Role of hormonal manipulations in patients with hormone-sensitive metastatic breast cancer

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Introduction

More than 90% of breast cancers are diagnosed at an early stage, when only a primary tumour and at most axillary lymph node metastases are detectable. Despite this, during the course of follow-up several patients will develop a recurrence, and patients with diffuse metastases in distant organs will then have to be considered incurable. Patients with oligo-metastatic disease (only few lesions) localised in one single organ may represent an exception to this dismal prognosis, however randomised trials are required in order to determine whether long survival is due to the aggressive pluridisciplinary approach or to the indolent course of the disease [1].

Several premenopausal patients and most of the postmenopausal patients present at diagnosis with a disease showing an expression of hormone receptors. At recurrence some patients maintain the level of hormone receptor expression, whereas in a certain percentage of patients hormone receptor status may change, either becoming less important or even negative [2,3]. This observation illustrates the importance of determining hormone receptor status in metastases (as far as possible) in order to avoid treatments without hope for activity.

The treatment of metastatic disease is mostly palliative and aims at maintaining the patient's quality of life by possibly reducing symptoms of the disease and preventing complications. Whether therapy at this stage of the disease has an impact on survival is still a matter of discussion.

For this reason the choice to treat a patient with metastatic disease by endocrine therapy alone is an important option in several circumstances: positive hormone receptors, low tumour burden, long interval between diagnosis of the primary and diagnosis of the metastatic process, patient asymptomatic or oligosymptomatic, little or no involvement of visceral organs. Hormonal therapy remains the mainstay of hormone receptor-positive metastatic breast cancer management (MBC) which is represented by new breast cancer molecular classification: Luminal A and B. This molecular profile is based upon variation in gene expression, which has identified several distinct breast cancer subtypes, of which Luminal A and B are hormone receptor-positive with a genetic profile similar to normal luminal cells. The prognosis of these subtypes, which are hormone sensitive, is better than basal-like and HER2 tumours.

In women with hormone receptor-positive metastatic breast cancer endocrine treatments are therefore often favoured as the initial treatment because they offer effective therapy without the toxicity of cytotoxic drugs.

Oestrogen deprivation is the key therapeutic approach in the treatment of metastatic hormone-sensitive breast cancer. The most important strategies employed are the reduction of oestrogen production (ovarian function suppression and inhibition of the aromatisation), the block of oestrogen at the receptor level (SERMs), or the degradation of the oestrogen receptor (SERDs).

The origin of hormonal manipulations in the treatment of advanced breast cancer

In 1896 Sir George Beatson reported in the Lancet [4] excellent responses in 3 patients with advanced breast cancer treated by surgical oophorectomy. The hospital records apparently show that while he was investigating the procedure he carried out ovarian removal on six patients, but his original article only reports on three. The other three, who remained anonymous, did not fare particularly well … The idea of performing oophorectomy for advanced breast cancer was not new and had already been described during a congress (but not published in a full paper) by a young German surgeon named Schinzinger.

Where did Beatson's idea come from? He had noted significant changes in the ovary of sheep during lactation, and postulated a non-nervous connection

between two organs, with one organ seeming to control the other (hormones were described by Ernst Starling only in 1905, and oestrogens were discovered in the 1920 and isolated and biochemically characterised in the 1930!). However, he incorrectly associated the changes in the pregnant breast with the pathological changes observed in malignancy. It was this serendipitous postulate that encouraged him to investigate ovarian removal in women with locally advanced breast cancer.

In 1958, by chance, the non-steroidal anti-oestrogens were discovered; the idea that they could be used as contraceptives or "morning after pill" did not translate to reality as they actually induced ovulation in sub-fertile women. In 1961 E. Jensen [5] first described the hormone receptors, and in 1966–67 Harper and Walpole discovered tamoxifen that was however not developed for breast cancer patients until 1975 [6].

More than 70 years after the first oophorectomy report, Richard Santen and Alan Lipton in 1972 started the first clinical trial with an aromatase inhibitor (aminoglutethimide) in breast cancer patients, after Ralph Dorfman, André Meyer and others had described aromatisation [7].

Hormonal therapies in premenopausal patients with metastatic disease

Oestrogen is a potent mitogen in several cells expressing oestrogen receptor and therefore the most powerful hormone stimulating breast cancer growth [8].

