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Breast Cancer

Endocrine Therapy in Premenopausal Hormone Receptor Positive/Human Epidermal Growth Receptor 2 Negative Metastatic Breast Cancer: Between Guidelines and Literature

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Disclosures of potential conflicts of interest may be found at the end of this article.

Key Words. Metastatic breast cancer • Hormone receptor positive • Premenopausal • Endocrine therapy

Abstract

There is growing interest in the endocrine treatment (ET) of premenopausal women with hormone receptor positive (HR+) metastatic breast cancer (MBC). This review summarizes available data on endocrine therapy for this patient subset and aims to define the most appropriate treatment approach. The combination of luteinizing hormone-releasing hormone (LHRH) agonists plus tamoxifen seems effective and safe and is considered as being superior to either approach alone; still, single-agent therapy remains an acceptable treatment option. Due to their mechanism of action, aromatase inhibitors alone are not suitable for the treatment of premenopausal patients, but the combination with LHRH agonists may result in excellent disease control. Fulvestrant, in conjunction with LHRH agonists, also yields interesting results regarding clinical benefit rate and time to progression; currently, other orally available selective estrogen receptor downregulators are under clinical evaluation. Recently, targeted drugs have been added to ET in order to reverse endocrine resistance, but only limited information regarding their activity in premenopausal patients is available. The cyclin dependent kinase 4 and 6 inhibitor palbociclib when combined with fulvestrant and LHRH agonists was shown to prolong progression-free survival over endocrine therapy alone in pretreated patients; similar results were obtained with the addition of abemacicilib or ribociclib to endocrine therapy. Currently, activity of the mammalian target of rapamycin inhibitor everolimus in combination with letrozole and goserelin is under assessment in premenopausal patients after progression on tamoxifen (MIRACLE trial). ***The Oncologist*** 2018;23:974–981

Implications for Practice: This review provides clinicians with an overview on the available data regarding endocrine treatment of hormone receptor positive (HR+) metastatic breast cancer (MBC) in premenopausal women and summarizes the treatment options available in routine clinical practice. Knowledge of an up-to-date therapeutic approach in women with premenopausal HR+ MBC will lead to better disease management, thereby improving disease control and quality of life while minimizing side effects.

Introduction

During the past 30 years, the incidence of metastatic breast cancer (MBC) in women aged 25–39 years has slightly increased from 1.53 (95% confidence interval [CI] 1.01–22.1) per 100,000 in 1976 to 1.9 (95% CI 2.31–3.59) per 100,000 in 2009 [1], increasing the interest in appropriate treatment strategies for this specific patient subset. In general, BC arising in young patients is characterized by a more aggressive phenotype [2], and several studies underline that young age is an independent predictor of adverse outcome [3, 4]; indeed, women diagnosed below the age of 40 are more likely to develop metastatic disease and die from BC [3, 5, 6]. As endogenous estrogens are clearly involved in BC development and progression [6], endocrine therapy (ET) remains the main pillar of systemic treatment [7]. Despite these facts, young MBC patients are underrepresented in endocrine therapy trials, and up to now, no comprehensive update review exists. Therefore, this overview aims to analyze the available data on ET in premenopausal women with hormone receptor positive (HR+) MBC and indicates potential future directions of research.

Endocrine Therapy for Metastatic Breast Cancer

In postmenopausal HR+/human epidermal growth receptor 2 (HER2) negative MBC, endocrine therapy is considered the treatment of choice, and this consideration applies for premenopausal patients as well. Clinical practice guidelines outline appropriate methods of treatment and care and address specific clinical situations [8–10]. Here, we summarize available evidence with regard to ET specifically in premenopausal

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patients. A potential treatment algorithm is provided in Figure 1.

