Endocrine Treatment of Metastatic Breast Cancer

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Key Words

Advanced breast cancer · Hormons · Tamoxifen ·
Aromatase inhibitor · Fulvestrant

Summary

Endocrine treatment represents the first choice in the treatment of endocrine-responsive non-life-threatening advanced breast cancer. Hormone receptor expression can be ascertained either on the metastasis (if biopsy can be taken easily) or on the primary tumor. The selection of endocrine therapy takes into account the menopausal status of the patient, the type of previous adjuvant endocrine treatment, the disease-free interval and past medical history. In premenopausal patients, the combination of LHRH (luteinizing hormone-releasing hormone) agonists and a second endocrine treatment (tamoxifen, anastrozole, fulvestrant, progestagens) is more effective than the single agents. In postmenopausal patients with recurrent disease progressing after or during adjuvant tamoxifen, third-generation aromatase inhibitors (AIs) are the preferred first-line endocrine treatment. In second-line treatment, fulvestrant, a second AI or tamoxifen again are reasonable options. There is no cross-resistance between steroidal and non-steroidal anti-aromatase agents. Steroidal AIs (exemestane) have shown activity after failure of non-steroidal AIs (anastrozole, letrozole). Vice versa, patients receiving exemestane as first anti-aromatase agent may also benefit from letrozole or anastrozole after disease progression. Simultaneous endocrine and cytostatic therapy is not recommended because the combination induces increased toxicity and does not improve overall survival. Maintenance endocrine therapy following chemotherapy appears to improve relapse-free and overall survival.

Schlüsselwörter

Metastasierter Brustkrebs · Hormone · Tamoxifen ·
Aromatasehemmer · Fulvestrant

Zusammenfassung

Die endokrine Therapie ist die erste Therapieoption beim metastasierten/rezidierten hormonsensitiven Mammakarzinom mit nicht lebensbedrohlicher Erkrankungssituation. Die Bestimmung der Hormonrezeptorexpression kann – falls leicht erreichbar – an der Metastase bzw. dem Rezidiv erfolgen. Die Bestimmung am Primärtumor ist jedoch ausreichend. Bei der Wahl der endokrinen Therapie müssen Menopausestatus, Vorbehandlung, krankheitsfreies Intervall und andere Risikofaktoren berücksichtigt werden. Bei prämenopausalen Patientinnen ist die Kombination eines LHRH (luteinizing hormone-releasing hormone)-Agonisten kombiniert mit einer zweiten endokrinen Therapie (Tamoxifen, Anastrozol, Fulvestrant, Gestagene) effektiver als diese Therapien alleine. Bei postmenopausalen Patientinnen mit Krankheitsrückfall unter/nach adjuvanter Tamoxifen-Gabe stellen Aromatasehemmer der 3. Generation den ersten endokrinen Therapieschritt dar. Für die Zweitlinientherapie sind Fulvestrant, ein weiterer Aromatasehemmer oder abermals Tamoxifen eine Option. Zwischen steroidal (Exemestan) und nicht-steroidal (Anastrozol, Letrozol) besteht keine Kreuzresistenz, d. h. Exemestan ist nach Anastrozol und Letrozol wirksam bzw. umgekehrt. Eine simultane chemo-endokrine Therapie kann nicht empfohlen werden, da sie zu mehr Nebenwirkungen führt, ohne dass das Gesamtüberleben verlängert wird. Eine endokrine Erhaltungstherapie nach erfolgter Chemotherapie scheint das rezidivfreie und auch das Gesamtüberleben zu verbessern.

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Basics of Endocrine Treatment

Endocrine therapy remains the first choice and most important part in the treatment of hormone-sensitive non-life-threatening advanced breast cancer. This approach has the advantage of combining efficacy, minimal toxicity, and good quality of life. However, a requirement for a successful endocrine therapy is a positive estrogen receptor (ER) and/or progesterone receptor (PR) status, either of the metastasis (if biopsy of the metastasis is possible and manageable) or of the primary tumor. One needs to consider that endocrine treatment takes 8–12 weeks to reveal a tumor response. The selection of the most appropriate endocrine therapy takes into account the menopausal status of the patient, the type of previous adjuvant endocrine treatment, the disease-free interval and the past medical history (e.g. thromboembolic disease). A meta-analysis of non-randomized observational trials suggests that HER2-positive metastatic breast cancer is less responsive to any type of endocrine treatment [1]. This issue is currently being addressed by the ELECTRA Study evaluating prospectively the efficacy of the aromatase inhibitor (AI) letrozole in metastatic hormone receptor-positive HER2-positive or negative breast cancer.