The endocrine treatment options for hormone-responsive metastatic breast cancer in premenopausal women are still limited compared with those available in postmenopausal women. Appropriate initial options include selective oestrogen receptor modulators such as tamoxifen or toremifen, ovarian ablation, or ovarian function suppression with luteinising hormone-releasing hormone (LHRH) agonists such as goserelin, leuprolide or triptorelin, or the combination of ovarian suppression and tamoxifen.

Tamoxifen

Tamoxifen is a selective oestrogen receptor modulator (SERM) that antagonises the action of oestrogen in certain tissues, such as the breast tissue. It inhibits the growth of breast cancer cells by competitive antagonism of oestrogen at its receptor, which leads to interrupted cell proliferation and ultimately to cell death.

However, its actions are multifaceted and tamoxifen also mimics the action of oestrogen in other tissues with a partial oestrogen agonist activity, such as the bone and uterus. These partial agonist effects can be beneficial – as in preventing bone demineralisation – but detrimental as well, for example by increasing the risk of uterine cancer by 2.4 times and of thromboembolic events by 1.9 times [9].

In premenopausal women with hormone receptor-positive MBC, who are tamoxifen-naive or who have relapsed more than 12 months after the end of adjuvant tamoxifen therapy, the first-line endocrine treatment recommended remains tamoxifen. In the adjuvant setting the overview by the Early Breast Cancer Trialist' Collaborative Group showed a clear benefit for adjuvant tamoxifen in terms of both survival and reduction in recurrence in premenopausal women with ER-positive tumours or tumours of unknown ER status [10]; however, the use of tamoxifen in premenopausal women with advanced disease has not been clearly demonstrated.

For premenopausal patients with tumours expressing oestrogen receptors (ER) and/or progesterone receptors (PR) the reported overall response rate is about 70% with tamoxifen [11]. The duration of response is usually between 12 and 18 months and benefit may persist for several years [11,12].

Some women have a remission lasting more than five years, but resistance to tamoxifen inevitably develops [13]. While in adjuvant treatment tamoxifen shows a clear benefit in terms of survival and reduction of recurrence in premenopausal women [14], with advanced disease the survival benefit of tamoxifen [15] has not been demonstrated so clearly. Compared with ovarian ablation, which has long been the hormonal treatment of choice for premenopausal women with metastatic breast cancer, the overall survival is similar between these two approaches, a median of 2.35 years for tamoxifen and 2.46 for ovarian ablatation [15,16].

A single oral, daily, 20 mg dose is recommended, as higher doses have not been shown to be more effective but are more toxic. Tamoxifen metabolites have long half-lives ranging from 7 to 14 days, which allows for a once-daily administration. Steady state levels are reached after about one month of therapy [13,16].

A transient "flare reaction", characterised by an increase in bone pain, skin erythema and/or an increase in the size and/or number of metastatic skin nodules occurs in 3–13% of patients, from two days to three weeks after starting tamoxifen [17]. The flare phenomenon appears to be limited to ER agonist therapies and this reaction is claimed

to be identifying a subset of women with a higher degree of binding to ERs, who are more likely to respond to endocrine therapy [18]. Drug resistance is the main limitation of all therapies in MBC and for tamoxifen the loss of ER expression is one possible explanation for the acquisition of resistance. However, between 15% and 30% of patients with tamoxifen resistance obtain clinical benefit from subsequent endocrine therapies, suggesting that breast cancer cells, despite becoming tamoxifen resistant, remain oestrogen-dependent and that ER signal transduction pathways could be effectively targeted for alternative endocrine therapies.

Toremifen

Toremifen is a SERM that is 40-fold less oestrogenic than tamoxifen. Several trials and a meta-analysis comparing toremifen versus tamoxifen in patients with untreated MBC have concluded that both agents have comparable activity and similar toxicity [19,20]. Toremifen is therefore an alternative to tamoxifen but does not provide any specific advantage over tamoxifen. In particular, in clinical trials no benefit in terms of endometrial cancer could be observed. Toremifen shows cross-resistance to tamoxifen and in second-line therapy after tamoxifen no benefit could be demonstrated [21].