Ovarian Ablation: Surgical Versus Medical Therapy

In premenopausal women, the ovaries are the predominant source of estrogen; oophorectomy has been suggested as the first systemic therapy for BC and has been used for over a century [11]. It promptly reduces circulating estrogens but causes permanent fertility loss and requires hospitalization. Oophorectomy and ovarian irradiation have been considered equally effective, with overall response rate (ORR) ranging from 30% [12, 13] to 79% [14, 15]. Reversible medical ovarian function suppression (OFS) can be accomplished via the administration of luteinizing hormone-releasing hormone (LHRH) agonists. The characterization of gonadotropin-releasing hormone in 1971 allowed for the development of synthetic LHRH analogues [16]. Chronic administration of these substances causes permanent internalization of pituitary LHRH receptors, rendering gonadotropic cells refractory to endogenous LHRH. Depot formulations of LHRH agonists showed similar effects with no difference in adverse events while allowing for a less frequent administration [17, 18]. In 1993, the monthly formulation of goserelin received U.S. Food and Drug Administration approval, although the 3-monthly formulation was approved for use in prostate cancer patients only, as insufficient data are available to support its use in BC. In line, current guidelines suggest caution as the suppression of estrogen production may be incomplete. A recent open-label, randomized phase III study, however, comparing a 3-monthly with monthly administration of goserelin in premenopausal women with HR+ MBC, observed similar pharmacodynamics and safety profiles with comparable suppression of estrogen levels [19]. Regarding the different available LHRH agonists, similar ORRs were seen: goserelin (31%) [20], buserelin (14%–42%) [21–23], leuprolide (34%–44%) [24, 25], and triptorelin (45%–70%) [26, 27].

Two trials compared goserelin with oophorectomy (or irradiation), both reporting no differences in terms of overall survival (OS; Table 1) [28, 32]. Nowadays, oophorectomy can be performed via laparoscopy with a relatively low complication rate (0%–6%) [33], is cost-effective [34], and can guarantee a good quality of life with a side-effect rate that seems to be not higher than with the use of LHRH analogues [35, 36]. Therefore, surgical castration should be considered as an alternative method of ovarian suppression, and the choice between the available options should be carefully taken considering patients' preferences.

Tamoxifen

Tamoxifen is a selective estrogen receptor (ER) modulator with an agonistic effect in certain tissue such as bone, liver, and the cardiovascular system and an antagonistic effect on other sites such as uterus and breast. Initially developed in the 1960s, it has been used as first-line therapy in MBC since the 1970s and was shown to harbor significant activity in premenopausal women [37–41]. Only two small trials have compared the efficacy of surgical castration with tamoxifen [38, 39]. In the trial by Ingle et al., treatment responses were seen in 37% of patients treated with oophorectomy and in 27% of patients receiving tamoxifen (10 mg twice daily); this difference was not statistically significant. In addition, progression-free survival (PFS) and OS did not differ between the two treatment arms

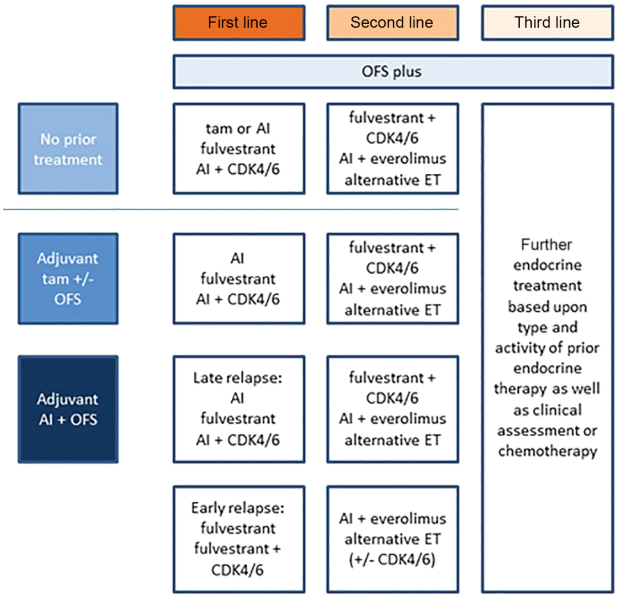

Figure 1. Endocrine therapy for premenopausal women with hormone receptor positive metastatic breast cancer.
Abbreviations: AI, aromatase inhibitor; ET, endocrine treatment; OFS, ovarian function suppression; tam, tamoxifen.

[40]. In the trial by Buchanan et al., a higher dose of tamoxifen was used (20 mg twice daily); again, no significant differences in terms of ORR (21% vs. 24%) or OS were observed [38].