Response to endocrine therapy increases with the amount of ER and PR receptor-positive cells. The effectiveness of endocrine treatment is measured by improvement of clinical symptoms and/or tumor response. Quantitative [¹⁸F]fluoroestradiol positron emission tomography (PET) or tumor markers can predict response to hormonal therapy and may help guide treatment selection [2]. Currently, there is no recommendation for routine use of PET or other diagnostic tools in monitoring endocrine therapy of advanced breast cancer. Patients responding to endocrine treatment should be treated until progression or occurrence of adverse effects. In the case of progression after long-lasting endocrine treatment, a further endocrine step is recommended. Early progress during endocrine treatment will usually require chemotherapy.

Drugs

All patients receiving endocrine treatment for advanced breast cancer will at some time progress, resulting in a need for new therapies that lack cross-resistance with existing agents. 3rd-generation aromatase agents are more effective than tamoxifen in the 1st-line treatment of patients with distant metastases. An overall survival benefit has not yet been demonstrated. Tamoxifen is superior to no endocrine therapy at all. Fulvestrant and toremifene are equivalent to tamoxifen in the first-line endocrine treatment of metastatic breast cancer [3]. There are several mechanisms of resistance that tumor cells can use to escape attempts to block their growth [4]. Enhancing the benefit of endocrine therapy by overcoming *de novo* or acquired resistance remains an important goal in sys-

Endocrine Therapy In Premenopausal Patients With Metastatic Breast Cancer		
	Oxford LOE / GR	AGO
➤ GnRH + tamoxifen (vs. OFS or Tam)	1a A	++
➤ Ovarian function suppression (OFS)	2b B	+
➤ Tamoxifen	2b B	+
➤ GnRH + anastrozole after GnRH + Tam	2b B	+
➤ Aromatase inhibitors without OFS	3 D	--

Fig. 1. Recommendations for endocrine therapy in premenopausal patients with metastatic breast cancer.

temic therapy of advanced breast cancer. Sequencing different endocrine steps may possibly sustain the endocrine responsiveness [5]. Otherwise, the increasing recognition of the roles of epidermal growth factor receptor (EGFR) and human EGFR2 (HER2) in cross-talk activation of ER signaling has led to studies aimed at identifying whether small-molecule tyrosine kinase inhibitors or monoclonal antibodies targeted against these receptors give additive or synergistic effects when combined with endocrine agents.

Premenopausal Patients

In premenopausal women with advanced breast cancer, the combination of LHRH (luteinizing hormone-releasing hormone) agonists plus tamoxifen is more effective than LHRH agonists or tamoxifen alone. Based on these data, the combination of an LHRH agonist plus tamoxifen is the recommended endocrine treatment in these patients [6]. If a patient shows tumor progression under this combination treatment and is still eligible for further hormonal treatment, she may benefit from ongoing ovarian suppression in combination with anastrozole [7]. Although there are no sufficient data regarding this situation, further ovarian function suppression accompanied by endocrine therapy similar to postmenopausal women is recommended (fig. 1).

Postmenopausal Metastatic Breast Cancer

After Adjuvant Tamoxifen

3rd-generation aromatase inhibitors (AIs) are the preferred 1st-line endocrine treatment in patients with recurrent disease progressing after or during adjuvant tamoxifen (fig. 2). In phase 3 trials, AIs were superior to tamoxifen in terms of re-

Endocrine Therapy In Postmenopausal Metastatic Breast Cancer Patients After Adjuvant Tamoxifen
		Oxford LOE	/ GR	AGO	
1 st line: aromatase inhibitors (3rd gen)*	1a	A		++	
2 nd line: fulvestrant	3b	C		+	
tamoxifen	3b	C		+	
aromatase inhibitor**	3b	C		+	
Further lines: MPA/MA	4	D		+	
repeating of previous treatments	5	D		+	

*The advantage of aromatase inhibitors has been proved mainly for TTP, CB, DOR and ORR. An overall survival benefit has not been demonstrated yet. Up to date, there is no evidence for superiority of a single aromatase inhibitor.
 ** steroidal or non-steroidal depending on previous AI

Fig. 2. Recommendations for endocrine therapy in postmenopausal metastatic breast cancer patients after adjuvant treatment with tamoxifen.