Pyrrhönen and colleagues, in a meta-analysis of trials comparing toremifen with tamoxifen, report a statistical equivalence between the both molecules, especially in terms of survival, with median survival times from 31.0 months in toremifen to 33.1 months in tamoxifen groups ($P = 0.758$). Relative risk for death (tamoxifen:toremifen) was 0.98 (95% CI of 0.83–1.15) indicating equivalent survival between the two treatments [20].

Oestrogen deprivation: oophorectomy or GnRH angonists

The predominant sites of oestrogen synthesis in premenopausal women are the ovaries. In order to create a state of oestrogen deprivation the classical endocrine manipulation for these patients with advanced breast cancer has been for several decades surgical oophorectomy, with removal of both ovaries [4]. It results in objective responses in about one-third of unselected premenopausal women with MBC [15,22]. Compared with tamoxifen, ovarian ablation is associated with similar response rates (16% vs 25% $P = 0.69$), time to progression (TTP) (median TTP = 0.34 year with ovarian ablation vs 0.5 with tamoxifen $P = 0.40$) and survival (median survival time = 2.46 years for ovarian ablation vs 2.35 years for tamoxifen, as first treatment) [15].

An alternative to surgery is the medical suppression of the ovarian function with a luteinising hormone-releasing hormone (LHRH) agonist such as goserelin or leuprolide [23,24]. The pituitary gland is stimulated by pulses of LHRH, producing pulsatile secretion of gonadotrophins and maintaining the cyclical activity of the gonads. Chronic administration of GnRH agonists – peptide analogs of LHRH, but 50–100-fold more potent than the natural hormone – results in an initial stimulation of gonadotrophin release, which is quickly followed by a fall of secretion and a subsequent decrease in the circulating oestrogen concentrations to postmenopausal levels [25]. In addition, in vitro work has demonstrated that LHRH agonists may have some direct antitumoral effect [26,27].

No large randomised trial has as yet compared surgical ovarian ablation versus medical ovarian suppression. A series of phase II studies with different LHRH agonists, including goserelin and buserelin, have demonstrated the activity of these agents in premenopausal women with advanced breast cancer, showing a response rate of about 30% with a duration of response of 4 months [24,25,28]. Furthermore, small randomised trials showed that treatment with the GnRH agonist, goserelin, provided a clinical benefit similar to surgical oophorectomy or tamoxifen in terms of both progression-free and overall survival [23,29–31]. A small prospective randomised trial compared the overall survival (OS) and failure-free-survival (FFS) in 138 premenopausal women with ER- or progesterone receptor (PR)-positive previously untreated MBC, treated with either oophorectomy or goserelin. There was no statistically significant difference between the two treatment arms regarding response rate, failure-free survival and overall survival [32]. However, surgical castration immediately reduced oestrogen levels to the postmenopausal range while medical ablation may take several weeks to take full effect and there is reversibility of postmenopausal state after the discontinuation of therapy.

Boccardo and colleagues [31] reported the results of a study in 85 premenopausal women with MBC with ER-positive and/or PR-positive or unknown receptor status and randomised to ovarian ablation (surgical or via radiation) with or without tamoxifen versus goserelin with or without tamoxifen. There was no statistically significant difference between the four different treatment arms. However, the study was terminated early due to poor accrual, preventing therefore the detectection of small differences. Patients' survival was comparable, irrespective of

allocated treatment. This indicates that oophorectomy (or ovarian irradiation) and goserelin have comparable efficacies.

As second line after failure with tamoxifen

For premenopausal women progressing after initial treatment with tamoxifen, ovarian function suppression is an alternative to chemotherapy, except in women who have rapidly progressive or visceral disease.

Especially if there was a response to the first-line therapy with tamoxifen, responses to oophorectomy or ovarian suppression can be observed [33].

Resistance to anti-oestrogens is one of the major challenges in breast cancer treatment. Various mechanisms can contribute to tamoxifen resistance, including kinase activity, that results in phosphorylation of oestrogen receptor alpha (ERα). It has been shown that phosphorylation of ERα at serine 305 (pERαSER305) [34] by protein kinase A (PKA) leads to an activation of ERα and to transcription of ERα-responsive genes in response to tamoxifen treatment, thus inducing resistance [35]. Some papers suggest that patients with tumours expressing PAK1 and pERαSER305 in combination are a group for which tamoxifen treatment could be insufficient [36] and that PAK1 and pERαSER305 could be associated with sensitivity to tamoxifen and could predict tamoxifen benefit [37]. This however must be confirmed before being used in clinical practice.