In order to test the hypothesis of providing complete estrogen blockade by combining tamoxifen with LHRH agonists, one study randomized 318 pre- and perimenopausal patients to goserelin with or without tamoxifen [28]. Similar ORRs (38% vs. 31%) were obtained, whereas a modest benefit in terms of median time to progression (TTP) in favor of the combination arm was observed (28 vs. 23 weeks; $p = .03$); median OS, however, was comparable between the groups. In another study by Klijn et al., the combination of buserelin and tamoxifen in premenopausal patients with MBC was compared with the sequence of upfront LHRH agonist therapy followed by tamoxifen or tamoxifen followed by buserelin [29]. Here, the combination demonstrated superiority in terms of ORR (48% vs. 34% vs. 28%, $p = .031$), median PFS (PFS 9.7 vs. 6.3 vs. 5.6 years, $p = .03$), and OS (3.7 vs. 2.5 vs. 2.9 years, $p = .01$). Moreover, in the combination arm, the tamoxifen-stimulated pituitary-ovarian axis was completely suppressed. In a meta-analysis [42] of four randomized trials ($n = 506$), the combination of tamoxifen and an LHRH agonist improved OS (hazard ratio = 0.70, 95% CI 0.58–0.85, test for heterogeneity $p = .5$), PFS (hazard ratio = 0.78, 95% CI 0.63–0.96, test for heterogeneity $p = .08$), and ORR compared with OFS alone. Still, some concerns have to be mentioned: The number of patients included was small; HR status was confirmed in 62% of patients only; patients had received different types of prior adjuvant chemo- and endocrine therapy; localization of metastatic disease was heterogeneous; no formal cross over to tamoxifen as second-line therapy existed in patients treated with LHRH agonists alone; and no toxicity and quality-of-life data were reported. Despite these limitations, the combination of tamoxifen and LHRH agonists may be considered the standard approach, with single-agent therapy remaining an acceptable treatment option.

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Table 1. Clinical trials including premenopausal breast cancer patients treated with LHRH and tamoxifen

Study (year) [reference]	Patients, *n*		Median age, years (range)	Treatment regimen	OS, years	ORR, % (CR + PR)	TTP, months	Adjuvant treatment	
	Total	For arm						ET, %	CT, %
International trial (1988) [28]	318	159	41 (24–55)	LHRH agonist (Gos)	2.6	31	5.7	4	52
		159	42 (28–55)	LHRH agonist (Gos) + TAM	2.9	38	7	4	39
EORTC trial (1988) [29]	161	54	42 (24–51)	TAM	2.9	28	5.6	0	30
		54	43 (28–58)	LHRH agonist (Bus)	2.5	34	6.3	6	36
		53	43 (31–50)	LHRH agonist (Bus) + TAM	3.7	48	9.7	2	29
Italian trial (1988) [30]	85	18	47 (35–53)	Oophorectomy	3.1	46.6	NS	44.5	0
		24	41 (35–53)	LHRH agonist (Gos)	3	27.2	NS	50	0
		19	47 (30–54)	Oophorectomy + TAM	3.1	11.1	NS	47.4	0
		24	44 (32–56)	LHRH agonist (Gos) + TAM	3	45	NS	80.2	0
Japanese trial (1994) [NP]	33	19	45 (32–51)	LHRH agonist (Gos)	NS	NS	NS	55	55
		14		LHRH agonist (Gos) + TAM	NS	NS	NS		
ITMO trial (1995) [31]	64	NS	43 (29–52)	LHRH agonist (Gos) + TAM	NS	41	3.2	0	32

Abbreviations: Bus, buserelin; CR, complete response; CT, chemotherapy; EORTC, European Organization for Research and Treatment of Cancer; ET, endocrine therapy; Gos, goserelin; ITMO, Italian Trials in Medical Oncology; LHRH, luteinizing hormone-releasing hormone; NS, not specified; NP, unpublished; ORR, overall response rate; OS, overall survival; PR, partial remission; TAM, tamoxifen; TTP, time to progression.

Aromatase Inhibitors

Although the current treatment algorithm in early-stage BC in premenopausal women is changing, many patients still receive tamoxifen with or without an LHRH agonist in the adjuvant setting, and a different endocrine therapy would be preferred for metastatic disease. Aromatase, a cytochrome P-450-dependent enzyme responsible for the conversion of adrenal androgen substrates to estrogens, is the unique source of estrogen after cessation of ovarian estrogen production; in postmenopausal women, the superiority of aromatase inhibitors (AIs) over tamoxifen as endocrine therapy for MBC has been established [43, 44]. In premenopausal patients, AIs must be used in combination with OFS, as otherwise, ovarian estrogen production remains unaffected. Limited data on first-generation AIs in premenopausal women with HR+ MBC are available with single-agent aminoglutethimide yielding a complete response (CR) or partial remission (PR) in 27.8% of patients. Of note, a CR was also observed in an HR-negative patient; therefore, these data need to be interpreted with due caution [45]. Further development of AIs in premenopausal patients occurred in combination with LHRH agonists due to the observation that LH and follicle-stimulating hormone levels may rise in patients treated with AIs alone [46]. Supporting this combination approach, two studies [46, 47] of formestane (a second-generation AI) plus an LHRH agonist reported a significant reduction of median estradiol levels compared with an LHRH agonist alone. Several phase II trials investigated the combination of third-generation AIs with LHRH agonists (Table 2). Based upon available data, such combinations are a viable treatment option even after tamoxifen failure. Still, the level of evidence supporting the use of AIs in premenopausal MBC patients remains lower as compared with early-stage disease [55, 57].

