER2CLIMB study of tucatanib versus placebo in combination with trastuzumab and capecitabine in patients who had received prior trastuzumab and T-DM1, there was a significant improvement in PFS, including in patients with active brain metastases.[183] The incidence of all-grade and grade >3 treatment-related adverse events was similar between arms with respect to LVEF reduction and QTc prolongation.[183] The ongoing COMPASS trial will assess the potential benefit of adjuvant tucatinib in combination with T-DM1 for high-risk patients; cardiotoxicity safety will be reported. For patients who develop cardiotoxicity on HER2-targeted therapy, the safety of continued treatment remains unclear.[184] SCHOLAR-2, a prospective randomized trial, will evaluate whether it is safe to continue trastuzumab, pertuzumab, or T-DM1 in patients with early-stage HER2+ breast cancer who develop mild, minimally symptomatic or asymptomatic systolic left ventricular (LV) dysfunction (ClinicalTrials.gov identifier: NCT04680442).

CDK4/6 Inhibitors

The combination of CDK4/6 inhibitors (palbociclib, ribociclib, and abemaciclib) and endocrine therapy are standard of care for patients with HR+/HER2− MBC. Although all CDK 4/6 inhibitors are associated with neutropenia, ribociclib has an FDA warning for QT prolongation which could lead to significant arrhythmias including Torsade de Pointes. In the pivotal MONALEESA trials, which led to approval of ribociclib in MBC, QT prolongation was observed in 7% of patients treated with ribociclib and ET versus 2% with ET alone.[73] Within the MONALEESA-7 trial in premenopausal women with MBC, there was a higher rate of QT prolongation

in patients prescribed ribociclib and tamoxifen (also QT-prolonging); thus, this combination is not recommended.[185]

Patients starting ribociclib are required to have a baseline and mid-cycle electrocardiogram because QT prolongation usually occurs within the first 30 days of treatment. The European Society of Cardiology (ESC) Cardio-Oncology guidelines currently recommend calculation of QTc using the Fredericia formula because of variability in heart rate of patients with cancer. Although monitoring is not required per package insert for abemaciclib and palbociclib, it is recommended to consider in patients with higher risk factors per the ESC Cardio-Oncology guidelines.[186] Supportive care drugs (eg, antiemetics, antibiotics), non–cancer-related medications (eg, for hypertension), and electrolyte abnormalities (eg, hypokalemia) may also prolong the QT interval. Pharmacovigilance and close collaboration with an oncology pharmacist is essential to avoid significant DDIs that increase the risk of significant QT prolongation. Patient education regarding DDIs should be a part of prescribing practices to avoid potential arrhythmias.

Immune Checkpoint Inhibitors

ICIs have revolutionized our approach to cancer treatment. Pembrolizumab in combination with chemotherapy has led to significant improvements in PFS in individuals with PD-L1–positive, metastatic TNBC (KEYNOTE-355) and pathologic complete response (pCR) rates and OS in those with high-risk early-stage TNBC (KEYNOTE-522).[187,188] Recent studies have also demonstrated improved pCR rates, with the addition of ICIs to neoadjuvant chemotherapy, in patients with early-stage HR+ breast cancer (CM7FL, KN756).[189,190] ICIs are associated with a robust host response which can lead to several irAE including the CV system. Although myocarditis is considered a rare irAE (1%-2%) and is more commonly associated with combination ICI therapy, the fatality rate is high (30%-50%), necessitating prompt intervention, often with high-dose steroids.[186] Other CV irAEs include pericarditis (2%), cardiac arrhythmias (4%), pericardial effusion (2%), myocardial infarction (2%), and rarely, heart failure (<1%). Early identification and treatment of CV irAEs requires a multidisciplinary approach. Rechallenging patients with ICIs after a diagnosis of myocarditis requires a multidisciplinary discussion and is generally not recommended.

Oral SERD

The development of oral SERDs has offered a more efficacious and bioavailable alternative to fulvestrant; however, some drugs within this class have shown concern for associated cardiotoxicity. Camizestrant had a reported bradycardia rate of 24.7% and grade 1 to 2 QTc prolongation within SERENA-2 at a 150 mg once daily dose although bradycardia was not demonstrated with a 75 mg once daily dose.[96] Additionally, giradestrant also showed asymptomatic grade 1 to 2 sinus bradycardia in 7% of patients at a dose >100 mg.[191] It is unclear what the associated cardiotoxicity may be with novel combinations that is, CDK4/6 inhibitors, PI3K inhibitors, AKT inhibitors with the potential for additive toxicity, reinforcing the need for awareness of potential cardiotoxicity.

TABLE 4. Breast Cancer Therapies and Associated Cardiotoxicity

Agent	Associated Cardiotoxicity	Frequency
ADCs		
T-DXd	Cardiomyopathy Decreased LVEF	Uncommon—common
T-DM1	Cardiomyopathy Reported drops in ejection fraction (EF)	Uncommon
SG	None	Rare
Dato-DXd	None	Rare
HER2 TKIs		
Tucatinib	None	Rare
Neratinib	None	Rare
Lapatinib	Decreased LVEF QTc prolongation	Uncommon
CDK4/6 inhibitors		
Ribociclib	QTc prolongation	Common
Abemaciclib	None	Rare
Palbociclib	None	Rare
Oral SERDs		
Camizestrant	Bradycardia	Common (dose-dependent)
Giradestrant	Bradycardia	Uncommon (dose-dependent)
ICIs		
Pembrolizumab	Myocarditis, pericarditis	Uncommon (fatal)

NOTE. Rare: not reported within clinical trials. Uncommon: reported within clinical trials but ≤5%. Common: reported within clinical trials >5%.

Abbreviations: ADCs, antibody-drug conjugates; CDK4/6, cyclin-dependent kinase 4 and 6; Dato-DXd, datopotamab deruxtecan; HER2, human epidermal growth factor receptor 2; ICIs, immune checkpoint inhibitors; LVEF, left ventricular ejection fraction; QTc, corrected QT; SERDs, selective estrogen receptor degraders; SG, sacituzumab govitecan; T-DM1, trastuzumab emtansine; TKIs, tyrosine kinase inhibitors; T-DXd, trastuzumab deruxtecan.

CV toxicity has traditionally been associated with anthracycline-based chemotherapy and HER2-targeted agents manifesting as LV dysfunction or heart failure. However, novel breast cancer therapies including ADCs, HER2 TKIs, CDK4/6 inhibitors, ICIs, and oral SERDs are also associated with an increased risk of CV toxicity including LV dysfunction, heart failure, QTc prolongation, myocarditis, and bradycardia. Table 4 summarizes the cardiotoxicity and associated prevalence of these novel breast cancer therapies. As novel combinations of these drugs are currently being explored, additional monitoring and awareness will be essential and necessitate a multidisciplinary approach to patient care.

CONCLUSION

Although the introduction of novel and emerging therapies in breast cancer has improved breast cancer outcomes, side effects of these agents must be reviewed and properly considered before treatment initiation. A comprehensive approach to mitigating side effects includes prevention strategies, close monitoring, and tailored pharmacologic and nonpharmacologic interventions. Clear communication with patients and health care providers is essential for early recognition and management of symptoms. Proactive symptom screening strategies, such as electronic patient-reported outcomes, can also help detect early symptom changes and prompt direct contact with the provider team leading to improved symptom management.[192-200] In the era of rapid development of novel therapies and combination strategies in breast cancer, increased awareness and proper management of adverse events is critical to preserve health-related quality of life and improve treatment outcomes.

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