Ovarian ablation or suppression in combination with tamoxifen

Combined therapy with tamoxifen and ovarian ablation/suppression is favoured over either approach alone for premenopausal women, because the combination results in higher response rates and a longer time to progression (TTP).

Four small randomised trials in pre- and perimenopausal women with metastatic breast cancer compared treatment with a LHRH analog alone versus the combination of tamoxifen and a LHRH analog. Klijn and colleagues reported a meta-analysis of the four randomised trials [30] at a median follow-up of 6.8 years including 506 patients. 79% of patients received goserelin as the LHRH agonist and the other 21% buserelin. 62% of patients were ER positive, 16% ER negative and 22% had an unknown ER status. The combination of tamoxifen and a LHRH analog was superior to a LHRH analog alone in terms of OS, overall response rate (ORR) and progression-free survival (PFS). Combination treatment was associated with a higher response rate (39% versus 30%), a significant 30% reduction in the hazard of progression, and 22% reduction of mortality over 6.8 years, which translated to an absolute improvement in median survival of 2 to 3 months.

The only trial that included a tamoxifen-alone control arm also concluded that combined therapy with buserelin plus tamoxifen was superior to either drug alone in terms of response rate (RR), PFS and OS [38].

Combined therapy does not seem to be associated with increased side effects [39].

Based on these trial results, the combination of ovarian ablation or suppression with tamoxifen as first-line endocrine therapy seems to be superior to either modality alone and it can be recommended for premenopausal women with hormone receptor-positive MBC who have either never received adjuvant tamoxifen or relapsed more than 12 months after completion of such therapy.

However, the overall survival benefit from the combination therapy is small. It is therefore a reasonable option to offer to pre- or perimenopausal patients sequential treatments with tamoxifen initially, followed by either a GnRH agonist or surgical oophorectomy at the time of disease progression.

Aromatase inhibitors (AIs)

AIs of the 3rd generation (anastrozole, letrozole, exemestane) are highly effective in postmenopausal women, but are generally not recommended in premenopausal women without concomitant ovarian function suppression. Aromatase inhibitors inactivate or block the peripheral conversion of androgen to oestrogen by inhibiting aromatase. The reduced feedback of oestrogen to the hypothalamus and pituitary gland in premenopausal patients increases gonadotrophin secretion, which stimulates the ovary, leading to an increase in androgen substrate and aromatase. AIs are not able to overcome ovarian aromatase activity. Therefore, only postmenopausal women or women with nonfunctioning ovaries, who underwent either medical or surgical ovarian suppression, can benefit from AIs.

A small randomised trial combining ovarian function suppression and anastrozole versus ovarian function suppression and tamoxifen was performed in 119 peri/premenopausal women with hormone-dependent MBC who had no previous endocrine therapy for advanced disease [40]. All patients received goserelin 3.6 mg depot injection every 28 days and were randomised to receive it concurrently with anastrozole

or tamoxifen. The ORR was greater for goserelin in combination with anastrozole than in combination with tamoxifen (80% vs 53%, $P = 0.0023$). The clinical benefit rate (CBR) was also superior for goserelin in combination with anastrozole (12.1 months for goserelin and anastrozole vs 8.3 months for goserelin and tamoxifen. The median time to death was also prolonged for goserelin and anastrozole (18.9 months vs 14.3 months, HR: 0.413, $P = 0.0001$). Interestingly enough no advantage in premenopausal patients could be detected for the combination LHRH-analogues and AIs versus LHRH-analogues and tamoxifen in a large trial in the adjuvant setting [41]. Results of the small trial in MBC need therefore further confirmation.

Recent data of a phase II study confirm that the combination of goserelin plus anastrozole has activity in the treatment of premenopausal women with hormone receptor-positive metastatic breast cancer. Of the 32 patients evaluable for response, 3.1% experienced a complete response, 34.4% a partial response and 34.4% experienced stable disease for 6 months or longer, with a clinical benefit rate of 71.9%. Median time to progression was 8.3 months and median survival was not reached (range 2.1 months to more than 63 months). One patient remains on treatment and has been in complete response for more than 63 months [42].