Selective Estrogen Receptor Downregulators

Fulvestrant is a first-generation selective estrogen receptor downregulator (SERD) that competitively binds to ER with greater affinity than tamoxifen and acts by downregulating ER and progesterone receptor (PgR). Therefore, in theory, it could be used as single agent in premenopausal patients. Despite this, several preclinical data suggested that fulvestrant worked better in the presence of a low-estrogen environment [58]. In postmenopausal patients, fulvestrant 250 mg and AIs have shown comparable efficacy as second-line treatment [59–62]. The first-line CONFIRM trial randomized postmenopausal MBC patients to fulvestrant 500 mg versus 250 mg, with longer PFS and OS observed with the high-dose, loading-dose regimen [63]. In premenopausal women, a single preoperative dose of fulvestrant 250 mg did not significantly alter the levels of ER, PgR, and Ki67; in contrast, fulvestrant 750 mg produced a significant change in the same markers. These observations led to the hypothesis that a higher dose of fulvestrant or a combination with LHRH agonists is required in premenopausal women in order to achieve an adequate estrogen blockade. The study by Bartsch et al. [64] therefore evaluated the combination of fulvestrant 250 mg plus goserelin in 26 premenopausal as first- to fourth-line ET in premenopausal MBC patients. This regimen

Table 2. Clinical trials with the combination of LHRH and aromatase inhibitor

Study (year) [reference]	Patients, *n*	Median age, years (range)	Treatment regimen	ORR, % (CR + PR)	CB, % (CR + PR + SD)	TTP, months	First-line ET, %
Forward et al. (2004) [48]	16	44 (32–52)	LHRH agonist (Gos) + AI (AZ)	6.2	75	NR	LHRH agonist (Gos) + TAM
Roche et al. (2009) [49]	33	44 (38–60)	LHRH agonist (Gos) + AI (LZ)	55	64	13	Adjuvant estrogens treatment (6%)
Cheung et al. (2010) [50]	36	44 (30–59)	LHRH agonist (Gos) + AI (AZ)	36	67	12	NR
	13	43 (33–54)	LHRH agonist (Gos) + EXE	NR	38	NR	LHRH agonist (Gos) + AI (AZ)
Carlson et al. (2010) [51]	35	43 (28–51)	LHRH agonist (Gos) + AI (AZ)	37	72	8.3	Adjuvant estrogens treatment (9%)
Park et al. (2010) [52]	35	41 (32–52)	LHRH agonist (Gos) + AI (LZ)	46	77	9.5	Adjuvant estrogens treatment (60%)
Yao et al. (2010) [53]	52	40 (29–49)	LHRH agonist (Gos) + AI (LZ)	21	71	10	LHRH agonist (Gos) + AI (LZ) First line: 69.2% Second line: 30.8% TAM 26.9%
Nishimura et al. (2012) [54]	37	43 (33–53)	LHRH agonist (Gos) + AI (LZ)	19	62	7.2	LHRH agonist (Gos) + TAM

Abbreviations: AI, aromatase inhibitor; AZ, anastrozole; CB, clinical benefit; CR, complete response; ET, endocrine therapy; EXE, exemestane; Gos, goserelin; LHRH, luteinizing hormone-releasing hormone; LZ, letrozole, NR, not reported; ORR, overall response rate; PR, partial remission; SD, stable disease; TAM, tamoxifen; TTP, time to progression.

yielded a CR in 1 patient, PR in 3 patients, and stable disease (>6 months) in 11 patients, resulting in a promising clinical benefit rate (CBR) (57.7%) and ORR (15.4%); median TTP was 6 months. Although limited by its nonrandomized design, long accrual period, low number of patients, and a suboptimal dose of fulvestrant (250 mg) as well as by the heterogeneous study population, these results are encouraging. Recently, the control arm of the PALOMA 3 trial obtained a comparable median PFS of 5.6 months with fulvestrant 500 mg plus goserelin in premenopausal patients who had progressed on prior ET.