Endocrine Therapy In Postmenopausal Metastatic Breast Cancer Patients After Adjuvant AI
		Oxford LOE	/ GR	AGO	
1 st line: tamoxifen	2b	B		++	
exemestan after non steroidal AI	2b	B		+	
2 nd line: fulvestrant	3b	C		+	
tamoxifen (if previously not given)	5	D		+	
Further lines:					
MPA/MA	4	C		+	
repeating of previous treatments	5	D		+/-	

Fig. 3. Recommendations for endocrine therapy in postmenopausal metastatic breast cancer patients after adjuvant treatment with an aromatase inhibitor (AI).

Endocrine Therapy In Postmenopausal Metastatic Breast Cancer Patients After Switch Adjuvant Tamoxifen → AI
		Oxford LOE	/ GR	AGO	
If short treatment free intervall:					
> fulvestrant	4	D		+	
> aromatase inhibitor*	4	D		+	
> tamoxifen	4	D		+/-	
If treatment free intervall > 1 year:					
> tamoxifen	4	D		+	
> aromatase inhibitor*	4	D		+	
> fulvestrant	4	D		+/-	

* Steroidal or non-steroidal depending on previous AI

Fig. 4. Recommendations for endocrine therapy in postmenopausal metastatic breast cancer patients after switch from adjuvant tamoxifen to an aromatase inhibitor (AI).

sponse rate, clinical benefit rate and time to progression. In second-line treatment, fulvestrant, a second AI or tamoxifen again are reasonable options. Steroidal AIs (exemestane) have shown activity after failure of non-steroidal AIs (letrozole, anastrozole) [8]. Vice versa, patients receiving exemestane as first anti-aromatase agent may also benefit from letrozole or anastrozole after disease progression [9]. There is a non-cross resistance between steroidal and non-steroidal anti-aromatase agents. It is therefore assumed that the partial non-cross resistance between steroidal and non-steroidal anti-aromatase agents is independent of the sequence employed. In phase III trials, fulvestrant has been shown to be at least as effective as the third-generation AI anastrozole in the treatment of postmenopausal women with advanced breast cancer progressing after prior tamoxifen therapy [3]. Fulvestrant is administered as a once-monthly 250 mg intramuscular injection into the gluteus muscle. Compared with AIs and tamoxifen, fulvestrant is equally well tolerated [10]. Also, after progression during fulvestrant treatment, tumor cells may retain their endocrine sensitivity (mainly when patients showed a tumor response to the preceding treatment) so that other endocrine drugs have shown activity, even in heavily endocrine-pretreated patients [5].

Because of their side effects, medroxyprogesterone acetate (MPA) and megestrol acetate (MA) are the last choice of endocrine treatment options. In patients treated with all available endocrine drugs, retreatment with previously applied agents may in some cases be a reasonable option. Selective ER modulators (SERMS), such as toremifene and raloxifene, have only poor efficacy following tamoxifen failure [11].

After Adjuvant AI

There are only few data regarding the efficacy of endocrine agents after progression during or following adjuvant AI treatment. Treatment options in this situation are tamoxifen (clinical benefit 50%) [12] or a non-cross-resistant AI (25–44%) (fig. 3) [8, 9]. Further treatment options are fulvestrant and MPA/MA.

After Switching from Adjuvant Tamoxifen to AI

As a result of the currently used switching of adjuvant endocrine treatment, this situation is new and will increase in the future. However, in postmenopausal women with advanced breast cancer and previous adjuvant tamoxifen and AI therapy, the treatment-free interval is an important issue. If relapse occurred during or shortly after switching, patients might benefit the most from fulvestrant or a non-cross resistant AI. It is assumed that patients who respond to fulvestrant could restore sensitivity to subsequent endocrine therapies [5]. If the treatment-free interval was 'long', tamoxifen, non-cross resistant AI or fulvestrant are the treatment options. The level of evidence is however low, since there are only few retrospective data and so far no prospectively randomized trials dealing with these issues (fig. 4).

Combination of endocrine and cytostatic therapy is not recommendable, because the combination induces rather increased toxicity and does not result in an improvement of disease-free interval or overall survival [13, 14]. Thus, endocrine and cytostatic therapy should be performed as sequential treatment modalities. There are unfortunately no data on HER2-positive hormone receptor-positive patients regarding the value of the upfront combination of endocrine therapy and trastuzumab in metastatic breast cancer. Studies with the AIs anastrozole and letrozole $\pm$ trastuzumab have been finished or are still ongoing.

There are only limited data about the effects of maintenance endocrine therapy following chemotherapy-induced response in hormone-sensitive tumors. Analyses by Berruti et al. [15] and Montemuro et al. [16] suggest a benefit in time to progression and overall survival for endocrine maintenance therapy. However, these are retrospective analyses so that the prognostic impact of maintenance endocrine therapy needs confirmation in randomized studies.

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