Trastuzumab in combination with hormonal treatment

HER2 is over-expressed by approximately 18–20% of all breast cancers. High expression levels identify patients who might respond to therapies targeting HER2, such as trastuzumab and lapatinib. Another option for initial treatment of women with ER/PR-positive, HER2-positive MBC is the combination of trastuzumab plus hormone therapy rather than hormone therapy alone. In the trastuzumab pivotal trials, approximately 50% of patients with HER2-positive metastatic disease were also ER positive [43]. Together, these data show that ER/HER2 co-positive disease is common, and it is of interest to explore specific treatment options for these patients. The TAnDEM trial of anastrozole plus trastuzumab versus anatrozole alone suggests that the addition of trastuzumab yielded a modest improvements in PFS in patient, 5.6 months vs 3.8 months, $P = 0.006$), and RR. The overall survival showed no statistically significant treatment difference (28.5 vs 23.9 months, $P = 0.325$). However 70% of the patients in the anastrozole arm crossed over to receive trastuzumab after progression on anastrozole alone [44].

Summary

For premenopausal women who have never received adjuvant tamoxifen or who relapsed more than 12 months after completion of such therapy, a combination of GnRH agonist and tamoxifen as first-line therapy is recommended. However the gain in OS from combination therapy is small and the alternative approach remains sequential treatment consisting of tamoxifen followed by a GnRH analog or ovariectomy at time of progression.

Women who relapse within 12 months of adjuvant tamoxifen will mostly need chemotherapy.

In case of progressive disease after ablation/suppression of ovarian function or after tamoxifen, alternative endocrine therapy could be proposed, including an AI if the patient has become menopausal or is concomitantly treated with GnRH analogs.

In case of MBC with overexpression of HER2 and expression of hormone receptor, there is an indication to apply simultaneously trastuzumab plus hormone therapy rather than an endocrine therapy alone.

Hormonal therapies in postmenopausal patients

The majority of postmenopausal patients have primary tumours expressing hormone receptors, and are therefore candidates in the metastatic setting for an endocrine therapy, except if a rapid response is needed due to impending complications of the tumour or its metastases.

Depending on the interval between the end of the adjuvant endocrine therapy and the relapse, and depending on the adjuvant treatment given to the patient, several options are available in this patient population.

Tamoxifen

This compound has been introduced in the treatment of metastatic breast cancer several decades ago: the first report on its use was published in 1971 [45].

Tamoxifen in the metastastic setting was shown to yield a response rate of about 35% (in patients with positive oestrogen receptors 46%, and patients with negative ones 12%), with an additional 20% of the patients experiencing a stabilisation of their disease, and a progression-free survival between 2 and 24 months [46,47]. Its contribution to prolongation of survival in patients with incurable disease is less investigated, as most of the trials only reported duration of response or progression-free survival.

In the 1980s Tamoxifen has been compared to several other endocrine therapies such as oestrogens,

androgens, progestins, aminoglutethimide, oophorectomy and adrenalectomy; response rates have been reported as generally similar between tamoxifen and these other compounds, but side effects of tamoxifen were mostly less severe and less disturbing to the patients [48–51].

In the same decade tamoxifen alone has been compared to combinations of endocrine therapies, and the results showed that response rates with the single agent were similar to those achieved with the more toxic combinations [52,53].

In recent years tamoxifen has been compared to aromatase inhibitors of the 3rd generation and the results will be described in the corresponding subsection.

Nowadays tamoxifen is used mostly in patients who recur after adjuvant aromatase inhibitors; its real value in this setting has however been less investigated. Tamoxifen can be re-introduced in patients who have received it in the adjuvant setting and who recur with an endocrine-responsive disease more than 12 months after the end of adjuvant tamoxifen.

Aromatase inhibitors

Aromatase inhibitors of the first and second generation (aminoglutethimide, 4-hydroxy-androstenedione) had severe side effects (somnolence, skin rashes, need to be applied i.m.), and were not selective in terms of inhibition of the aromatase enzymes; consequently, they have been replaced completely by the compounds of the 3rd generation (the non-steroidal compounds letrozole and anastrozole and the steroidal compound exemestane).