Obviously, the dose of fulvestrant is one of the key points: The phase II FIRST trial indicated superior activity of fulvestrant 500 mg over anastrozole in terms of TTP in postmenopausal patients [65]. In the phase III FALCON trial, PFS was significantly longer in the fulvestrant 500 mg arm compared with the anastrozole arm. The only available data regarding high-dose fulvestrant in premenopausal patients with MBC were derived from the aforementioned PALOMA 3 study. In summary, these results suggested that the combination of fulvestrant 500 mg plus goserelin is a reasonable treatment approach in premenopausal women. Recently, the KCSG BR10-04 study showed that premenopausal patients with advanced BC treated with fulvestrant plus goserelin had an increased PFS (hazard ratio = 0.61, 95% CI 0.370–0.998, $p = .049$) but not OS compared with goserelin alone, especially in patients younger than 40 years (hazard ratio = 0.41, 95% CI 0.181–0.936, $p = .034$). No difference was observed in terms of PFS and OS when anastrozole was added to goserelin compared with goserelin alone [66].

Different combinations of ET were also assessed. The FACT trial showed no benefit for the combination of fulvestrant and anastrozole as first-line treatment in post- and premenopausal women, the latter receiving a combination with LHRH agonists [67]. In contrast, in the SWOG 0226 study, an improvement in terms of TTP (13.5 vs. 15 months) and OS (41.3 vs. 47.7 months) was obtained when fulvestrant 250 mg was added to anastrozole [68]; of note, this effect was mainly driven by endocrine-naïve patients. Finally, in the SoFEA study, the combination of fulvestrant 250 mg with anastrozole compared with fulvestrant plus placebo or exemestane alone yielded comparable results in terms of PFS and OS [69]. Therefore, the combination of fulvestrant with AIs is currently not considered as treatment standard.

Despite the considerable activity of fulvestrant, there is evidence to suggest that even at the 500 mg dose, suboptimal occupancy of the ER may occur in some patients, which may correlate with rapid disease progression [70]. These data, combined with the intramuscular route of administration, underscore the need for novel SERDs. Recently, data on Elacestrant were published; this orally available SERD exhibited significant antitumor activity both as a single agent and in combination with palbociclib or everolimus in patient-derived BC xenograft models [71]; therefore, further investigation of this compound is warranted.

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Combinations and New Directions: mTOR, CDK4/6, and PI3KCA Inhibitors

Signal transduction inhibitors have been added to ET in order to overcome endocrine resistance. The mammalian target of

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rapamycin (mTOR) is a signaling kinase in the PI3K/mTOR/akt-pathway that mediates cell growth and metabolism; it is commonly dysregulated in BC. In the BOLERO-2 trial, postmenopausal women with HR+ MBC progressing after or on therapy with AIs were randomized to exemestane plus everolimus or placebo; a clinically relevant PFS prolongation (7.8 vs. 3.2 months) and a higher ORR was observed in the everolimus group [72, 73]. Currently, the ongoing MIRACLE trial (NCT02313051) randomizes premenopausal HR+ MBC patients after progression on tamoxifen to receive goserelin plus letrozole with or without everolimus.

Cell proliferation requires the progression from the G1 phase to the S phase, which is regulated by the cyclin-dependent-kinases 4 and 6 (CDK4/CDK6). Palbociclib, an oral small molecule inhibitor of CDK4/CDK6, has shown relevant activity when combined with ET [74]. The phase II PALOMA-1/Trio-18 study randomized postmenopausal patients to letrozole plus palbociclib or letrozole alone as first-line treatment; the combination obtained significantly longer PFS and higher CBR in all subgroups, including patients who had previously received ET [75, 76]. The phase III PALOMA-2 study confirmed these results; both studies, however, were conducted in postmenopausal patients only. In contrast, the PALOMA-3 trial assessed the combination of fulvestrant with palbociclib or placebo in patients who had failed on previous endocrine treatment, including 108 premenopausal patients, who received additional goserelin. Of note, results in the premenopausal cohort were comparable to the overall population, with a clinically relevant improvement in median PFS (9.5 vs. 5.6 months) and CBR (69% vs. 44%) in favor of the palbociclib group [77, 78].