The 3rd generation of these compounds has been shown in several randomised trials to be equivalent or superior to tamoxifen (first line) and to progestins (second line after failure of tamoxifen) in terms of progression-free survival [54,55]. Overall survival in the different comparisons has not shown statistically significant differences in favour of aromatase inhibitors.

In addition, they show a different toxicity profile than tamoxifen and progestins: arthralgia and myalgia are the most common side effects, and they do not increase thrombo-embolisms or endometrial cancer, as does tamoxifen, or induce weight gain and liquid retention, as do progestins.

After the publication of several trials showing their superiority to tamoxifen in the adjuvant situation, aromatase inhibitors are nowadays frequently used in early breast cancer. For patients recurring after adjuvant steroidal or non-steroidal aromatase inhibitors who are still endocrine responsive, treatment may consist in the switch to non-steroidal or steroidal compounds (if the therapy-free interval is exceeding 1 year), fulvestrant or tamoxifen.

Fulvestrant

This drug prevents the binding of endogenous oestrogens to ER and thus abrogates the oestrogen-regulated gene transcription pathways that drive cell proliferation [56]. Unlike tamoxifen, fulvestrant is a pure receptor antagonist and it blocks the dimerisation of the receptor, limiting therefore its nuclear translocation [57].

The first investigations were conducted in second-line application following progression after prior endocrine therapy, using monthly regimes of 250 mg and 500 mg. In some of the trials an additional loading dose of 250 or 500 mg was administered on day 14.

Most of the trials investigating 250 mg per month compared fulvestrant to either steroidal or non-steroidal AIs, showing comparable results in terms of time to progression and response rates for the different modalities [58]. Time to treatment failure was between 3.7 and 5.5 months and the overall response rate between 10% and 20.7%, with a clinical benefit for about 42–48% of the patients.

When the loading dose was added fulvestrant had the same efficacy as exemestane [59] with a time to progression of 3.7 months for both treatments and similar response rates, durations of response and quality of life assessments. As in many trials in the metastatic setting, overall survival was not the primary endpoint. Conclusions about the impact of fulvestrant on overall survival cannot be drawn with the available data.

Fulvestrant was compared to tamoxifen in the first-line setting in one large randomised trial. It was inferior to tamoxifen in terms of time to progression (6.8 months compared to 8.3 for tamoxifen) and clinical benefit (54.3% versus 62% for tamoxifen). In this trial overall survival was similar with tamoxifen and fulvestrant (40.7 versus 39.3 months) [60]. These results have prevented the development of the compound for the adjuvant setting.

Fulvestrant has also been investigated in the second-line setting at a dose of 500 mg/month compared to the same compound at 250 mg/month with or without loading dose, and as first-line compared to anastrozole in a phase II study. In second line the higher dose showed in 2 trials a benefit in terms of time to progression and clinical benefit for western but not for Japanese, women, and in a phase III trial overall

survival was non-significantly longer with 500 mg (25.1 months versus 22.8) [61–63].

In untreated patients the primary endpoint (clinical benefit) and response rate did not differ between fulvestrant and anastrozole [64] but time to progression was prolonged with 500 mg fulvestrant (23.4 months) as compared to anastrozole (13.1 months; $P = 0.01$) (San Antonio Breast Cancer Conference 2010).

Progestins

Progestins have been used in the treatment of metastatic breast cancer for several years. The mechanism of action of these compounds is still not entirely clear, and is a matter of debate. Several compounds (medroxyprogesterone acetate, megestrol acetate, norethistrone, hydroxyprogesterone caproate) have been shown to produce a response rate in unselected patients of 10–40% [65]. In general a high-dose schedule has been applied in order to reach these results. Several randomised trials have compared progestins to tamoxifen and aminoglutethimide, and results in terms of response rate and time to treatment failure as well as duration of response and overall survival have been comparable. In more recent years they have been compared to aromatase inhibitors as second-line therapy after failure with anti-oestrogens. Aromatase inhibitors have shown significant gains in efficacy and improved tolerability, leading to the nearly complete disappearance of the more toxic progestins [66].

Oestrogens

Oestrogens have been the treatment of choice for metastatic breast cancer in postmenopausal women together with ovarian ablation for premenopusal patients in the period before the introduction of tamoxifen, progestins and aromatase-inhibitors.