Similar to the results of PALOMA-2, the MonaLEEsa-2 trial established that the addition of the CDK4/6-inhibitor ribociclib to letrozole resulted in a significant prolongation of PFS in postmenopausal woman who had received no prior therapy for advanced HR+ BC [79]. The MonaLEEsa-7 trial is the first phase III trial investigating CDK4/6 inhibitor-based regimens as frontline treatment specifically for pre/perimenopausal women with advanced BC. The addition of ribociclib to tamoxifen/nonsteroidal AI (NSAI) and goserelin led to an increased PFS (median PFS 23.8 vs. 13.0, hazard ratio = 0.55, 95% CI 0.44–0.69, $p < .001$) and CBR (79.8% vs. 67.3%, $p < .001$) compared with placebo tamoxifen/NSAI and goserelin, with a manageable safety profile [80].

Finally, the MONARCH 2 study showed an improvement in PFS and ORR with a tolerable safety profile in women with HR+/HER2-negative MBC when the CDK4/6-inhibitor abemaciclib was added to fulvestrant. Importantly, results were independent from the menopausal status, and peri-/premenopausal patients received an LHRH agonist in addition [81].

Phosphatidylinositol 3-kinase (PI3K) pathway activation is a hallmark of endocrine-resistant HR+ MBC. The BELLE-2 trial demonstrated that the addition of the pan-class I PI3K inhibitor buparlisib to fulvestrant in postmenopausal patients with MBC whose disease had progressed on or after AI treatment improved PFS over ET alone; on the downside, a relevant increase of toxicity was observed as well. In a post hoc analysis, a greater effect of buparlisib was reported in patients harboring *PIK3CA* mutations [82]. The results of the BELLE-3 trial are consistent, but again, the clinical use of buparlisib appeared limited by its unfavorable toxicity profile [83]. Tolerability of α-isoform-specific PI3K inhibitors is apparently superior, and such drugs are currently under clinical investigation in the SOLAR 1 (alpelisib) [84] and SANDPIPER (taselisib) trials [85]. Data regarding the activity of PI3K inhibitors in premenopausal women are still lacking.

Discussion

The optimal endocrine treatment approach in premenopausal patients with MBC is still poorly defined. Current clinical guidelines recommend that patients with luminal disease should be treated preferentially with ET, whereas chemotherapy should be reserved for rapidly progressing, symptomatic or endocrine-resistant disease. Still, in many countries, chemotherapy is the preferred first-line option in younger patients [86]. Information regarding the efficacy of endocrine therapy in premenopausal patients is limited by the small number of patients enrolled into clinical trials, long accrual time, and lack of stratification for previous adjuvant therapy or for relevant prognostic factors; in addition, no information concerning postprogression treatment is available. The vast majority of trials evaluating novel endocrine treatment options included postmenopausal patients only. Therefore, no corresponding results are available for women who remain premenopausal.

Information regarding the efficacy of endocrine therapy in premenopausal patients is limited by the small number of patients enrolled into clinical trials, long accrual time, and lack of stratification for previous adjuvant therapy or for relevant prognostic factors; in addition, no information concerning postprogression treatment is available.

Given available data, the combination of LHRH agonists with tamoxifen is preferred compared with the use of either agent alone; oophorectomy is a valid alternative approach to LHRH agonists, especially in the metastatic setting, where fertility preservation might be less important for the patients. Moreover, it is the option of choice for those patients who would like to avoid monthly injections. Despite these considerations, it is of major importance to carefully discuss with each patient which approach to choose, considering the pros and cons of both methods and the patient's preference. The combination of AIs or fulvestrant with LHRH agonists harbors promising activity even after prior tamoxifen exposure. Furthermore, in premenopausal patients who have failed on previous endocrine treatment, palbociclib plus fulvestrant and goserelin was superior to endocrine treatment alone, and this effect was similar to the outcome in postmenopausal patients. Finally, ribociclib added to tamoxifen or NSAI and goserelin is a potential new treatment option for premenopausal patients not previously treated with ET for advanced disease. Therefore, current guidelines recommend starting OFS in order to induce menopause; thereafter, recommended treatment mirrors that of postmenopausal patients.

In summary, endocrine therapy should be considered a standard first-line treatment option for the majority of premenopausal patients with MBC because of its favorable

efficacy/safety balance as compared with chemotherapy. Several endocrine therapy options as well as combinations of endocrine therapy with targeted agents are available today, and treatment should be chosen considering risk factors, response to previous therapy, and patient preference.

Conclusion

Similar to options for postmenopausal patients, endocrine therapy is an active and safe treatment option with limited side effects in premenopausal women with HR+ MBC. Further data regarding the combination of endocrine treatment with novel targeted agents will help to define the best treatment strategy for this population. Currently, OFS with LHRH agonists or surgical castration is preferred, and patients should be treated according to recommendations for postmenopausal women.

Author Contributions

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Disclosures

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