A randomised trial including more than 500 patients showed that the best response (21%) was associated with the highest dose of diethyl-stilbestrol (DES) [67]. Interesting is the observation that about one quarter of patients treated with oestrogens will show a withdrawal response when oestrogens are terminated [68]. The partly prohibitive side effects (nausea, vomiting, thrombo-embolic events in particular) discourage its use currently, even though nowadays, with deeper insight in cellular pathways, its use is frequently discussed in sequence with targeted treatments for resuming hormonal sensitivity of tumours.

Androgens

Androgens have been shown to have activity in breast cancer, and have been compared to oestrogens in randomised trials. The results showed significantly less activity of androgens than oestrogens (remission rate 10% as compared to 16% for oestrogens) and the side effects, in particular masculinisation, prevent their wide use [69].

Special populations

Oligometastatic patients

It is still a matter of debate whether for these patients a real possibility of cure exists. Endocrine therapy is a valid option for this state and can be applied for reaching a complete remission of the disease or as a “maintenance” therapy after reaching complete remission by other means like chemotherapy or radiation therapy. It has however to be kept in mind that there is no scientific evidence that this approach yields benefits in terms of progression-free or overall survival.

Elderly

The treatment of elderly patients with metastatic breast cancer does not differ from the treatment of younger patients. Careful attention has however to be dedicated to the organ function and to the possible side effects of a palliative therapy in order to avoid cumulation of symptoms from pre-existing diseases and of systemic therapy. Response rate and time to progression of endocrine therapies have not been reported to be influenced by age.

Duration of hormonal treatment in the metastatic setting

The median time to progression for first-line endocrine therapy is generally between some months and 1 year, and frequently can exceed 2 years. Responses to second-line endocrine therapies are generally less frequent (~20%) and duration of response decreases with each additional therapeutic line [70].

Sequences

Optimal sequencing of endocrine agents becomes very important in the therapeutic strategy of metastatic breast cancer. Since the move to aromatase inhibitors in the adjuvant setting there is no consensus on the sequence of endocrine therapy to be used in the metastatic setting.

A possible algorithm could be to use, after non-steroidal aromatase inhibitors in the adjuvant setting, and if the therapy-free interval is exceeding 12 months as is usual in the population of patients with hormone-responsive disease, a steroidal aromatase

inhibitor [71], and to continue with tamoxifen or fulvestrant. In case of shorter therapy-free interval patients could benefit after aromatase inhibitors from tamoxifen or fulvestrant [72].

Some patients maintain endocrine responsiveness for a very long time and in these rare cases additional attempts can be made with progestins, oestrogens or androgens.

How many different courses?

If the patient maintains response to endocrine therapy several different courses can be applied. It is however infrequent that more than 3 different courses can be applied.

Outlook

One of the most important research fields in breast cancer and particularly in the metastatic stage of the disease will be the overcoming of primary endocrine resistance for patients who do not respond to hormonal manipulations despite expressing hormone receptors in their primary tumours and the maintenance of endocrine sensitivity, allowing for a longer application of hormonal therapy and leading therefore to a prolongation of survival for patients in this nowadays still incurable state. Several hypotheses exist on the cellular pathways that may lead to hormonal resistance in breast cancer, considering that hormonal resistance does not automatically mean also loss of oestrogen dependency by the tumour cells. Mutations of *PIK3CA* or oxidative stress of tumour cells have been described as possible mechanisms that may induce this resistance and which could be targeted by novel treatment options [73,74]. Combinations of targeted therapies like trastuzumab, pertuzumab, lapatinib and gefitinib have also been mentioned in the discussion as they could help blocking escape cellular pathways.

Other attempts are obviously ongoing to improve selectivity of available endocrine treatments and in particular to decrease toxicity and side effects of these therapies that can considerably decrease patients' quality of life.

Conclusion

Metastatic breast cancer remains an incurable situation, but systemic treatments can often control the disease and provide palliation, sometimes for several years. Endocrine treatment remains the most important approach for patients with tumours expressing hormone receptors, as their side effects are generally less distressing than those of chemotherapies. It remains controversial whether endocrine treatment for metastatic breast cancer can extend survival, but in general this is not the primary goal of these therapies.

Conflict of interest statement

The authors have no potential conflict of interest to disclose.

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